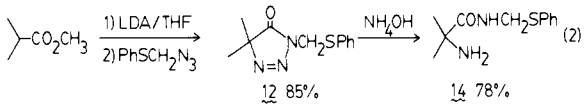
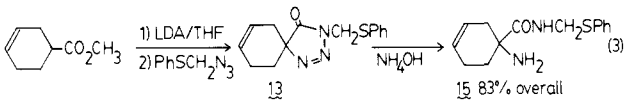
of **10**.[15] Formation of heterocycles is demonstrated by the indole synthesis (Table I, entry 5).

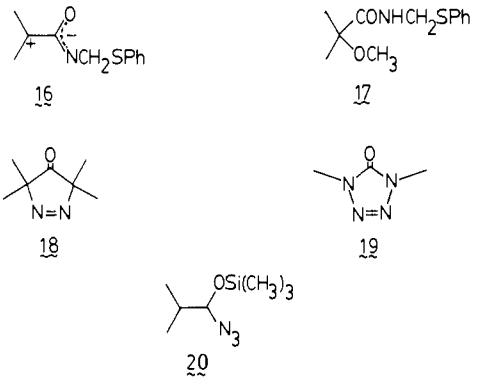
Initial efforts to extend this amination reaction to aliphatic and heteroaromatic (furan, thiophene, indole) organometallic reagents have not been fruitful. Formation of the triazenes occurred smoothly with aliphatic Grignard reagents, but satisfactory yields of amines upon hydrolysis have not been obtained.

On the other hand, enolates derived from α,α-disubstituted esters reacted smoothly to give a new heterocycle, a 5*H*-1,2,3-triazol-4-one (eq 2 and 3).[16] While in the case of **12**,[17] this





heterocycle was isolated as a crystalline solid, mp 78.5–79.5° (dec), their general instability (thermally decompose well below 100 °C) led us to react the crude triazolones immediately. For α-amination, a THF solution of the triazolones **12** and **13** was treated with aqueous ammonium hydroxide which gave the α-amino amides **14**[18] and **15**[18] in excellent overall yields.[19] In fact, these heterocycles behave as if they are a functional equivalent of a zwitterion such as **16**. For example, dissolution of **12** in methanol containing magnesium methoxide led to a quantitative yield of **17**.[20] The thermal lability of the triazolones is further highlighted by the exceptional stability of the carbon and nitrogen analogues **18**[21] and **19**.[22]



(15) For lithiation of anilides, see: Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133.

(16) (a) The marked difference in physical and chemical properties between the heterocycles **12** and **13** and a related tautomer i[16b] and isomer ii[16b] emphasize the uniqueness of this heterocyclic system.

(b) Begtrup, M.; Pedersen, C. *Acta Chem. Scand.* **1969**, *23*, 633.

(17) IR ($CDCl_3$) 1730, 1667, 1575 cm^{-1}; NMR ($CDCl_3$) δ 7.40–7.65 (6 H, m), 5.30 (2 H, s), 1.31 (6 H, s). Mass spectrum, *m/z* (relative intensity) 151 (23), 123 (27), 110 (35), 109 (21), 98 (19), 84 (16), 70 (100). Anal. Calcd for $C_{11}H_{13}N_3OS$: 235.0777. Found: 235.0782.

(18) This compound has been characteirzed by IR and NMR spectroscopy. For complete characterization, the α-amino substituent was acetylated to give the crystalline acetamide derivatives, mp 127.5–128.0 and 136.5–137.0 °C from **14** and **15**, respectively. The amides were fully characterized spectrally and elemental composition established by high-resolution mass spectroscopy.

(19) For example, the triazolone **12** (3.2 mmol) was dissolved in THF (3.5 mL) and aqueous ammonium hydroxide (4.5 mL of 30% solution) was added. After stirring vigorously at room temperature overnight, aqueous workup and Florisil chromatography gave 0.56 g (78%) of **14**.

(20) The triazalone **12** (1.06 mmol) in THF (1 mL) was added to magnesium methoxide (1.17 mmol) in methanol (4 mL). After stirring 24 h at room temperature, ether was added, the mixture was filtered, and the filtrate was washed with 5% HCl. Workup followed by Florisil chromatography gave 235 mg (100%) of **17**.

(21) Engel, P. S.; Shen, L. *Can. J. Chem.* **1974**, *52*, 4040. Crawford, R. J.; Tokunaga, H. *Ibid.* **1974**, *52*, 4033. Pirkle, W. H.; Hoover, D. J. *J. Org. Chem.* **1980**, *45*, 3407.

Previous work has demonstrated the utility of substituted α-azido sulfides in molecular rearrangements to lactams and imino thioethers.[5] The present work demonstrates the utility of the parent system as a NH_2^+ equivalent. The uniqueness of this sulfur substituted reagent is further indicated by the recovery of the oxygen analogue[21] **20** unchanged after treatment with phenylmagnesium bromide. Further synthetic applications of this class of compounds is under investigation.

Acknowledgment. We thank the National Science Foundation for their generous support of our programs.

(22) Wadsworth, W. S. *J. Org. Chem.* **1969**, *34*, 2994.

(23) Vorbrüggen, H.; Krolikiewicz, K. *Synthesis* **1979**, 35.

On the Stereo- and Regiochemistry of a Palladium-Catalyzed O to C Migration

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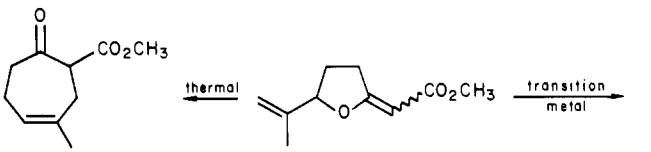
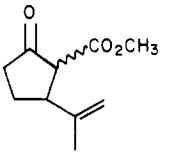
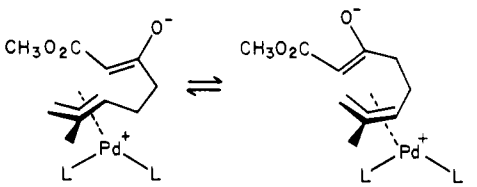
The ability to isomerize allyl vinyl ethers such as **1** to cyclopentanones under the influence of a transition-metal catalyst represents a reordering of the normal chemical reactivity of such compounds which, under thermolysis conditions, rearrange to cycloheptenones.[1-3] Such a reaction also can resolve a classic



1



problem of O vs. C alkylation of β-keto esters.[1] Mechanistic insight into this novel isomerization, especially its stereochemistry and regiochemistry, is required in order to apply it. In particular, if a π-allylpalladium complex such as **2** is an intermediate, the



2

(1) Trost, B. M.; Runge, T. A.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 2840.

(2) See: Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, 1475.

(3) Balavoine, G.; Guibe, F. *Tetrahedron Lett.* **1979**, 3949. Balavoine, G.; Bram, G.; Guibe, F. *Nouv. J. Chim.* **1978**, *2*, 207.

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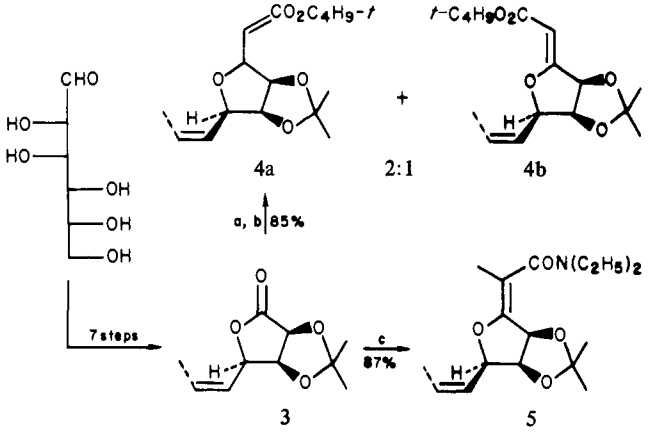
Scheme I. Synthesis of Alkylidenetetrahydrofurans[a]



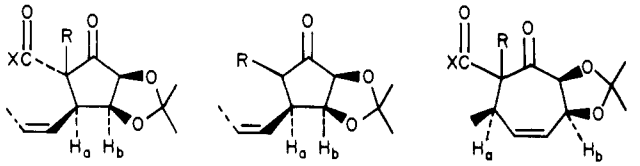
[a] (a) $LiCH_2CO_2C_4H_9t$, THF, −78 °C. (b) CH_3SO_2Cl, 3 equiv of DBU, THF, 0 °C. (c) $CH_3C{\equiv}CN(C_2H_5)_2$, $MgBr_2$, THF, 10 °C (cf. ref 7).

regioselectivity is quite surprising, since previous work in our laboratories suggested that palladium-catalyzed cyclizations normally preferred the larger of the two possible rings.[4] In this communication we not only delve into these questions but also report a new approach to alkylidenetetrahydrofurans and thus a new cyclopentanone and cycloheptenone synthesis.

Carbohydrates represent excellent substrates to examine the questions of stereo- and regiochemistry as well as to illustrate the particular applicability of this methodology in chiral synthesis.[5] Mannose was converted to the crystalline vinyl lactone **3** (see Scheme I) by a known seven-step sequence.[6] Olefination procedures using phosphonium ylides or phosphonate anions were unqualified failures. Two alternatives outlined in Scheme I proved highly successful and thus allowed excellent conversion of vinyl lactones to the requisite alkylidenetetrahydrofurans **4**[8] and **5**.[8]

Isomerization of (*Z*)-**4** with tetrakis(triphenylphosphine)palladium in Me_2SO gave a mixture of the seven-membered-ring compound **8** and the decarboalkoxylated five-membered-ring compound **7** (see Scheme II) in stark contrast to our earlier observations which led only to five-membered-ring compounds.[1] Utilizing a sterically less demanding catalyst, $(dppe)_2Pd$,[9a] produced only the seven-membered-ring compound **8**, whereas a polymer-bound catalyst[9b] (presumably a sterically hindered catalyst) gave virtually exclusively the five-membered-ring compounds **6** (17% isolated yield) and **7** (79% isolated yield) with a small amount of **8** (4% isolated yield). Assuming the source of the decarboalkoxylation was the presence of adventitious acid, we performed the reaction with the polymer catalyst in toluene in the presence of *O,N*-bis(trimethylsilyl)acetamide which allowed isolation of the cyclopentanone without decarboalkoxylation as its enol silyl ether in 98% isolated yield (see Scheme II). Direct

Scheme II. Rearrangement of Alkylidenetetrahydrofurans



6, R = H, X = OC_4H_9-*t*
9, R = CH_3, X = $N(C_2H_5)_2$

7, R = H

8, R = H, X = OC_4H_9-*t*
10, R = CH_3, X = $N(C_2H_5)_2$

rearrangement of **4**[e]	% yield	% **6**[f]	% **7**[f]	% **8**[f]
6% $(dppe)_2Pd$,[a] Me_2SO, 100 °C	64%			100
6% $(Ph_3P)_4Pd$,[b] Me_2SO, 60 °C	85%		59	41
P-Pd,[b,c] $PhCH_3$, 100 °C	Q	98[d]		2

rearrangement of **5**[e]	% yield	% **9**[f]	% **10**[f]
6% $(dppe)_2Pd$, Me_2SO	62%	56	44
6% $(dppe)_2Pd$, dioxane	93%	100	

[a] *E* isomer of **4** used for this run. [b] *Z* isomer of **4** used for this run. [c] *O,N*-Bis(trimethylsilyl)acetamide added. [d] Isolated as its trimethylsilyl enol ether. [e] The concentration of **4** and **5** varied from 0.2 to 0.02 M with no observable effect. [f] The products were isolated pure by preparative TLC on silica gel utilizing 50% C_2H_5OAc in hexane.

heating of this product at 70 °C in Me_2SO led to the decarboalkoxylated **7** in 82% isolated yield (overall from **4**). The ability to effect such a decarboalkoxylation under such mild conditions represents a useful new approach for such a process.

The amide **5** gave a 1.3:1 mixture of the five- and seven-membered-ring products **9** and **10** with $(dppe)_2Pd$ in Me_2SO but only the cyclopentanone **9** when dioxane was the solvent.

Since the β-keto ester **6**[8] exists as a 64:36 mixture of its keto and enol forms, respectively, it was best characterized after decarboalkoxylation to **7**,[8] mp 70–71 °C. A cyclopentanone carbonyl group was verified by the 1755-cm^{-1} carbonyl frequency. ^1H and ^{13}C data fully confirm the structural and geometrical assignments [*Z* olefinic protons at δ 5.48 and 5.62, J = 10.6 Hz; ^{13}C of CH_3 on (*Z*)-olefin at δ 13.2;[10a] *Z* ring stereochemistry with H_a at δ 3.13 and H_b at δ 4.63, J_{ab} = 4.3 Hz[10b]]. The cycloheptenone (IR 1740, 1715 cm^{-1}) structure **8**[8] was also verified spectrally. The cis relationship of the methyl group to the acetonide was indicated by the homoallylic coupling of H_a (δ 3.07) and H_b (δ 5.19) of J_{ab} = 1.7 Hz—a coupling that is geometrically precluded in the alternative isomer[11]—and by analogy to the amide case (vide infra).

Similar spectral arguments apply to cyclopentanone **9**[8] (IR 1760 and 1620 cm^{-1}). ^1H and ^{13}C NMR spectra indicate a *Z*-propenyl group (^1H: δ 5.82 and 5.48, J = 11.0 Hz, ^{13}C of CH_3: δ 13.3[10a]) and the cis relationship of this group to the acetonide group (H_a at δ 3.73 and H_b at δ 4.73, J = 4.9 Hz[10b]). The stereochemistry of the quaternary methyl group is established by a 16.5% NOE[12] between this angular methyl group and the proximal vinyl proton which indicates their cis orientation as well as the upfield ^{13}C shift of this methyl group (δ 17.8) as a result of the γ effect with the propenyl group. Cycloheptenone **10** (IR 1725 and 1620 cm^{-1}) shows a homoallylic coupling between H_a (δ 3.54) and H_b (δ 5.14)

(4) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743 and references cited therein.

(5) For recent reviews of the use of carbohydrates in synthesis, see: Fraser-Reid, B.; Anderson, R. C. *Prog. Chem. Org. Nat. Prod.* **1980**, *30*, 1. Hanessian, S. *Acc. Chem. Res.* **1979**, *5*, 159.

(6) Trost, B. M.; Klun, T. P. *J. Org. Chem.* **1980**, *45*, 4256.

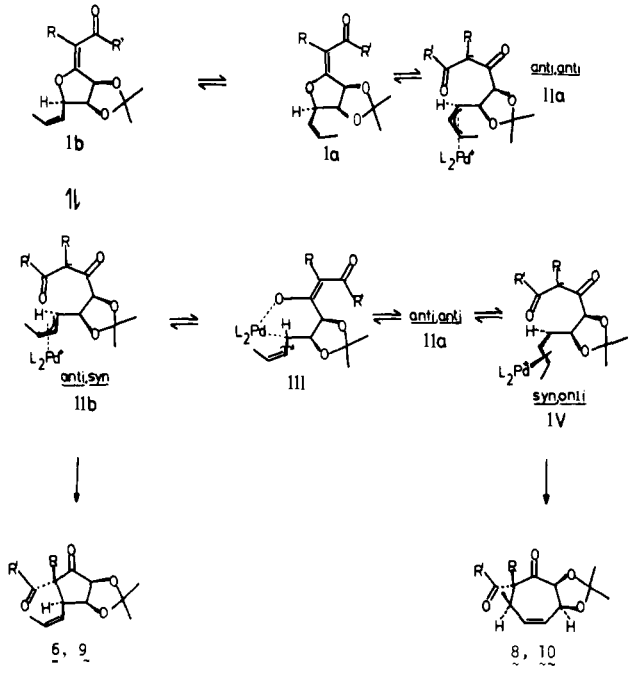
(7) Ficini, J.; Genet, J. P.; Depezay, J. C. *Bull. Soc. Chim. Fr.* **1973**, 3367. Ficini, J. *Tetrahedron* **1976**, *32*, 1449. We have found that significantly higher yields than previously reported are obtained by using THF rather than ether as solvent.

(8) This compound has been fully characterized by spectral means and for elemental composition either by high-resolution mass spectroscopy or by combustion analyses. These details appear as supplementary material.

(9) (a) $(dppe)_2Pd$ = bis[1,2-bis(diphenylphosphino)ethane]palladium. (b) This catalyst, developed by Mr. S. Springer in these laboratories, derived from phosphinylated polystyrene was prepared by the method of: Card, R. J.; Neckers, D. C. *J. Org. Chem.* **1978**, *43*, 2958. Schwartz, R. H. *Ibid.* **1979**, *44*, 2705.

(10) (a) In related *E* isomers, this chemical shift is observed at >δ18. (b) In related *E* isomers, $J \sim 0$ Hz.

Scheme III. Mechanistic Rationale for Pd(0)-Induced Rearrangements

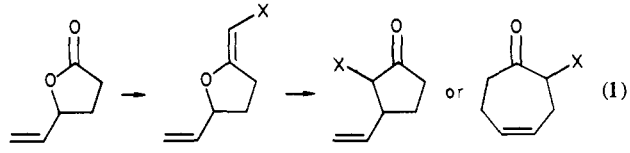


of J = 1.3 Hz—a coupling geometrically possible only in the isomer having the secondary methyl group cis to the acetonide.[11] The cis relationship of H_a to the amide group is supported by its abnormally low chemical shift due to deshielding by the amide carbonyl group; the cis relationship of the two methyl groups of the cycloheptenone ring is suggested by their high field shifts in the ^{13}C spectra at δ 13.5 and 16.5 for the methyl carbons at the secondary and tertiary centers, respectively. These spectral interpretations were fully confirmed by a single-crystal X-ray structural determination.[13]

The stereospecificity of this reaction is extraordinary. The stereochemistry of the cyclopentanones indicate that the C–O bond broken is replaced by the new C–C bond with complete retention of configuration—a result in accord with both the ionization initiated by palladium and the attack of the resultant enolate on the π-allylpalladium intermediate proceeding by inversion as in the case of palladium-mediated allylic alkylations.[14,15] The stereocontrol for a disubstituted olefin is unlike the intermolecular cases where substantial stereorandomization occurs for (*Z*)-olefins (although not (*E*)-olefins).[14a] The formation of a single stereoisomer at the quaternary center of **9** implies the stereochemistry of the alkylidene group of **5** may be the controlling factor. Regardless, this degree of stereochemical control at each center should prove of great synthetic utility.

Most remarkable has been the degree of control of regioselectivity that can be rationally exercised. Scheme III presents the overall picture. Previous work on vinyl lactones suggests that ionization occurs from conformer Ib rather than Ia to avoid formation of the unfavorable anti,anti-π-allyl complex IIa.[16] Formation of the cyclopentanones **6** and **9** occurs directly from the *anti,syn*-complex IIb. Creation of a cycloheptenone from IIb is precluded due to the fact that such a reaction requires creation of an (*E*)-olefin in the seven-membered ring. However, due to steric hindrance by the acetonide, attack to form such cyclopentanones is slowed. Thus, in this case, unlike our earlier simpler cases, syn–anti interconversion of the π-allyl unit can begin to compete with the desired cyclization. Such a syn–anti interconversion proceeds through σ-bonded intermediates such as III and can ultimately lead to IV. In IV, there are no geometric reasons why seven-membered-ring formation would be disfavored. Considering the steric hindrance associated with five-membered-ring formation, IV would be expected to collapse only to cycloheptenones. Thus, the effects of the change of ligands and solvents on the ratio of five- to seven-membered-ring formation arise from the effect of such changes on the rate of cyclization to cyclopentenones compared to the rate of syn–anti interconversion. Since Me_2SO is known to enhance syn–anti interconversion,[17a,c] simply switching from Me_2SO to dioxane totally eliminates cycloheptenone formation in the case of **5**. Switching from dppe to triphenylphosphine also slows syn–anti interconversion due to increased steric inhibition to form the σ complex.[17] In the case of **4**, this change effected an alteration in product ratio from exclusive formation of cycloheptenone **8** to a 1:1.3 ratio of the seven- and five-membered-ring products. By using an even bulkier catalyst and switching to toluene, the seven-membered-ring product was almost totally eliminated. Thus, from the same substrate total regiochemical control by simple and rational manipulation of reaction conditions is possible.

Cycloheptenone formation represents a Pd(0)-catalyzed version of the Claisen rearrangement which allows the reaction to be done under much milder conditions than the direct thermal method.[18] Most significantly, the results herein demonstrate an extraordinarily high level of control of the selectivity of organic reactions by transition-metal templates. In addition, this work extends the usefulness of this approach to both five- and seven-membered-ring compounds by utilizing the readily available vinyl lactones as precursors of the alkylidenetetrahydrofurans as summarized in eq 1.



(1)

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. We are especially indebted to Dr. Ken Haller for determining the X-ray crystal structure of **10**.

Supplementary Material Available: ^1H NMR, ^{13}C NMR, IR, and MS spectra as well as elemental analyses of compounds **4–10** (6 pages). Ordering information is given on any current masthead page.

(11) For maximum homoallylic coupling, both C–H bonds must be oriented parallel to the olefinic p orbitals. Chow, Y. L.; Streith, J.; Taurand, G. *Org. Magn. Reson.* **1973**, *5*, 155. Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; p 316.

(12) Noggle, J. H.; Shirmer, R. E. "The Nuclear Overhauser Effect: Chemical Applications"; Academic Press: New York, 1971.

(13) The X-ray structural determination was performed by Dr. K. Haller of the Instrumentation Center of the Department of Chemistry.

(14) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730. (b) *Ibid.* **1978**, *100*, 3435. (c) Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J.; Dietsche, T. J. *Ibid.* **1978**, *100*, 3416. (d) Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* **1976**, *41*, 3215. (e) *J. Am. Chem. Soc.* **1976**, *98*, 630.

(15) Other likely mechanisms including one proceeding through a π-allyl-oxa-π-allylpalladium intermediate are effectively eliminated by these results. For a case which may involve such an intermediate, see: Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199. Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381.

(16) Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* **1979**, *101*, 6756.

(17) (a) Cotton, F. A.; Faller, J. W.; Musco, A. *Inorg. Chem.* **1967**, *6*, 179. (b) Oslinger, M.; Powell, J. *Can. J. Chem.* **1973**, *51*, 284. (c) For reviews, see: Faller, J. W. *Adv. Organomet. Chem.* **1977**, *16*, 211. Tsutsui, M.; Courtney, A. *Ibid.* **1977**, *16*, 241.

(18) For a Pt(0)-catalyzed version, see ref 3. For a Pd(2+)-catalyzed Cope rearrangement, the all carbon analogue of the Claisen rearrangement, see: Overman, L. E.; Knoll, F. M. *J. Am. Chem. Soc.* **1980**, *102*, 865.