May CUME

Department of Chemistry
University of Missouri—Columbia
Saturday, May 10, 1997
@Nine O'Clock
Chemistry Reading Room

Dr. Rainer Glaser

Announced Reading

The Chemistry of
Amir Hoveyda, Boston College, Boston &
Cynthia Burrows, University of Utah, Salt Lake City
as presented at the 10th Annual Organic Chemistry Day at MU

Question 1. Asymmetric Zirconium-Catalyzed Ethylmagnesation. (35 points)

Ref. 1. "Zirconium-Catalyzed Asymmetric Carbomagnesation" J. P. Morken, M. T. Didiuk, A. H. Hoveyda, *J. Am. Chem. Soc.* **1993**, *115*, 6997-8.
Ref. 2. "Catalytic and Enantioselective Route to Medium-Ring Heterocycles. Asymmetric Zirconium-Catalyzed Ethylmagnesation of Seven- and Eight-Membered Rings." Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291-4298.

(a) Consider the addition reaction of EtMgCl to propene. Draw the structures of the two potentially formed addition products. Which one of the regioisomers do you consider to be more likely and why?

(6 points)

(b) Consider the addition reaction of EtMgCl to 3-hydroxy-1-propene. Draw the structures of the two potentially formed addition products. Which one of the regioisomers do you consider to be more likely and why?

(6 points)

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(c) The nucleophilic addition of EtMgCl to 4-oxacyclohexene in the presence of (*R*)-**1**—(*R*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)zirconiumdichloride—affords a chiral product in 73% yield and 95% enantiomeric excess. Provide a detailed mechanism for the reaction. Note that the function of EtMgCl in this reaction is entirely different from the simple addition considered in (a) and (b); EtMgCl never adds to a C=C bond. Explicitly state the two functions of the EtMgCl. Explicitely state in what step the regiochemistry and the stereochemistry are decided and what features determine the outcomes.

Give a detailed mechanism: (12 points)

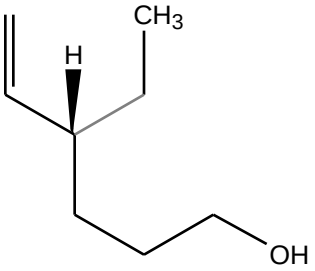
(*R*)-**1**

Function of EtMgCl: (2 points)

Explain the regiochemistry: (2 points)

Explain the stereochemistry: (2 points)

(d) The catalytic Zirconium-catalyzed asymmetric carbo-magnesation of 4-hetero-cycloalkenes can be combined with the formation of the 4-hetero-cycloalkenes via diene metathesis. For the chiral alcohol shown, complete the retrosynthesis, that is provide the structure of the cyclic intermediate which serves as the substrate for the catalytic Zirconium-catalyzed asymmetric carbomagnesation and the structure of the starting material for the diene metathesis and. [No need to specify any of the reagents needed.] (5 points)



Question 2. Discovery of Chiral Catalysts Through Ligand Diversity. (15 points)

"Discovery of Chiral Catalysts Through Ligand Diversity: Ti-Catalyzed Enantioselective Addition of TMSCN to *meso* Epoxides." Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668-1671.

(a) Give reagents, catalyst (Ti compound and Schiff base), solvent, reaction conditions and the structures of the products for the ring-opening of the epoxide of cyclohexene that leads to racemic *beta*-cyanohydrines. Describe the absolute configurations of all chiral centers in the products using the *R/S* nomenclature. (6 points)

(b) Snapper, Hoyeda, et al. turned the reaction in (a) enantioselective through the use of chiral and enantiomerically pure catalysts. The novelty lies with the discovery of this chiral catalyst through simple combinatorial techniques. Briefly describe how these authors proceed to optimize their dipeptide catalyst of the constitution **MeO-Gly-AA2-AA1** where AA1 and AA2 are amino acids. (6 points)

(c) The approach described does suffer from one significant methodological drawback with regard to "additivity effects". Briefly explain. (3 points)

Question 3. DNA and RNA Modifications by Sulfate Radical Anion. (50 points)

Ref. 1: "DNA and RNA Modification Promoted by $[Co(H_2O)_6]Cl_2$ and $KHSO_5$: Guanine Selectivity, Temperature Dependence, and Mechanism." Muller, James G.; Zheng, Ping; Rokita, Steven E.; Burrows, Cynthia J. *J. Am. Chem. Soc.* **1996**, *118*, 2320-5.

Abstract: Reaction of a single-stranded oligodeoxynucleotide or a 17-base hairpin-forming oligodeoxynucleotide with $CoCl_2$ and $KHSO_5$ produced guanine-specific cleavage after piperidine treatment. The obsd. reactivity is shown to be nearly twice that obtained for NiCR (CR = 2,12-dimethyl-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),2,11,13,15-pentaene) under equivalent conditions, although NiCR displays a slightly higher degree of selectivity for unpaired guanine residues. Cobalt-induced DNA modification was catalytic with respect to the metal complex and was obsd. at temps. up to 80C, conditions under which NiCR was ineffective. Mechanistic studies of the cobalt-mediated reaction suggest that $SO_4^{\cdot -}$ is responsible for guanine oxidn. Reaction with tRNAPhe induced aniline.cntdot.HOAc-labile (pH 4.5) lesions also at accessible guanine sites. The high reactivities of G20 and G34 are consistent with attack of $SO_4^{\cdot -}$ on the π-face of the guanine heterocycle as opposed to recognition of G N7 as proposed for NiCR. $CoCl_2$ should become an extremely attractive probe of nucleic acid structure since it induces base-specific and conformation-specific cleavage of DNA under a much wider variety of exptl. conditions than NiCR, acts with a different mode of guanine selectivity than do nickel complexes, and is com. available.

Ref. 2: "DNA Damage from Sulfite Autoxidation Catalyzed by a Nickel(II) Peptide."
Muller, J. G.; Hickerson, R. P.; Perez, R. J.; Burrows, C. J. *J. Am. Chem. Soc.* **1997**, *119*, 1501-1506.

Abstract: Guanine-specific modification of both single- and double-stranded oligodeoxynucleotides via the autoxidation of sulfite is shown to be catalyzed by $[NiCR]^{2+}$ (where CR = 2,12-dimethyl-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),2,11,13,15-pentaene) and $[NiKGH\text{-}NH_2]^+$ (where KGH = lysylglycylhistidine). In the latter case, the nickel complex is proposed to act as a catalyst in three separate steps of sulfur oxide chemistry. Oxidative damage of guanines led to strand scission after piperidine treatment. The observed reactivity represents the first demonstration of DNA damage by sulfite and nickel(II) complexes. Importantly, these reactions were conducted using sulfite concentrations relevant to levels known to be cytotoxic. Mechanistic studies suggest the importance of both monoperoxysulfate and sulfate radical anion in the observed DNA damage. Evidence for formation of guanine radical cation as the initial product of DNA oxidation was found by comparison of the sequence dependence of guanine reactivity in a duplex restriction fragment. These studies underscore a role for sulfite in nickel toxicity and suggest a new method of site-specific oxidation with bioconjugates using sulfite rather than highly reactive oxidants such as monoperoxysulfate.

(a) Draw Lewis structures for the following compounds. All of these species occur somewhere in the discussions of Burrows et al. (12 easy points)

SO_3^{2-}	SO_4^{2-}	$S_2O_{10}^{2-}$
$SO_3^{\cdot -}$	$SO_4^{\cdot -}$	HSO_5^-

(b) Treatment of oligodeoxynucleotides with $CoCl_2$ and $KHSO_5$ followed by treatment with piperidine leads to strand breaking and indicates that the strandbreaking occurs at guanines. It was claimed that $SO_4^{\cdot -}$ is the DNA damaging species. How is $SO_4^{\cdot -}$ formed by $CoCl_2$ catalytic action on $KHSO_5$? (4 p.)

(c) It was shown that $SO_4^{\cdot -}$ formed in another reaction gave the same damage to oligodeoxynucleotides. What was that reaction? (4 points)

(d) The radical anion $SO_3^{\cdot -}$, $SO_4^{\cdot -}$, and $SO_5^{\cdot -}$ are discussed as potential DNA damaging species in ref. 2. Suggest reactions by which these species can be formed from sulfite in the presence of the Nickel catalyst. Refer to the catalyst as "M(OS)" where OS indicates the oxidation state. (8 points)

(e) For the Cobalt catalyzed reactions discussed in ref. 1, there was a question as to whether the reactive species is the sulfate radical anion or whether it might be the hydroxyl radical. Quenching experiments with ethanol and *tert*.-butanol were carried out to examine this question and to argue in favor of the sulfate radical anion. Briefly, clearly and precisely explain the logic behind the argument. (8 points)

(f) Alcohol quenching studies also were used in the Nickel catalyzed reactions to make deductions as to the involvement of the radical anion $SO_4^{\cdot -}$. This radical is said to react 10,000 times faster with alcohols as compared to the other radical anions $SO_3^{\cdot -}$ and $SO_5^{\cdot -}$. In ref. 2 it is stated that (i) ethanol (25ml) quenched the reaction of Na_2SO_3 (100μM) and $[NiKGH\text{-}NH_2]^+$ (10μM) with single strand oligodeoxynucleotide only <u>modestly</u> (<20%) while (ii) ethanol (25ml) quenched the reaction of Na_2SO_3 (1000μM) and $[NiCR]^{2+}$ (10μM) with single strand oligodeoxynucleotide almost <u>completely</u> (87%). Explain how this data has been interpreted. Do you consider the argument to be strong or weak? (6 p.)

(g) The "$CoCl_2$ induced conformational specificity" of the guanine damage is discussed in ref. 1 and compared to similar studies with Nickel complexes. Explain what is meant by the term "conformational specificity" and explain how "hairpin-forming oligodeoxynucleotides" are used to study this stereochemical issue. (8 points)