rate of hydrolysis in the antibody–substrate complex, $v_{complex} = k_{complex}[complex][OH^-]$.[19] The ratio of $k_{complex}/k_{uncat}$, which reflects the acceleration of hydrolysis by the antibody, is 810. We are carrying out additional experiments to unravel the mechanism of the antibody-catalyzed hydrolysis and are screening 20 additional IgGs for catalytic activity.[20]

We have described the rational generation of a catalytic antibody with predefined specificity. Much work remains to be done to define those elements necessary for the generation of catalytic antibodies with high-turnover numbers and specificity. At the same time we are pursuing additional strategies for introducing catalytic activity into antibodies, including chemical and genetic modification of antibodies. In conclusion, the diversity of receptors that can be generated by the immune system offers tremendous opportunities for investigations of the chemical mechanism of molecular recognition and catalysis.

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(19) The value of $k_{uncat}[OH^-]$ was determined to be 1.75×10^{-3} min^{-1} at 30 °C in 10 mM Tris·HCl, pH 8.5, by extrapolation of the rate of the uncatalyzed reaction to zero buffer concentration.

(20) Generation of monoclonal antibodies against the KLH–phosphonate **2** adduct afforded 20 IgG's, which were inhibitable in a competition ELISA assay. One such IgG catalyzes the hydrolysis of carbonate **1** with $k_{cat} = 29$ min^{-1} and $K_M = 350$ μM, a rate acceleration of 16000 above background.

Unusual Chemoselectivity Using Difunctional Allylic Alkylating Agents

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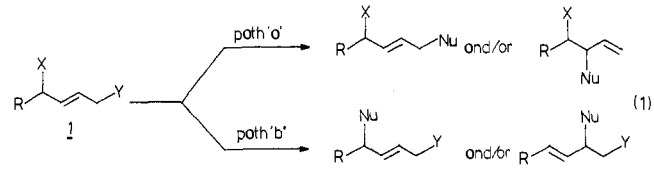
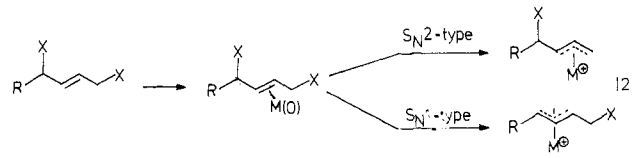
Chemoselective alkylations using difunctional alkylating agents like **1** require differentiating the two leaving groups[1]—a task that may be very cumbersome. A more appealing solution to such a problem would be to have identical leaving groups which may be differentiated simply by modification of reaction conditions to favor path "a" or path "b" (eq 1). An auxillary problem is the question

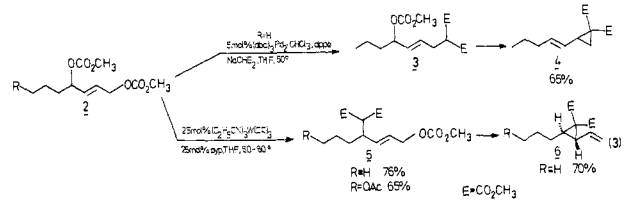


of regioselectivity in such alkylations. Thus, from a single substrate such as **1**, four different constitutional isomers in addition to the stereoisomer and geometrical isomers possible (for a total of eight isomers) may arise. In this paper, we report the remarkable ability to fully control the reactivity of such substrates by appropriate catalyst choice.

In examining the question of metal-catalyzed alkylations, the effect of both olefin substitution and the degree of substitution of the carbon bearing the leaving group must be evaluated. However, for substrates like **1**, only the latter concerns us since ionization of either leaving group occurs from the same olefin–metal(0) complex (see eq 2). The sensitivity of palladium-catalyzed reactions to steric effects[2] led us to propose its ability to ionize would resemble an S_N2-type displacement and, thereby, favor cleavage of the leaving group at the primary carbon. On the other hand, tungsten catalysts showed a greater dependence on electronic effects[3] which should more closely resemble an S_N1-type displacement and, thereby, favor cleavage of the leaving group at the more substituted carbon.

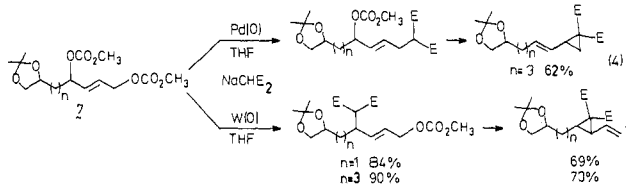


In the event, treatment of the dicarbonate **2** with dimethyl sodiomalonate in the presence of a Pd(0) catalyst at 50 °C led to a mixture of **3** and **4**, the latter arising from further reaction of the former. Allowing the reaction to proceed to completion



produced the vinylcyclopropane **4**[4] as the sole product.[5] Clearly, initial ionization occurred cleanly at the primary carbon. On the other hand, a tungsten catalyst generated by mixing 25 mol % of $(C_2H_5CN)_3W(CO)_3$,[6] 25 mol % of bpy, and 75 mol % of additional propionitrile with the nucleophile[7] and then adding the dicarbonate **2** led cleanly to only **5**.[4,8] While cyclopropane **6**[4] may arise by further treatment with a tungsten catalyst, a smoother conversion occurred using typical Pd(0) conditions.

A similar complementarity occurred with the dicarbonate **7** ($n = 3$) as summarized in eq 4. The W(0)-catalyzed reactions



showed a strong dependence on inductive effects. The electron-withdrawing effect of placing the acetonide directly on the secondary carbon bearing the leaving group (i.e., **7**, $n = 0$) led only

(1) For excellent illustrations of this point related to transition metals, see: Backvall, J. E.; Nystrom, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676. Ferroud, D.; Genet, J. P.; Kiolle, R. *Tetrahedron Lett.* **1986**, *27*, 23. Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523. Colobert, F.; Genet, J.-P. *Tetrahedron Lett.* **1985**, *26*, 2779. Genet, J. P.; Ferroud, D. *Tetrahedron Lett.* **1984**, *25*, 3579. Tanigawa, Y.; Nishimura, K.; Kawasaki, A.; Murahashi, S. *Tetrahedron Lett.* **1982**, *23*, 5549.

(2) For reviews, see: Trost, B. M.; Verhoeven, T. R. *Compr. Organomet. Chem.* **1982**, *8*, 799. Tsuji, J. *Organic Synthesis with Palladium Compounds*, Springer-Verlag: New York, 1980.

(3) Trost, B. M.; Hung, M. H. *J. Am. Chem. Soc.* **1983**, *105*, 7757; **1984**, *106*, 6837.

(4) All new compounds have been fully characterized spectrally and elemental compositions determined by combustion analysis and/or high-resolution mass spectroscopy.

(5) During the course of our studies, the formation of the parent vinylcyclopropane from the dicarbonate of 2-butene-1,4-diol has been reported. However, the question of chemoselectivity of substituted systems has not been addressed. See: Burgess, K. *Tetrahedron Lett.* **1985**, *26*, 3049. Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 3835. Also see: Tsuda, T.; Okada, M.; Nishi, S.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 421.

(6) Cf.: Kubas, G. J. *Inorg. Chem.* **1983**, *22*, 692. We prefer to prepare the catalyst by exchange from $(CH_3CN)_3W(CO)_3$ and propionitrile, analogous to preparation of the benzonitrile analogue. See: Werner, H.; Deckelmann, K.; Schonenberger, U. *Helv. Chim. Acta* **1970**, *53*, 2002.

(7) It is critical to react the tungsten complex with the nucleophile prior to adding the electrophile for optimum results. The exact structure of the active catalyst, presumably an anionic species, will be the focus of future work.

(8) The effect of an adjacent oxygen substituent on the regioselectivity of allylic alkylations has been previously noted for palladium-catalyzed reactions. See ref 1 and: Trost, B. M.; Molander, G. *J. Am. Chem. Soc.* **1981**, *103*, 5969. Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575.

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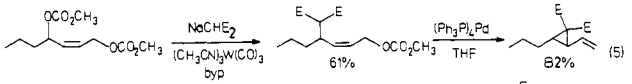
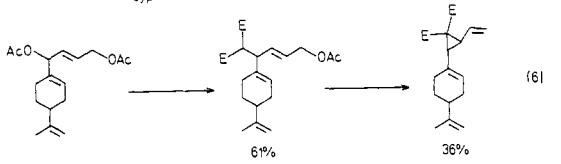
to recovered starting material. Simply inserting a single methylene group (i.e., **7**, n = 1) is sufficient to reduce the destablizing inductive effect to permit smooth alkylation.

The unusual ability to effect chemoselective displacements at a more substituted carbon led us to focus our efforts on the tungsten-catalyzed reaction. Equations **5** and **6** illustrate some



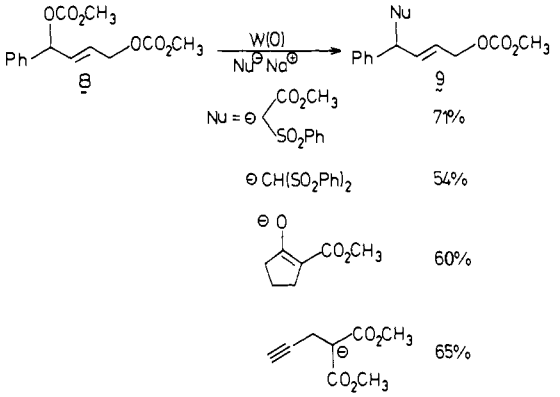
(5)



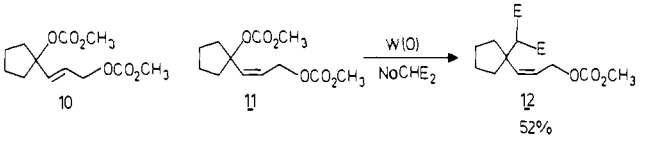
(6)

additional examples of the selective displacement and further substitution. Note the retention of olefin geometry in reactions 3 and 5 which contrasts to palladium-catalyzed reactions[9] where olefin geometry is frequently scrambled. In the disubstituted example of eq 6, the diacetate sufficed. While these last two examples employed the acetonitrile complex of tungsten, we now prefer the propionitrile complex because of its better stability and higher catalytic activity.

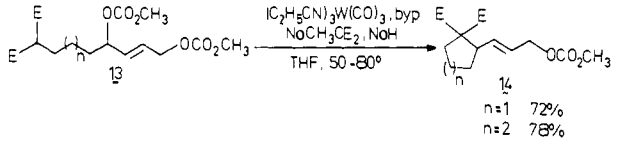
A wide range of nucleophiles has been examined by using the dicarbonate **8**. In each and every case, chemo- and regioselective alkylation occurred to give **9**.[4] The success of the acetylenic



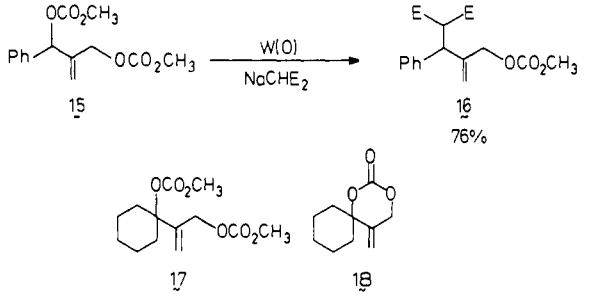
malonate stands in contrast to molybdenum-catalyzed reactions[10] whereby the presence of an acetylene prevented alkylation reactions. Steric hindrance around the olefin may be important. Whereas the *E*-olefin dicarbonate **10** only returned starting material, the *Z*-olefin **11** led to the desired alkylation product **12** (52% yield) in addition to an elimination product (37% yield).



Initial attempts to extend this chemoselective alkylation reaction to a cyclization of **13** failed—only starting material was recovered. During our preliminary examination of the W(0) reactions, we determined that the order of addition of the nucleophile and electrophile was critical. As stated earlier, the nucleophile was added *prior* to the electrophile—a requirement that cannot be met in the case of **13** which, of necessity, adds both simultaneously. This dilemma was resolved by initially reacting the tungsten complex with dimethyl sodiomethylmalonate (1 equiv with respect to substrate) and then adding the sodium salt of the cyclization substrate generated by treating **13** with sodium hydride. While, obviously, the possibility of an intermolecular alkylation arose, no such products were detected. Excellent chemo- and regioselective cyclization occurred to form the five-[11] and six-membered rings **14**,[4] n = 1 and 2.



Other types of dicarbonates may be envisioned to require similar chemoselectivity. Thus, **15** led smoothly to the monoalkylation product **16**.[4] On the other hand, the dicarbonate **17** or **18** failed to give any reaction whatsoever. Presumable the steric hindrance



of these latter systems precluces their ability to serve as substrates for tungsten. The demonstration that such subtle selectivity can be achieved by rational catalyst choice whereby the nature of the transition state of displacement may be altered from a S_N2 type to a S_N1 type encourages us to seek such solutions to other problems of chemoselectivity.

Acknowledgment. We thank the National Science Foundation for their generous support of our programs.

Supplementary Material Available: General procedures for the reactions **2** → **4**, **2** → **5**, **5** → **6**, and **13** → **14** (3 pages). Ordering information is given on any current masthead page.

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(10) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1982**, *104*, 5543; **1983**, *105*, 3343.
(11) In this case the cyclization product contained some of the transesterified dimer (carbonate related to **14**, n = 1).

Device for Simultaneous Measurements of Transient Raman and Absorption Spectra of Enzymic Reactions: Application to Compound I of Horseradish Peroxidase

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Application of resonance Raman (RR) spectroscopy to intermediates of enzymic reactions, is a fascinating subject since it brings about structural information essential to elucidate a catalytic mechanism,[1] but a problem arises when the intermediate is photolabile. For compound II of horseradish peroxidase (HRP) with a ferryl heme,[2] which is the second intermediate in the reaction of ferric HRP with H_2O_2, the RR spectra reported by several groups[3-6] are in agreement with each other and the

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(4) Rakhit, G.; Spiro, T. G.; Uyeda, M. *Biochem. Biophys. Res. Commun.* **1976**, *71*, 803-807.

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