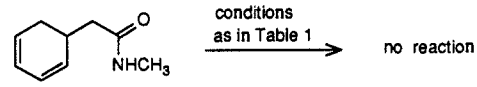
l). In several of these cases, the catalytic intermediates related to **14** were observed by ^1H NMR.[7] Nucleophilic attack by chloride on these intermediates gives the products observed. In one case, the chloride dimer of **14** (R = $COCH_3$) was isolated and characterized.[8]

Amides have previously been utilized as nucleophiles in palladium-catalyzed additions to monoolefins.[9,10] For example, carbamates and sulfonamides were applied in palladium-catalyzed intramolecular reactions to produce heterocycles,[9] and various amides were used in palladium-catalyzed intramolecular amidocarbonylations.[10] The results here are the first-described selective oxidations of conjugated dienes where amides serve as nucleophiles. It is remarkable that the amide nitrogen can act as a nucleophile under the slightly acidic conditions.[11] Dienic amides such as **16**, which on cyclization would give γ-lactams, did not give the desired amidation products. Attempts to cyclize **16**, readily available from **1**,[12] gave only recovered starting material. Apparently the ring strain caused by the carbonyl group makes the rate too slow to be synthetically useful.



16

In conclusion, these 1,4-oxidations in which one nitrogen nucleophile and one oxygen or halide nucleophile are added across the diene should make a number of nonaromatic nitrogen heterocycles available from amino dienes. The fact that the chloro group can be subsequently regioselectively substituted with either retention or inversion[1,2a,13] should make the present methodology useful in the synthesis of natural products.[14]

Acknowledgment. We are grateful to the Swedish Natural Science Research Council for financial support and to Johnson Matthey for a loan of palladium chloride. We also thank Dr. Adolf Gogoll for assistance with the NOE experiments.

Registry No. **1** (*n* = 1), 125974-25-6; **1** (*n* = 2), 125974-26-7; **2** (*n* = 1), 125974-27-8; **2** (*n* = 2), 125974-28-9; **3a**, 125974-29-0; **3b**, 125974-30-3; **3c**, 125974-31-4; **3d**, 125974-32-5; **3e**, 125974-33-6; **4a**, 125974-34-7; **5**, 125974-35-8; **6**, 125974-36-9; **7**, 125974-37-0; **8**, 125974-38-1; *trans*-**9**, 125974-39-2; *cis*-**9**, 126060-07-9; **10**, 125974-40-5; **11**, 125974-41-6; **12**, 125974-42-7; **13**, 125974-43-8; **14** (R = $COCH_3$), 125995-62-2; **16**, 125995-63-3; $TsNH_2$·Na, 18522-92-4; $AcNH_2$·Na, 2620-30-6; benzyl chloroformate, 501-53-1; benzyl isocyanate, 3173-56-6.

Supplementary Material Available: Experimental details of the preparation of **5** and spectroscopic (^1H and ^{13}C NMR, IR, and MS) and analytical data for **5**-**13** (4 pages). Ordering information is given on any current masthead page.

(7) For the mechanistic studies, the reactions were run in acetone-d_6 and CD_3COOD (4:1) in an NMR tube. ^1H NMR spectra were then recorded periodically. The catalytic intermediate π-allyl complex was observed at a steady-state concentration close to that of the catalyst, indicating that the first step is rapid. The spectrum of the π-allyl complex was very similar to that of the isolated dimer.[8]

(8) $[C_{10}H_{14}OPdCl]_2$ (**14**, R = $COCH_3$). This π-allyl complex consisted of two rotamers (2:1 ratio) due to hindered rotation around the acyl-nitrogen bond. ^1H NMR (300 MHz, $CDCl_3$): δ (major rotamer) 5.55 (dd, *J* = 7.0 and 6.0 Hz, 1 H, CH of π-allyl), 5.10 (dd, *J* = 6.5 and 6.0 Hz, 1 H, CH of π-allyl), 4.67 (d, *J* = 7.0 Hz, 1 H, CH of π-allyl), 4.36 (d, *J* = 7.8 Hz, 1 H, CHN bridgehead), 3.53 (br q, 1 H, one of CH_2N), 3.36 (br q, 1 H, one of CH_2N), 3.41 (m, 1 H, CH bridgehead), 2.20 (s, 3 H, CH_3CO), 2.02 (br s, 2 H), 1.95-1.65 (m, 2 H); δ (minor rotamer) 5.48 (dd, *J* = 6.0 and 5.4 Hz, 1 H, CH of π-allyl), 5.21 (d, *J* = 5.4 Hz, H2, 1 H, CH of π-allyl), 4.99 (dd, *J* = 6.0 and 5.4 Hz, 1 H, CH of π-allyl), 4.52 (d, *J* = 7.2 Hz, 1 H, CHN bridgehead), the rest of the shifts coincide with the major rotamer.

(9) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444.

(10) (a) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, *110*, 3994. (b) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5731.

(11) A similar reactivity of amides under acidic conditions was observed by Tamaru et al. in palladium-catalyzed intramolecular amidocarbonylation of olefins.[10a]

(12) Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 2033.

(13) Bäckvall, J. E. *Bull. Soc. Chim. Fr.* **1987**, 665.

(14) (a) Preliminary experiments showed that *N*-((benzyloxy)carbonyl)- and *N*-((benzylamino)carbonyl)- protected 1-(4-aminobutyl)-1,3-cyclohexadiene resulted in a palladium-catalyzed spiroamidocyclization under the reaction conditions of Table I. These products are of potential interest for the synthesis of histrionicotoxins.[14b,c] (b) Daly, J. W. In *Progress in the Chemistry of Organic Natural Products*; Springer: Berlin, 1982; Vol. 41, p 205. (c) Tanner, D.; Sellén, M.; Bäckvall, J. E. *J. Org. Chem.* **1989**, *54*, 3374.

Stereoelectronic Effects in Cyclization Reactions

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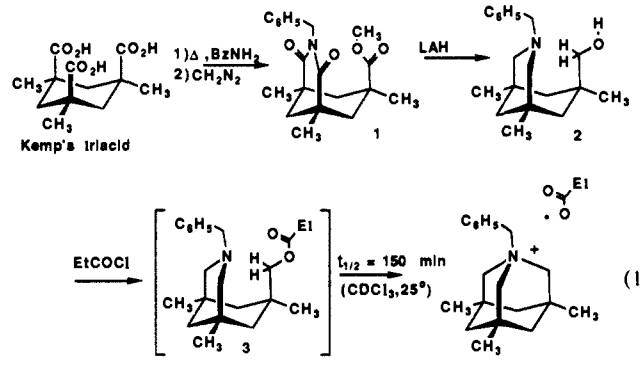
Derivatives of the Kemp Triacid[1] are useful as scaffolds for molecular recognition[2] and as probes for stereoelectronic effects at carboxyl oxygen.[3] The diaxial relationship enforced between any two carboxyl groups encourages neighboring-group participation, leading to enormous rate enhancements in amide hydrolysis.[4] We report here some other unusual manifestations of this unique skeleton as they apply to stereoelectronic effects in cyclization reactions.

The first involves the peculiar behavior of the bicyclic ester **3**. This is readily prepared from the imide methyl ester **1**[5] by LAH reduction followed by acylation[6] (eq 1). Despite the poor leaving group and the nonlinear arrangement of nucleophile, carbon, and the leaving group, the intermediate **3** cyclizes rapidly to the azaadamantane salt. Specifically, the half-life for the cyclization in $CDCl_3$ at room temperature is 150 min. There is no obvious bimolecular counterpart for this reaction.



(1)

The second involves a less nucleophilic nitrogen derivative of the same skeleton, namely, the lactam of the bicyclic acid **4**. This is readily prepared as described previously,[7] and it is available in optically active form. Treatment of the optically active form with excess $SOCl_2$ in $CHCl_3$ *results in racemization*. For example, quenching with water gave the racemic acid, while quenching with

(1) Kemp, D. S.; Petrakis, K. S. *J. Org. Chem.* **1981**, *46*, 5140. Commercially available from the Aldrich Chemical Co. For a convenient synthesis, see: Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426-2431.

(2) Rebek, J., Jr. *Pure Appl. Chem* **1989**, *61*, 1517-1522.

(3) Tadayoni, B. M.; Parris, K.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 4503.

(4) Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* **1988**, *110*, 6794.

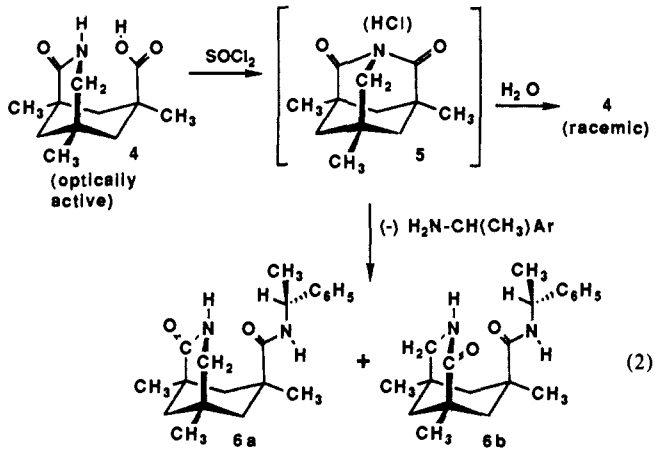
(5) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K.-S.; Jones, S.; Parris, K.; Williams, K.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1082-1090.

(6) All new compounds were characterized by a full complement of high-resolution spectra. For **2**, mp 62 °C. For **6a**, mp 63-65 °C. For **6b**, mp 196-197 °C. The absolute configuration of **6a** was established by the X-ray structure of a derivative.[7] For **7** (optically active), mp 183-184 °C.

(7) Jeong, K.-S.; Parris, K.; Ballester, P.; Rebek, J., Jr. *Angew. Chem.*, in press.

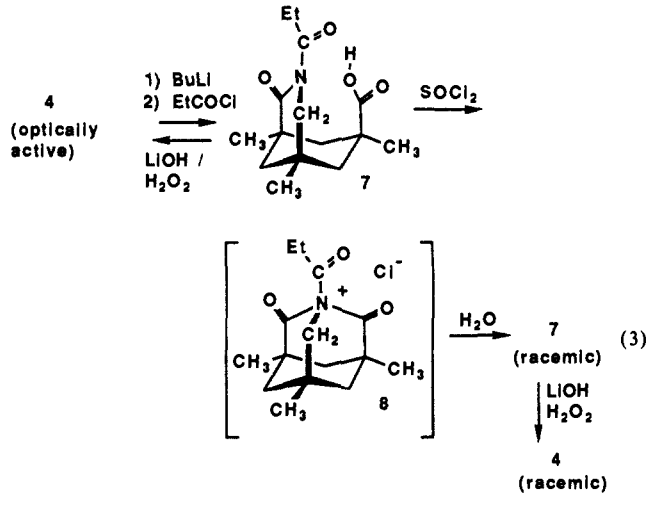
0002-7863/90/1512-3685$02.50/0

optically active (*S*)-α-phenylethylamine gave the diastereomeric lactam amides **6** (eq 2). A symmetrical intermediate cannot be avoided by this evidence.[8] One possibility is the tricyclic **5**, a decidedly nonplanar imide.[9] It could arise from an acylium ion, but even the cyclization of the acylium species is less than optimal from a stereoelectronic point of view.[10]



(2)

Finally, the participation of an even less nucleophilic nitrogen, a neighboring imide, was observed. The optically active lactam acid **4** was treated first with BuLi and then with propionyl chloride (eq 3) to give the imide acid **7**. This, on mild hydrolysis,[11] regenerated optically active lactam acid **4**. However, treatment of the *N*-propionyl lactam **7** with $SOCl_2$ followed by quenching with H_2O *gave racemic* **7**. Mild hydrolysis of this material gave racemic **4**. The intermediate that summarizes these results most economically is the unusual structure **8**.



(3)

In summary, the relief of strain or other factors[12] involved in neighboring-group participation on this rigid template results in some bizarre intermediates. Lactams and imides become involved in a "face" sense rather than the "edge" or in-plane sense usually required by their lone pairs, and even carboxyl carbons undergo reactions involving unusual stereoelectronics.

Acknowledgment. We thank the National Institutes of Health for support, Kyu-Sung Jeong for experimental assistance, and Professor A. Greenberg for helpful discussions.

(8) Labeling experiments bear this out. Quenching of **5** with $H_2{}^{18}O$ gave the label only in the acid. Resubmission of this material to $SOCl_2$ then H_2O *gave label in the lactam* as well as the acid, as determined by ^{13}C NMR spectroscopy: Vederdas, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 374-376. Chloro derivatives of **5** are also likely intermediates, particularly since the initial reaction of **4** with $SOCl_2$ is at the lactam function.

(9) For studies on nonplanar (bridgehead) lactams, see: Pracejus, H.; Kehlen, M.; Kehlen, H.; Matschiner, H. *Tetrahedron* **1965**, *21*, 2257-2270. For imides, see: Brouillette, W. J.; Einspahr, H. M. *J. Org. Chem.* **1984**, *49*, 5113-5116. For a recent review, see: Greenberg, A. *Structure and Reactivity*; Liebman, J. F., Greenberg, A., Eds.; VCH Publishers, Inc.: New York, 1988; Chapter 4, p 138-179.

(10) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. See also: Strozier, R. W.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 1340-1343. Wallis, J. D.; Dunitz, J. D. *J. Chem. Soc., Chem. Commun.* **1984**, 671-672.

(11) Evans, D. A.; Ellman, J. A.; Britton, J. C. *Tetrahedron Lett.* **1987**, *28*, 6141.

(12) Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128-134.

Bifunctional Zinc-Imidazole and Zinc-Thiophenol Catalysts

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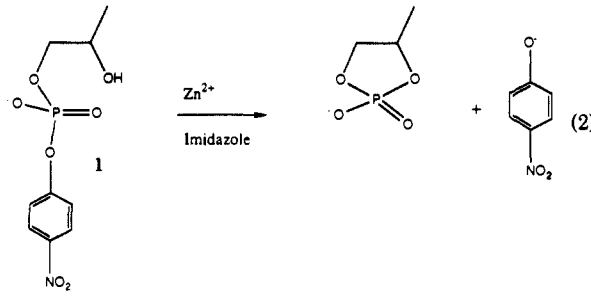
Many enzymes perform bifunctional catalysis using a metal ion and a basic group. Electron flow from base to metal occurs through the atoms of the transition state for the reaction catalyzed. For attack of a hydroxyl group on the central atom of a carboxylic acid derivative or of a phosphate derivative, the bridge has an H, two O's, and the carbon or phosphorus atom (eq 1).

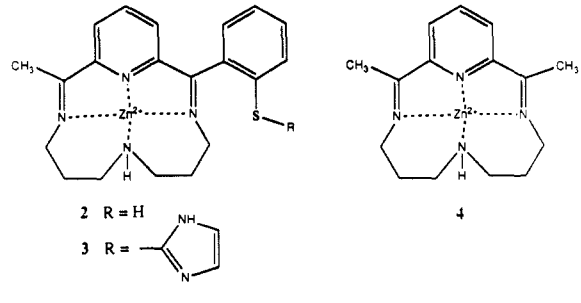
(1)

We have described intracomplex catalysis of amide cleavage by a metal ion and a base[1] and bifunctional catalysis of the cyclization of **1** by the combined action of Zn^{2+} or its complexes with free imidazole acting as a base[2] (eq 2). We have now designed and constructed a new class of catalysts, with a metal ion rigidly complexed by a strong multidentate ligand and the auxiliary catalytic group held so that it cannot directly bond to the metal.



(2)

The first examples are catalysts **2** and **3**, with a fixed Zn^{2+} and either a thiophenol/thiophenoxide group or a somewhat more flexibly held imidazole group. Molecular models show that no internal base-metal short circuit is possible and that the catalysts can readily accommodate to the binding of a transition state symbolized in eq 1. The additional catalytic group indeed increases the effectiveness of the Zn^{2+} complex.



(1) Schepartz, A.; Breslow, R. *J. Am. Chem. Soc.* **1987**, *109*, 1814.

(2) Breslow, R.; Huang, D.-L.; Anslyn, E. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 1746. In that paper the structure of compound **1** is misprinted; it should be shown as the *p*-nitrophenyl phosphate ester of the *primary* hydroxyl of propylene glycol, as in this paper.

0002-7863/90/1512-3686$02.50/0