Scheme I

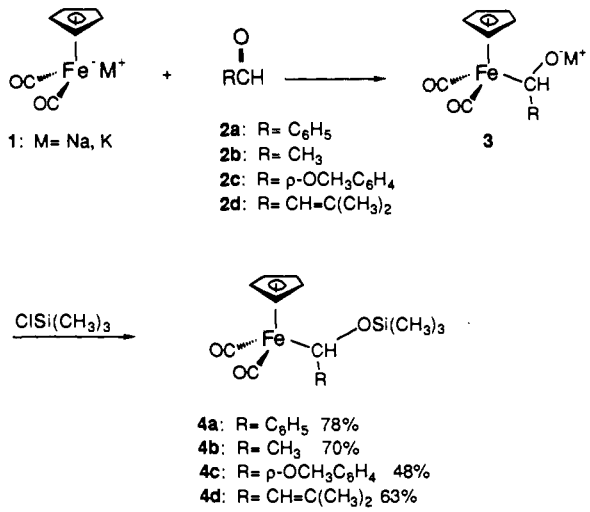


Table I. Cyclopropanes from Precursors 4

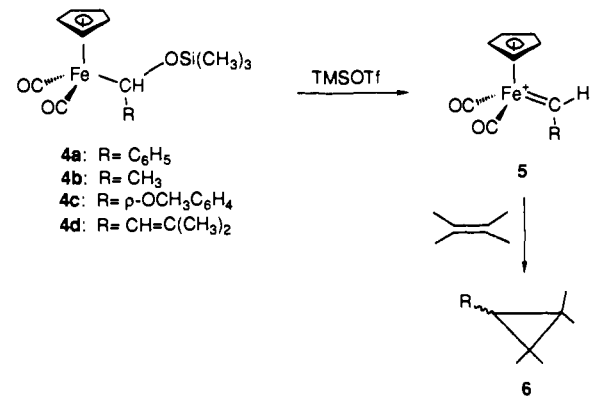
precursor	olefin	yield (%)
4a	styrene	68 (all cis)[a,b]
	cyclopentene	62 (all endo)[a,b]
	2-methyl-2-butene	88 (all cis)[a,b]
4b	styrene	72 (all cis)[b,c]
4c	styrene	38 (4:1)[a,b,d]
4d	styrene	44 (1:2)[a,b,d]

[a] Isolated, unoptimized yield. [b] Ratios were determined by GC and/or ^{1}H NMR spectroscopy.[3] [c] Determined by GC with results calibrated against an internal standard. [d] Cis:trans ratio.

pentacarbonyl anion and benzaldehyde at room temperature. However, he did propose the existence of a related manganese alkoxide anion $(CO)_5Mn(C_6H_5CHO^-Li^+)$ as a fleeting intermediate in the reduction of the manganese pentacarbonyl acyl complex by trialkylborohydrides.[8] Gladysz's findings and the following observations are consistent with the chemistry described in Scheme I, although the mechanism of this reaction has not yet been defined. There is no apparent reaction between chlorotrimethylsilane and the aldehyde nor between silyl complex $Cp(CO)_2FeSi(CH_3)_3$ and the aldehyde under the reaction conditions. Despite some uncertainty as to the exact mechanism, this reaction provides an efficient and convenient synthetic approach to various (siloxyalkyl)iron complexes.

To determine the potential utility of this strategy, the (siloxyalkyl)irons **4** were separately treated with 1.1-1.7 equiv of trimethylsilyl triflate at -78 °C in the presence of 2-4 equiv of olefin (Scheme II). In situ generation of the carbene complex **5**[9] produced the corresponding cyclopropane **6**.[1c,f,g,10] The results are summarized in Table I. It is readily apparent from the unoptimized results for the new precursors **4a**,**b** that they are efficient. They also exhibit very high cis selectivity[11] when reacted with acyclic alkenes. In addition, precursor **4a** shows very high endo selectivity with cyclopentene. Reaction of styrene with both

Scheme II



4c and **4d** gave different selectivities. Precursor **4d** provided the trans isomer as the major product, which is consistent with a related precursor reported previously.[1f,10e] Precursor **4c** preferred the cis isomer, exhibiting higher selectivity than a related precursor with propene.[10f]

The synthesis of (siloxyalkyl)iron complexes **4** from inexpensive and readily available aldehydes demonstrates rather clearly a new, simple synthetic technique for the preparation of electrophilic iron carbene complexes. More importantly, a new reaction for the Fp anion has been developed which has potential synthetic utility. Work is underway to determine the versatility of this method by utilizing a greater variety of aldehydes and extending the study to ketones. In addition, mechanistic studies of the reaction are being pursued.

Supplementary Material Available: Experimental procedures and spectral data for the syntheses of **4a-d** and their reactions with alkenes (8 pages). Ordering information is given on any current masthead page.

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(11) The stereoselectivity of our results differs from that obtained by Brookhart[10b,c] for cyclopropanation of the Fp-(α-methoxymethyl) precursor with styrene versus our **4b** with styrene. However, our results are consistent with those of Helquist et al.[1c,10d]

Selective Coloration of Spiro Pyridopyrans for Guanosine Derivatives

Masahiko Inouye,* Kwangshik Kim, and Teijiro Kitao

Department of Applied Chemistry
University of Osaka Prefecture
Sakai, Osaka 591, Japan

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The artificial receptors that recognize and bind to specific nucleoside bases are of current interest.[1] Especially, recent discoveries of the role of GTP-binding regulatory proteins (G-proteins)[2] and of the cap-binding protein (CBP)[3] have stimulated the investigation on the chemical recognition of guanine.[4] We recently introduced a new type of spiro benzopyran possessing a monoaza-crown ring as a recognition site, isomerization of which to the colored merocyanines was induced by recognition of al-

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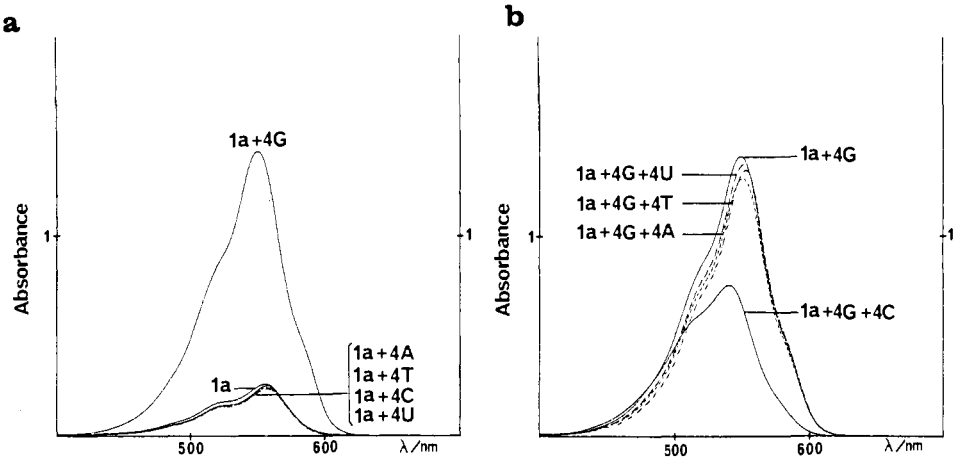
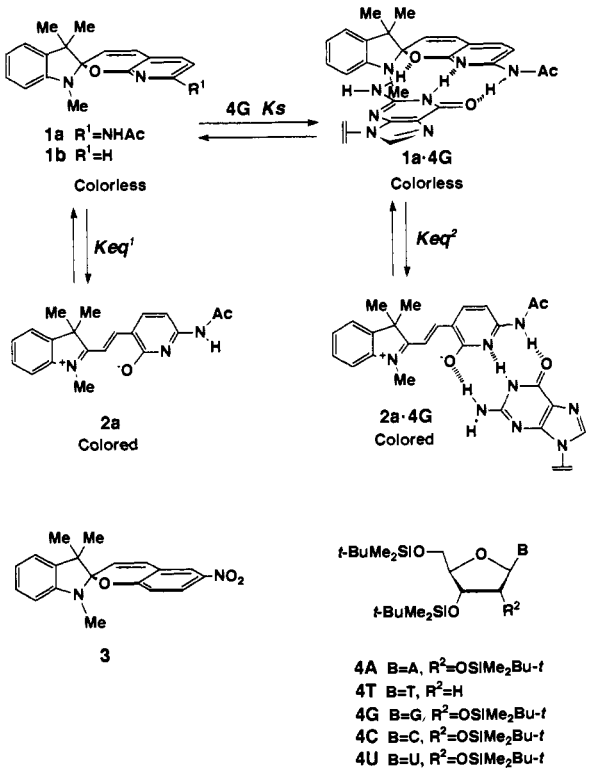
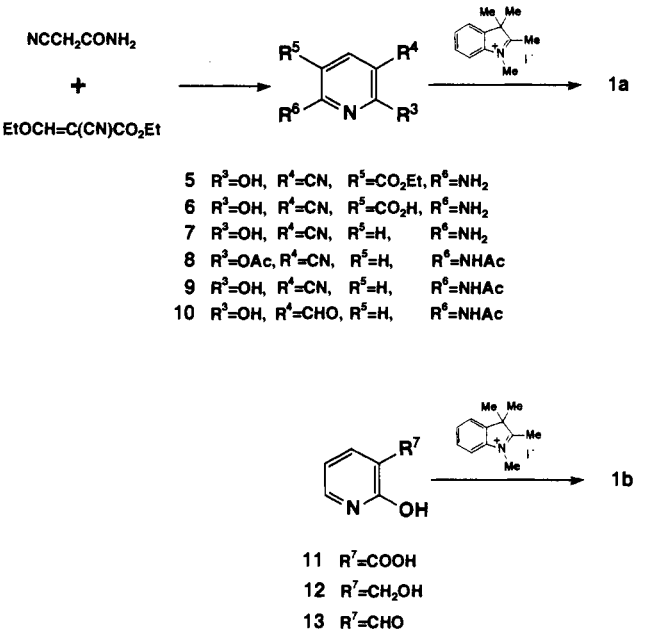


Figure 1. (a) The electronic absorption spectra of **1a** (3.0×10^{-2} mM) in the presence or absence of nucleoside derivatives in CH_2Cl_2. (b) The electronic absorption spectra of **1a** + **4G** in the presence or absence of other nucleoside derivatives in CH_2Cl_2.

Scheme I



Scheme II



kali-metal cations.[5] In order to develop further artificial receptors for other biologically important species, in which guest recognition induces a change in the molecular structure, which in turn causes development of a spectral signal, we sought to construct hosts for nucleoside bases. Here we present the synthesis and selective coloration of spiro pyridopyrans for guanosine derivatives.

The design of the spiro pyridopyran **1a** was based on the triple hydrogen bond complementarity between the acetamidopyridopyran unit of **1a** or the acetamidopyridone anion unit of the open merocyanine form **2a** and guanine. We might expect that equilibrium between the colorless spiro pyridopyran and the colored merocyanine would be affected by recognition of guanine and that this change ($K_{eq^1} \neq K_{eq^2}$) could be detected using a UV–vis spectrophotometer (Scheme I). Reaction of α-cyanoacetamide with ethyl 2-(ethoxymethylene)-2-cyanoacetate gave the tetrasubstituted pyridine derivative **5**, which was then hydrolyzed to **6**. Decarboxylation of **6** with urea produced **7**.[6] Acetylation of **7** gave **8**, which was selectively hydrolyzed to **9**, followed by hydrogenation to **10**. Treatment of **10** with 1,2,3,3-tetramethyl-3*H*-indolium iodide afforded the desired spiro pyridopyran **1a**. A parent spiro pyridopyran **1b** was also synthesized, aiming at comparison of its coloration with that of **1a** (Scheme II).

The spiro pyridopyran **1a** thus prepared showed only weak absorption bands above 350 nm in nonhydroxylic solvents (hexane, CH_3CN, CH_2Cl_2, etc.), indicating that **1a** exists mainly as the closed spiro pyran form. In CH_2Cl_2, however, addition of 2′,3′,5′-tris-*O*-(*tert*-butyldimethylsilyl)guanosine[7] (**4G**, 10 equiv) to **1a** produced changes in the absorption spectra, and strong absorption bands appeared ($\lambda_{max} = 550$ nm, $\epsilon = 4.8 \times 10^4$). On the other hand, only negligible changes were observed upon addition of other nucleoside derivatives (**4A**, **4T**, **4C**, and **4U**)[7] (Figure 1a). The increasing absorption bands were attributed to the increasing proportion of the merocyanine form to that of the spiro pyran form (i.e., $K_{eq^1} < K_{eq^2}$) by recognition of **4G**. Indeed, ca. 10, 43, and 56% of the spiro pyran (12.5 mM in $CDCl_3$) exists as the merocyanine form in the absence or presence of **4G**, 0, 6.3, and 12.5 mM, respectively, as judged by integrations

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of the *N*-Me protons (**1a** and **1a·4G**, 2.77 ppm; **2a** and **2a·4G**, 3.67 ppm) in the ^{1}H NMR spectra. The complexation was also shown on the basis of the following NMR experiments. To a $CDCl_3$ solution (0.8 mL) of **1a** (20 μmol) was added **4G** (20 μmol), and ^{1}H NMR spectra were measured. The NH protons on both **1a** and **4G** were shifted downfield by 1.83 (**1a**-NH), 1.25 (**4G**-NH_2), and 0.82 (**4G**-NH) ppm, reflecting the formation of **1a·4G**, and new broad peaks, which might be assigned to NH protons of **2a·4G**, appeared. The association constant (K_s) of 280 ± 20 M^{-1} was determined by the Foster–Fyfe analysis.[8]

As expected, the presence of the cytidine derivative interfered with this selective coloration of **1a** for the guanosine derivative because of the competitive formation of the Watson–Crick G–C base pairs. Thus, addition of **4C** (3.0 equiv to **4G**) to the colored solution caused dramatic fading of the color, but other nucleoside derivatives (**4A**, **4T**, and **4U**) had little influence on it (Figure 1b). While **1b**, which was expected to bind guanine via two hydrogen bonds, also revealed substantially selective coloration for **4G**, the corresponding spiro benzopyran **3** showed no changes in its absorption spectrum in the presence of any nucleoside derivatives.

In summary, we have developed multifunctional artificial receptors for guanosine derivatives, namely, "recognition/structural change/signaling" receptors. In future investigations, the design of receptors which bind native nucleosides and nucleotides is expected to show great practical value.

Acknowledgment. We thank A. Iwamoto for technical assistance and N. Nakayama for encouragement. We are also indebted to Dr. K. Kobayashi (Nagaoka University of Technology) for discussions. K.K. was supported by a Rotary Yoneyama scholarship.

Supplementary Material Available: Preparation and spectral data for **1a**, **1b**, **8–12**, and **13** (4 pages). Ordering information is given on any current masthead page.

(8) Foster, R.; Fyfe, C. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **1969**, *4*, 1–89. K_s measurements were made by monitoring the chemical shifts of the **4G**-NH proton as a function of **1a** concentration. In such conditions ([**1a**] ≫ [**4G**]), the presence of the opened merocyanines (**2a** and **2a·4G**) was negligible; see text.

Stereospecific Antibody-Catalyzed Reduction of an α-Keto Amide

Grace R. Nakayama and Peter G. Schultz*

Department of Chemistry, University of California Berkeley, California 94720

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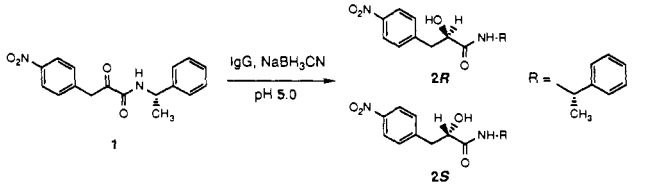
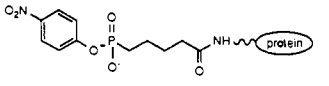
The development of catalytic enantioselective reactions for the synthesis of pure chiral compounds has become an important focus of synthetic organic chemistry.[1] Enzymes are being used in an increasing number of applications by virtue of their remarkable specificities.[2] However, only a limited number of enzymes are available, and in many cases cofactor recycling complicates the use of a biocatalyst. A number of powerful synthetic chiral catalysts have also been developed including epoxidation,[3] hydrogenation,[4] and hydride transfer[5] catalysts. However, the rational design of such catalysts is still at a very early state. An alternate approach to the generation of chiral catalysts exploits nature's ability to generate high-affinity, highly selective receptors by means of the highly evolved machinery of the immune system.[6] We now report the use of antibodies to carry out the catalytic stereospecific reduction of an α-keto amide using the reductant $NaBH_3CN$, a first step toward the generation of a family of catalytic antibodies for chiral alcohol and amine synthesis.

We anticipated that antibodies specific for phosphonate **3** might catalyze the stereospecific, $NaBH_3CN$-dependent reduction of α-keto amide **1** to α-hydroxy amide **2** on the basis of the following considerations: (1) The negatively-charged tetrahedral phosphonate moiety, which can be readily incorporated into haptens, should induce a combining site capable of polarizing a carbonyl group for attack by a hydride reagent. (2) The antibody combining site should provide a chiral environment that discriminates the transition states arising from attack of hydride on the two faces of the carbonyl group.[7] The ability to generate antibodies with any desired specificity (or lack thereof) should ensure the production of antibodies with high enantioselectivities (regioselectivities or substrate specificities). (3) Conjugation of hapten to carrier protein at or near the phosphonate group should ensure accessibility of a relatively small reductant to the carbonyl group (second-generation haptens might incorporate a "reductant site"). Although many enzymes[2] and enzyme mimics[8] for the stereospecific reduction of α-keto acids and their derivatives utilize nicotinamide cofactors, we chose a less expensive, more powerful metal hydride reductant that is capable of reducing a large array of carbonyl groups and carbonyl derivatives.[9]





3

Monoclonal antibodies specific for phosphonate **3**[10] were purified to homogeneity by affinity chromatography on protein A coupled sepharose[11] as determined by SDS–polyacrylamide gel electrophoresis. Eight antibodies were then assayed for their ability to reduce α-keto amide **1** by high-performance liquid chromatography (HPLC). The (*S*)-(−)-α-methylbenzylamine group was incorporated into the α-keto acid substrate to facilitate analysis of reaction stereospecificity (it has been previously shown that antibodies specific for phosphonate **3** are relatively insensitive to substitutions in the aliphatic linker[10b]). α-Keto amide **1** was prepared by a modification[12] of the method of Westerberg and co-workers for the preparation of (4-nitrophenyl)pyruvic acid.[13]

* Author to whom correspondence should be addressed.

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(12) Pyruvamide **1** was synthesized from α-acetamido-4-nitrocinnamic acid[13] by treatment with isobutylchloroformate/4-methylmorpholine to form the mixed anhydride, followed by reaction with (*S*)-(−)-α-methylbenzylamine. Subsequent hydrolysis and chromatography on silica gel (hexanes/*i*-PrOH) afforded α-keto amide **1**.

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