nistically viewed as a thermally activated process, as previously established for many triplet ketones.[4,21]

In conclusion, the combined experimental and theoretical data for the solvent-induced quenching of n,π* excited singlet azoalkanes support a hydrogen abstraction in which a transition state is followed by a conical intersection as the reaction coordinate. This photochemical reaction mechanism should be general for n,π* singlet excited chromophores and provides an important rationale for their reactivity and efficiency in hydrogen abstractions.

Received: June 11, 1997 [Z10537IE]
German version: *Angew. Chem.* **1998**, *110*, 103–107

Keywords: ab initio calculations · azo compounds · hydrogen transfer · isotope effects · photochemistry

---

[1] L. Salem, C. Leforestier, G. Segal, R. Wetmore, *J. Am. Chem. Soc.* **1975**, *97*, 479–487.

[2] N. J. Turro, J. McVey, V. Ramamurthy, P. Lechtken, *Angew. Chem.* **1979**, *91*, 597–612; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 572–586.

[3] W. M. Nau, F. L. Cozens, J. C. Scaiano, *J. Am. Chem. Soc.* **1996**, *118*, 2275–2282, and references therein.

[4] M. A. Garcia-Garibay, A. Gamarnik, R. Bise, L. Pang, W. S. Jenks, *J. Am. Chem. Soc.* **1995**, *117*, 10264–10275.

[5] D. Severance, H. Morrison, *Chem. Phys. Lett.* **1989**, *163*, 545–548.

[6] A. E. Dorigo, M. A. McCarrick, R. J. Loncharich, K. N. Houk, *J. Am. Chem. Soc.* **1990**, *112*, 7508–7514.

[7] P. S. Engel, D. W. Horsey, J. N. Scholz, T. Karatsu, A. Kitamura, *J. Phys. Chem.* **1992**, *96*, 7524–7535.

[8] P. S. Engel, D. W. Horsey, D. E. Keys, C. J. Nalepa, L. R. Soltero, *J. Am. Chem. Soc.* **1983**, *105*, 7108–7114.

[9] W. M. Nau, W. Adam, J. C. Scaiano, *Chem. Phys. Lett.* **1996**, *253*, 92–96.

[10] M. J. Mirbach, M. F. Mirbach, W. R. Cherry, N. J. Turro, P. Engel, *Chem. Phys. Lett.* **1978**, *53*, 266–269.

[11] P. S. Engel, C. J. Nalepa, *Pure Appl. Chem.* **1980**, *52*, 2621–2632.

[12] M. Klessinger, *Angew. Chem.* **1995**, *107*, 597–599; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 549–551, and references therein.

[13] F. Bernardi, M. Olivucci, M. A. Robb, *Chem. Soc. Rev.* **1996**, 321–328.

[14] B. S. Solomon, T. F. Thomas, C. Steel, *J. Am. Chem. Soc.* **1968**, *90*, 2249–2258.

[15] H. Rau, *Angew. Chem.* **1973**, *85*, 248–258; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 224–239.

[16] R. P. Bell, *The Tunnel Effect in Chemistry*, Chapman und Hall, London, **1980**.

[17] For the calculation of k_q the ambient-temperature value of τ_0 ((930 ± 30) ns, gas phase) was employed for all temperatures. Inclusion of the much smaller temperature dependence of τ_0, which implicitly includes any temperature dependence of k_f and k_d and the possible contribution due to photodecomposition, does not affect the activation parameters within the limits of statistical regression error. For comparison, the gas-phase lifetimes are 950 and 885 ns at −20 and 65 °C, respectively; that is, they are within the limits of error of or very close to the ambient value.

[18] All MCSCF geometry optimizations were carried out with a complete active space (CAS) including 12 electrons in 10 orbitals (CAS(12,10)). The CAS orbitals comprise the π and π* N=N orbitals, the four σ and σ* C–N orbitals, the two nitrogen lone pair orbitals of the pyrazoline fragment, and the σ and σ* orbitals of the reactive C–H bond of CH_2Cl_2. To improve the description of the H transfer the standard 6-31G* basis set (double-ζ + d-type polarization function for atoms of the first and seconds rows of the periodic system) was augmented with p-type polarization and s-type diffuse functions on the CH_2Cl_2 hydrogen atoms and with sp-type diffuse functions (included in Gaussian 94)[19b] on the nitrogen centers. To improve the energetics by including the effect of dynamic electron correlation, the S_1 energies of MIN, TS, and LP were recomputed using multireference Møller–Plesset perturbation theory with the PT2F method included in MOLCAS.[20] To reduce the computational cost we used a CAS(8,7) with the 6-31G* basis set for the reaction coordinate and frequency computations. This reduced CAS does not include the σ and σ* orbitals of the "short" C–N bond and the lone-pair orbital on the alternative N atom. CAS(8,7) produces optimized geometries of MIN, TS, and LP which differ only slightly from that of CAS(12,10) (see Figure 1, top). The reaction coordinate was determined with the IRC method available in Gaussian 94. The conical intersection is easily located by computing the reaction coordinate until degeneracy of S_1 and S_0 is achieved. This manifests itself in failure of the MCSCF calculation to converge owing to S_1–S_0 near-degeneracy. The last reaction coordinate point before degeneracy (LP) is taken as representative of the conical intersection.

[19] a) B. O. Roos, *Adv. Chem. Phys.* **1987**, *69*, 399–446; b) the MCSCF program used is implemented in Gaussian 94, Revision B.2: M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, USA, **1995**.

[20] a) K. Andersson, P.-A. Malmqvist, B. O. Ross, *J. Chem. Phys.* **1992**, *96*, 1218–1226; b) MOLCAS, Version 3: K. Andersson, M. R. A. Blomberg, M. Fülscher, V. Kellö, R. Lindh, P.-A. Malmqvist, J. Noga, J. Olsen, B. O. Roos, A. J. Sadlej, P. E. M. Siegbahn, M. Urban, P. O. Widmark, University of Lund, Sweden, **1994**.

[21] P. J. Wagner, Q. Cao, R. Pabon, *J. Am. Chem. Soc.* **1992**, *114*, 346–348.

[22] P. S. Engel, L. R. Soltero, S. A. Baughman, C. J. Nalepa, P. A. Cahill, R. B. Weisman, *J. Am. Chem. Soc.* **1982**, *104*, 1698–1700.

[23] M. F. Mirbach, M. J. Mirbach, K.–C. Liu, N. J. Turro, *J. Photochem.* **1978**, *8*, 299–306.

Catalytic, Highly Regio- and Chemoselective Generation of Radicals from Epoxides: Titanocene Dichloride as an Electron Transfer Catalyst in Transition Metal Catalyzed Radical Reactions**

Andreas Gansäuer,* Marianna Pierobon, and
Harald Bluhm

During the last two decades the development of efficient chain reactions has led to an explosive growth in free radical chemistry.[1] Although the understanding of how substrate control determines the stereo- and chemoselectivity of these reactions has reached a high level,[2] to the best of our knowledge little is known about reagent-controlled, catalytic transformations of radicals not proceeding as chain reactions.[3] The advantage of this type of reaction is broader application because the influence of the substrate on the chemo- and stereoselectivity can ideally be overruled and the course of the reaction determined solely by the reagent in catalytic amounts. Therefore a reagent-controlled catalytic reaction would extend the synthetic utility of free radicals even further.

---

[*] Dr. A. Gansäuer, M. Pierobon, H. Bluhm
Institut für Organische Chemie der Universität
Tammannstrasse 2, D-37077 Göttingen (Germany)
Fax: Int. code + (49) 551-392944
e-mail:agansae@gwdg.de

[**] This work was supported by the Fonds der Chemischen Industrie and the Socrates Program. We thank Prof. R. Brückner for constant support and encouragement.

An interesting alternative to radical chain reactions is the reductive opening of epoxides by single electron transfer (SET) from titanocene chloride dimers.[4] The β-titanoxy radical thus formed can undergo the typical radical reactions. Epoxides can be prepared conveniently from a number of functional groups, for example olefins[5] and carbonyl compounds,[6] and can thus serve as radical precursors. An attractive feature of this reaction is that an alcohol is formed after hydrolysis rather than a hydrocarbon, as in the reactions of halides with stannanes.[7] However, both the electron transfer reagent precursor, titanocene dichloride, and the reductant, usually zinc powder, are employed in at least stoichiometric quantities. This is clearly disadvantageous when more complex titanocenes are used.[8] If the reaction could be conducted with a catalytic amount of titanocene, this problem would be solved, and the way would be paved for transition metal catalyzed radical reactions with the potential for efficient reagent control. To achieve this goal the titanocene alkoxide formed must be converted into a derivative of the alcohol or the alcohol itself and titanocene dichloride, the catalyst precursor. In situ reduction by the stoichiometric reductant would yield the redox-active titanium(III) complex[9] and complete the catalytic cycle.

Recently Fürstner et al. have devised efficient catalytic McMurry[10] and Nozaki–Hiyama couplings[11] by adding chlorotrimethylsilane to the reaction mixture. The metal alkoxides and oxides formed in the couplings are thus silylated and the catalytically active metal species are regenerated. This method is, however, not applicable to epoxides because silylated chlorohydrins would form by Lewis acid initiated ring opening. We reasoned that protonation of the titanium-bound oxygen atom should also allow efficient regeneration of the catalyst. For this purpose the acid must be strong enough for the protonation, but neither may the metal powder be oxidized nor the catalyst deactivated by complexation of the resulting base. Pyridinium hydrochlorides (Py-HCl) seemed to be appropriate based on their pK_a values[12] and were therefore tested as acids in the reaction of **1** with cyclohexadiene as the hydrogen atom donor, a stoichiometric reductant, and 5 mol% titanocene dichloride (Table 1).

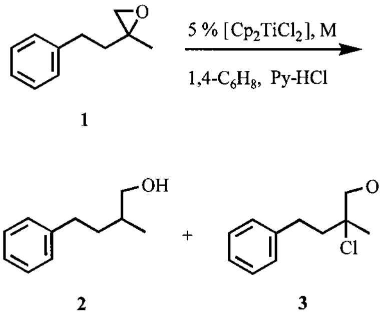


Table 1. Optimization of the reductive opening of epoxide **1** with 5 mol% [Cp$_2$TiCl$_2$] and 1,4-cyclohexadiene.

Hydrochloride	M	t[h]	**1**:**2**:**3**[a]
Py-HCl	Zn	35	28:32:26
2,4-Me$_2$Py-HCl	Zn	36	30:43:22
2,4,6-Me$_3$Py-HCl	Zn	36	15:71[b]:12
2,4,6-Me$_3$Py-HCl	Mn	16	0:88[b]:0.5

[a] Determined from the ^{1}H NMR spectrum of the crude mixture. [b] Yield of the isolated product.

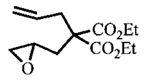
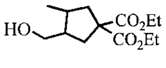
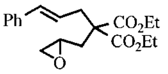
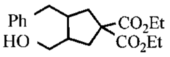
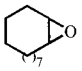
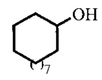
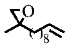
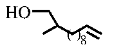
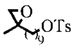
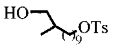
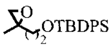
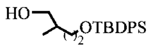
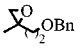
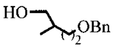
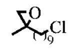
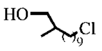
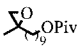
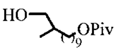
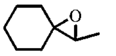
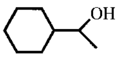
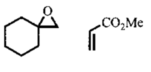
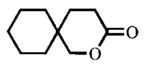
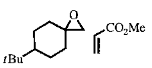
All of the pyridine hydrochlorides tested, except the bulky 2,6-di-*tert*-butylpyridine hydrochloride, led to conversion. 2,4,6-Trimethylpyridine hydrochloride (collidine hydrochloride) was the most efficient. In addition to the milder reaction conditions required, there are two more general advantages to having protonation as the key step in the catalytic cycle: 1. Protonations are amongst the fastest reactions. 2. 2,4,6-Collidine can be recovered simply by acid–base extraction or distillation; treatment with HCl then provides the hydrochloride. Hydrolysis of the silylated alcohols yields hexamethyldisiloxane, which cannot be reconverted to chlorotrimethylsilane in a straightforward manner. These advantages should become especially important in large-scale applications.

In hydrogen atom abstraction reactions with 1,4-cyclohexadiene, manganese is superior to zinc as the stoichiometric reductant in two respects. When manganese is used, no chlorohydrin **3** is formed by Lewis acid initiated ring opening of the epoxides, and the reaction proceeds significantly faster. Apparently the zinc chloride formed in the reaction complexes the epoxide, prevents complete conversion into product, and allows the slow chloride-mediated ring opening to compete. Gratifyingly the much less Lewis-acidic manganese dichloride[11] does not interfer with the catalytic reaction and thus the products are obtained cleanly in a reasonable time. It should be noted that other metals such as aluminum[13] do not lead to fast reduction of titanocene dichloride and are therefore not suitable as stoichiometric reductants.

To explore the generality of the optimized reaction conditions a number of epoxides were tested in inter- and intramolecular C–C bond forming reactions and reductions (Table 2). Terminal, 1,1- and 1,2-disubstituted (*cis* and *trans*, entry 3), and trisubstituted epoxides give the desired products in good yields. It should be noted that deoxygenation of the epoxide was not detected for any substrate. The regioselectivity of the epoxide opening is opposite to that of S$_N$2 reactions and seems to be governed only by the stability of the radical formed. Therefore the radical is produced only on the more substituted carbon atom of the epoxide. The observed diastereoselectivities of the cyclizations are typical for radical reactions and their well-known conformational effects.

For the intermolecular addition of the radical to methyl acrylate, zinc was used as the stoichiometric reductant (entries 12 and 13). The lactones were isolated in 75–80% yield after 40 h but the corresponding chlorohydrins (roughly 5%) were also detected. The reaction was much slower with manganese. After 40 h the conversion was estimated at 15%. This is presumably due to deactivation of the titanium catalyst by the MeOH generated. Zinc chloride seems to be Lewis-acidic enough to complex MeOH and thus prevent catalyst deactivation. When manganese was employed in combination with zinc chloride, essentially the same results were obtained

Table 2. Titanocene-catalyzed reductive opening of epoxides under the optimized conditions.[a]

Entry	Substrate	t[h]	Yield[%]	Product
1		30	78[b]	
2		30	55[c]	
3		30	83[d]	
4		16	72	
5		18	58	
6		18	86	
7		12	67	
8		18	74	
9		18	69	
10	1 4-phenyl-2-butanone	60	70 95	2 4-phenyl-2-butanone
11		30	76[e]	
12		40	77[e]	
13		40	82[e,f]	

[a] See Experimental Section. [b] *cis*:*trans* = 88:12. [c] *cis*:*trans* = 85:15. [d] Substrate was a mixture of *cis* und *trans* isomers. [e] Zn was used as reductant. [f] *cis*:*trans* = 14:86.

as with zinc as reductant. This result supports the abovementioned hypothesis of catalyst deactivation.

Since titanocene-mediated SET is the key step in the epoxide opening, a number of functional groups sensitive to electron transfer reagents such as samarium diiodide[14] were subjected to the optimized conditions. Gratifyingly benzyl ethers, chlorides, and even ketones (see Table 2, entry 10 for the competition experiment) are perfectly stable under the reaction conditions, and the corresponding products were isolated in good yields. Chlorides are not tolerated in radical chain reactions using tributylstannane (dehalogenation), and therefore the reaction described here allows a mild and highly chemoselective entry to radical chemistry.[7] Protecting groups that can migrate under basic conditions like pivalate (Piv), tosylate (Ts), and *tert*-butyldiphenylsilyl ether (OTBDPS) do not migrate even when it would be kinetically favorable, as in the case of the TBDPS ethers.[15] Also elimination of tosylate was not observed. Although these alcohols can also be obtained by hydroboration and oxidation, the method described here is superior because distant double bonds and ketones are not tolerated by the hydroboration protocol.[16] Also hydroboration of 2-methyl-1,11-dodecadiene takes place preferentially at the less substituted double bond and is therefore complementary to our reaction (entry 4).[17]

We have demonstrated that the reductive opening of epoxides with concommitant hydrogen atom abstraction and inter- or intramolecular C–C bond formation can be catalyzed efficiently and in a highly chemoselective manner by titanocene dichloride if manganese or zinc is used as the stoichiometric reductant and 2,4,6-collidine hydrochloride is used as an acid to protonate the titanium oxide and regenerate titanocene dichloride.

Experimental Section

All new compounds were characterized by the usual means. Preparation of cyclododecanol: A suspension of collidine hydrochloride (197 mg, 1.25 mmol), titanocene dichloride (12.4 mg, 0.05 mmol), manganese (60.0 mg, 1.1 mmol), 1,4-cyclohexadiene (0.425 mL, 4.5 mmol), and cyclododecene oxide (182 mg, 1.0 mmol) in THF (10 mL) was stirred at room temperature for 32 h. After extraction (5 mL 2 M HCl, 2 × 20 mL H_2O) and chromatography on silica gel (diethyl ether/petroleum ether 1/3) cyclododecanol (153 mg, 0.83 mmol) was obtained in 83 % yield.

Received: July 18, 1997 [Z 10701 IE]
German version: *Angew. Chem.* **1998**, *110*, 107–109

Keywords: chemoselectivity · epoxides · homogeneous catalysis · radical reactions · regioselectivity

[1] a) B. Giese, *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Oxford, **1986**; b) W. B. Motherwell, D. Crich, *Free Radical Chain Reactions in Organic Synthesis*, Academic Press, London, **1991**.

[2] a) A. L. J. Beckwith, C. J. Easton, A. K. Serelis, *J. Chem. Soc. Chem. Commun.* **1980**, 482; b) W. Smadja, *Synlett* **1994**, 1; D. P. Curran, N. A. Porter, B. Giese, *Stereochemistry of Radical Reactions*, VCH, Weinheim, **1996**.

[3] a) A. Gansäuer, *Chem. Commun.* **1997**, 457; b) *Synlett* **1997**, 363.

[4] a) W. A. Nugent, T. V. RajanBabu, *J. Am. Chem. Soc.* **1988**, *110*, 8561; b) T. V. RajanBabu, W. A. Nugent, *ibid.* **1989**, *111*, 4525; c) T. V. RajanBabu, W. A. Nugent, M. S. Beattie, *ibid.* **1990**, *112*, 6408; d) T. V. RajanBabu, W. A. Nugent, *ibid.* **1994**, *116*, 986.

[5] A. S. Rao in *Comprehensive Organic Synthesis*, *Vol. 7* (Eds.: B. M. Trost, I. Fleming, G. Pattenden), Pergamon, Oxford, **1991**, pp. 358–375.

[6] J. Aubé in *Comprehensive Organic Synthesis*, *Vol. 1* (Eds.: B. M. Trost, I. Fleming, G. Pattenden), Pergamon, Oxford, **1991**, pp. 819–834.

[7] J. O. Metzger, *Methoden Org. Chem. (Houben-Weyl) 4th ed. 1952–*, Vol. E19a/1, pp. 147–168.

[8] R. L. Halterman, *Chem. Rev.* **1992**, *92*, 965.

[9] M. L. H. Green, C. R. Lucas, *J. Chem. Soc. Dalton Trans.* **1972**, 1000.

[10] A. Fürstner, A. Hupperts, *J. Am. Chem. Soc.* **1995**, *117*, 4468.

[11] A. Fürstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 2533, 12349.

[12] *Handbook of Chemistry and Physics*, 66th ed. (Ed.: R. C. Weast), CRC, Boca Raton, FL, **1985**, D159–D161.

[13] R. S. P. Coutts, P. C. Wailes, R. L. Martin, *J. Organomet. Chem.* **1973**, *47*, 375.

[14] G. A. Molander, *Chem. Rev.* **1992**, *92*, 29.

[15] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., Wiley, New York, **1991**, p. 83, p. 98.

[16] a) H. C. Brown, P. Heim, *J. Am. Chem. Soc.* **1970**, *92*, 1637; b) E.-I. Negishi in *Comprehensive Organometallic Chemistry*, *Vol. 7* (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982**, p. 255; c) H. Molin, B. G. Pring, *Tetrahedron Lett.* **1985**, *26*, 677.

[17] J. A. Soderquist in *Encyclopedia of Reagents for Organic Synthesis*, *Vol. 2* (Ed.: L. Paquette), Wiley, New York, **1995**, pp. 622–630.