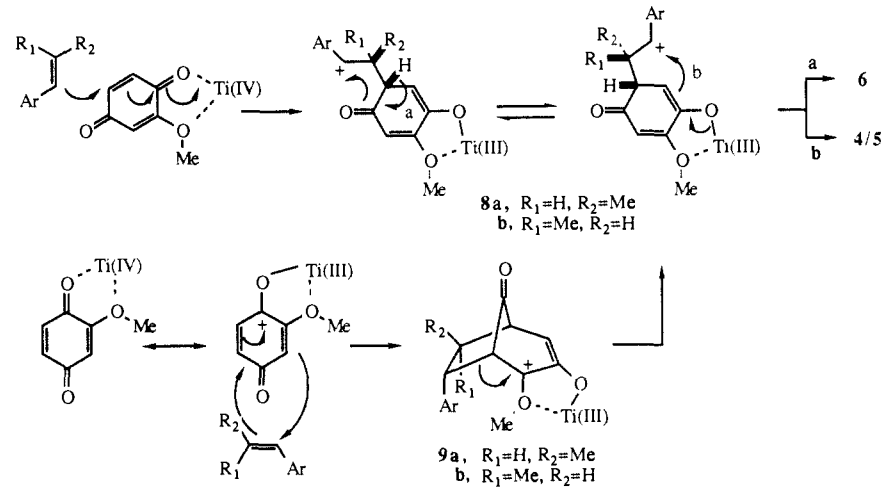
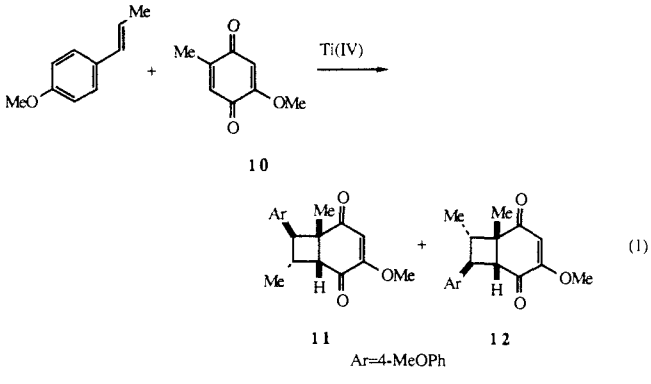
**Scheme II**



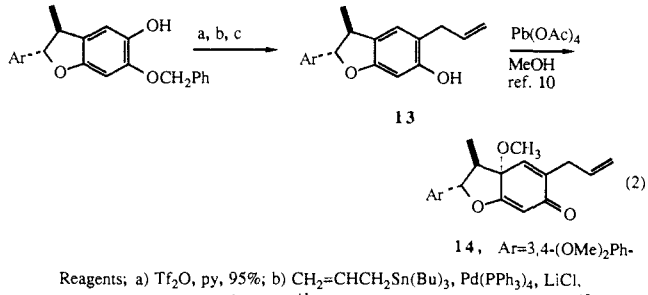

give **6** upon workup or via path **b** to give **4/5**. The stereospecific formation of **8** may be the result of an initial symmetry-allowed 5 + 2 ($4\pi + 2\pi$) cycloaddition between the quinone–titanium(IV) complex and the sytrenes **1/2** to give **9a/b**, respectively, which then rearrange to **8a/b**. Cycloadditions of alkenes and pentadienyl cations have ample literature precedence, and the aryl group of a styrene would be expected to occupy an endo position in similar cycloadditions with the quinone–titanium(IV) complex.[7-9] Intermediates analogous to **9** are known to rearrange under acidic conditions to give dihydrobenzofuran products.[8] Thus, the stereochemistry of the initial cycloaddition explains the specific formation of **4** and **5**.

Reactions of 2-methoxy-5-methyl-1,4-benzoquinone (**10**), with *trans*-β-methylsytrenes are stereoselective but not regioselective (eq 1). Treatment of **10** with a 3:1 mixture of $TiCl_4/Ti(O\mathit{i}Pr)_4$




(1)

(0.8 equiv) and then anethole (**1**) (X = 4-OMe) gives a 2:1 ratio of cyclobutanes **11** and **12** in 76% combined yield. Stereochemical assignments of **11** and **12** are based on $^1H$ NMR NOE data.[6]




(2)

Reagents; a) $Tf_2O$, py, 95%; b) $CH_2{=}CHCH_2Sn(Bu)_3$, $Pd(PPh_3)_4$, LiCl, DMF, 100°C, 95%;[11] c) $BF_3Et_2O$, $DMS/CH_2Cl_2$, rt, 67%.[12]

As an application of this new methodology, a total synthesis of (±)-kadsurenone (**14**),[10] a potent platelet activating factor antagonist, has been accomplished (eq 2). Phenol **13** is produced in four steps in 48% overall yield, and **13** has been oxidized directly to **14**. We are continuing to explore the synthetic utility and mechanism of the reactions described herein.

**Acknowledgment.** We thank Dr. Fusao Takusagawa for the crystal structure determination, Dr. David Vander Velde for help with the NOE experiments, and Dr. Mitree Ponpipom for copies of the NMR spectra of **13** and **14**. We gratefully acknowledge financial support from the University of Kansas General Research Fund, Research Corporation, Petroleum Research Fund, administered by the American Chemical Society, and, in part, the National Institutes of Health.

**Supplementary Material Available:** Summary of the NOE data on **4b**, **5b**, **11**, and **12** and an ORTEP diagram of **4b** [X = 3,4-$(OMe)_2$] (1 page). Ordering information is given on any current masthead page.

(7) (a) Heilmann, W.; Koschinsky, R.; Mayr, H. *J. Org. Chem.* **1987**, *52*, 1989. (b) Büchi, G.; Chu, P.-S. *Ibid.* **1981**, *46*, 1. (c) Sanchez, I. H.; Yanez, R.; Enriquez, R.; Joseph-Nathan, P. *Ibid.* **1981**, *46*, 2818. (d) Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1983**, *24*, 5011. (e) Wagner, E. R.; Moss, R. D.; Brooker, R. M.; Heeschen, J. P.; Potts, W. J.; Dilling, M. L. *Ibid.* **1965**, 4233. (f) Mamont, P. *Bull. Chim. Soc. Fr.* **1970**, 1557. (g) McGregor, H. H., Jr. Ph.D. Thesis, Harvard University, 1971 and references cited in the above.

(8) (a) Büchi, G.; Mak, C.-P. *J. Am. Chem. Soc.* **1977**, *99*, 8073. (b) Büchi, G.; Chu, P.-S. *J. Org. Chem.* **1978**, *43*, 3717. (c) de Alvarenga, M. A.; Brocksom, U.; Gottlieb, O. R.; Yoshida, M.; Filho, R.; Figliuolo, R. *J. Chem. Soc., Chem. Commun.* **1978**, 831.

(9) (a) Mori, M.; Hayamizu, A.; Kanematsu, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1259. (b) Ojima, I.; Yatabe, M.; Fuchikami, T. *J. Org. Chem.* **1982**, *47*, 2051 and ref 8.

(10) Ponpipom, M. M.; Bugianesi, R. L.; Brooker, D. R.; Yue, B.-Z.; Hwang, S.-B.; Shen, T.-Y. *J. Med. Chem.* **1987**, *30*, 136.

(11) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

(12) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull. Jpn.* **1980**, *28*, 3662.

## A Stereoselective Contrasteric Conversion of Epoxides to *cis*-Oxazolidin-2-ones

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The stereocontrolled introduction of heteroatoms represents a common synthetic challenge. The formation of vicinal amino alcohols via intermediate epoxides[1,2] is an attractive strategy

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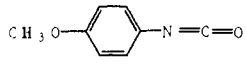
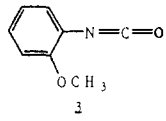
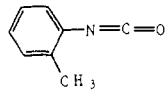
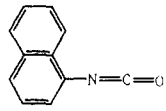
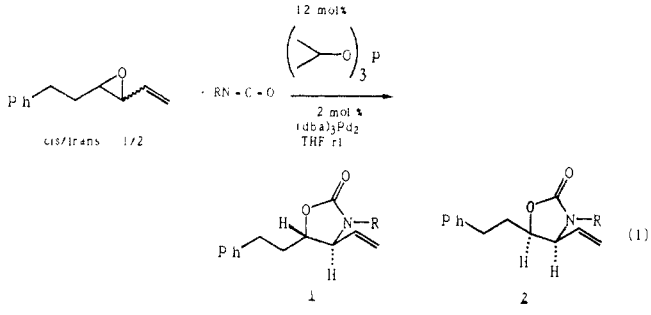
**Table I.** Dependence of Stereochemistry on Isocyanate

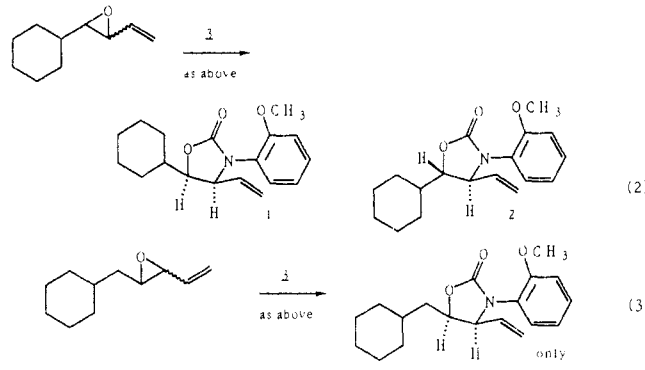
| entry | isocyanate | cis/trans | isolated yield (%) |
|---|---|---|---|
| 1 | TsN=C=O | 1/3 | 92 |
| 2 | PhN=C=O | 3.1/1 | 88 |
| 3 |  | 3.7/1 | 81 |
| 4 |  | 11/1 | 85 |
| 5 |  | 5.3/11 | 72 |
| 6 |  | 10/1 | 75 |

because of the ready availability of the substrates using the condensation of sulfur ylides with carbonyl groups[3] and of enantiomerically pure epoxides from olefins.[4] We previously noted the reaction of vinyl epoxides with *p*-toluenesulfonyl isocyanate in the presence of a Pd(0) catalyst is a very effective approach to vinyloxazolidin-2-ones.[5] In the course of our further studies, we observed an unexpected strong dependence of the stereochemistry of this reaction on the nature of the isocyanate substituent. We wish to report a most unexpected development in which vinyl epoxides are stereoselectively converted to the thermodynamically less stable (*Z*)-oxazolidin-2-ones regardless of the stereochemistry of the vinyl epoxides.



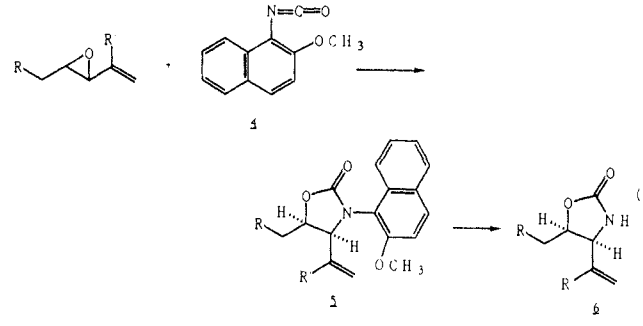
(1)

Equation 1 and Table I reveal the remarkable dependence of stereochemistry of the reaction of vinyl epoxides with isocyanates on the nature of the substituent. All the isocyanates except for *p*-toluenesulfonyl isocyanate, which produces a cis/trans product ratio reflective of that of starting epoxide, condense to produce preferentially the cis product even though the starting epoxide was mainly the trans isomer. While a strict correlation is lacking, the data suggests that steric more than electronic effects are responsible. Some dependence of steric hindrance around the epoxide also plays a role as revealed in eq 2 and 3.




The synthetic utility of this sequence relies on the removal of the substituent from nitrogen. The *p*-anisyl group is easily removed oxidatively using CAN,[6] but the diastereoselectivity using the corresponding isocyanate is modest. On the other hand, the *o*-anisyl isocyanate condenses to give excellent cis selectivity, but the oxidative cleavage fails. Rationalizing the failure of the oxidative cleavage as arising from hydroxylation para to the methoxy group, we designed 2-methoxy-1-naphthyl isocyanate (**4**),[7] available from the known amine[8] by reaction with the phosgene surrogate trichloromethyl chloroformate, as a reagent to provide high cis stereoselectivity and to possess a cleavable aryl substituent.

The sequence is summarized in eq 4 and Table II. To a yellow solution of the catalyst prepared by simply stirring 0.12 mmol of triisopropyl phosphite with 0.01 mmol of $(dba)_3Pd_2 \cdot CHCl_3$[9] in




0.5–1.0 mL of THF is added 1.1 mmol of isocyanate **4**. The epoxide (1 mmol) is added all at once, either neat or dissolved in 1 mL of THF, and the reaction is stirred 12–24 h until complete. Evaporation in vacuo and flash chromatography gives the pure *N*-aryloxazolidin-2-one.[10] Oxidative cleavage on a 0.5-mmol scale involves adding an aqueous solution of 1.5 mmol of CAN in 3 mL of water to the oxazolidinone in 3 mL of acetonitrile at 0 °C. After 20 min, the reaction is diluted with water and extracted with

(1) (a) For alternative approaches, see: Shibata, I.; Baba, A.; Iwasaki, H.; Matsuda, H. *J. Org. Chem.* **1986**, *51*, 2177. Fujiwara, M.; Baba, A.; Tomohisa, Y.; Matsuda, H. *Chem. Lett.* **1986**, 1963. Mereyala, H. B.; Frei, B. *Helv. Chim. Acta* **1986**, *69*, 415. Julina, R.; Herzig, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta.* **1986**, *69*, 368. Baba, A.; Fujiwara, M.; Matsuda, H. *Tetrahedron Lett.* **1986**, *27*, 77. Faroogi, J. A.; Ahmad, M. *Chem. Ind. (London)* **1985**, 598. Baba, A.; Shibata, I.; Masuda, K.; Matsuda, H. *Synthesis* **1985**, 1144 and references therein. (b) For a review, see: Dyen, M. E.; Swern, D. *Chem. Rev.* **1967**, *67*, 197. Also, see: Roush, W. R.; Adam, M. A. *J. Org. Chem.* **1985**, *50*, 3752. (c) For reactions of chlorosulfonyl isocyanate, see: Lorincz, T.; Erden, I.; Nader, R.; deMeijere, A. *Synth. Commun.* **1986**, *16*, 123. Murthy, K. S. K.; Dhar, D. N. *Synth. Commun.* **1984**, *14*, 7, 687.

(2) For a novel synthesis of oxazolidin-2-ones from alkenes, see: Hu, N. X.; Aso, Y.; Otsubo, T.; Ogura, F. *Chem. Commun.* **1987**, 1447.

(3) Rosenberger, M.; Neukom, C.; Aig, E. R. *J. Am. Chem. Soc.* **1983**, *105*, 3656. Yoshimoto, M.; Ishida, N.; Kishida, Y. *Chem. Pharm. Bull.* **1971**, *19*, 863.

(4) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(5) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792. Also, see: Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 99.

(6) CAN = ceric ammonium nitrate. Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

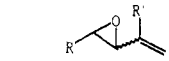
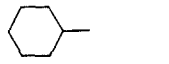
(7) Mp 75–6°C. A solution of 20 mmol of trichloromethyl chloroformate in 10 mL of dioxane was added to 20 mmol of the amine in 20 mL of dioxane over 10 min. After heating at reflux for 2 h, the dioxane was removed in vacuo, and the residue was distilled to give the isocyanate which crystallized upon standing.

(8) Maehr, H.; Smallheer, J. *J. Am. Chem. Soc.* **1985**, *107*, 2943. Bradley, W.; Robinson, R. *J. Am. Chem. Soc.* **1934**, 1484. We found the workup for the reduction of 2-methoxy-1-nitronaphthalene was simplified by replacing zinc with stannous chloride. See: Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839.

(9) dba = dibenzylideneacetone. Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253.

(10) This compound has been characterized spectrally, and elemental composition was established by high resolution mass spectroscopy.

**Table II.** Stereoselective *cis*-Oxazolidin-2-one Synthesis

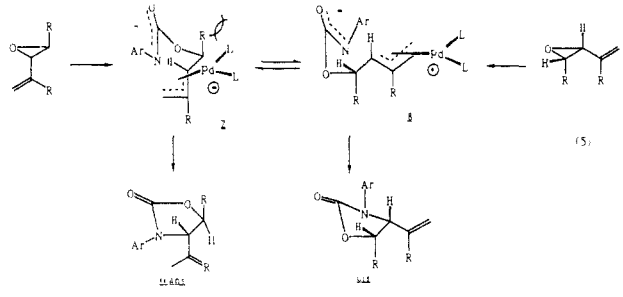
| entry | R | R′ |  | isolated yields (%) 5 | isolated yields (%) 6 | ratio cis/trans |
|---|---|---|---|---|---|---|
| 1 | $PhCH_2CH_2$ | H | 1/2 | 79 | 67 | 10:1[a,b] |
| 2 | $PhCH_2CH_2$ | $CH_3$ | 1/1.2 | 72 | 86 | 8:1[a,b] |
| 3 |  | H | 1/1 | 82 | 75 | 9:1[a,b] |
| 4 | $n\text{-}C_{11}H_{23}$ | H | 2/3 | 76 | 72 | 9:1[b] |
| 5 | $Cl(CH_2)_3$ | H | 1/1 | 87 | 77 | 11:1[a,b] |
| 6 | $TBDMSOCH_2CH_2$ | H | trans only | 80 | nd[d] | cis only[b,c] |
| 7 | $TBDMSOCH_2CH_2$ | H | cis only | 100[e] | nd[d] | cis only[b] |
| 8 | $HC{=}C(CH_2)_3$ | H | 1/1 | 71 | 70 | 10:1[a,b] |

[a] The ratio was determined on unpurified product by capillary gas chromatography with a SE-30 column. [b] The ratio was determined on crude product by NMR spectroscopy. [c] Verification of the absence of the trans isomer was obtained by conversion to **6**, R = $AcOCH_2CH_2$, R′ = H in 70% overall yield by (i) $FeCl_3/Ac_2O$, then (ii) CAN, $CH_3CN$, $H_2O$, 0 °C, and by comparison of the latter by VPC and NMR to an authentic sample of the corresponding trans isomer. [d] nd = not determined. [e] Yield of crude material only.

ether, and the resultant combined ether layers are washed with aqueous sodium bisulfite. After the usual workup and silica gel chromatography, the pure dearylated oxazolidin-2-one[10] is isolated.

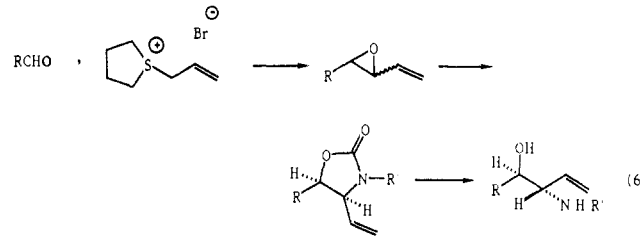
To prove unambiguously that the stereochemistry of the process is independent of the stereochemistry of the starting material, we demonstrated that the pure trans (Table II, entry 6) and pure cis (Table II, entry 7) stereoisomer of the same epoxide both gave the same product which was exclusively the cis isomer in this case.

The source of this remarkable stereoselectivity is unclear. Since both *cis*- and *trans*-epoxides give identical stereochemical results, the two intermediate diastereomeric $\pi$-allylpalladium complexes must be interconverting faster than cyclization to form the oxazolidin-2-ones.[11] Equation 5 depicts a possible rationale. A



(5)

transition state leading from **7** encounters two unfavorable interactions: (1) the R group resides on the concave face of the envelope and (2) the R group is brought into close contact with the palladium complex. On the other hand, the vicinal eclipsing interaction between the R group and the vinyl substituent destabilizes transition states proceeding from **8**. Apparently, the destabilizing interactions associated with **7** outweigh those related to **8** to give an overall cis selectivity. It appears, therefore, that steric interactions evolving within the organic reacting moiety, which would be expected to favor formation of the *trans*-oxazolidin-2-one, do not play a major role. On the contrary, the steric course appears dictated primarily by the ability of the organic moiety to conform to the steric requirements of the metal template. Minimization of such interactions in the reactive complex ultimately leads to a product which, when freed from the template, corresponds to the thermodynamically less stable one. The stereoconvergence in this reaction has special synthetic utility in that the obtention of geometrically defined epoxides is unnecessary. For example, the condensation of sulfur ylides with aldehydes generally produces cis, trans mixtures. As shown in eq 6, this lack of stereocontrol in the first step becomes corrected by the metal template in forming the oxazolidin-2-ones and ultimately vicinal amino alcohols.



(6)

**Acknowledgment.** We thank the National Institutes of Health, Institute of General Medical Sciences, and the National Science Foundation for their generous support of our programs.

(11) We assume that epoxide opening by palladium to form the $\pi$-allyl complex and cyclization by attack of N on this complex both occur with inversion of configuration. Such assumptions stem from good precedent in Pd-catalyzed reactions and the fact that epoxides from cyclic olefins which are constrained to react in such a manner participate smoothly. Nevertheless, we cannot rule out a mechanism whereby the urethane anion coordinates to the palladium of the $\pi$-allyl complex and then suffers reductive elimination. In such an event, the structural features of the reductive elimination would determine the stereochemical outcome.