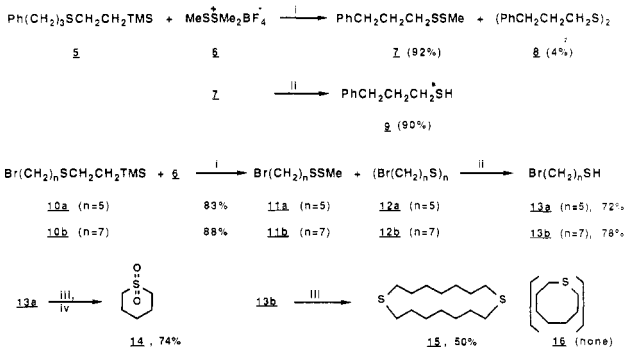
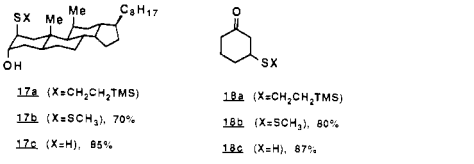
Scheme II[a]



[a] (i) MeSSMe (5 equiv), CH_2Cl_2, 0 °C, 4 h; (ii) *n*-Bu_3P, 10% aqueous CH_3OH, 25 °C, 1 h; (iii) NaH, THF; (iv) MCPBA, CH_2Cl_2, 0 °C, 30 min.

symmetrical disulfides **11a/12a** and **11b/12b** which were separated for characterization purposes. Cleavage of **11a** and **11b** with tri-*n*-butylphosphine in aqueous methanol provides ω-bromo mercaptans **13a,b** in 72% and 78% yield, respectively. Treatment of **13a** with sodium hydride in THF at room temperature provides the pentamethylene sulfide which was not purified but directly oxidized with MCPBA to give sulfone **14** in 74% overall yield. Repetition of the cyclization procedure with the 7-bromo-1-mercaptoheptane (**13b**) (even using extremely slow addition of a 0.005 M solution of the bromo mercaptan to a large volume of THF containing excess NaH) afforded only the 16-membered disulfide **15** (50%) with no indication for the presence of the monomeric sulfide **16** as assayed by mass spectrometry.

The same cleavage protocol was applied to two additional 2-(trimethylsilyl)ethyl sulfides: steroidal sulfide-alcohol **17a** (98% yield from 2α,3α-cholestane oxide and mercaptan **1**) and β-substituted ketone **18a** (85% yield from cyclohexenone and **1**). These substrates are sequentially transformed to disulfides **17b,18b** and the mercaptans **17c,18c** in the yields indicated.

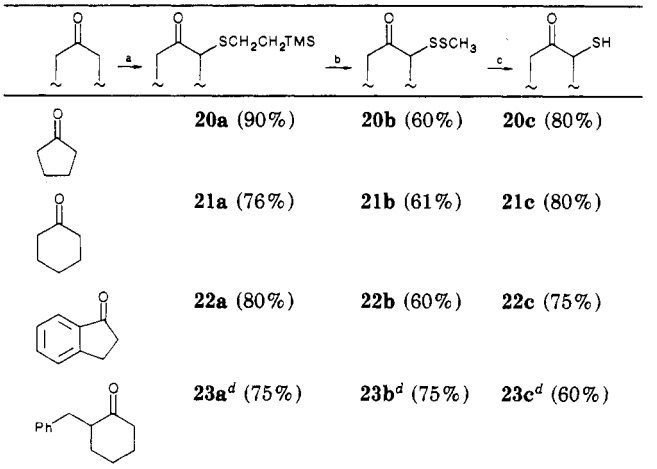


Electrophilic introduction of the mercaptan moiety can be effected by a sulfenylation/cleavage sequence. Treatment of a variety of ketone enolates (Table III) under standard conditions[18] with the thiolsulfonate reagent (**19**[19]) derived from **1** affords the α-sulfenylated ketones **20–25a** in very good yield. Conversion of these materials to the disulfides **20–23b** and then to the α-mercapto ketones **20–23c** proceeds smoothly.

A final example of the versatility of this methodology is shown in Scheme III. Metalation of cyclohexyl sulfone **24** followed by sulfenylation with thiolsulfonate **19** affords α-sulfenylated sulfone **25** in 83% yield. Chemospecific reductive cleavage of the *arylsulfonyl* moiety[20] of both **25** and **26** affords the 2-(trimethylsilyl)ethyl-substituted sulfide **27** and sulfone **28** without any trace of the aryl sulfone **24** which would have resulted from the alternative

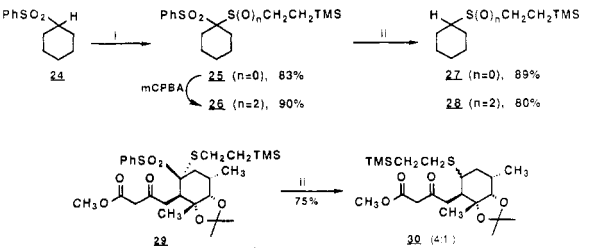
(17) Compounds **10a,b** were prepared from 5-acetoxy-1-chloropentane and methyl 7-bromoheptanoate via (i) reaction with **1**, (ii) LAH reduction, and triphenyl phosphine/CBr_4 reaction in 48% and 64% overall yield, respectively.
(18) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363.
(19) See ref 1 for further elucidation.
(20) Trost, B. M.; Arndt, H. C.; Strenge, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

Table III



[a] (a) i. LDA, −78 °C, THF; ii. $TMSCH_2CH_2STs$ (**19**); (b) $MeS^+SMe_2BF_4^-$, MeSSMe, CH_2Cl_2, 0 °C; (c) *n*-Bu_3P, 10% aqueous CH_3OH, 25 °C, 2 h; (d) ~1:1 mixture of diastereomers.

Scheme III



[a] (i) a, *n*-BuLi, THF, −30 °C; (b) $TMSCH_2CH_2STs$ (**19**); (ii) Na-(Hg), 1:1 THF/CH_3OH.

mode of cleavage. Application of this strategy to the more highly functionalized sulfone **29** provides desulfonylated β-keto ester **30** in 75% yield as a 4:1 mixture of diastereomers.

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Supplementary Material Available: Experimental procedures along with NMR, IR, and mass spectroscopy data (19 pages). Ordering information is given on any current masthead page.

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Lipase-Catalyzed Irreversible Transesterification for Preparative Synthesis of Chiral Glycerol Derivatives[1]

Summary: An irreversible, lipase-catalyzed transesterification using enol ester as an acylating agent has been developed for preparative enantioselective acylation of *meso*-1,3-diols.

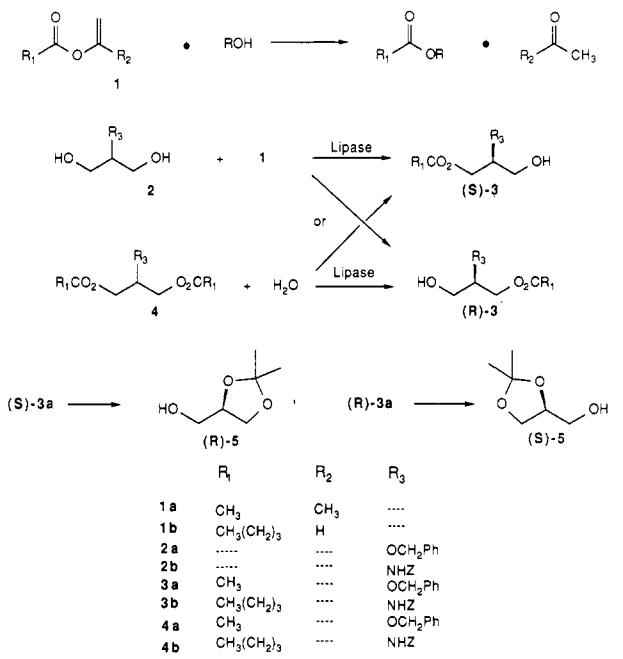
Sir: Lipase-catalyzed esterifications and transesterifications in organic solvents have proven very useful for enantioselective synthesis.[2] Certain reactions which are sensitive to water can now be carried out in organic media. Potential drawbacks in these processes are that the reactions are often very slow[2c] and that due to the reversible nature of esterification and transesterification in enzyme-catalyzed kinetic resolutions and the same enantioselectivity of the enzyme catalysis in both directions, the optical purity of the desired product obtained decreases as the reverse reaction proceeds.[3] This problem has been clearly illustrated in the enantioselective esterification of racemic menthol.[3] Illustrated in eq 1 is a racemic alcohol

$$(RS)\text{-ROH} + \text{R}'\text{CO}_2\text{R}'' \rightleftarrows (R)\text{-R}'\text{CO}_2\text{R} + \text{R}''\text{OH} + (S)\text{-ROH} \quad (1)$$

to be resolved via an enzymatic esterification (R″ = H) or transesterification. If the *R* isomer is a better substrate than the *S* isomer for the enzyme, accumulation of the *R* ester and the unreacted alcohol (L-ROH) will be observed. In the reverse reaction, however, the *R* ester will react with R″OH preferentially to give (*R*)-ROH. The optical purities of both the R ester and (*S*)-ROH will therefore decrease progressively as the extent of the reverse reaction increases. The same situation can be seen in reactions with meso compounds. This problem can be overcome if the reaction is irreversible. Also, it is easier to control and optimize the irreversible reaction process to achieve high enantioselectivity. We have reported in a preliminary study the use of isopropenyl acetate (**1a**) as an acyl transfer reagent in lipase-catalyzed irreversible and regioselective acetylation of sugars.[1,4a] We report here the use of this and other enol esters[4b] as irreversible acyl transfer reagents in lipase-catalyzed enantioselective acylation of *meso*-1,3-diols; the leaving group of such reagents tautomerizes to ketone (R″OH → acetone or acetaldehyde) which is volatile and does not undergo the reverse reaction.

In a representative procedure, a solution of 2-*O*-benzylglycerol (**2a**) (1.09 g, 6 mmol) and **1a** (2.64 mL, 24 mmol) in 12 mL of chloroform was mixed with 60 mg of lipase from *Pseudomonas* sp. (EC 3.1.1.3, Sigma L-9518, Type XIII) and stirred for 24 h at 28 °C (Scheme I). The enzyme was then filtered off and washed with dichloromethane. The combined filtrate was evaporated and the products were analyzed by GC.[5] The ratio of diacetate, monoacetate, and the remaining diol was 43:57:0.1. After column chromatography on silica gel (EtOAc:hexane = 1:3 v/v), the monoacetate was obtained in 53% yield (0.7 g): $[\alpha]^{23}_D$ −20.1° (*c* 3.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.071 (3 H, s), 3.58–3.76 (3 H, m), 4.23 (2 H, d, *J* = 4.6 Hz), 4.60 (1 H, d, *J* = 11.7 Hz), 4.71 (1 H, d, *J* = 11.7 Hz), 7.35 (5 H, s). The optimal purity of the monoester was determined to be 96% ee by ^1H NMR analysis in the presence of Eu(hfc)$_3$ (a major peak at 3.02 and a minor peak at 2.88 ppm, both for CH_3COO). To determine the absolute stereochemistry of the monoester, it was converted[6] to 2,2-dimethyl-1,3-dioxolane-4-methanol (**5**) (glycerol acetonide) which has the *R* configuration based on rotation, indicating that the compound has the *S* configuration.

Scheme I



	R_1	R_2	R_3
1a	CH_3	CH_3	----
1b	$CH_3(CH_2)_3$	H	----
2a	-----	----	OCH_2Ph
2b	-----	----	NHZ
3a	CH_3	----	OCH_2Ph
3b	$CH_3(CH_2)_3$	----	NHZ
4a	CH_3	----	OCH_2Ph
4b	$CH_3(CH_2)_3$	----	NHZ

For preparation of **2a**, glycerol was treated with trityl chloride (2 equiv) and triethylamine (2.4 equiv) in the presence of 4-(dimethylamino)pyridine (0.1 equiv) in dichloromethane to yield 1,3-di-*O*-tritylglycerol (**6**). Reaction of **6** with benzyl bromide and NaH in tetrahydrofuran yielded the 2-*O*-benzyl derivative, which was converted to **2a** in 75% overall yield after removal of the trityl group (*p*-toluenesulfonic acid/CH_3OH).

We notice that (*R*)-**3** can be prepared from 2-*O*-benzylglycerol diacetate (**4a**) via a lipoprotein lipase catalyzed hydrolysis.[7] Compound (*S*)-**5** can thus be obtained from (*R*)-**3a** with known chemistry.[6] The same enantioselectivity in the hydrolysis of **4a** was observed with this lipase and (*R*)-**3a** was obtained in 52% yield with 71% ee.[8]

In another example, 2-*N*-(benzyloxycarbonyl)serinol (**2b**) (0.3 g, 1.1 mmol) and vinyl valerate (**1b**) (0.51 g, 4 mmol)[9] in 23 mL of tetrahydrofuran was incubated with 0.9 g of porcine pancreatic lipase at 28 °C with stirring. After 11 h, the mixture was filtered and the filtrate was evaporated

(1) Supported by the NSF Grant CHE8318217. This work was presented at the 194th National Meeting of the American *Chemical Society*, New Orleans, September 1, 1987: "Symposium on Asymmetric Synthesis of Carbohydrates from Acyclic Precursors" which will appear in an ACS Symposium Series (Hawkins, L. D., McGarvey, G. J., Eds.) and at the US–Japan Joint Biotechnology Conference, Lake Biwa, 1986 (*Adv. Biochem. Eng.*, in press). The identity of all new compounds has been established by IR, NMR, and mass spectroscopy. The purity and elemental composition were verified by elemental analysis or HRMS.

(2) (a) Kirchner, G.; Scollar, M. B.; Klibanov, A. M. *J. Am. Chem. Soc.* **1985**, *107*, 7072. Therisod, M.; Klibanov, A. M. *Ibid.* **1986**, *108*, 5638; **1987**, *109*, 3977. Riva, S.; Chopineau, J.; Kieboom, A. P. G.; Klibanov, A. M. *Ibid.* **1988**, *110*, 584. (b) Stokes, T. M.; Oehlschlaher, A. C. *Tetrahedron Lett.* **1987**, 28, 2091. (c) Langrand, G.; Baratti, J.; Buono, G.; Triantaphylides, C. *Tetrahedron Lett.* **1986**, *27*, 29. Gil, G.; Ferre, E.; Meou, A.; Petit, J. L.; Triantaphylides, C. *Ibid.* **1987**, *28*, 1647 and references cited therein. (d) Tombo, G. M. R.; Schar, H.-P.; Busquets, X. F.; Ghisalba, O. *Ibid.* **1986**, *27*, 5707. Sonnet, P. E. *J. Org. Chem.* **1987**, *52*, 3477. Belan, A.; Bolte, J.; Fauve, A.; Gourcy, J. G.; Veschambre, H. *Ibid.* **1987**, *52*, 256.

(3) Chen, C.-S.; Wu, S.-H.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 2812–7.

(4) (a) Sweers, H. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1986**, *108*, 6421. (b) For transesterification of vinyl butyrate to ethanol, see: Degueil-Castaing, M.; Jeso, B. D.; Drouillard, S.; Maillard, B. *Tetrahedron Lett.* **1987**, *28*, 953.

(5) GC analyses were performed on a Hewlett-Packard 5890 gas chromatograph equipped with a 20-m DB-5 megabore column: initial temperature, 150 °C; final temperature, 250 °C; rate, 10 °C/min; flow rate, 15 mL/min.

(6) Suemune, H.; Mizuhara, Y.; Akita, H.; Sakai, K. *Chem. Pharm. Bull.* **1986**, *34*, 3440–48.

(7) Breitgoff, D.; Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1523. An opposite enantioselectivity was observed when the lipase from *Candida cylindracea* was used as catalyst in the transesterification. The resulting monoester (*R*)-**3** has 40% ee.

(8) The hydrolysis was carried out in 0.1 M phosphate buffer (pH 7) at 28 °C. The pH was controlled at 7.0 during the reaction by addition of 1 N NaOH. The extent of conversion was determined by GC. After reaction, the mixture was extracted with ether and purified by column chromatography as described in the esterification.

and purified on a silica gel column chromatography (ethyl acetate:*n*-hexane = 1:4–1:1 v/v) to give 0.24 g (77% yield) of monovalerate **3b**: $[\alpha]^{23}_D$ +3.3° (*c* 1, $CHCl_3$); ^1H NMR δ 0.91 (3 H, t, *J* = 7.2 Hz), 1.34 (2 H, tq, *J* = 7.2, 7.2 Hz), 1.60 (2 H, tt, *J* = 7.2, 7.2 Hz), 2.33 (2 H, t, *J* = 7.2 Hz), 3.65 (2 H, m), 3.94 (1 H, m), 4.23 (2 H, d, *J* = 5.6 Hz), 5.11 (2 H, s), 5.20 (1 H, br), 7.36 (5 H, s). For determination of the optical purity, compound **3b** was converted to the (+)-MTPA ester[10] and analyzed by ^1H NMR in the presence of $Eu(hfc)_3$ to establish an enantiomeric excess greater than 97% (a single peak for OCH_2 at 4.85 ppm). The configuration was determined to be *R* after correlation with authentic (*S*)-**3b** prepared from *N*-(benzyloxycarbonyl)-L-serine methyl ester; thus a complete reversal of enantioselectivity was observed in this case. For preparation of the *S* monovalerate, divalerate **4b** was subjected to hydrolysis[8] catalyzed by the same enzyme to give, as expected, the *S* enantiomer in 55% isolated yield and >97% ee (a single peak for OCH_2 at 4.65 ppm).

With regard to the rate of enzymatic transesterification, the ratio of ethyl acetate:isopropenyl acetate:vinyl acetate:vinyl valerate is about 1:100:400:2000. The enol esters are readily available and easy to manipulate. If necessary, the ester with a long acyl chain can be prepared from a carboxylic acid and propyne catalyzed by $Ru(COD)_2$/PR.[11]

In summary, these *irreversible* enzymatic acylation and hydrolysis processes provide new routes to useful chirons in both enantiomeric forms.[12] Application of this procedure to the resolution of other chiral and prochiral alcohols is in progress.

(9) Of the enol esters tested, vinyl valerate gave the best enantioselectivity and rate.

(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(11) Watanabe, Y.; Yamakawa, Y.; Hori, Y.; Mitsudo, T. *J. Org. Chem.* **1987**, *52*, 2230–9.

(12) The compounds prepared are useful chiral building blocks. Compound (*S*)-**3a** is useful for the syntheses of platelet activating factor and other phospholipids (ref 6). Compound (*S*)-**3b** can be used in the synthesis of phospholipase A2 inhibitors (Dennis, E. A. *Bio/Technology* **1987**, *5*, 1294. Chandrakumar, N. S.; Hajdu, J. *J. Org. Chem.* **1983**, *48*, 1197). Currently, compound (*S*)-**5** is prepared from D-mannitol (Hirth, G.; Walther, W. *Helv. Chim. Acta* **1985**, *68*, 1863. Fisher, H. O. L.; Baer, E. *Ibid.* **1934**, *17*, 622); compound (*R*)-**5** is prepared from ascorbic acid (Jung, M. E.; Shaw, *J. Am. Chem. Soc.* **1980**, *102*, 6304. Morgenlie, S. *Carbohydr. Res.* **1982**, *107*, 137), L-serine (Hirth, G. et al. as described above), and others (Wilde, H. D.; Clercg, P. D.; Vandewalle, M.; Roper, H. *Tetrahedron Lett.* **1987**, *28*, 4757–8 and references cited therein).

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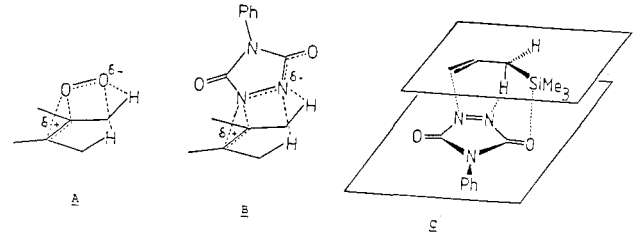
How Mechanistically Equivalent Are Singlet Oxygen and Triazolinedione? Regiochemical and Stereochemical Differences in Their Ene Reactions with Allylsilanes†

Summary: The usual syn regioselectivity of $^1O_2$ is observed and the gem regioselectivity of PTAD is also observed for these enophiles with allylsilanes, but while $^1O_2$ leads to trans product, PTAD affords cis product; coordination of the silyl groups with these enophiles is thought to be responsible for this mechanistic dichotomy.

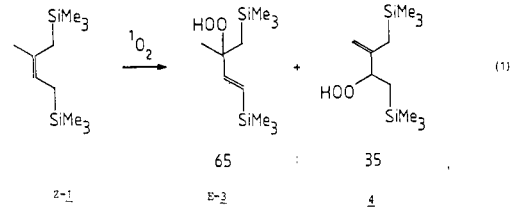
†Dedicated to Prof. F. D. Greene on the occasion of his 60th birthday for his pioneering contributions in this area.

Sir: Presently we report preliminary stereochemical results for the ene reactions of (*E*)- and (*Z*)-1,4-bis(trimethylsilyl)-2-methylbut-2-ene (**1**) with $^1O_2$ and PTAD, which suggest that the mechanistic equivalence of these two enophiles, i.e. the perepoxide-type (A) and the aziridinium



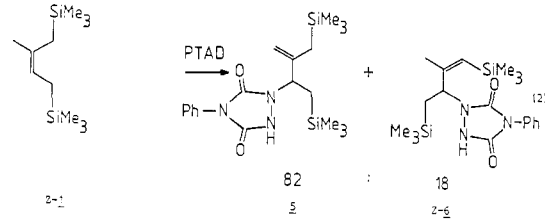
imide type (B) activated complexes, respectively, is not as general as previously implied.[1] As for the alkene diastereomers (*E*/*Z*)-**2**, with $^1O_2$ syn selectivity[2,3] and with PTAD gem selectivity[1,4] is exercised, of course the trimethylsilyl groups causing substantial changes in the regioisomeric composition.[5] More significantly, while $^1O_2$ affords the *E* product for both substrates **1** and **2**, PTAD leads to the *Z* product with the disilylated alkene **1**, but the *E* product with the alkene **2** (cf. regioisomeric and diastereoisomeric fingerprints in Scheme I).

Tetraphenylporphine (TPP) sensitized photooxygenation of the pure (*Z*)-**1** diastereomer in CCl_4 at 0 °C led to the regioisomers **3** and **4** in 65:35 relative proportion (eq 1), as calculated from the 200-MHz ^1H NMR



spectrum of the crude photooxygenation mixture. The trans stereochemistry in (*E*)-**3** was evident from the AB pattern of the olefinic protons at 5.87 ppm with a large coupling of J_{AB} = 19.1 Hz, while cis-configurated vinylsilanes typically show a coupling of ca. 15 Hz.[5a,b] No significant quantities of the cis stereoisomer could be detected by ^1H and ^{13}C NMR.

In contrast to $^1O_2$, the ene reaction of pure (*Z*)-**1** with PTAD in CH_2Cl_2 at ca. 20 °C gave a 82:18 mixture (by ^1H NMR taken on the crude product mixture) of the two regioisomeric urazoles **5** and **6** (eq 2). The stereochemistry



of the minor regioisomer (*Z*)-**6** was assessed by an X-ray structure determination.[6] The ^1H and ^{13}C NMR spectra

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(3) Stephenson, L. M.; Grdina, M. J.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, *13*, 419.

(4) Griesbeck, A. Dissertation, University of Munich (1984).

(5) (a) Shimizu, N.; Shibata, F.; Imazu, S.; Tsuno, Y. *Chem. Lett.* **1987**, 1071. (b) Dubac, J.; Laporterie, A.; Iloughmane, H.; Pillot, J. P.; Deleris, G., Dunogues, J. *J. Organomet. Chem.* **1985**, *281*, 149. (c) Dubac, J.; Laporterie, A. *Chem. Rev.* **1987**, *87*, 319.

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