Table I. Percentage Yield of Material at Origin (Tetramer and Longer)[a]

no.	concn of monomer, M	R_1 = H, R_2 = H	R_1 = Me, R_2 = H	R_1 = H, R_2 = Me	R_1 = Et R_2 = H
1	0.0125	13	46	6	9
2	0.025	32	74	23	20
3	0.05	39	89	45	34
4	0.05 (no template)	0	0	0	0

[a] 2,6-Lutidine-HNO_3 buffer, pH 7.0, 0.4 M; $NaNO_3$, 0.4 M; $Mg(NO_3)_2$, 0.8 M. Imidazolide poly(C) ratio is 1:2. Yields after 14 days at 0 °C.

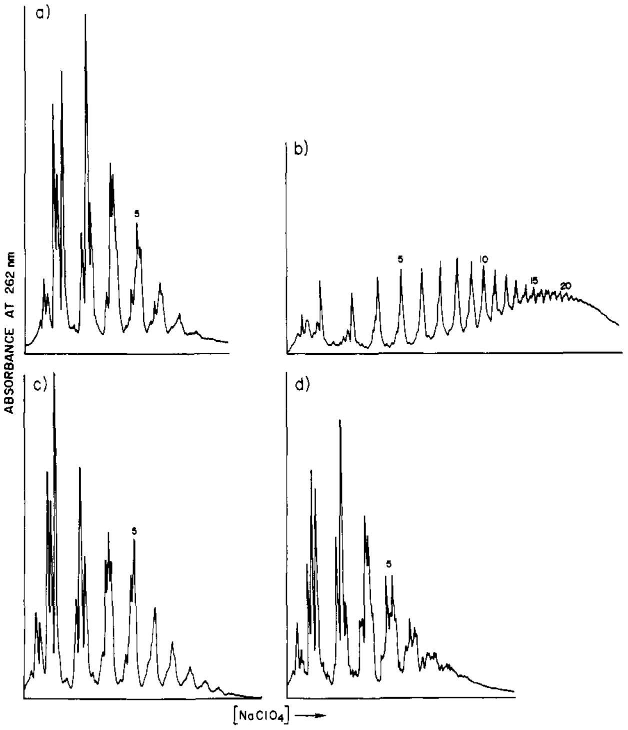

Figure 1. HPLC elution profile of guanosine-5′-phosphorimidazolide derivatives on a poly(C) template after 14 days (Table I, row 3). (a) $R_1 = R_2 = R_3$ = H; (b) R_1 = Me, $R_2 = R_3$ = H; (c) R_1 = Et, $R_2 = R_3$ = H; (d) $R_1 = R_3$ = H, R_2 = Me (or $R_1 = R_2$ = H, R_3 = Me). For reaction conditions see footnote to Table I.

on the column. The all 3′,5′-linked oligomers were identified by cochromatography with authentic samples obtained by degrading poly(G) with ribonuclease P_1.

Elution profiles of the products obtained from the four imidazolides under identical conditions are shown in Figure 1. It is clear that substantial amounts of oligomers up to the 50-mer are obtained from **2**, while the oligomers obtained from **1**, **3**, and **4** are much shorter. Furthermore, the isomeric purity of the products from **2** is greater than that from any other imidazolide, as revealed by a comparison of peak height corresponding to the all 3′,5′-linked compounds with the peaks to the left of them on the HPLC elution profile. We confirmed that the products from **2** are almost exclusively 3′,5′ linked by degrading a sample with ribonuclease T_2 before application to the column. Negligible amounts of material longer than trimer were detected.

The greatly enhanced yield of oligomers obtained in the reaction of **2** in the presence of poly(C) and the extreme sensitivity of the efficiency and regioselectivity of the reactions to minor changes in the nature of the imidazole moiety are unusual for an organic condensation reaction in solution. Presumably, the rigid orientation of monomers imposed by the poly(C) template makes possible a degree of specificity which is rarely encountered, except with highly constrained reactants or in enzyme-catalyzed reactions. We believe that the 2-methyl group controls the detailed structure of the exterior of the helix so as to bring the P–N bond in line with 3′-O···P direction. Larger substituents at the 2-position or a 4-(5-)methyl group lead to a less favorable geometry.

We have also studied the time course of the template-directed reaction of **2** at various temperatures. The terminal yield falls from 89% to 54% and the half-life of the reaction from 4 days to 18 h as the temperature increases from 0 to 20 °C. In other experiments we found that the concentration of Na^+ and Mg^{2+} ions profoundly affects the efficiency and regioselectivity of the reaction, as revealed by the HPLC profile of the products. In solutions containing 0.4 M $NaNO_3$ and 0.2 M $Mg(NO_3)_2$, for example, we find very sharp peaks corresponding to all 3′,5′-linked oligomers up to the 20-mer, while in solutions containing 0.4 M $NaNO_3$ and 1.2 M $Mg(NO_3)_2$ we observe much broader peaks corresponding to oligomers at least as long as the 40-mer but containing more 2′,5′ linkages.

In a previous study of a related Zn^{2+} condensation of **1** on poly(C), we concluded, tentatively, that the Zn^{2+} ion functions by changing the geometry of the helix rather than by activating the 3′-OH group.[2] The results reported here strengthen that conclusion, since they show that orientation alone can greatly increase the efficiency of the reaction.

The sensitivity of the reaction to minor changes in the concentration of reactants and metal ions may have significance in the context of the chemistry of the prebiotic earth. It suggests that short peptides that interacted with polynucleotides might have had profound effects on the efficiency and regiospecificity of the earliest prebiotic template-directed replication reactions.

Full details of these and related reactions will be reported in due course.

Acknowledgment. This work was supported by National Institutes of Health Grant GM 13435. We thank A. R. Hill for technical assistance and R. Brown for secretarial help.

Ketone Methylenation with Optical Resolution. Total Synthesis of the Ginseng Sesquiterpene (−)-β-Panasinsene and Its Enantiomer

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(−)-β-Panasinsene (**1**) is a principal component of the volatile oil from the root of ginseng (*Panax ginseng*) which is highly valued in Chinese folk medicine. The compound was identified and found to be present in both fresh and dried ginseng by Yoshihara and Hirose in 1975.[1] The synthesis of (±)-**1** has recently been reported by McMurry and Choy.[2] We were intrigued primarily by the unique 4-5-6 fused tricyclic system of **1** and secondly by the comment of McMurry and Choy that "total synthesis of panasinsenes turned out to be a considerably more difficult task than we had originally thought and more than a few synthetic plans came to naught". The most apparent penult in the synthesis of **1** is ketone **2** which McMurry and Choy found to be "inert to methylenetriphenylphosphorane in DMSO". This lack of reactivity of ketone **2** in the Wittig reaction indicated to us that **2** would be a good vehicle for demonstrating the efficacy of a new methylenation–resolution scheme based on sulfoximine chemistry.

Conjugate addition of 4-methyl-3-pentenylmagnesium bromide[3] to 3-methyl-2-cyclohexenone in the presence of 5 mol % of copper(I) bromide/dimethyl sulfide complex in tetrahydrofuran (THF) at 0 °C followed by trapping of the intermediate enolate

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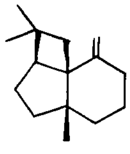
[1] Yoshihara, K.; Hirose, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2078.

[2] McMurry, J. E.; Choy, W. *Tetrahedron Lett.* **1980**, 2477. Their synthesis involved intramolecular cuprous triflate catalyzed photocyclization of 2-methylene-3-(4-methyl-3-pentenyl)-1-cyclohexanol (elaborated from 2-methylcyclohexanone), oxidation of the photoproduct to ketone **2**, addition of methyllithium, and dehydration to a mixture of α- and β-panasinsenes.

[3] Julia, M.; Julia S.; Guegan, R. *Bull. Soc. Chim. Fr.* **1960**, 1072.



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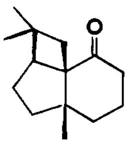
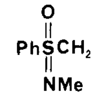


2

with gaseous formaldehyde gave hydroxy ketones **3** and **4** (90%, 1:1) which were separated on a silica gel column for characterization purposes (Scheme I).[4] The ^{1}H NMR spectrum of the compound of higher R_f exhibited the ring methyl singlet at δ 0.8; the ring methyl of the diastereomer appeared at δ 1.1. On the basis of the general trend that axial methyl groups are deshielded relative to a corresponding equatorial methyl group,[5] structure **3** was assigned to the more mobile diastereomer and structure **4** to the less mobile. As a model system, 2-(hydroxymethyl)-3,3-dimethylcyclohexanone was prepared; the geminal methyols appeared at δ0.8 and 1.1.

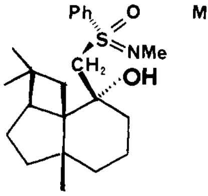
A mixture of **3** and **4** was converted into the tosylates in 82% yield by treatment with *p*-toluenesulfonyl chloride in pyridine. The relatively unstable tosylates were purified by flash chromatography and exposed to potassium *tert*-butoxide in THF/*tert*-butyl alcohol at −78 °C to give the enone **5** in 78% yield. Upon irradiation in refluxing pentane enone **5** slowly underwent intramolecular photocyclization to yield ketone **2**; after 1 week a 67% yield of **2** was obtained. Models indicated that the photoadditon should occur with the desired stereochemistry. The ^{1}H NMR spectrum of our ketone **2** was identical with a spectrum of **2** provided by McMurry who obtained **2** by synthesis and degradation of caryophyllene.[2]

In a reaction exhibiting remarkable diastereoselectivity, the addition of (±)-(*N*-methylphenylsulfonimidoyl)methyllithium (**6**) to (±)-ketone **2** occurred at −78 °C to give (±)-**7** with only a trace of a second diastereomer (±)-**8** (ratio >30:1). The (+)-(*S*)-sulfoximine reagent **6** kinetically selects a single carbonyl face of the (−)-enantiomer of **2** and the (−)-(*R*)-**6** selects the same carbonyl face of (+)-**2** to give (±)-**7** as the major product. Additions to ketone **2** are apparently completely diastereoface selective, and the addition of the chiral reagent (±)-**6** results in mutual kinetic resolution.[6] Treatment of crude (±)-**7** with aluminum amalgam and acetic acid in aqueous tetrahydrofuran[7] gave (±)-β-panasinsene (**1**) in 67% yield based on ketone **2** (the ^{1}H NMR of our **1** and that prepared by McMurry and Choy[2] were identical). None of the isomeric α-panasinsene could be detected. (In α-panasinsene[1] the double bond is shifted to give the 1-methylcyclohexane derivative).



$\mathrm{Ph\overset{O}{\underset{NMe}{S}}CH_2Li}$

6



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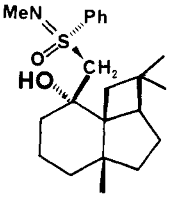

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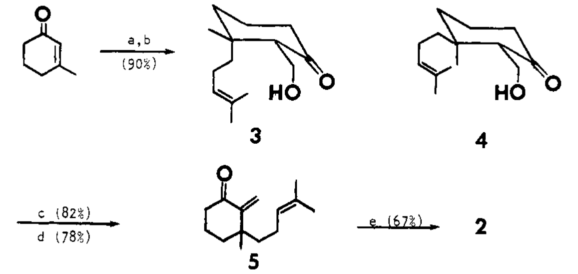
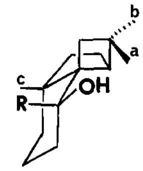
Scheme I[a]



[a] (a) 4-Methyl-3-pentenylmagnesium bromide, 5 mol % CuBr/Me$_2$S, THF, 0 °C, 45 min. (b) Gaseous CH$_2$O, 0 °C, 60 min. (c) *p*-TolSO$_2$Cl, pyridine, 25 °C, 16 h. (d) *t*-BuOK, THF *t*-BuOH (9:1), −78 °C, 1 h. (e) $h\nu$ (GE 250-W E-Z Merc) in refluxing pentane 0.02 M in **5**, 1 week.

The addition of (*S*)-(*N*-methylphenylsulfonimidoyl)methyllithium (**6**) (99% optically pure)[8] to (±)-**2** resulted in the production of two diastereomers (+)-**7** and (+)-**8** which were readily separated by flash chromatography. Diastereomer **7** was obtained in 42% yield as a gum, $[\alpha]^{25}{}_{\mathrm{D}}$ +11.0 (*c* 1.14, CHCl$_3$). Diastereomer **8** was obtained in 33% yield as a crystalline solid, mp 143–148 °C, $[\alpha]^{25}{}_{\mathrm{D}}$ +108.9° (*c* 1.07, CHCl$_3$). Treatment of diastereomer (+)-**7** with aluminum amalgam and acetic acid in aqueous tetrahydrofuran gave (−)-β-panasinsene (**1**), $[\alpha]^{25}{}_{\mathrm{D}}$ −27.7° (*c* 1.11, CHCl$_3$) and −24.6° (*c* 1.05, MeOH) in 96% yield. The β-panasinsene, isolated from ginseng and reported to have $[\alpha]^{25}{}_{\mathrm{D}}$ −3° (MeOH) (concentration not recorded),[1] is apparently of low optical purity. Treatment of diastereomer (+)-**8** as above gave the unnatural enantiomeric (+)-β-panasinsene, $[\alpha]^{25}{}_{\mathrm{D}}$ +29.7° (*c* 1.11, CHCl$_3$) and +27.3 (*c* 1.06, MeOH), in 92% yield.

Raney nickel desulfurization[9] of adduct **7** gave, in 78% yield, tertiary alcohol **9**, $[\alpha]^{20}{}_{\mathrm{D}}$ −52.1° (*c* 0.47, CHCl$_3$). It has been previously reported that addition of methylmagnesium bromide to (−)-**2** (obtained from natural caryophyllene of known absolute configuration[10]) resulted in a single alcohol (stereochemistry at the carbinol center undetermined) with spectral characteristic matching our **9** and $[\alpha]^{20}{}_{\mathrm{D}}$ −56.5° (*c* 0.44, CHCl$_3$).[11] Desulfurization of adduct **8** gave the enantiomer of **9**, $[\alpha]^{20}{}_{\mathrm{D}}$ +53.0° (*c* 0.49, CHCl$_3$), in 94% yield.



9 R = CH$_3$

10 R = H

The relative configuration at the carbinol center in **9** and its enantiomer as well as their predecessors **7** and **8** is tenuous. The choice shown is based on the following lines of evidence: On the basis of the model systems we believe the ^{1}H NMR assignments for the methyl groups in **9** are a and b, a singlet at δ 0.92, R at δ 1.13, and c at δ 1.22. Upon addition of the shift reagent tris(2,2,6,6-tetramethylheptane-3,5-dionato)europium(III) the resonance of the carbinol methyl R moved rapidly downfield, the geminal methyl signal separated, and one singlet (a) moved downfield at a moderate pace, crossing the signal of c. The shifts of b and c, which are almost equidistant from the hydroxyl, moved slowly downfield in a parallel manner. These shifts are in accord with expectations for the structure shown as **9**. In the ^{13}C NMR spectrum of **7** the *S*-methylene carbon appears at δ 58 which appears to be characteristic for axial orientation of this group.[12] Finally, the reduction of ketone **2** with lithium aluminum hydride resulted in a single alcohol, presumably **10**, with ^{1}H NMR singlets at δ 0.85, 0.90, and 1.19 and IR bands at 1046 and 1029 cm^{-1} (CHCl$_3$) in the region characteristic of equatorial C–O stretch.[13]

The method for ketone methylenation with optical resolution which we have used in the above sequence should have wide applicability in the total synthesis of optically active natural

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(4) Satisfactory microanalytical data was obtained for all compounds in the sequence except for the tosylates of **3** and **4** which decomposed during shipment.

(5) Jackman, L. M.; Sternhill, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; Pergamon Press: Oxford, 1969.

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(7) Johnson, C. R.; Kirchhoff, R. A. *J. Am. Chem. Soc.* **1979**, *101*, 3602.

(8) Based on $[\alpha]^{25}{}_{\mathrm{D}}$ +184°(*c*3, acetone) for (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine.

(9) Johnson, C. R.; Stark, C. J. *J. Org. Chem.*, in press.

(10) Barton, D. H. R.; Nickon, A. *J. Chem. Soc.* **1954**, 4665.

(11) McKillop, T. F. W.; Martin, J.; Parker, W.; Roberts, J. S.; Stevenson, J. R. *J. Chem. Soc. C* **1971**, 3375.

(12) Zeller, J. R.; Johnson, C. R., unpublished results.

(13) Conley, R. T. "Infrared Spectroscopy"; Allyn and Bacon: Boston, 1969; p 129.

products containing exocyclic methylene groups as well as groups derived from the methylene by diastereoface selective additions, e.g., hydrogenation, hydroboration, epoxidation. The procedure will be most effective when applied to ketones which will exhibit high diastereoface selectivity upon the addition of reagent **6**, as this will limit to two the diastereomeric β-hydroxysulfoximines to be separated.

Acknowledgment. This work was supported by a grant from the National Science Foundation. We thank Professor John E. McMurry for providing spectra of **1** and **2** and James R. Zeller for valuable discussions.

Base Catalysis in a Photochemical Smiles Rearrangement. A Case of General Base Catalysis of a Photoreaction

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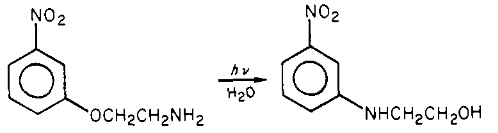
While phenomena identified as catalytic have been reported often for photochemical reactions,[2] fundamental criteria for the assessment of catalytic effects in photochemistry have not been defined. We wish to report the novel observation of base catalysis of a photochemical Smiles rearrangement[3] and to argue that our observations are best interpreted as a case of general base catalysis of an excited-state reaction.

The kinetic effect of sodium hydroxide on the photo-Smiles rearrangement of **1**, giving **2** in quantitative yield, was determined



1 **2**

by measuring quantum yields at 313 nm with a merry-go-round apparatus. The reactions were conducted in carbonate-free aqueous solutions containing 2.5×10^{-3} M **1** and varying amounts of sodium hydroxide (0.0001 to 0.02 M) at constant ionic strength (0.625 M KCl) and at 23 °C. The reactions were monitored by the absorbance at 405 nm (ϵ_{405} of **2** 1110); the actinometer was degassed 0.100 M valerophenone in benzene.[4] A double reciprocal plot of the data from these experiments is shown in Figure 1.

Inspection of the plot discloses two facts about the kinetic effect of hydroxide ion: (i) the linear region at high base concentrations indicates that the reaction is subject to base catalysis and (ii) the plateau at low base concentrations indicates that an uncatalyzed reaction, or one catalyzed weakly by water, also occurs.

We next inquired whether the catalysis was general or specific. Solutions of **1** at pH 10.04 containing 0.1 M concentrations of a variety of weak bases were irradiated in parallel on the wheel, and quantum yields were determined. As shown in Table I, the added bases are effective catalysts at constant pH. Observations of this kind constitute a classical experimental test for general base catalysis in the ground state,[5] and we conclude accordingly that the photoreaction is subject to general base catalysis.

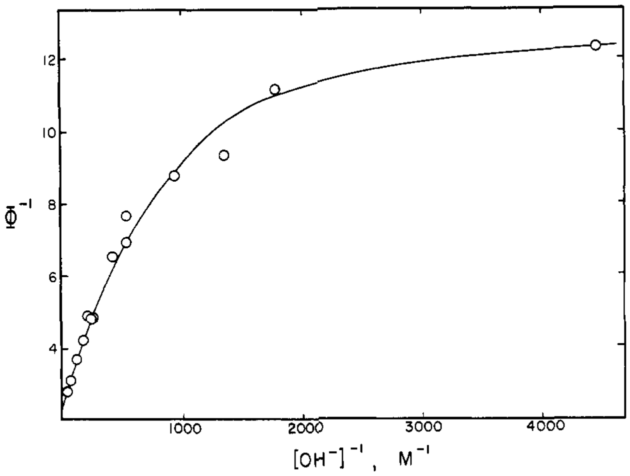


Figure 1. Dependence of quantum yields for photo-Smiles rearrangement of **1** on the concentration of NaOH.

Table I. Dependence of Quantum Yields on Bases[a]

base	conjugate acid pK_a	concn, M	Φ_{Smiles}
none			0.0880
NaOAc	4.76	0.100	0.103
$NaHCO_3$-Na_2CO_3	6.37 10.25	0.100[b]	0.200
Na_2HPO_4	7.21	0.100	0.206
morpholine	8.33	0.100	0.152[c]
$HOCH_2CH_2NH_2$	9.50	0.077	0.168[c]

[a] All reactions conducted at pH 10.04 ± 0.02. [b] Expresses total carbonate concentration. [c] Morpholine and ethanolamine may quench the excited state.

Before considering the kinetic description of the reaction, we wish to justify our use of the quantum yield as the experimental measure of catalysis. A ground-state catalyst may be defined as a substance which appears in the rate expression to a power higher than it appears in the stoichiometry.[6] The photochemist's measurement analogous to rate is quantum yield, which may be thought of as a ratio of rates—the rate of product formation divided by the rate of light absorption. We propose, analogous to the ground-state definition, that a photochemical catalyst be defined as a substance which appears in the quantum yield expression to a power higher than it appears in the stoichiometry.[7] We anticipate that, as is the case in the ground state,[6] explanations of photochemical catalysis will be couched in terms of rate constants for new and more efficient reaction pathways which the catalyst makes available.

The mechanism presented in Scheme I is consistent with all of our findings. The triplet state is implicated as the reactive excited state since the reaction sensitized by 0.043 M p-methoxyacetophenone in 50% CH_3CN-H_2O containing 0.01 M NaOH proceeds cleanly with a quantum yield 1.09 times greater than that of the comparable direct photoreaction. The quantum yield

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(1) Before August 1, 1982, direct correspondence to Gorlaeus Laboratories, P.O. Box 9502, State University, 2300 RA Leiden, Netherlands.

(2) (a) Stoll, A.; Schlientz, W. *Helv. Chim. Acta* **1955**, *38*, 585-594. (b) Marshall, J. A.; Carroll, R. D. *J. Am. Chem. Soc.* **1966**, *88*, 4092-4093. (c) Kropp, P. J. *Ibid.* **1966**, *88*, 4091-4092. (d) Letsinger, R. L.; Wubbels, G. G. *Ibid.* **1966**, *88*, 5041-5042; **1974**, *96*, 6698-6706. (e) Bryce-Smith, D.; Deshpande, R.; Gilbert, A.; Grzonka, J. *J. Chem. Soc., Chem. Commun.* **1970**, 561-562. (f) Wubbels, G. G.; Jordan, J. W.; Mills, N. S. *J. Am. Chem. Soc.* **1973**, *95*, 1281-1285. (g) Wubbels, G. G.; Monaco, W. J.; Johnson, D. E.; Meredith, R. S.; *Ibid.* **1976**, *98*, 1036-1037. (h) Nylund, T.; Morrison, H. *Ibid.* **1978**, *100*, 7364-7374. (i) Yokoyama, K.; Nakagaki, R.; Nakamura, J.; Mutai, K.; Nagakura, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2472-2475. (j) Wagner, P. J.; Thomas, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 4173-4182. (k) Stone, P. G.; Cohen, S. *Ibid.* **1980**, *102*, 5685-5686. (l) Scaiano, J. C.; Neta, P. *Ibid.* **1980**, *102*, 1608-1611. (m) Mariano, P. S.; Leone, A. A. *Ibid.* **1979**, *101*, 3607-3617.

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(6) Bender, M. L.; "Mechanisms of Homogeneous Catalysis from Protons to Proteins"; Wiley: New York, 1971; pp 3-5.

(7) The definition could be qualified by specifying a particular reactive state as the starting state, thereby excluding sensitizers and promoters of intersystem crossing from the category "catalyst". Medium effects will not qualify as catalysis since they will have no term in the rate expression. A paper exploring in more detail a definition of excited-state catalysis is in preparation, and we invite readers to draw our attention to novel examples of catalysis and related phenomena for excited-state reactions.

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