

## 9 Synthetic Methods

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### 1 Introduction

*'The problem with organic synthesis is that it is literally creative and that its practitioners range from the master builder who uses only the best materials (in extreme cases only materials and methods he has invented) to the scrap merchant who is prepared to knock you up a molecule out of any old synthons.'*<sup>1</sup>

The award of the Nobel prize to E. J. Corey<sup>2</sup> in 1991, possibly marks the maturation of organic synthesis<sup>3</sup> from a pure science with internal goals to an applied science which can tackle significant problems in biology and make new materials with predictable properties.<sup>4</sup>

There is certainly a wealth of techniques available, particularly for asymmetric transformations. Artificial (abiotic) catalysts are now competitive with yeast<sup>5</sup> and enzymes<sup>6</sup> in terms of selectivity and yield. But the ability to change the reactivity of enzymes using protein engineering,<sup>7</sup> substrate imprinting<sup>8</sup> and non-aqueous solvents<sup>9</sup> means they are currently more versatile and this position will be augmented when catalytic antibodies (abzymes)<sup>10</sup> are available 'off the shelf'. 'Biotransformations'<sup>11</sup> have a further advantage that (with some exceptions) they all act under more or less the same conditions and so it is possible to perform multiple reactions

<sup>1</sup> S. Warren, *Chem. Ind.*, 1991, 796.

<sup>2</sup> E. J. Corey, *Angew. Chem. Int. Ed. Engl.*, 1991, **30**, 455.

<sup>3</sup> J. Mulzer, H. J. Altenbach, M. Braun, K. Krohn, and H. U. Reissig, *Organic Synthesis Highlights*, VCH, Weinheim, 1991.

<sup>4</sup> G. W. Gokel, J. C. Medina, and C. Li, *SYNLETT.*, 1991, 677.

<sup>5</sup> R. Cszuk and B. I. Glanzner, *Chem. Rev.*, 1991, **91**, 49.

<sup>6</sup> *Biocatalysis in Organic Chemistry*, 'a symposium in print', *Recl. Trav. Chim. Pays-Bas.*, 1991, **110** (5), 151–263, 63; *Biotransformations of organometallics* A. D. Ryabov, *Angew. Chem. Int. Ed. Engl.*, 1991, **30**, 931.

<sup>7</sup> Z. Zhong, J. L.-C. Liu, L. M. Dinterman, M. A. J. Finkelman, W. T. Mueller, M. L. Rollence, M. Whitlow, and C.-H. Wong, *J. Am. Chem. Soc.*, 1991, **113**, 683; Z. Zhong, J. A. Bibbs, W. Yuan, and C.-H. Wong, *J. Am. Chem. Soc.*, 1991, **113**, 2259.

<sup>8</sup> M. Stahl, U. Jeppsson-Wistrand, M.-O. Mansson, and K. Mosbach, *J. Am. Chem. Soc.*, 1991, **113**, 9366.

<sup>9</sup> E. Rubio, A. Fernandez-Moyorales, and A. M. Klivanov, *J. Am. Chem. Soc.*, 1991, **113**, 695; A. L. Gutman and M. Shapira, *J. Chem. Soc., Chem. Commun.*, 1991, 1467; P. Z. Fitzpatrick and A. M. Klivanov, *J. Am. Chem. Soc.*, 1991, **113**, 3166; S. Parida, and J. S. Dordick, *J. Am. Chem. Soc.*, 1991, **113**, 2253.

<sup>10</sup> 'Catalytic Antibodies', Ciba Foundation Symposium 159, Chairman, W. P. Jencks, Wiley, Chichester, 1991; R. A. Lerner, S. J. Benkovic, and P. G. Schultz, *Science*, 1991, **252** (5006), 659.

<sup>11</sup> The activity in this area can be judged by the launch of the new journal *Preparative Biotransformations*.

in one pot e.g. ester hydrolysis,<sup>12</sup> oxidation of the alcohol to an aldehyde, cis-trans isomerization,<sup>13</sup> and carbon-carbon bond formation with an aldolase could all be achieved concurrently.

There are intriguing possibilities offered by molecular recognition using supramolecular systems<sup>14</sup> or self assembling structures<sup>15</sup> such as micelles or monolayers which can be visualized and modelled using computer graphics.<sup>16</sup> However although there are a plethora of supramolecular abiotic systems capable of selective binding, precious few are capable of effecting a chemical change.<sup>17</sup> One system with enormous potential is the carcerands which are large hollow spherical molecules constructed by dimerization of two hemispherical units (cavitands<sup>18</sup>). At least one molecule of solvent is always imprisoned<sup>19</sup> during closure and if a solvent mixture is used, the most polar solvent (assuming it is small enough) is preferentially incorporated. The linkages between the cavitands are typically acetals<sup>20</sup> or thioethers<sup>21</sup> which are formed by nucleophilic substitution on alkyl chlorides. The imprisoned solvent molecule(s) stabilize the polar  $S_N2$  transition state which otherwise would have to take place in a vacuum. Cram has revolutionized isolation technology by infiltrating  $\alpha$ -pyrone (2) into a hemicarcerand (1)<sup>22</sup> at high temperature and then photolysing it to give a trapped molecule of cyclobutadiene (3) and carbon dioxide which escaped. Prolonged photolysis effected retro [2 + 2] cycloaddition to give acetylene which also escaped the confines of the hemicarcerand (1).<sup>23</sup> The hemicarcerands have much larger portals than the carcerands and guests as large as ferrocene can be incorporated,<sup>24</sup> with discrimination between enantiomers.<sup>25</sup>

<sup>12</sup> I. Weinhouse, R. A. Lerner, R. A. Gibbs, P. A. Benkovic, R. Hilhorst, and S. J. Benkovic, *J. Am. Chem. Soc.*, 1991, **113**, 291; K. D. Janda, M. I. Weinhouse, T. Danon, K. A. Pacelli, and D. M. Schloeder, *J. Am. Chem. Soc.*, 1991, **113**, 5427; S. Ikeda, M. I. Weinhouse, K. D. Janda, R. A. Lerner, and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1991, **113**, 7763; T. Kitazume, J. T. Lin, M. Takeda, and T. Yamazaki, *J. Am. Chem. Soc.*, 1991, **113**, 2123.

<sup>13</sup> D. Y. Jackson and P. G. Schultz, *J. Am. Chem. Soc.*, 1991, **113**, 2319.

<sup>14</sup> F. Vogtle, 'Supramolecular Chemistry, an Introduction', Wiley, Chichester, 1991; ed. H.-J. Schneider and H. Durr, 'Frontiers of Supramolecular Organic Chemistry and Photochemistry', VCH, Weinheim, 1991.

<sup>15</sup> F. M. Menger, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1086.

<sup>16</sup> Interactions computation, W. L. Jorgensen, Chemtracts: Organic Chemistry, 1991, **4**, 91; W. C. Ripka and J. M. Blaney, *Top. Stereochem.*, 1991, **20**, 1.

<sup>17</sup> Ten news items and articles describing prospects for nanotechnology, *Science*, 1991, **254**(5036), 1300-1342.

<sup>18</sup> These are essentially calixarenes with functional groups on one face, see J. Vicens and V. Bothmer, 'Calixarenes a Versatile Class of Macrocyclic Compounds' (Topics in Inclusion Science 3), Kluwer, Dordrecht, 1991.

<sup>19</sup> 'Host-Guest molecular Interactions: From Chemistry to Biology', Ciba foundation Symposium 158, Chairman, I. O. Sutherland, Wiley, Chichester, 1991.

<sup>20</sup> J. C. Sherman, C. B. Knobler, and D. J. Cram, *J. Am. Chem. Soc.*, 1991, **113**, 2194.

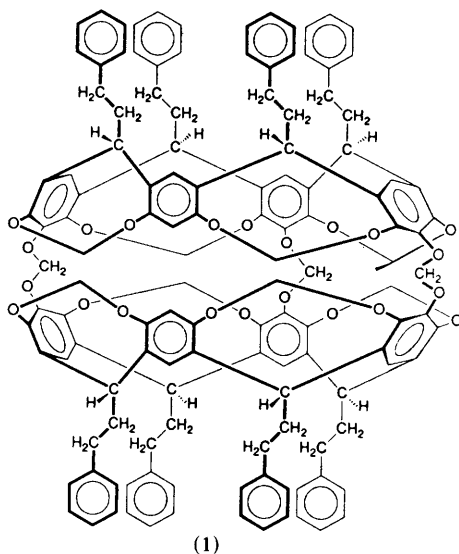
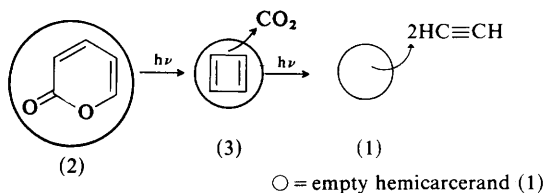
<sup>21</sup> J. A. Bryant, M. T. Blanda, M. Vincenti, and D. J. Cram, *J. Am. Chem. Soc.*, 1991, **113**, 2167.

<sup>22</sup> Hemicarcerands differ from carcerands in having portals through which guests can enter and leave.

<sup>23</sup> D. J. Cram, M. E. Tanner, and R. Thomas, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1024; H. Hopf, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1117.

<sup>24</sup> M. L. C. Quan and D. J. Cram, *J. Am. Chem. Soc.*, 1991, **113**, 2754; D. J. Cram, M. E. Tanner, and C. B. Knobler, *J. Am. Chem. Soc.*, 1991, **113**, 7717.

<sup>25</sup> J. K. Judice and D. J. Cram, *J. Am. Chem. Soc.*, 1991, **113**, 2790.



**Buckminsterfullerene.**—The most vigorous area of research (as judged by citation analysis of papers published in 1991) continues to be the chemistry of buckminsterfullerene.<sup>26</sup> The simple construction of the carbon spark generator<sup>27</sup> enables even a novice to make practical amounts of fullerite (the raw mixture of  $\text{C}_{60}$ ,  $\text{C}_{70}$ , and higher homologues) which can be separated crudely by soxhlet extraction<sup>28</sup> and purified by HPLC.<sup>29</sup> The spark generator appears to operate by formation of individual carbon atoms because mixtures of  $^{12}\text{C}$  and  $^{13}\text{C}$  graphite give  $\text{C}_{60}$  in which the  $^{13}\text{C}$  atoms are randomly incorporated.<sup>30</sup>

<sup>26</sup> Reviews, H. W. Kroto, A. W. Allaf, and S. P. Balm, *Chem. Rev.*, 1991, **91**, 1213; J. F. Stoddart, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 70; A. Moody, *Chem. Ind.*, 1991, (10), 346; R. Lee, *ibid.*, 349; J. S. Miller, *Adv. Mater.*, 1991, **3**, 262; F. Diederich and R. L. Whetten, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 678.

<sup>27</sup> A. S. Koch, K. C. Khemani, and F. Wudl, *J. Org. Chem.*, 1991, **56**, 4543.

<sup>28</sup> D. H. Parker, P. Wurz, K. Chatterjee, K. R. Lykke, J. E. Hunt, M. J. Pellin, J. C. Hemminger, D. M. Gruen, and L. M. Stock, *J. Am. Chem. Soc.*, 1991, **113**, 7499.

<sup>29</sup> W. Pirkle and C. J. Welch, *J. Org. Chem.*, 1991, **56**, 6973.

<sup>30</sup> J. M. Hawkins, A. Meyer, S. Loren, and R. Nunlist, *J. Am. Chem. Soc.*, 1991, **113**, 9394; C. S. Yannoni, P. P. Bernier, D. S. Bethune, G. Meijer, and J. R. Salem, *J. Am. Chem. Soc.*, 1991, **113**, 3190; for complete 2D NMR studies see J. M. Hawkins, S. Loren, A. Meyer, and R. Nunlist, *J. Am. Chem. Soc.*, 1991, **113**, 7770; R. D. Johnson, G. Meijer, J. R. Salem, and D. S. Bethune, *J. Am. Chem. Soc.*, 1991, **113**, 3619.

$C_{60}$  and  $C_{70}$  have eluded structural characterization by X-ray crystallography because these nearly spherical molecules spin too quickly in the crystal lattice,<sup>31</sup> however, the cyclohexanone solvates reduce this rotation sufficiently to define the positions and general shape<sup>32</sup> and the osmium tetroxide dipyrindine adduct was sufficiently ordered that the 'football' structure could finally be proven.<sup>33</sup> A hexa(diethylphosphino platinum) adduct of  $C_{60}$  is formed with octahedral symmetry and  $n^2$ -bonding at the electron rich 6:6 fusions;<sup>34</sup> similarly,  $C_{70}$  reacts with  $Ir(CO)Cl(Ph_3P)_2$  to give a mono  $n^2$ -adduct at the most non-planar 6:6 fusion.<sup>35</sup> In both cases the adducts were characterized by X-ray crystallography. The situation for  $p$ -block derivatives is much less satisfactory. The  $C_{60}O$  and  $C_{70}O$ ,<sup>36</sup> the monoepoxides have been characterized well but other derivatives such as  $C_{60}(CH_3)_{1-24}$ ,<sup>37</sup>  $C_{60}F_{60}$ ,<sup>38</sup>  $C_{60}F_{36}$ ,  $C_{70}F_{40}$ , amongst other fluoro derivatives,<sup>39</sup>  $C_{60}Cl_{12}$ ,<sup>40</sup>  $C_{60}Cl_2$ ,  $C_{60}Br$ ,  $C_{60}(OCH_3)_{1-26}$ ,  $C_{60}Ph_{>22}$ ,<sup>41</sup>  $C_{60}HPh_{12}$ ,<sup>42</sup>  $C_{60}(\text{morpholine})_6$ <sup>43</sup> are only characterized as amorphous mixtures.

$C_{60}$  readily forms stable radical anion salts<sup>44</sup> which are semiconductors. It is reduced to a trianion<sup>45</sup> with alkali metals<sup>46</sup> to produce materials that are superconducting at 18 K, which is unprecedentedly high for an 'organic superconductor',<sup>47</sup>

<sup>31</sup> J. M. Hawkins, T. A. Lewis, S. D. Loren, A. Meyer, J. R. Heath, R. J. Saykally, and F. J. Hollander, *J. Chem. Soc., Chem. Commun.*, 1991, 775; W. I. F. David, R. M. Ibberson, J. C. Matthewman, K. Prassides, T. J. S. Dennis, J. P. Hare, H. W. Kroto, R. Taylor, and D. R. M. Walton, *Nature*, 1991, **353**, 147.

<sup>32</sup> S. M. Gorun, K. M. Creegan, R. D. Sherwood, D. M. Cox, V. W. Day, C. S. Day, R. M. Upton, and C. E. Briant, *J. Chem. Soc., Chem. Commun.*, 1991, 1556.

<sup>33</sup> J. M. Hawkins, A. Meyer, T. A. Lewis, S. Loren, and F. J. Hollander, *Science*, 1991, **252**(5003), 312.

<sup>34</sup> P. J. Fagan, J. C. Calabrese, and B. Malone, *J. Am. Chem. Soc.*, 1991, **113**, 9408; J. M. Hawkins, A. Meyer, T. A. Lewis, S. Loren, F. J. Hollander, *Science*, 1991, **252**, 312; P. J. Fagan, J. C. Calabrese, and B. Malone, *Science*, 1991, **252**, 1160.

<sup>35</sup> A. L. Balch, V. J. Catalano, J. W. Lee, M. M. Olmstead, and S. R. Parkin, *J. Am. Chem. Soc.*, 1991, **113**, 8953.

<sup>36</sup> F. Diederich, R. Ettl, Y. Rubin, R. L. Whetten, R. Beck, M. Alvarez, A. Anz, D. Sensharma, F. Wudl, K. C. Khemani, and A. Koch, *Science*, 1991, **252**, 548.

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<sup>38</sup> J. H. Holloway, E. G. Hope, R. Taylor, J. Langley, A. G. Avent, T. J. Dennis, J. P. Hare, H. W. Kroto, and D. R. M. Walton, *J. Chem. Soc., Chem. Commun.*, 1991, 966.

<sup>39</sup> H. Selig, C. Lifshitz, T. Peres, J. E. Fischer, A. R. McGhie, W. J. Romanow, J. P. Cauley, Jr., and A. B. Smith, III, *J. Am. Chem. Soc.*, 1991, **113**, 5475.

<sup>40</sup> F. N. Tebbe, J. Y. Becker, D. B. Chase, L. E. Firment, E. R. Holler, B. S. Malone, P. J. Krusic, and E. Wasserman, *J. Am. Chem. Soc.*, 1991, **113**, 9900.

<sup>41</sup> G. A. Olah, I. Bucci, C. Lambert, R. Aniszfeld, N. J. Trivedi, D. K. Sensharma, and G. K. S. Prakash, *J. Am. Chem. Soc.*, 1991, **113**, 9385.

<sup>42</sup> G. A. Olah, I. Bucci, C. Lambert, R. Aniszfeld, N. J. Trivedi, D. K. Sensharma, and G. K. S. Prakash, *J. Am. Chem. Soc.*, 1991, **113**, 9387.

<sup>43</sup> A. Hirsch, Q. Li, and F. Wudl, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1309.

<sup>44</sup> P.-M. Allemand, G. Srdanov, A. Koch, K. Khemani, F. Wudl, Y. Rubin, F. Diederich, M. M. Alvarez, S. J. Anz, and R. L. Whetten, *J. Am. Chem. Soc.*, 1991, **113**, 2780.

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<sup>47</sup> A. F. Hedard *et al.*, *Nature*, 1991, **350**(6319), 600; This was the most highly cited paper published in 1991, with 89 citations; see also R. C. Haddon *et al.*, *Nature*, 1991, **350**(6318), 920; J. H. Weaver *et al.*, *Chem. Phys. Lett.*, 1991, **66**, 1741.

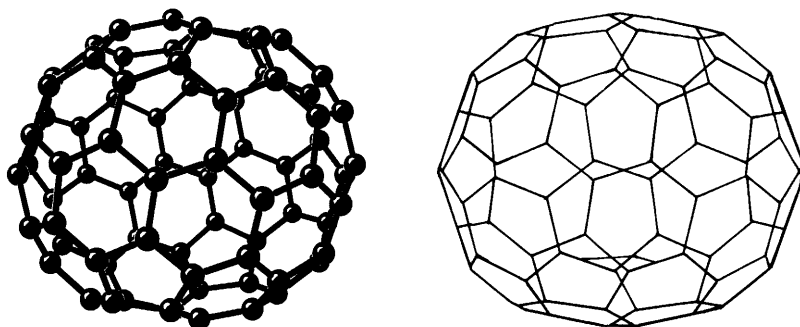
## Synthetic Methods

whereas the tetra-anions are not superconductors.<sup>48</sup>  $C_{60}^{4-}$  and  $C_{60}^{5-}$  can be generated reversibly but only in benzonitrile.<sup>49</sup>

$C_{60}$  and  $C_{70}$  are stable to light and readily yield the triplet states<sup>50</sup> which are good sensitizers for singlet oxygen formation.<sup>51</sup>

Species such as  $AgC_{60}$ ,<sup>52</sup>  $FeC_{60}^{+}$ ,<sup>53</sup> and the 'dumbbell'  $Ni(C_{60})_2^{+}$ <sup>54</sup> have the metal bound on the outer surface of the fullerene, however,  $C_{60}He^{+}$ <sup>55</sup> and  $C_{60}Ne^{+}$ , produced by collision in ion beams<sup>56</sup> may be the long sought after endohedral complexes.<sup>57</sup>

In another surprise in this area  $C_{76}$  (4)<sup>58</sup> and  $C_{84}$ <sup>59</sup> both appear to have  $D_2$  symmetry and exist as pairs of enantiomers. By analogy with the helicenes, they are expected to have extremely high optical rotations.



(4)

The carbon oxides (5) are precursors of 'cyclic carbon' (6) (7).<sup>60</sup> *Ab initio* calculations suggest that the most stable valence isomer of  $C_{18}$  is the cummulene (7) rather than the polyacetylene (6).<sup>61</sup> Intriguingly, the  $C_{30}$  (6c) (7c) homologue gives an extremely intense peak at 720 amu in the positive ion laser desorption Fourier transform mass spectrum, implying dimerization to  $C_{60}$ .

A new synthesis of corannulene (13) ([5]circulene) has two particularly striking steps (Scheme 1): Double Knoevenagel condensation yields a cyclopentadienone

<sup>48</sup> R. M. Fleming, M. J. Rosseinsky, A. P. Ramirez, D. W. Murphy, J. C. Tully, R. C. Haddon, T. Siegrist, R. Tycko, S. H. Zahurak, A. V. Makhija, and C. Hampton, *Nature*, 1991, **352**, 701.

<sup>49</sup> D. Dubois, K. M. Kardish, S. Flanagan, and L. J. Wilson, *J. Am. Chem. Soc.*, 1991, **113**, 7773.

<sup>50</sup> M. R. Wasielewski, M. P. O'Neil, K. R. Lykke, M. J. Pelin, and D. M. Gruen, *J. Am. Chem. Soc.*, 1991, **113**, 2774.

<sup>51</sup> J. W. Arbogast and C. S. Foote, *J. Am. Chem. Soc.*, 1991, **113**, 8886.

<sup>52</sup> J. A. Howard, M. Tomietto, and D. A. Wilkinson, *J. Am. Chem. Soc.*, 1991, **113**, 7870.

<sup>53</sup> L. M. Roth, Y. Huang, J. T. Schwedler, C. J. Cassidy, D. Ben-Amotz, B. Kahr, and B. S. Freiser, *J. Am. Chem. Soc.*, 1991, **113**, 6298.

<sup>54</sup> Y. Huang and B. S. Freiser, *J. Am. Chem. Soc.*, 1991, **113**, 8186.

<sup>55</sup> T. Weiske, D. K. Bohme, J. Hrusak, W. Kratschmer, and H. Schwarz, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 884.

<sup>56</sup> K. A. Caldwell, D. E. Giblin, C. S. Hsu, D. Cox, and M. L. Gross, *J. Am. Chem. Soc.*, 1991, **113**, 8519.

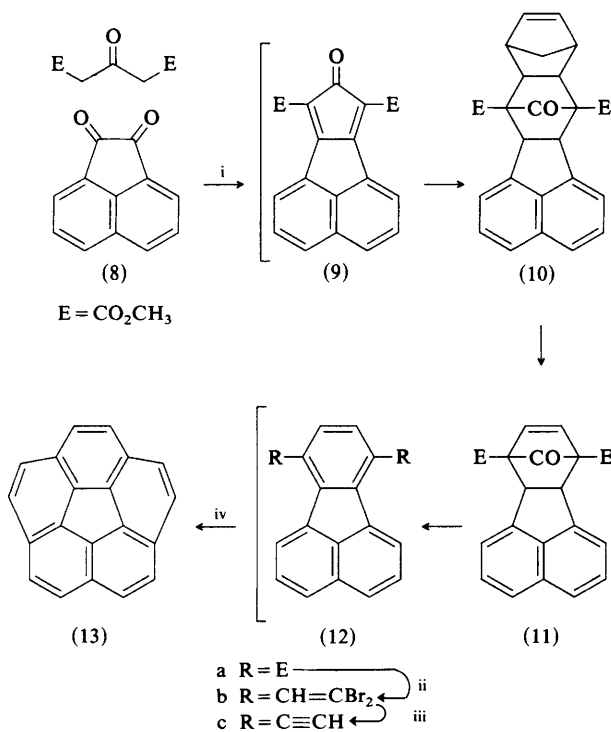
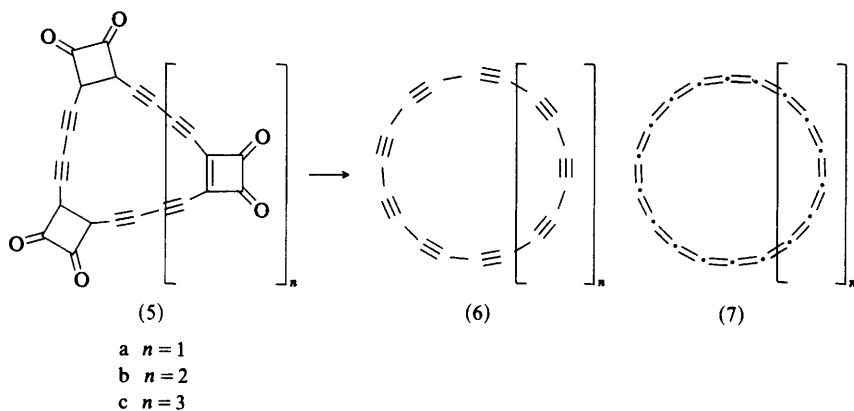
<sup>57</sup> J. Cioslowski and E. D. Fleischmann, *J. Chem. Phys.*, 1991, **94**, 3730; J. Cioslowski, *J. Am. Chem. Soc.*, 1991, **113**, 4139; J. Cioslowski, and S. T. Mixon, *J. Am. Chem. Soc.*, 1991, **113**, 4142.

<sup>58</sup> R. Etti, I. Chao, F. Diederich, and R. L. Whetten, *Nature*, 1991, **353**, 149.

<sup>59</sup> P. W. Fowler, *J. Chem. Soc. Faraday Trans.*, 1991, **87**, 1945.

<sup>60</sup> Y. Rubin, M. Kahr, C. B. Knobler, F. Diederich, and C. L. Wilkins, *J. Am. Chem. Soc.*, 1991, **113**, 495.

<sup>61</sup> V. Parasuk, J. Almlof, and M. W. Feyereisen, *J. Am. Chem. Soc.*, 1991, **113**, 1049.

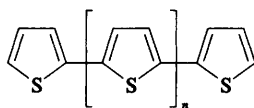


Reagents: i, Glycine, norbornadiene; ii, (a) LiAlH<sub>4</sub> (b) PCC (c) Ph<sub>3</sub>P, Zn, CBr<sub>4</sub>; iii, LDA; iv, Flash vacuum pyrolysis

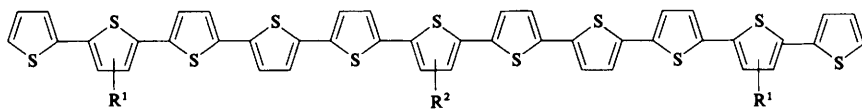
Scheme 1

(9) which undergoes a Diels–Alder reaction *in situ* with nonbornadiene. The adduct (10) eliminates cyclopentadiene by a retro Diels–Alder reaction and extrudes carbon monoxide to give diester (12a). This was converted to the tetrabromide (12b) or the diacetylene (12c), both of which gave corannulene (13) in about 10% yield upon flash vacuum pyrolysis.<sup>62</sup> Low temperature NMR studies show that corannulene has a bowl like structure which inverts rapidly through the planar form at room temperature.<sup>63</sup>

**Thiophenes**—There has been a renaissance in the chemistry of oligothiophenes<sup>64</sup> due to their potential as electrical conductors<sup>65</sup> and occurrence in plants of the *Compositae* family<sup>66</sup> where they act as phototoxic<sup>67</sup> nematocides (e.g.  $\alpha$ -terthiophene (14a) and  $\alpha$ -quinquethiophene (14b)<sup>68</sup>). Typically these systems are prepared by acylation of thiophenes with succinyl chloride to give 1,4 diketones which are converted to a thiophene ring with Lawesson's reagent. The longest characterized oligothiophene is the undecithiophene (15), which was substituted with aliphatic



(14) a  $n = 1$   
b  $n = 3$



(15) a  $R^1 = R^2 = C_{12}H_{25}$   
b  $R^1 = n-C_{12}H_{25}$ ,  $R^2 = n-C_4H_9$

sidechains to enhance solubility<sup>69</sup> and has comparable conductivity to polythiophene or poly(benzo[*c*]thiophene).<sup>70</sup> The bis(terthiophene) (16) in which the two  $\pi$ -systems are orthogonal has been proposed as a molecular switch<sup>71</sup> and an extraordinary 'insulated wire' consisting of a fully conjugated porphyrin core almost 65 Å long with an insulating sheath of *t*-butyl groups has been prepared.<sup>72</sup>

<sup>62</sup> L. T. Scott, M. M. Hasemi, D. T. Meyer, and H. P. Warren, *J. Am. Chem. Soc.*, 1991, **113**, 7082. Although corannulene was first made in 1966, the synthesis has apparently never been repeated and so for example the <sup>13</sup>C NMR spectrum had never been recorded prior to the current work.

<sup>63</sup> For a comparable study of [7]circulene and [7.7]circulene see K. Yamamoto, Y. Saitho, D. Iwaki, and T. Ooka, *Angew. Chem., Int. Ed. Engl.* 1991, **30**, 1173.

<sup>64</sup> S. Gronowitz, 'Thiophene and its Derivatives Pt 4' (Chemistry of Heterocyclic Compounds, **44**), Wiley, New York, 1991.

<sup>65</sup> Review of organic conductors, K. Davidson, *Educ. Chem.*, 1991, **28**, 155.

<sup>66</sup> J. Kagan, *Prog. Chem. Org. Nat. Prod.*, 1991, **56**, 88.

<sup>67</sup> D. M. Perrine, D. M. Bush, E. P. Kornak, M. Zhang, Y. H. Cho, and J. Kagan, *J. Org. Chem.*, 1991, **56**, 5095.

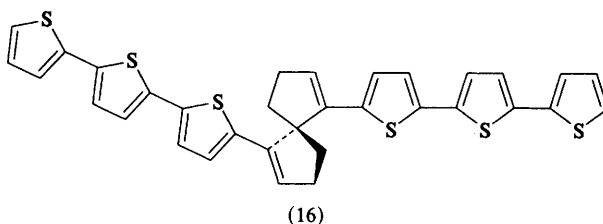
<sup>68</sup> A. Merz and F. Ellinger, *Synthesis*, 1991, 462.

<sup>69</sup> W. ten Hoeve, H. Wynberg, E. E. Havinger, and E. W. Meijer, *J. Am. Chem. Soc.*, 1991, **113**, 5887.

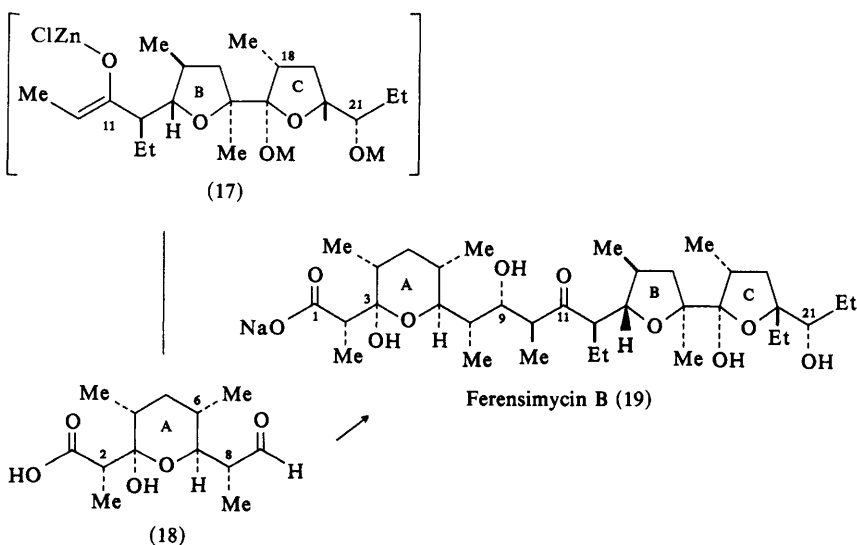
<sup>70</sup> T. Iyoda, M. Kitano, and T. Shimidzu, *J. Chem. Soc., Chem. Commun.*, 1991, 1618.

<sup>71</sup> J. Nakayama and T. Fujimori, *J. Chem. Soc., Chem. Commun.*, 1991, 1614; For the benzanoid analogue see N. Harada, H. Ono, Y. Nishiwaki, and H. Uda, *J. Chem. Soc., Chem. Commun.*, 1991, 1753.

<sup>72</sup> M. J. Crossley, P. L. Burn, S. S. Chew, F. B. Cuttance, and I. A. Newsom, *J. Chem. Soc., Chem. Commun.*, 1991, 1564; M. J. Crossley, P. L. Burn, S. J. Langford, S. M. Pyke, and A. G. Stark, *J. Chem. Soc., Chem. Commun.*, 1991, 1567; M. J. Crossley and P. L. Burn, *J. Chem. Soc., Chem. Commun.*, 1991, 1569.



**Natural Products Synthesis.**—Evans has achieved the synthesis of Ferensimycin B which bears a total of 16 chiral centres on a 24 carbon backbone. In the last step aldol reaction of the zinc enolate (17) and aldehyde (18) gave a mixture of adducts (65% yield), in which Ferensimycin (19) (the threo-Cram adduct) was the largest



component (41%).<sup>73</sup> Nicolaou has completed the synthesis of the FGHIJ rings of brevetoxin A<sup>74</sup> in about 100 steps starting from common sugars.<sup>75</sup> The ABCD and E ring fragments were finished last year. Assembly and a one carbon homologation at the aldehyde terminus should complete this monumental task. A nine year study has culminated in the syntheses of all members of the phyllanthostatin family (23). A key bond construction was addition of the vinyl lithium (21) to the aldehyde (20) to give the pivitol intermediate (22).<sup>76</sup>

<sup>73</sup> D. A. Evans, R. P. Polniaszek, K. M. DeVries, D. E. Guinn, and D. J. Mathre, *J. Am. Chem. Soc.*, 1991, **113**, 7613.

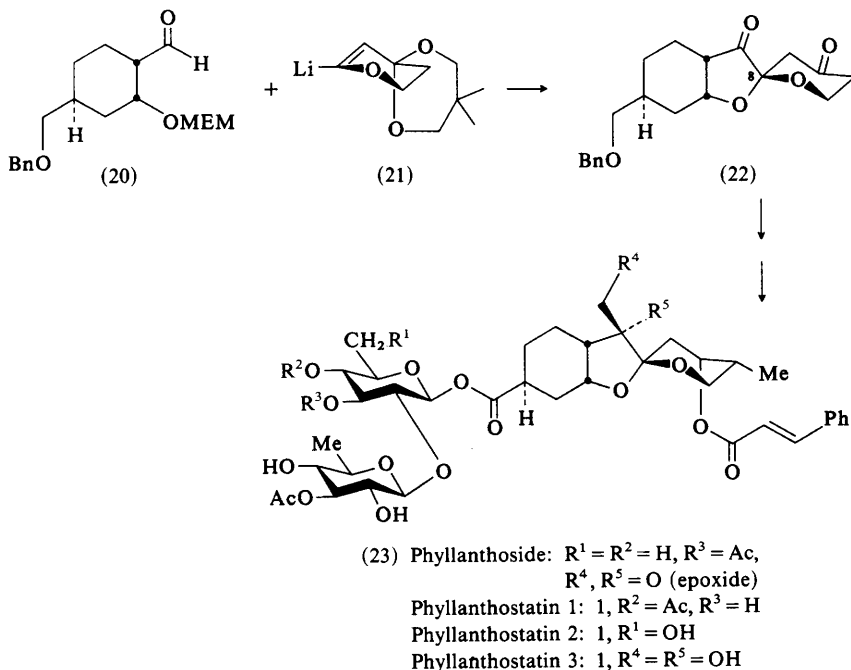
<sup>74</sup> For a review of polyether antibiotics see J. A. Robinson, *Prog. Chem. Org. Nat. Prod.*, 1991, **58**, 1.

<sup>75</sup> K. C. Nicolaou, A. C. Veale, C.-K. Hwang, J. Hutchinson, C. V. C. Prasad, and W. W. Ogilvie, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 299.

<sup>76</sup> A. B. Smith, III, M. Fukui, H. Vaccaro, and J. R. Empfield, *J. Am. Chem. Soc.*, 1991, **113**, 2071; A. B. Smith, III, R. A. Rivero, K. J. Hale, and H. Vaccaro, *ibid.*, 2092; A. B. Smith, K. J. Hale, H. Vaccaro, and R. A. Rivero, *ibid.*, 2112.



## Synthetic Methods



**Chiral Analysis.**—The developments in chiral<sup>77</sup> synthesis<sup>78</sup> have severely tested the techniques for the determination of enantiomeric excess. HPLC,<sup>79,80</sup> SFC,<sup>81</sup> GLC,<sup>82</sup> and capillary zone electrophoresis (CZE)<sup>83</sup> give the most accurate results, but NMR spectroscopy<sup>84</sup> is usually quicker. Circular dichroism is restricted to compounds with good chromophores but enables the absolute configuration to be determined.<sup>85</sup>

2,2,2-Trifluoro-1-(9-anthryl)ethanol (24) (which is widely used as a chiral solvating agent and as the stationary phase in chiral HPLC), adopts a conformation in solution which places the trifluoro group orthogonal to the anthracene ring and locks the

<sup>77</sup> 'New Developments in Molecular Chirality', ed. P. C. Mezey, Kluwer Academic Publishers, Dordrecht, 1991.

<sup>78</sup> For industrial chiral synthesis see J. Crosby, *Tetrahedron*, 1991, **47**, 4789.

<sup>79</sup> 'Chiral Separations by Liquid Chromatography', ed. S. Ahuja, ACS Symposium series 471, ACS, Washington, 1991; N. Krause and G. Handke, *Tetrahedron Lett.*, 1991, **32**, 7225; W. H. Porter, *Pure Appl. Chem.*, 1992, **63**, 1119; J. N. Kinkel, U. Gysel, D. Blase, and D. Seebach, *Helv. Chim. Acta*, 1991, **74**, 1622.

<sup>80</sup> For the determination of absolute configuration by HPLC see K. S. Rein and R. E. Gawley, *J. Org. Chem.*, 1991, **56**, 839; K. Nilsson, A. Hallberg, R. Isaksson and J. Sandstrom, *Acta Chem. Scand.*, 1991, **45**, 716.

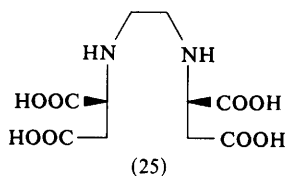
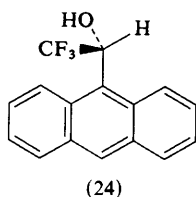
<sup>81</sup> V. Schurig, D. Schmalzing, and M. Schleimer, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 987.

<sup>82</sup> Y. Dobashi, K. Nakamura, T. Saeki, M. Matsuo, S. Hara, and A. Dobashi, *J. Org. Chem.*, 1991, **56**, 3299.

<sup>83</sup> P. Camilleri and G. N. Okafo, *J. Chem. Soc., Chem. Commun.*, 1991, 196.

<sup>84</sup> D. Parker, *Chem. Rev.*, 1991, **91**, 1441; for a new techniques using <sup>77</sup>Se NMR see L. A. Silks III, J. Peng, J. D. Odom, and R. B. Dunlap, *J. Chem. Soc., Perk. Trans.*, 1, 1991, 2495.

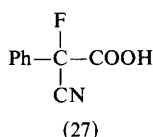
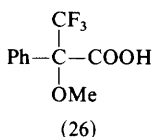
<sup>85</sup> H. E. Smith and L. P. Fontana, *J. Org. Chem.*, 1991, **56**, 432; T. Hargitai, P. Rheinholdsson, and J. Sandstrom, *Acta Chem. Scand.*, 1991, **45**, 1076; D. F. Colon and S. T. Pickard, *J. Org. Chem.*, 1991, **56**, 2322.



hydroxyl group in a highly asymmetric environment.<sup>86</sup> In the solid state homochiral material forms face to face dimers with the hydroxyl groups facing inwards and the hydroxyl proton engaged in an unusual  $\pi$ -facial hydrogen bond.<sup>87</sup>

Chiral lanthanide shift reagents are convenient to use but are highly unpredictable, cause line broadening, and can only be used in very dry organic solvents. However, the Europium(III) complex of (*S,S*)-ethylenediamine-*N,N'*-disuccinic acid (25) discriminates the <sup>1</sup>H NMR signals of enantiomeric amino acids in aqueous solution.<sup>88</sup>

It is remarkable that after 22 years Mosher's acid chloride (26)<sup>89</sup> is still the paramount derivatizing reagent<sup>90</sup> for assessing enantiomeric purity and for determining absolute stereochemistry.<sup>91</sup> The cyano fluoro analogue (27) has been suggested



as a substitute because it gives larger  $\Delta\delta$  values in the <sup>19</sup>F NMR spectrum.<sup>92</sup> Chiral derivatives are not necessarily required. Achiral diphenyldichlorosilane forms diastereomeric silyl acetals with chiral alcohols. If the *dl* and meso compounds can be distinguished the enantiomeric ratio can be calculated.<sup>93</sup> Similarly, if the enantiomers associate in solution (e.g. by hydrogen bonding) the enantiomeric ratio can be determined in the same way!<sup>94</sup>

Cholesteric liquid crystals attached to steroidal crown ethers change colour when they bind enantiomeric ammonium salts. In the best case the difference in  $\langle\Delta\rangle\langle\lambda\rangle_{\max}$  was only 81 nm, but it is not difficult to imagine that this could be developed into the chiral equivalent of pH paper!<sup>95</sup>

<sup>86</sup> C. Jaime, A. Virgili, R. M. Claramunt, C. Lopez, and J. Elguero, *J. Org. Chem.*, 1991, **56**, 6521.

<sup>87</sup> H. S. Rzepa, M. L. Webb, A. M. Z. Slawin, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1991, 765.

<sup>88</sup> J. Kido, Y. Okamoto, and H. G. Brittain, *J. Org. Chem.*, 1991, **56**, 1412.

<sup>89</sup> J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

<sup>90</sup> D. E. Ward and C. K. Rhee, *Tetrahedron Lett.*, 1991, **32**, 7165.

<sup>91</sup> I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092; T. Kusumi, Y. Fujita, I. Ohtani, and H. Kakisawa, *Tetrahedron Lett.*, 1991, **32**, 2923; I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Org. Chem.*, 1991, **56**, 1296; T. Kusumi, T. Fukushima, I. Ohtani, and H. Kakisawa, *Tetrahedron Lett.*, 1991, **32**, 2939.

<sup>92</sup> Y. Takeuchi, N. Itoh, H. Note, T. Koizumi, and K. Yamaguchi, *J. Am. Chem. Soc.*, 1991, **113**, 6318.

<sup>93</sup> X. Wang, *Tetrahedron Lett.*, 1991, **32**, 3651.

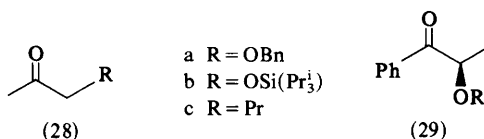
<sup>94</sup> C. Giordano, A. Restelli, M. Villa, and R. Annunziata, *J. Org. Chem.*, 1991, **56**, 2270.

<sup>95</sup> T. Nishi, A. Ikeda, T. Matsuda, and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, 1991, 339; F. Vogtle and P. Knops, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 958.

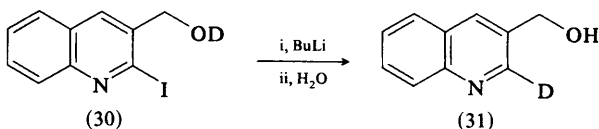
**New Publications.**—The Organic Syntheses Reaction Guide<sup>96</sup> has been brought up to date and collectives will occur at five yearly intervals in future rather than ten yearly as at present. Wilen's excellent review of reviews is also appearing more frequently.<sup>97</sup> A reasonably priced 4 volume compilation of drug syntheses<sup>98</sup> has been published as well as second editions of Greene's 'Protective Groups in Organic Synthesis'<sup>99</sup> and Lowenthal's 'Guide for the Perplexed Experimentalist'.<sup>100</sup>

## 2 CC Connection and Disconnection

**Ketones.**—A careful study has for the first time given convincing proof that chelation increases the rate of nucleophilic addition to ketones.<sup>101</sup> Thus the chelating benzyl ether (28a) reacts 140 times faster with dimethyl magnesium<sup>102</sup> at  $-78^{\circ}\text{C}$  than the non-chelating silyl ether (28b). In fact the latter is about as reactive as methyl butyl ketone (28c). A similar study with the chiral ethers (29a–c) showed a direct correlation between diastereoselectivity and reaction rate.<sup>103</sup>



**Organolithiums.**—When the O-deutero quinoline (30) was treated with butyl lithium and then quenched with H<sub>2</sub>O the C-deutero quinoline (31) (66% incorporation of deuterium) was formed,<sup>104</sup> repetition of this work under slightly different conditions gave a 27–32% incorporation.<sup>105</sup> This result was attributed to initial halogen-lithium exchange followed by intramolecular transfer of deuterium, however, it is also possible that individual molecules undergo alkoxide formation, followed by halogen-lithium exchange and the aryl lithium is quenched by unreacted O-deuteroquinoline (30). These two possibilities can only be resolved by a double labelling experiment which shows the extent of intermolecular transfer of deuterium.



<sup>96</sup> D. C. Liotta and M. Volmer, 'Organic Syntheses. Reaction Guide': Incorporating Collective Volumes 1–7 and Annual Volumes 65–68, John Wiley and Sons Inc., New York, 1991.

<sup>97</sup> S. H. Wilen, *J. Org. Chem.*, 1991, **56**, 477, 2597, 4580, 5966; 1992, **57**, 412, 2203.

<sup>98</sup> D. Lednicher and L. A. Mitscher, 'Organic Chemistry of Drug Synthesis', Wiley, New York, 1991.

<sup>99</sup> T. W. Greene and P. G. M. Wuts, 'Protective Groups in Organic Synthesis', Wiley, New York, 1991.

<sup>100</sup> H. J. E. Loewenthal, 'Guide for the Perplexed Experimentalist', J. Wiley and Sons, Chichester, 2nd edition, 1990.

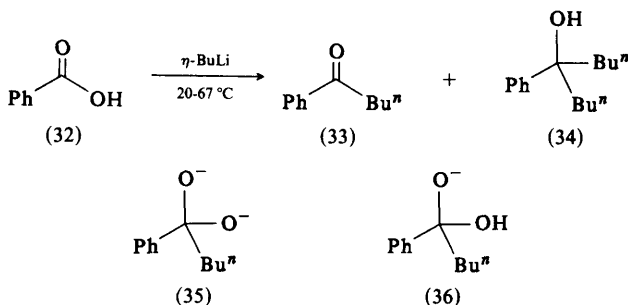
<sup>101</sup> For acyl silanes see S. Bienz and A. Chapeaurouge, *Helv. Chim. Acta*, 1991, **74**, 1477; aldol condensation R. Carlson, A. Nordahl, and W. Kraus, *Acta Chem. Scand.*, 1991, **45**, 46.

<sup>102</sup> For boron enolates as nucleophiles see A. Bernardi, A. M. Capelli, A. Comotti, G. Gennari, M. Gardner, J. M. Goodman, and I. Paterson, *Tetrahedron*, 1991, **47**, 3471.

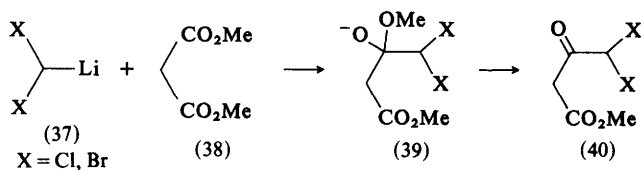
<sup>103</sup> E. L. Eliel, S. V. Frye, E. R. Hortelano, X. Chen, and X. Bai, *Pure Appl. Chem.*, 1992, **63**, 1591.

<sup>104</sup> N. S. Narasimhan, N. M. Sunder, R. Ammanamanchi, and B. D. Bonde, *J. Am. Chem. Soc.*, 1990, **112**, 4431.

<sup>105</sup> D. J. Gallagher and P. Beak, *J. Am. Chem. Soc.*, 1991, **113**, 7984.



An intriguing, similar, result has been obtained during the addition of butyl lithium to benzoic acid (32) which yields roughly equal amounts of the ketone (33) and the alcohol (34). The conventional wisdom is that deprotonation is followed by nucleophilic attack to give the stable dialkoxide (35). It has been suggested in this case that nucleophilic attack occurs prior to deprotonation (36) and that loss of lithium hydroxide gives the ketone (33) which then undergoes a second addition, but it is also possible that lithium oxide is eliminated from the dialkoxide (35).<sup>106</sup> Dihalo-organolithiums<sup>107</sup> (37) add to diesters (38), without elimination of the alkoxy group (39), (40),<sup>108</sup> as do acyl anions.<sup>109</sup>



Lithium naphthalenide and lithium *p,p'*-di-*tert*-butylbiphenyl (LiDBB)<sup>110</sup> are normally used stoichiometrically for the preparation of organolithium<sup>111</sup> reagents from alkyl halides, but a new catalytic procedure is claimed to be equally efficient.<sup>112</sup> *para*-Dilithium hexakis(trimethylsilyl)benzenide has been isolated as a bis-THF adduct<sup>113</sup> with both lithium atoms located on the concave side of the boat shaped aromatic ring.<sup>114</sup> Addition of D<sub>2</sub>O gives the expected 'Birch' 1,4-dihydrobenzene.

Association between cation and carbanion,<sup>115</sup> and the degree of aggregation<sup>116</sup>

<sup>106</sup> C. Einhorn, J. Einhorn and J.-L. Luche, *Tetrahedron Lett.*, 1991, **32**, 2771.

<sup>107</sup>  $\alpha,\alpha$ -halolithiums are configurationally stable at  $-120\text{ }^\circ\text{C}$ , R. W. Hoffmann, T. Ruhland, and M. Bewersdorf, *J. Chem. Soc., Chem. Commun.*, 1991, 195.

<sup>108</sup> J. Barluenga, L. Llavona, M. Yus, and J. M. Concellon, *Tetrahedron*, 1991, **47**, 7875; J. Barluenga, L. Llavona, J. Concellon, and M. Yus, *J. Chem. Soc., Perkin Trans.*, 1, 1991, 297.

<sup>109</sup> D. Seyferth, R. M. Weinstein, R. C. Hui, W.-L. Wang, and C. M. Archer, *J. Org. Chem.*, 1991, **56**, 5768.

<sup>110</sup> D. J. Rawson and A. I. Meyers, *Tetrahedron Lett.*, 1991, **32**, 2095; N. J. R. van Eikem Hommes, F. Bickelhaupt and G. W. Klumpp, *J. Chem. Soc., Chem. Commun.*, 1991, 438.

<sup>111</sup> For a new analytical method see H. Kiljunen and T. A. Hase, *J. Org. Chem.*, 1991, **56**, 6950.

<sup>112</sup> M. Yus and D. J. Ramon, *J. Chem. Soc., Chem. Commun.*, 1991, 398.

<sup>113</sup> A. Sekiguchi, K. Ebata, C. Kabuto, and H. Sakurai, *J. Am. Chem. Soc.*, 1991, **113**, 1464.

<sup>114</sup> A. Sygula and P. W. Rabideau, *J. Am. Chem. Soc.*, 1991, **113**, 7797.

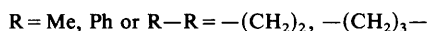
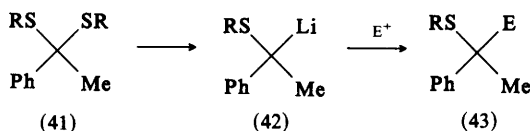
<sup>115</sup> H. J. Reich and J. P. Borst, *J. Am. Chem. Soc.*, 1991, **113**, 1835.

<sup>116</sup> M. Buhl, N. J. R. van Eikema Hommes, P. von R. Schleyer, U. Fleischer, and W. Kutzelnigg, *J. Am. Chem. Soc.*, 1991, **113**, 2459; L. M. Jackman, E. F. Rakiewicz and A. J. Benesi, *J. Am. Chem. Soc.*, 1991, **113**, 4101; H.-J. Gais, J. Muller, J. Volhardt, and H. J. Lindner, *J. Am. Chem. Soc.*, 1991, **113**, 4002.

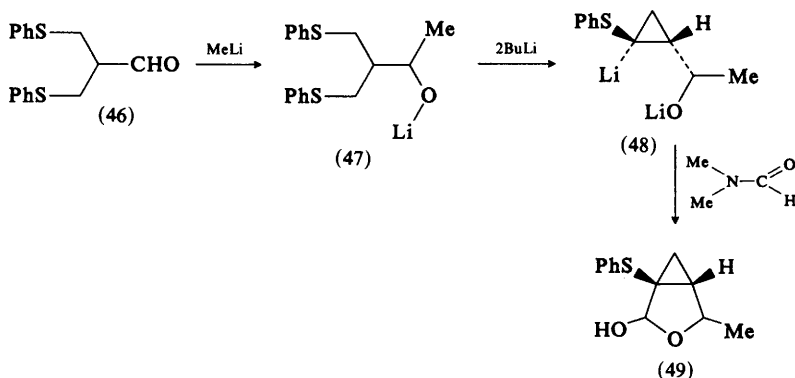
## Synthetic Methods

profoundly affect the reactivity of organometallics, but these factors are not readily predictable. The enthalpies of deprotonation of isopropanol by alkyl lithiums and lithium amides in the presence and absence of lithium t-butoxide are the same, indicating that the alkoxide does not associate with the base.<sup>117</sup> But the rates of deprotonation of toluene and ethyl benzene increase when more sterically hindered potassium alkoxides are used with alkyl lithiums.<sup>118</sup>

Dithioacetals derived from aromatic ketones (41) undergo reductive cleavage by alkyl lithiums to give a benzylic anion (42);<sup>119</sup> similarly the allyl thioether (44) is cleaved by lithium 1-(dimethylamino)naphthalenide to give the allyl methyl anion (45) which is a useful reagent for terpene synthesis.<sup>120</sup> In a more complex example,



addition to the aldehyde (46) gives an alkoxide (47) which undergoes deprotonation adjacent to one thioether and intramolecular nucleophilic displacement of the other thioether group. A second deprotonation directed by the alkoxide gives the *cis*-dilithiocyclopropane (48), which can be trapped with dimethylformamide to give the lactol (49).<sup>121</sup> Reductive cleavage of  $\text{BF}_3$ -THF complex (50) with LDBB at room temperature yields a versatile  $\delta$ -alkoxy organolithium (51) used in a synthesis of



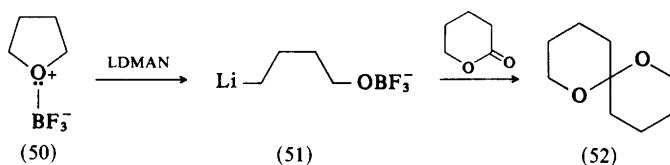
<sup>117</sup> E. M. Arnett and K. D. Moe, *J. Am. Chem. Soc.*, 1991, 113, 7068.

<sup>118</sup> L. Lochmann and J. Petranek, *Tetrahedron Lett.*, 1991, 32, 1483.

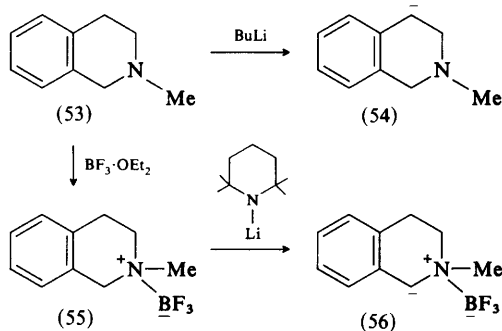
<sup>119</sup> A. Kreif, B. Kenda, and P. Barbeaux, *Tetrahedron Lett.*, 1991, 32, 2509.

<sup>120</sup> D. W. McCullough, M. Bhupathy, E. Piccolino, and T. Cohen, *Tetrahedron*, 1991, 47, 9727.

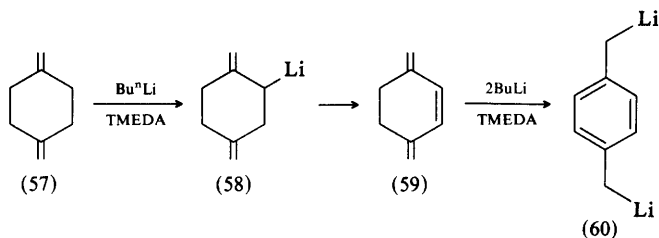
<sup>121</sup> K. Tanaka, H. Matsuura, I. Funaki, and H. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1991, 1145.



the olive fly sex pheromone (52).<sup>122</sup> *N*-methyl tetrahydroisoquinoline (53) is deprotonated by butyl lithium at C-4 (54), but the  $\text{BF}_3$  complex (55) is deprotonated adjacent to the amino group by lithium tetramethyl piperide.<sup>123</sup>



The diene (57) undergoes initial deprotonation to give an allyl lithium (58), which eliminates lithium hydride<sup>124</sup> to give the triene (59). Double deprotonation then gives a product best formulated as the *p*-xylene dianion (60).<sup>125</sup>



Intermolecular addition of organolithiums to unactivated alkenes is generally very slow,<sup>126</sup> but the kinetically controlled 5-exo-trig cyclization of 5-hexen-1-yl lithiums<sup>127</sup> is much faster and has been used in a novel synthesis of racemic

<sup>122</sup> B. Mudryk and T. Cohen, *J. Am. Chem. Soc.*, 1991, 113, 1866; for a related cleavage of oxetane with  $\text{K}^+(18\text{-Crown-6})\text{K}^-$  see Z. Jedlinski, A. Misiolek, A. Jankowski, and H. Janeczka, *J. Chem. Soc., Chem. Commun.*, 1991, 1513.

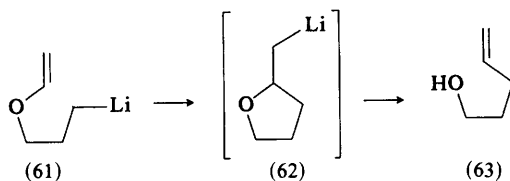
<sup>123</sup> S. V. Kessar, P. Singh, R. Vohra, N. P. Kaur, and K. N. Singh, *J. Chem. Soc., Chem. Commun.*, 1991, 568; S. V. Kessar, P. Singh, K. N. Singh, and M. Dutt, *J. Chem. Soc., Chem. Commun.*, 1991, 570.

<sup>124</sup> J. J. Novoa, M.-H. Whangbo, and G. D. Stucky, *J. Org. Chem.*, 1991, 56, 3181.

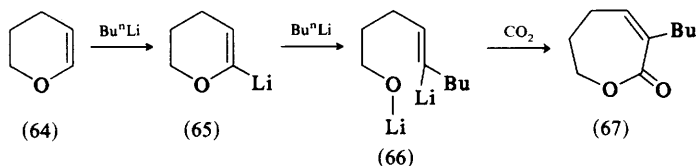
<sup>125</sup> S. D. Meyer, N. S. Nills, J. B. Runnels, B. de la Torre, C. C. Ruud, and D. K. Johnson, *J. Org. Chem.*, 1991, 56, 947.

<sup>126</sup> B. O. T. Kammermeier, G. W. Klumpp, K. Kolthof, and M. Vos, *Tetrahedron Lett.*, 1991, 32, 3111; T. Hattori, T. Suzuki, and S. Miyano, *J. Chem. Soc., Chem. Commun.*, 1991, 1375.

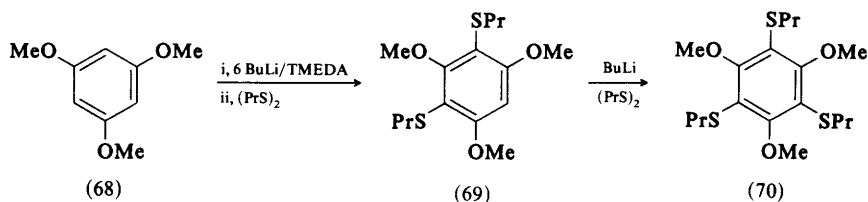
<sup>127</sup> W. F. Bailey, A. D. Khanolkar, K. Gavaskar, T. V. Ovaska, K. Rossi, Y. Thiel, and K. Wiberg, *J. Am. Chem. Soc.*, 1991, 113, 5720; for a comparable epoxide cyclization see V. Cere, C. Paolucci, P. Pollicino, E. Sandri, and A. Fava, *J. Org. Chem.*, 1991, 56, 4513.



cuparene.<sup>128</sup> Cyclization of the vinyl ether (61) effected  $\beta$ -elimination of the alkoxide (62) to give a novel [1,4]-Wittig rearrangement<sup>129</sup> to (63). Similarly, dihydropyran (64) can be deprotonated to give the  $\alpha$ -lithiated vinyl ether (65),<sup>130</sup> which undergoes nucleophilic addition of alkyl lithiums to the carbanionic centre (!) and alkoxide elimination to give the ring opened, vinyl lithium (66).<sup>131</sup>



Polyolithio aromatics have been sought by several groups, but at present dilithio derivatives<sup>132</sup> seem to be the practical limit. Treatment of 1,3,5-trimethoxybenzene (68) with 6 equivalents of  $\text{BuLi}$ /TMEDA complex and trapping with propyl disulfide gave only the *bis* adduct (69), but *in situ* repetition of the reaction allowed a third group to be introduced (70).<sup>133</sup> Direct lithiation of the diphenol (71a) gave insoluble



TMEDA = *N,N,N',N'*-tetramethyl-1,2-ethane diamine

precipitates, but halogen-lithium exchange<sup>134</sup> gave the sulfide (73) *via* (72), plus reduced starting material (71a).<sup>135</sup> Attempted halogen-lithium exchange with the sterically congested bromide (74), gave the unexpected plumbane (75), a diplumbane, and the alcohol (76), presumably *via* single electron transfer and hydrogen

<sup>128</sup> W. F. Bailey and A. D. Khanolkar, *Tetrahedron*, 1991, **47**, 7727.

<sup>129</sup> W. F. Bailey and L. M. J. Zarcone, *Tetrahedron Lett.*, 1991, **32**, 4425.

<sup>130</sup> N. J. Harris and J. F. Sebastian, *Tetrahedron Lett.*, 1991, **32**, 6069.

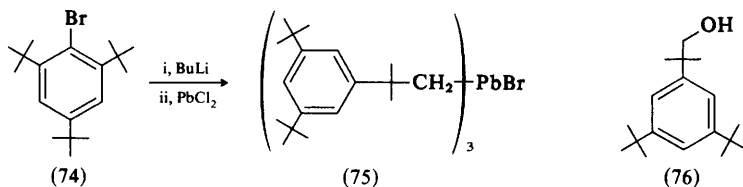
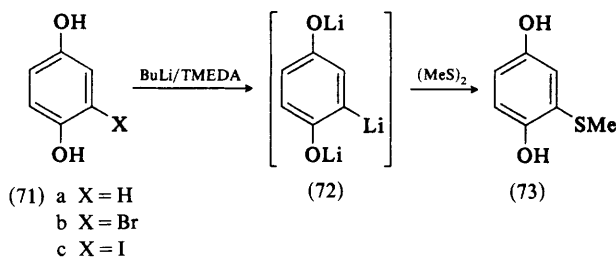
<sup>131</sup> T. Nguyen and E. Negishi, *Tetrahedron Lett.*, 1991, **32**, 5903.

<sup>132</sup> L. Lochmann, M. Fossatelli, and L. Brandsma, *Recl. Trav. Chim. Pays-Bas.*, 1990, **109**, 529; T. Lund and H. Lund, *Acta Chem. Scand.*, 1991, **45**, 655.

<sup>133</sup> S. Cabiddu, L. Contini, C. Fattuoni, C. Floris, and G. Gelli, *Tetrahedron*, 1991, **47**, 9279.

<sup>134</sup> H. J. Reich, D. P. Green, and N. H. Phillips, *J. Am. Chem. Soc.*, 1991, **113**, 1414.

<sup>135</sup> J. M. Saa, J. Morey, G. Suner, A. Frontera, and A. Costa, *Tetrahedron Lett.*, 1991, **32**, 7313.



radical migration.<sup>136</sup>  $\pi$ -Deficient aromatics normally undergo nucleophilic addition of organolithiums,<sup>137</sup> but if a directing group is present *ortho* metallation occurs.<sup>138</sup>

**Grignard Reagents.**—Butyl magnesium bromide and butyl lithium react in surprisingly different ways with para-substituted benzophenones. BuMgBr produces increasing amounts of 1-phenyl ethanols as the electronegativity of the substituents increases and the rate increases ( $\rho = 1.45$ ), whereas the rate of reaction of BuLi is virtually independent of the substituents and the ratio of addition to reduction is more or less constant (70:30).<sup>139</sup>

Dry magnetic stirring of magnesium powder under an inert atmosphere causes fragmentation to give a micro-crystalline powder which is much more reactive than conventional 'turnings'. This enables 0.4M solutions of Grignard reagents to be produced free from coupling products.<sup>140</sup> Cyclopropyl magnesium bromide is notorious difficult to prepare, because the intermediate cyclopropyl radicals<sup>141</sup> attack the solvent to give cyclopropane, but if it is prepared in the presence of hexyl bromide or hexyl magnesium bromide (entrainment) the yield is greatly enhanced.<sup>142</sup>

Reduction of magnesium chloride with lithium naphthalenide gives extremely fine magnesium powder which undergoes cycloaddition to 1,4 dienes to give a magnesium metallocycle,<sup>143</sup> which in turn reacts with dihalides to give fused<sup>144</sup> or

<sup>136</sup> R. Okazaki, K. Shibata, and N. Tokitoh, *Tetrahedron Lett.*, 1991, **32**, 6601; cf. B. Dhawan and D. Redmore, *J. Org. Chem.*, 1991, **56**, 833.

<sup>137</sup> For addition reactions of Grignard reagents see T. Holm, *Acta Chem. Scand.*, 1991, **45**, 276 or thiols see S. Prachayasittikul, G. Doss, and L. Bauer, *J. Het. Chem.*, 1991, **28**, 1051.

<sup>138</sup> G. Queguiner, F. Marsais, V. Snieckus, and J. Epszajn, *Adv. Het. Chem.*, 1991, **52**, 189; J. A. Lepoivre, *Janssen Chemica Acta*, 1991, **9**(1), 20.

<sup>139</sup> H. Yamataka, N. Miyano, and T. Hanafusa, *J. Org. Chem.*, 1991, **56**, 2573.

<sup>140</sup> K. V. Baker, J. M. Brown, N. Hughes, A. J. Skarnulis, and A. Sexton, *J. Org. Chem.*, 1991, **56**, 698.

<sup>141</sup> J. F. Garst, *Acc. Chem. Res.*, 1991, **24**, 95.

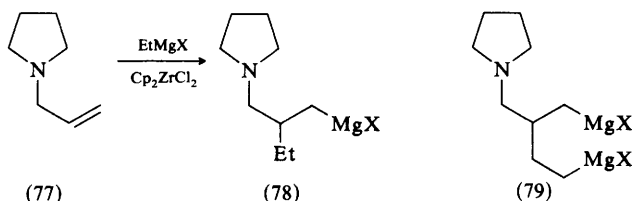
<sup>142</sup> J. F. Garst, F. Ungvary, R. Batlaw, and K. E. Lawrence, *J. Am. Chem. Soc.*, 1991, **113**, 5392, 6697.

<sup>143</sup> *o*-Phenylenemagnesium tetramer, M. A. G. M. Tinga, O. S. Akkerman, F. Bickelhaupt, E. Horn, and A. L. Spek, *J. Am. Chem. Soc.*, 1991, **113**, 3604.

<sup>144</sup> R. D. Rieke and H. Xiong, *J. Org. Chem.*, 1991, **56**, 3109.

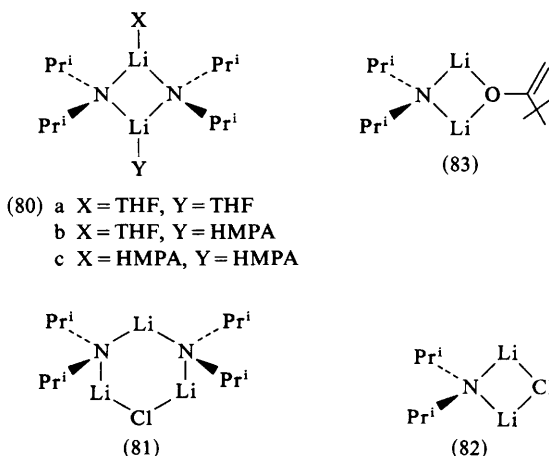


## Synthetic Methods



spiro<sup>145</sup> carbocycles. A curious double metallation was observed during zirconocene dichloride catalysed addition of ethyl magnesium halides to the allyl pyrrolidine (77).<sup>146</sup>

**Amide Bases.**—Crystalline LDA exists as a helical polymer<sup>147</sup> in which the ‘backbone’ consists of unprecedented near linear N–C–N bonds.<sup>148</sup> In hexane it exists as a mixture of at least five different types of aggregate, however, in THF solution it is present exclusively as the cyclic dimer (80a).<sup>149</sup> Addition of lithium chloride gives the dimer adduct (81) at low concentrations and the monomer adduct (82) at high concentrations, whereas addition of an enolate gives the 1 : 1 dimer (83).<sup>150</sup> HMPA is purported to enhance reactivity by acting as a disaggregating agent; however,



<sup>145</sup> H. Xiong and R. D. Rieke, *Tetrahedron Lett.*, 1991, **32**, 5269.

<sup>146</sup> D. P. Lewis, P. M. Muller, R. J. Whitby, and R. V. H. Jones, *Tetrahedron Lett.*, 1991, **32**, 6797; *cf.* P. Canonne, R. Boulanger, and P. Angers, *Tetrahedron Lett.*, 1991, **32**, 5861.

<sup>147</sup> R. E. Mulvey, *Chem. Soc. Rev.*, 1991, **20**, 167; U. Olsher, R. M. Izatt, J. S. Bradshaw, and N. K. Dalley, *Chem. Rev.*, 1991, **91**, 137; *cf.* organomagnesium compounds, P. R. Markies, O. S. Akkerman, F. Bickelhaupt, W. J. J. Smeets, and A. L. Spek, *Adv. Organometallic Chem.*, 1991, **32**, 147.

<sup>148</sup> N. D. R. Barnett, R. E. Mulvey, W. Clegg, and P. A. O’Neil, *J. Am. Chem. Soc.*, 1991, **113**, 8187.

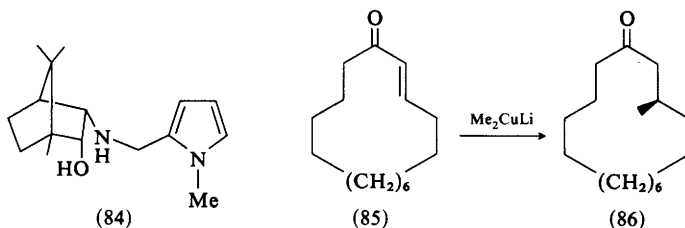
<sup>149</sup> The crystal structure of this dimer has been reported but the details were not published, however, comparable structures have been reported for bis(trimethylsilyl) amide bases, P. G. Williard and M. A. Nichols, *J. Am. Chem. Soc.*, 1991, **113**, 9671; and a sodium amide, P. C. Andrews, D. R. Armstrong, W. Clegg, M. MacGregor, and R. E. Mulvey, *J. Chem. Soc., Chem. Commun.*, 1991, 497. For a comparable study of silaamidate salts see G. E. Underiner, R. P. Tan, D. R. Powell, and R. West, *J. Am. Chem. Soc.*, 1991, **113**, 8437.

<sup>150</sup> A. S. Galiano-Roth, Y.-J. Kim, J. H. Gilchrist, A. T. Harrison, D. J. Fuller, and D. B. Collum, *J. Am. Chem. Soc.*, 1991, **113**, 5053.

spectroscopic studies demonstrate that it sequentially (80b) (80c) replaces the THF ligands in the dimer (80a) without changing the state of aggregation.<sup>151</sup> In fact even an amide base incorporating a crown ether group exists as the dimer in the solid state.<sup>152</sup> Crystalline unsolvated enolates can be isolated from hexane solutions of LDA<sup>153</sup> (up to 0.1 M at  $-78^{\circ}\text{C}$ ) and ketones, esters, or carboxamides.<sup>154</sup> The elusive isoprene<sup>155</sup> anion<sup>156</sup> has now been prepared using LDA and potassium t-butoxide.

**Cuprates.**—Organocoppers can be prepared directly by the reaction of alkyl halides and dispersed Cu(O). In a new procedure lithium naphthalenide reduction of CuCN·2LiBr rather than copper iodide phosphine complexes,<sup>157</sup> enables the preparation of organocopper reagents free from phosphine ligands, which are appreciably more reactive, particularly in conjugate additions.<sup>158</sup> The cuprate reagent prepared from  $^{13}\text{C}$  labelled ethyl lithium and  $^{13}\text{C}$  labelled copper cyanide has a  $^{13}\text{C}$ – $^{13}\text{C}$  two bond NMR coupling. This indicates that both moieties are attached to the copper atom (Et(CN)CuLi), however, addition of further ethyl lithium abolishes the coupling to the cyanide carbon and so this reagent must be formulated as a dialkyl cuprate lithium cyanide complex (Et<sub>2</sub>CuLi·LiCN), rather than a higher order cuprate; R<sub>2</sub>(CN)CuLi<sub>2</sub>.<sup>159</sup> Curiously when lithio silanes are added to these complexes, an alkyl lithium is displaced and can be detected uncomplexed in solution.<sup>160</sup>

Considerable effort has been expended in the design of chiral amino<sup>161</sup> and phosphine<sup>162</sup> ligands for asymmetric conjugate addition. One extremely successful example is the synthesis of the highly prized fragrance muscone. Conjugate addition of dimeric chiral complex formed from the ligand (84) and dimethyl cuprate, to the enone (85), gives (*R*)-(–)-muscone (86) enantiomerically pure, with non-

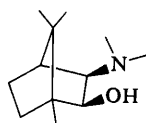


- <sup>151</sup> F. E. Romberg, J. H. Gilchrist, A. T. Harrison, D. J. Fuller, and D. B. Collum, *J. Am. Chem. Soc.*, 1991, **113**, 5751.
- <sup>152</sup> D. Barr, D. J. Berrisford, L. Mendez, A. M. Z. Slawin, R. Snaith, J. F. Stoddart, D. J. Williams, and D. S. Wright, *Angew. Chem. Int. Ed. Engl.*, 1991, **30**, 82.
- <sup>153</sup> For a new analytical method see R. E. Ireland and R. S. Meissner, *J. Org. Chem.*, 1991, **56**, 4566.
- <sup>154</sup> Y.-J. Kim, M. P. Bernstein, A. S. Galiano-Roth, F. E. Romberg, P. G. Williard, D. J. Fuller, A. T. Harrison, and D. B. Collum, *J. Org. Chem.*, 1991, **56**, 4435.
- <sup>155</sup> M. Bertrand, B. Waegell, and J. P. Zahra, *Bull. Soc. Chim. Fr.*, 1991, **128**, 904.
- <sup>156</sup> P. A. A. Klusener, L. Tip, and L. Brandsma, *Tetrahedron*, 1991, **47**, 2041.
- <sup>157</sup> G. W. Ebert and W. R. Klein, *J. Org. Chem.*, 1991, **56**, 4744.
- <sup>158</sup> D. E. Stack, B. T. Dawson and R. D. Rieke, *J. Am. Chem. Soc.*, 1991, **113**, 4672.
- <sup>159</sup> S. H. Bertz, *J. Am. Chem. Soc.*, 1991, **113**, 5470; S. H. Bertz, G. Dabbagh and A. M. Majsce, *J. Am. Chem. Soc.*, 1991, **113**, 631.
- <sup>160</sup> R. D. Singer and A. C. Oehlschlager, *J. Org. Chem.*, 1991, **56**, 3510; S. Sharma and A. C. Oehlschlager, *J. Org. Chem.*, 1991, **56**, 770; S. Sharma and A. C. Oehlschlager, *Tetrahedron*, 1991, **47**, 1177; R. D. Singer, M. W. Hutzinger, and A. C. Oehlschlager, *J. Org. Chem.*, 1991, **56**, 4933.
- <sup>161</sup> B. E. Rossiter, M. Eguchi, A. E. Hernandez, D. Vickers, J. Medich, J. Marr, and D. Heinis, *Tetrahedron Lett.*, 1991, **32**, 3973.
- <sup>162</sup> A. Alexakis, S. Mutti, and J. F. Normant, *J. Am. Chem. Soc.*, 1991, **113**, 6332.

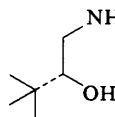
enantiomerically pure catalyst.<sup>163</sup> This phenomenon, known as chiral amplification, comes about when the *heterodimeric catalytic complex is more stable* and the *homodimeric complex is more reactive* and enantioselective. In essence all of the less abundant enantiomer is trapped in the heterodimeric complex and hence the reactive homodimer is enantiomerically pure.

**Zinc.**—The formation of organozincs by reaction of an organohalide and zinc metal is normally very slow, however, the reaction with alkyl iodides is accelerated by primary amines<sup>164</sup> and using precipitated zinc<sup>165</sup> even alkyl chlorides can be converted quantitatively.

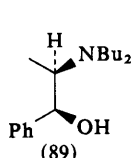
Diorganozincs are unreactive with aldehydes, however, the complexes<sup>166</sup> formed with catalytic amounts of amine ligands (e.g. (87),<sup>167</sup> (88),<sup>168</sup> (89),<sup>169</sup> (90)<sup>170</sup>) or the titanium complex (91)<sup>171</sup> promote highly enantioselective addition.



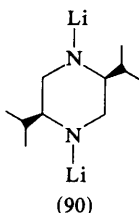
(87) = (–)-DAIB  
(–)-3-*exo*-(dimethylamino)isoborneol



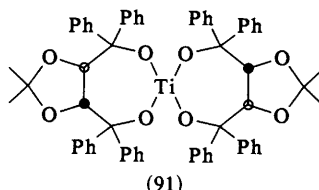
(88)



(89)  
(1*R*,2*S*)-(+)-dibutyl  
norephedrine



(90)



(91)

The reactivity of organozinc halides can be modified by transmetalation with a mixture of lithium chloride and copper cyanide to give reagents<sup>172</sup> with a similar, but attenuated reactivity, reminiscent of organocoppers or cuprates, such as *syn*

<sup>163</sup> K. Tanaka and H. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1991, 101; K. Tanaka, H. Ushio, Y. Kawabata, and H. Suzuki, *J. Chem. Soc., Perk. Trans.*, 1, 1991, 1445; K. Tanaka, J. Matsui, Y. Kawabata, H. Suzuki, and A. Watanabe, *J. Chem. Soc., Chem. Commun.*, 1991, 1632; for an alternative approach see T. Ogawa, C.-L. Fang, H. Seumune, and K. Sakai, *J. Chem. Soc., Chem. Commun.*, 1991, 1438.

<sup>164</sup> H. P. Knoess, M. T. Furlong, M. J. Rozeman, and P. Knochel, *J. Org. Chem.*, 1991, **56**, 5974.

<sup>165</sup> L. Zhu, R. M. Wehmeyer, and R. D. Rieke, *J. Org. Chem.*, 1991, **56**, 1445.

<sup>166</sup> For an X-ray crystal structure of a zinc aldehyde complex see M. Bochmann, K. J. Webb, M. B. Hursthouse, and M. Mazid, *J. Chem. Soc., Chem. Commun.*, 1991, 1735.

<sup>167</sup> R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 49.

<sup>168</sup> M. Hayashi, T. Kanekp, and N. Oguni, *J. Chem. Soc., Perk. Trans.*, 1, 1991, 25.

<sup>169</sup> K. Soai, Y. Kawase, and A. Oshio, *J. Chem. Soc., Perk. Trans.*, 1, 1991, 1613; S. Niwa, T. Hatanaka, and K. Soai, *J. Chem. Soc., Perk. Trans.*, 1, 1991, 2025; P. Chaloner, E. Langadianou, and S. A. R. Perera, *J. Chem. Soc., Perk. Trans.*, 1, 1991, 2731; for conjugate additions to enones see K. Soai, M. Okudo, and M. Okamoto, *Tetrahedron Lett.*, 1991, **32**, 95.

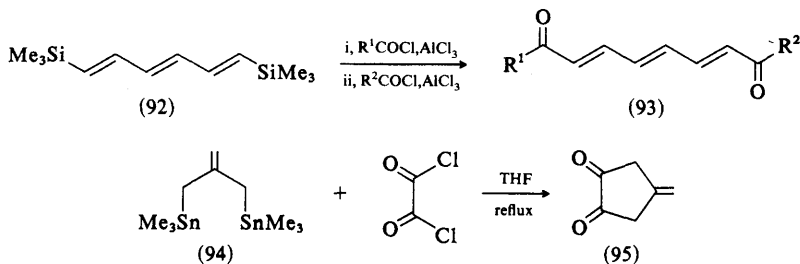
<sup>170</sup> S. Niwa and K. Soai, *J. Chem. Soc., Perk. Trans.*, 1, 1991, 2717; T. Shono, N. Kise, E. Shirakawa, H. Matsumoyo, and E. Okazaki, *J. Org. Chem.*, 1991, **56**, 3063.

<sup>171</sup> B. Schmidt and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 99, 1321; D. Seebach, L. Behrendt and D. Felix, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1008.

<sup>172</sup> S. A. Rao and P. Knochel, *J. Org. Chem.*, 1991, **56**, 4591.

addition to acetylenes,<sup>173</sup> addition-elimination with nitroalkenes<sup>174</sup> and coupling with vinyl halides.<sup>175</sup>

**Allyl Silanes and Stannanes.**<sup>176</sup>—An ultrasonicated mixture of allyl bromide and tin powder in ethanol–water effects diastereoselective addition (threo:erythro approx 5:1) of an allyl group to aldoses with good to excellent yields.<sup>177</sup> Similar results can be obtained with aldehydes and ketones by blending them with allyl bromide<sup>178</sup> or propargyl bromide,<sup>179</sup> zinc and ammonium chloride in a mortar and pestle. The triene disilane (92) was acylated twice in one pot to give a diketotrienes (93)<sup>180</sup> and the distannane (94) reacted with oxalyl chloride in refluxing THF to give the useful cyclopentanone (95).<sup>181</sup>



The addition of alkoxy substituted allyl species<sup>182</sup> to aldehydes<sup>183</sup> and  $\alpha,\beta$  unsaturated ketones<sup>184</sup> has been a major theme this year and some perplexing results have been obtained. Addition of  $\alpha$ -alkoxyallyl silanes and stannanes (96) to aliphatic aldehydes (97a) gives predominantly the *syn E*-isomer (98a), whereas aromatic aldehydes (97b) give the *syn Z*-isomer (99b) with the opposite facial selectivity,<sup>185</sup> which was attributed to diastereomeric boron trifluoride complexes (102), (101).<sup>186</sup> But in general bidentate Lewis acids (e.g.  $\text{TiCl}_4$ )<sup>187</sup> give much better stereoselectivity

<sup>173</sup> S. A. Rao and P. Knochel, *J. Am. Chem. Soc.*, 1991, **113**, 5735; cf. G. Courtemanche and J.-F. Normant, *Tetrahedron Lett.*, 1991, **32**, 5317.

<sup>174</sup> C. Retherford and P. Knochel, *Tetrahedron Lett.*, 1991, **32**, 441.

<sup>175</sup> S. A. Rao and P. Knochel, *J. Org. Chem.*, 1991, **56**, 4593.

<sup>176</sup> V. J. Jephcote and E. J. Thomas, *J. Chem. Soc., Perkin Trans. I*, 1991, 429; see also allyl indiums S. Araki, T. Shimizu, P. S. Johar, S.-J. Jin, and Y. Butsugan, *J. Org. Chem.*, 1991, **56**, 2538; allyl bariums, A. Yanagisawa, S. Habaue, and H. Yamamoto, *J. Am. Chem. Soc.*, 1991, **113**, 8955; and allyl trifluorosilanes Y. Hatanaka, Y. Ebina, and T. Hiyama, *J. Am. Chem. Soc.*, 1991, **113**, 7075.

<sup>177</sup> W. Schmid and G. M. Whitesides, *J. Am. Chem. Soc.*, 1991, **113**, 6674.

<sup>178</sup> K. Tanaka, S. Kishigama, and F. Toda, *J. Org. Chem.*, 1991, **56**, 4333.

<sup>179</sup> J. J. DeVozz, J. F. Jamie, J. T. Blanchfield, M. T. Fletcher, M. G. O'Shea, and W. Kitching, *Tetrahedron*, 1991, **47**, 1985; C. Chen and D. Crich, *J. Chem. Soc., Chem. Commun.*, 1991, 1289.

<sup>180</sup> F. Babudri, V. Fiandanese, and F. Naso, *J. Org. Chem.*, 1991, **56**, 6245.

<sup>181</sup> A. Degl'Innocenti, P. Dembach, A. Mordini, A. Ricci, and G. Seconi, *Synthesis*, 1991, 267.

<sup>182</sup> J. A. Marshall and G. S. Welmaker, *Tetrahedron Lett.*, 1991, **32**, 2101; J. A. Marshall, G. S. Welmaker and B. Gung, *J. Am. Chem. Soc.*, 1991, **113**, 647.

<sup>183</sup> J. A. Marshall and D. V. Yashunsky, *J. Org. Chem.*, 1991, **56**, 5493; J. A. Marshall and G. P. Luke, *J. Org. Chem.*, 1991, **56**, 483.

<sup>184</sup> L. O. Jeroncio, M.-P. Cabal, S. J. Danishefsky, and G. M. Schulte, *J. Org. Chem.*, 1991, **56**, 387.

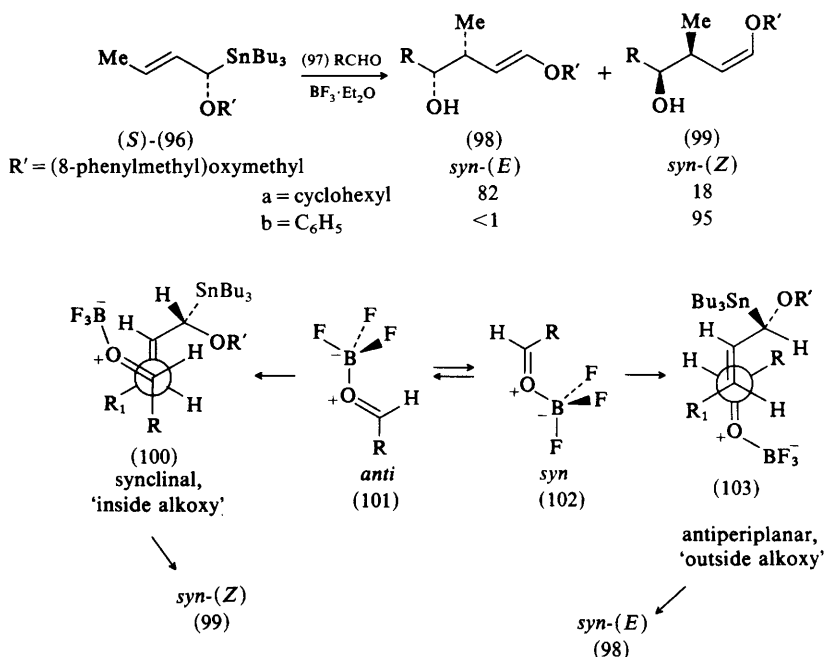
<sup>185</sup> B. W. Gung, D. T. Smith, and M. A. Wolf, *Tetrahedron Lett.*, 1991, **32**, 13; B. W. Gung, A. J. Peat,

B. M. Snook, and D. T. Smith, *Tetrahedron Lett.*, 1991, **32**, 453.

<sup>186</sup> B. W. Gung, *Tetrahedron Lett.*, 1991, **32**, 2867.

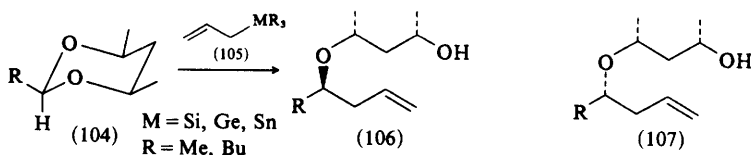
<sup>187</sup> C. Nativi, G. Palio, and M. Taddei, *Tetrahedron Lett.*, 1991, **32**, 1583.

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than moderate Lewis acids (e.g.  $\text{BF}_3$ ), in which the stereocontrol results solely from steric interactions.<sup>188</sup>

The stereoselectivity of ring opening of acetals (104) to (106) and (107) is lower with allyl silanes than allyl stannanes (105)<sup>189</sup> because the acetals undergo reversible ring opening<sup>190</sup> prior to attack of the less reactive allyl silanes.<sup>191</sup> Similar oxonium ion intermediates can be generated *in situ* from aldehydes and trimethylsilyl ethers<sup>192</sup> and the intramolecular reaction has been used for a synthesis of medium ring ethers.<sup>193</sup>



<sup>188</sup> Y. Nishigaichi, A. Takuwa, and A. Jodai, *Tetrahedron Lett.*, 1991, **32**, 2383; J. A. Marshall and X. Wang, *J. Org. Chem.*, 1991, **56**, 3211; 6264.

<sup>189</sup> G. Hagen and H. Mayr, *J. Am. Chem. Soc.*, 1991, **113**, 4954.

<sup>190</sup> S. E. Denmark and N. G. Almstead, *J. Am. Chem. Soc.*, 1991, **113**, 8089.

<sup>191</sup> S. E. Denmark and N. G. Almstead, *J. Org. Chem.*, 1991, **56**, 6458, 6485.

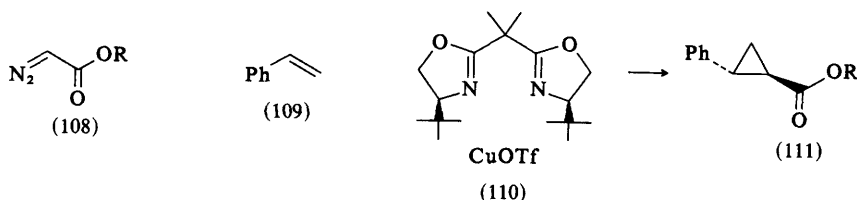
<sup>192</sup> A. Mekhalifa and I. E. Marko, *Tetrahedron Lett.*, 1991, **32**, 4779.

<sup>193</sup> R. Chakraborty and N. S. Simpkins, *Tetrahedron*, 1991, **47**, 7689; for other cyclizations involving imminium ions H. H. Mooiweer, H. Hiemstra, and W. N. Spekamp, *Tetrahedron*, 1991, **47**, 3451; epoxides M. Yoshitake, M. Yamamoto, S. Kohmoto, and K. Yamada, *J. Chem. Soc., Perkin Trans. I*, 1991, 2157, 2161; enones G. Majetich, J.-S. Song, C. Ringold, G. A. Nemeth, and M. G. Newton, *J. Org. Chem.*, 1991, **56**, 3973.

**Cycloadditions.**<sup>194</sup>—[2 + 1]. A stable crystalline carbene has been prepared, it melts at 240–241 °C without decomposition<sup>195</sup> and gives a ‘reverse’ ylide with iodopentafluorobenzene<sup>196</sup> but no reactions with alkenes have been reported thus far. It was anticipated that methoxytrifluoromethylcarbene would be stabilized by a push-pull effect (*cf.* captodative radicals), but in fact it is much more reactive than most other carbenes and fails to discriminate between electron deficient and electron rich alkenes.<sup>197</sup>

Highly reactive Simmons–Smith reagents<sup>198</sup> can be prepared from chloriodomethane and diethylzinc in 1,2 dichloroethane,<sup>199</sup> but the reagents are less stable than in ethereal solvents<sup>200</sup> and less regioselective.<sup>201</sup> This method can also be applied to iodoform, for the generation of iodocarbene.<sup>202</sup>

The metal complex catalysed<sup>203</sup> asymmetric cyclopropanation of alkenes with diazoalkenes is a notoriously difficult reaction. The enantioselectivity is usually poor and *cis/trans* mixtures are produced. Accordingly, most workers have effected double differentiation by using both a chiral catalyst and a chiral diazoester. However, the technology has now progressed sufficiently far that the chirality in the diazoester can be dispensed with<sup>204</sup> although a sterically hindered ester (108) is still required for *trans/cis* selectivity. In the best case, styrene (109) gave 95% of the *trans* cyclopropane (111) (97% ee).<sup>205</sup> Intramolecular cyclopropanation<sup>206</sup> with rhodium catalysts does not seem to suffer from the formation of *cis/trans* mixtures and the enantioselectivities are excellent.<sup>207</sup>



<sup>194</sup> Enantiocontrolled Cycloadditions, ed. L. M. Harwood a ‘symposium in print’, *Tetrahedron: Asymmetry*, 1991, 2, 1173–1444.

<sup>195</sup> A. J. Arduengo III, R. L. Harlow, and M. Kline, *J. Am. Chem. Soc.*, 1991, 113, 361, 2801; M. Regitz, *Angew. Chem., Int. Ed. Engl.*, 1991, 30, 674.

<sup>196</sup> A. J. Arduengo III, M. Kline, J. C. Calabrese, and F. Davidson, *J. Am. Chem. Soc.*, 1991, 113, 9704.

<sup>197</sup> R. A. Moss, T. Zdrojewski and G.-J. Ho, *J. Chem. Soc., Chem. Commun.*, 1991, 946.

<sup>198</sup> S. Durandetti, S. Sibille, and J. Perichon, *J. Org. Chem.*, 1991, 56, 3255.

<sup>199</sup> S. E. Denmark and J. P. Edwards, *J. Org. Chem.*, 1991, 56, 6974.

<sup>200</sup> The crystal structure of bis(iodomethyl) zinc coordinated to a bornane ether has been determined. S. E. Denmark, J. P. Edwards, and S. R. Wilson, *J. Am. Chem. Soc.*, 1991, 113, 723.

<sup>201</sup> E. C. Freidrich and F. Niyati-Shirkhodae, *J. Org. Chem.*, 1991, 56, 2202.

<sup>202</sup> E. V. Dehmloew and J. Suttén, *Tetrahedron Lett.*, 1991, 32, 6105.

<sup>203</sup> Review, M. P. Doyle, *Recl. Trav. Chim. Pays-Bas.*, 1991, 110, 305; for reusable polymer bound rhodium carboxylates see D. E. Bergbreiter, M. Morvant, and B. Chen, *Tetrahedron Lett.*, 1991, 32, 2731.

<sup>204</sup> R. E. Lowenthal and S. Masamune, *Tetrahedron Lett.*, 1991, 32, 7373; some of the structural assignments in this paper have been criticised see D. A. Evans *et al.*, next citation.

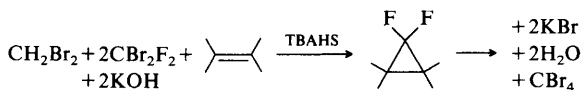
<sup>205</sup> D. A. Evans, K. A. Woerpel, M. M. Hinman, and M. M. Faul, *J. Am. Chem. Soc.*, 1991, 113, 726.

<sup>206</sup> For racemic and achiral examples see J. Adams, C. Lepine-Frenette, and D. M. Spero, *J. Org. Chem.*, 1991, 56, 4494; W. Kirmse and G. Homberger, *J. Am. Chem. Soc.*, 1991, 113, 3925.

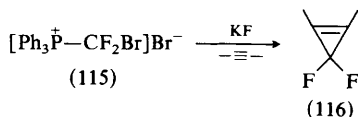
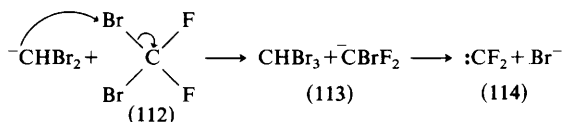
<sup>207</sup> M. P. Doyle, R. J. Peiters, S. F. Martin, R. E. Austin, C. J. Oalman, and P. Muller, *J. Am. Chem. Soc.*, 1991, 113, 1423.

## Synthetic Methods

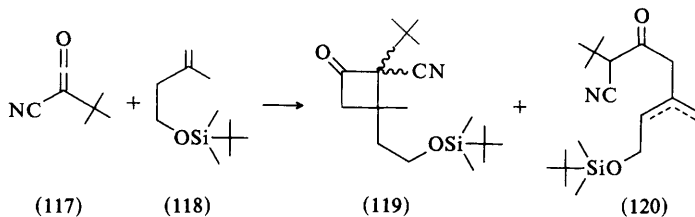
Dichlorocarbene is easily generated under phase transfer conditions by the deprotonation of chloroform with aqueous sodium hydroxide and subsequent elimination of chloride;<sup>208</sup> however, difluorocarbene generated under the same conditions reacts with water, before it can be intercepted by an alkene. Consequently, in an attempt to generate it in the organic bulk phase, dibromomethane anion (112) was used as a halogenophile to generate the difluorobromo anion (113), elimination of bromide gave difluorocarbene (114), which was efficiently trapped by alkenes.<sup>209</sup> Alternatively, treatment of the phosphonium salt (115) with potassium fluoride gives difluorocarbene which was trapped with alkynes to give difluorocyclopropenes (116).<sup>210</sup>



TBAH = tetrabutyl ammonium hydrogen sulfate



[2 + 2], Thermal. Cycloaddition of the cyanoketene (117) to the alkene (118), gave the expected cyclobutanones (119) plus the regioisomeric ene reaction products (120).<sup>211</sup> These were attributed to the anion stabilizing ability of the cyano group<sup>212</sup> which enables a stepwise zwitterionic mechanism to operate.<sup>213</sup> *Ab initio* calculations now favour a  $[\pi 2s + (\pi 2s + \pi 2s)]$  description over the Woodward-Hofmann  $[\pi 2s + \pi 2a]$  mechanism, for ketene-alkene cycloadditions.<sup>214</sup> Whatever the precise



<sup>208</sup> J. D. Winkler and E. A. Gretler, *Tetrahedron Lett.*, 1991, **32**, 5733.

<sup>209</sup> P. Balcerzak, M. Fedorynski, and A. Jonczyk, *J. Chem. Soc., Chem. Commun.*, 1991, 826.

<sup>210</sup> Y. Bessard and M. Schlosser, *Tetrahedron*, 1991, **47**, 7323; H. Burger and S. Sommer, *J. Chem. Soc., Chem. Commun.*, 1991, 456.

<sup>211</sup> A. H. Al-Husaini, M. Muqtar, and Sk. A. Ali, *Tetrahedron*, 1991, **47**, 3845, 7719.

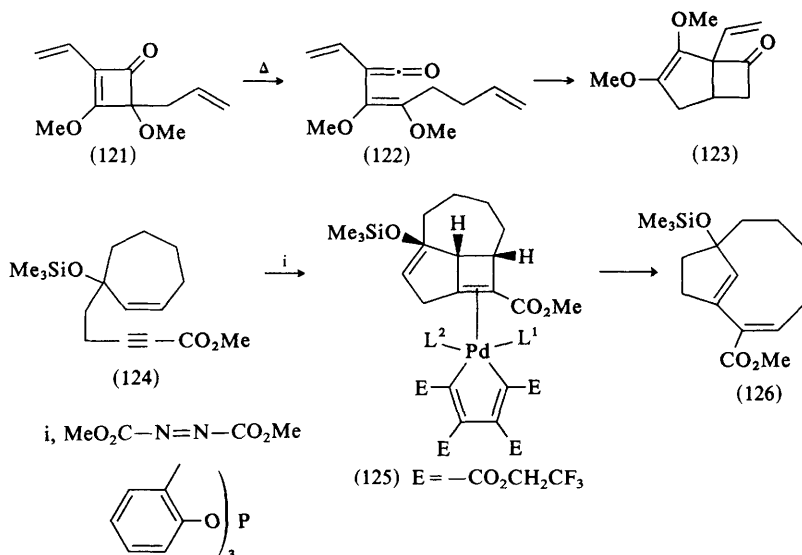
<sup>212</sup> For a general discussion of the effect of substituents on ketene structure see L. Gong, M. A. McAllister, and T. T. Tidwell, *J. Am. Chem. Soc.*, 1991, **113**, 6021.

<sup>213</sup> W. T. Brady and M. M. Dad, *J. Org. Chem.*, 1991, **56**, 6118; T. Gotoh, A. B. Padias, and H. K. Hall, Jr., *J. Am. Chem. Soc.*, 1991, **113**, 1308.

<sup>214</sup> E. T. Seidl and H. F. Schaefer III, *J. Am. Chem. Soc.*, 1991, **113**, 5195.

nature of the transition state it is clearly highly ordered. The addition of oxazolidine substituted ketenes to imines is essentially stereospecific<sup>215</sup> (>97%, absolute stereochemistry unknown) and similarly the cycloaddition of the keteniminium salt gives a single stereoisomer at the bridgehead positions completely overwhelming the stereorandom elements present.<sup>216</sup>

Electrocyclic ring opening of cyclobutenes has been used in two novel ring transformation reactions.<sup>217</sup> Thermolysis of the cyclobutenone (121) gives the vinyl ketene (122) which undergoes cycloaddition to the distal alkene to give (123), a bicyclo[3.2.0]heptanone.<sup>218</sup> Similarly, Trost used palladium catalysed olefin metathesis<sup>219</sup> to give the tricyclic complex (125) which underwent ring opening to give the bicyclo[6.2.1]undecane (126).<sup>220</sup>



The sulfonyl allene framework (127) demonstrates the subtle balance between the [2 + 2] and [4 + 2] cycloaddition pathways.<sup>221</sup> When there is no substituent at C-2 (127a), fast (2 + 2) cycloaddition gives the cyclobutene (128a), whereas with a methyl substituent (127b), slow [4 + 2] cycloaddition gives the decalin (129b).<sup>222</sup>

<sup>215</sup> L. S. Hegedus, J. Montgomery, Y. Narukawa, and D. C. Snustard, *J. Am. Chem. Soc.*, 1991, **113**, 5784; cf. B. C. Borer and D. W. Balogh, *Tetrahedron Lett.*, 1991, **32**, 1039.

<sup>216</sup> L. Chen and L. Ghosez, *Tetrahedron: Asymmetry*, 1991, **2**, 1181.

<sup>217</sup> H. Hesse, *Ring Enlargements in Organic Chemistry*, VCH, Weinheim, 1991.

<sup>218</sup> S. L. Xu, H. Xia, and H. W. Moore, *J. Org. Chem.*, 1991, **56**, 6094.

<sup>219</sup> R. Hertel, J. Mattay, and J. Runsink, *J. Am. Chem. Soc.*, 1991, **113**, 657.

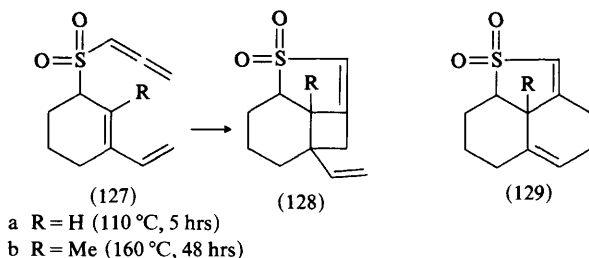
<sup>220</sup> B. M. Trost and M. K. Trost, *J. Am. Chem. Soc.*, 1991, **113**, 1850; for the metal mediated [2 + 2] dimerization of benzene see R. L. Thompson, S. J. Geib, and N. J. Cooper, *J. Am. Chem. Soc.*, 1991, **113**, 8961.

<sup>221</sup> S. J. Getty and W. T. Borden, *J. Am. Chem. Soc.*, 1991, **113**, 4334.

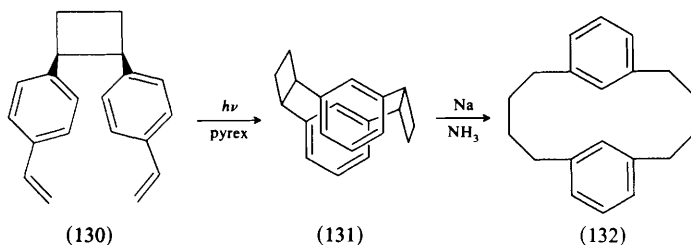
<sup>222</sup> K. Kanematsu, N. Sugimoto, M. Kawaoka, S. Teo, and M. Shiro, *Tetrahedron Lett.*, 1991, **32**, 1351 for intermolecular [2 + 2] cycloadditions to allenes see D. J. Pasto, K. D. Sugi, and J. L. Malandra, *J. Org. Chem.*, 1991, **56**, 3781, 3795; 6216.



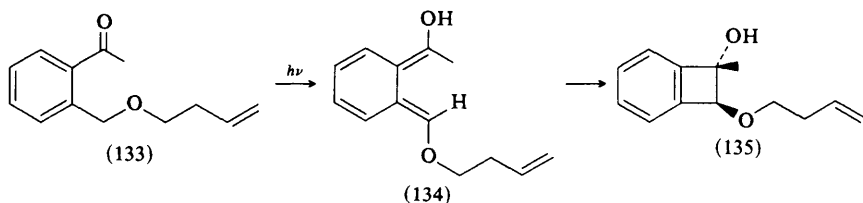
## Synthetic Methods



[2 + 2], *Photochemical*. Photolysis of the *bis*-styrene (130) gave a mixture of all the possible *cis* cyclobutane stereoisomers (131) in low yield, however, the mixture was quantitatively converted to [4.4] metacyclophane (132) by Birch reduction.<sup>223</sup>



Photoenolization of the ketone (133) and thermal ring closure gives the cyclobutenols (135) as single diastereoisomers;<sup>224</sup> in contrast photochemical ring disrotatory opening of cyclobutenes is only partially stereoselective.<sup>225</sup>



The photoaddition<sup>226</sup> of alkenes to enones is particularly useful, because it can give the highly prized *trans* adducts, but the reaction is frequently complicated by isomerization of the alkene. In an attempt to overcome this intramolecular photoaddition of the *Z*-alkene (136) (or the *E*-isomer) was attempted, but an equal amount of diastereomeric products (137) were obtained due to non-stereospecific ring closure of the 1,4 diradical intermediate.<sup>227</sup> The photoaddition of cyclopentene to cyclohexenone gives four adducts (138)–(141) (68 : <1 : 7 : 25), which were isomer-

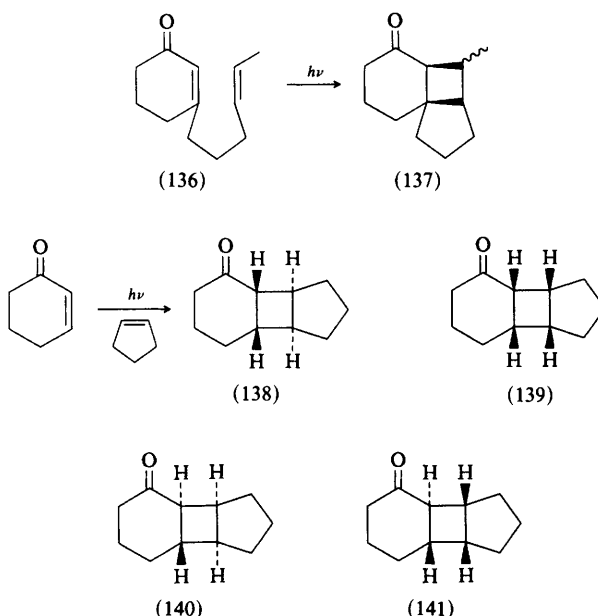
<sup>223</sup> J. Nishimura, Y. Horikoshi, Y. Wada, H. Takahashi, and M. Sato, *J. Am. Chem. Soc.*, 1991, **113**, 3485  
see also K. Nakanishi, K. Mizuno, and Y. Otsuji, *J. Chem. Soc., Chem. Commun.*, 1991, 90.

<sup>224</sup> P. J. Wagner, D. Subrahmanyam, and B.-S. Park, *J. Am. Chem. Soc.*, 1991, **113**, 709.

<sup>225</sup> W. J. Leigh and K. Zheng, *J. Am. Chem. Soc.*, 1991, **113**, 4019.

<sup>226</sup> D. I. Schuster, G. E. Heibel, and J. Woning, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1345.

<sup>227</sup> D. Becker, M. Nagler, Y. Sahali, and N. Haddad, *J. Org. Chem.*, 1991, **56**, 4537.



ized by base to the *cis*-isomers (138), (139) (75:25) in contradiction to an earlier report.<sup>228</sup>

[3 + 2]. The [2 + 2] cycloaddition of  $\alpha,\beta$ -unsaturated ketones and alkenes has been extended in a novel way by placing an alkyne group at the  $\beta$ -position of the enone. 1,5 closure gives the carbene (146) which abstracts hydrogen to give a mixture of dienes or reacts with excess alkene to give a cyclopropane.<sup>229</sup> Reviews have appeared of the addition of diazomethane to nitrogen heterocycles<sup>230</sup> and the Weiss reaction.<sup>231</sup>

[4 + 2]. There have been two major issues in Diels–Alder chemistry this year, the use of novel solvents<sup>232</sup> and enantioselective catalysis.<sup>233</sup> Several reactions including the Diels–Alder reaction are accelerated if run in water<sup>234</sup> or laterly lithium perchlor-

<sup>228</sup> D. I. Schuster, N. Kaprinidis, D. J. Wink, and J. C. Dewan, *J. Org. Chem.*, 1991, **56**, 561.

<sup>229</sup> H.-J. Rathjen, P. Margaretha, S. Wolff, and W. C. Agosta, *J. Am. Chem. Soc.*, 1991, **113**, 3904.

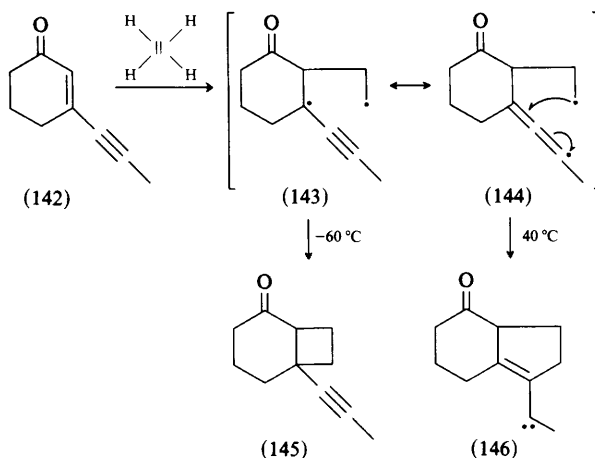
<sup>230</sup> B. Stanovnik, *Tetrahedron*, 1991, **47**, 2925; for other heterocyclic [3 + 2] cycloadditions see A. Ando, M. Kato, and T. Akasaka, *J. Am. Chem. Soc.*, 1991, **113**, 6286; T. Hudlicky and G. Barbieri, *J. Org. Chem.*, 1991, **56**, 4598; H. H. Karsch, K. Zellner, and G. Muller, *J. Chem. Soc., Chem. Commun.*, 1991, 466; P. J. Smith, D. J. Soose, and C. S. Wilcox, *J. Am. Chem. Soc.*, 1991, **113**, 7412; P. A. Wender and J. L. Mascarenas, *J. Org. Chem.*, 1991, **56**, 6267.

<sup>231</sup> A. K. Gupta, X. Fu, J. P. Synder, and J. M. Cook, *Tetrahedron*, 1991, **47**, 3665; for other carbocyclic [3 + 2] annulations see F. Fellga, P. Nitti, G. Pitacco, and E. Valentin, *J. Chem. Soc., Perk. Trans. I*, 1991, 1645; J. Boivin, C. Tailhan, and S. Z. Zard, *J. Am. Chem. Soc.*, 1991, **113**, 5874; D. A. Singleton, C. C. Huval, K. M. Church, and E. S. Priestly, *Tetrahedron Lett.*, 1991, **32**, 5765; M. P. Collins, J. Mann, N. Capps, and H. Finch, *J. Chem. Soc., Perk. Trans. I*, 1991, 239.

<sup>232</sup> C. Reichardt, 'Solvents and Solvent Effects in Organic Synthesis', VCH, Weinheim, 1988.

<sup>233</sup> K. Naraska, *Synthesis*, 1991, 1.

<sup>234</sup> R. Breslow, *Acc. Chem. Res.*, 1991, **24**, 159; W. Blokzijl, M. J. Blandamer, and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, 1991, **113**, 4241; A. Lubineau, J. Auge, and N. Lubin, *Tetrahedron Lett.*, 1991, **32**, 7529; I. Hunt and C. D. Johnson, *J. Chem. Soc., Perk. Trans. II*, 1991, 1051.



ate-diethyl ether.<sup>235</sup> This has been attributed to solvoconstriction (hydrophobic effect); the forcing together of the reactants by the cohesive forces between the water molecules,<sup>236</sup> hydrogen bonding,<sup>237</sup> and catalysis by lithium ions.<sup>238</sup> Similar effects are claimed for the surface of clay<sup>239</sup> (in non-aqueous solvents).

The current strength of chiral Diels-Alder technology can be demonstrated by three syntheses of the prostaglandin intermediate (149). Corey<sup>240</sup> used the achiral amide (148a) and either of two chiral catalysts (150)<sup>241</sup> (151)<sup>242</sup> and in both cases obtained the endo adduct (149) (>95% endo, >95% ee). Whereas Arai used the chiral ester (148b) and titanium tetrachloride<sup>243</sup> as catalyst and obtained essentially identical results (endo adduct only, de 95%).<sup>244</sup>

$\alpha$ -Methylene  $\beta$ -lactones (152)<sup>245</sup> are versatile substitutes<sup>246</sup> for allenes.<sup>247</sup> They

<sup>235</sup> P. A. Greico, *Aldrichimica Acta*, 1991, **24**, 59; H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1306; P. A. Greico, R. J. Cooke, K. J. Henry, and J. M. VanderRoest, *Tetrahedron Lett.*, 1991, **32**, 4665; P. A. Greico, J. D. Clark, and C. T. Jagoe, *J. Am. Chem. Soc.*, 1991, **113**, 5488; A. Thaler, D. Seebach, and F. Cardinoux, *Helv. Chim. Acta*, 1991, **74**, 617, 628.

<sup>236</sup> R. Brewlow and C. J. Rizzo, *J. Am. Chem. Soc.*, 1991, **113**, 4340.

<sup>237</sup> J. F. Blake and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1991, **113**, 7430.

<sup>238</sup> M. A. Forman and W. P. Dailey, *J. Am. Chem. Soc.*, 1991, **113**, 2761; G. Desimoni, G. Faiti and P. P. Righetti, *Tetrahedron*, 1991, **47**, 5857; G. Desimoni, G. Faita, P. P. Righetti, and G. Tacconi, *Tetrahedron*, 1991, **47**, 8399; D. A. Smith, and K. N. Houk, *Tetrahedron Lett.*, 1991, **32**, 1549.

<sup>239</sup> C. Collet and P. Laszlo, *Tetrahedron Lett.*, 1991, **32**, 2905.

<sup>240</sup> For closely related studies using other catalysts see E. J. Corey, N. Imai, and H.-Y. Zhang, *J. Am. Chem. Soc.*, 1991, **113**, 728; E. J. Corey and T.-P. Loh, *J. Am. Chem. Soc.*, 1991, **113**, 8966.

<sup>241</sup> E. J. Corey, N. Imai, and S. Pikul, *Tetrahedron Lett.*, 1991, **32**, 7517; for borane based catalysts and auxiliaries see J. M. Hawkins and S. Loren, *J. Am. Chem. Soc.*, 1991, **113**, 7794; X. Wang, *J. Chem. Soc., Chem. Commun.*, 1991, 1515.

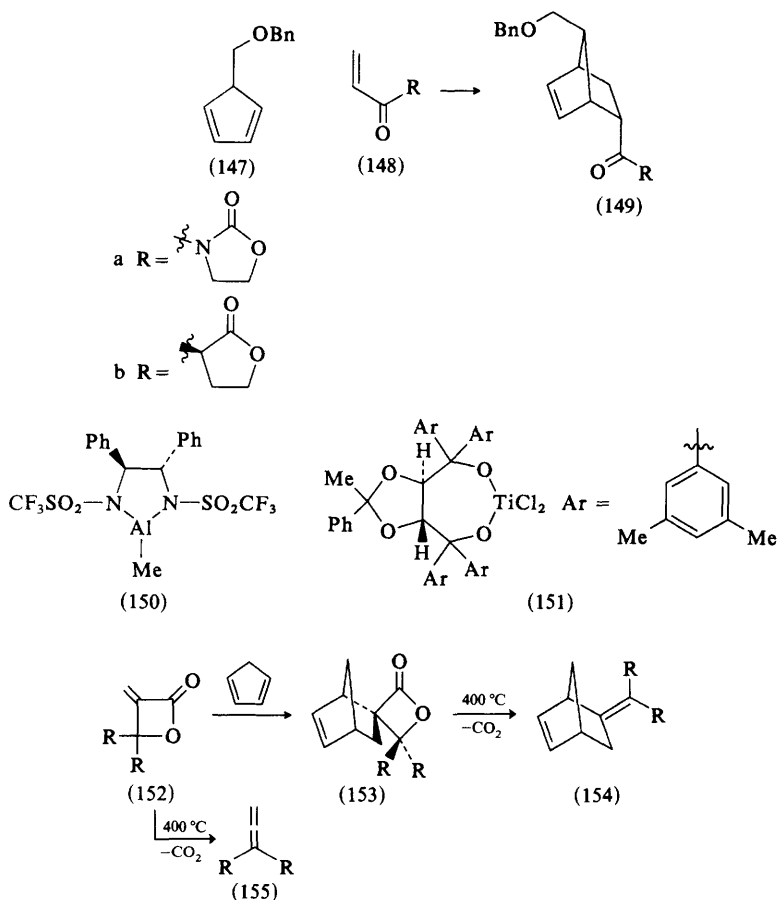
<sup>242</sup> E. J. Corey and Y. Matsumura, *Tetrahedron Lett.*, 1991, **32**, 6289; for the use of this catalyst with 1,4 benzoquinones see T. A. Enger, M. A. Letavic, and J. P. Reddy, *J. Am. Chem. Soc.*, 1991, **113**, 5068; and BINOL titanium dichloride M. Terada, K. Mikami, and T. Nakai, *Tetrahedron Lett.*, 1991, **32**, 935.

<sup>243</sup> R. C. Corcoran and J. Ma, *J. Am. Chem. Soc.*, 1991, **113**, 8973.

<sup>244</sup> K. Miyaji, Y. Ohara, T. Tabahashi, T. Tsuruda, and K. Arai, *Tetrahedron Lett.*, 1991, **32**, 4557.

<sup>245</sup> W. Adams, R. Albert, N. D. Grau, L. Hasemann, B. Nestler, E.-M. Peters, K. Peters, F. Prechtel, and H. G. von Schnering, *J. Org. Chem.*, 1991, **56**, 5778.

<sup>246</sup> For the use of vinyl sulfoxides as allene equivalents see R. V. Williams and K. Chauhan, *J. Chem. Soc., Chem. Commun.*, 1991, 1672 or as acetylene equivalents see A. Sekiguchi, I. Maruki, E. Ebata, C. Kabuto, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 1991, 341.



readily undergo cycloaddition and cleanly generate either allenes (155) or alkenes (154), albeit at high temperatures.<sup>248</sup>

The furan (156) undergoes cycloaddition with ethyl acrylate<sup>249</sup> at room temperature to yield (157) whereas the phorbol precursor (158) required 19 kbar pressure<sup>250</sup> to produce (159), but with a shorter tether, cyclization occurred so readily that the open chain compound (160) could not be isolated.<sup>251</sup>

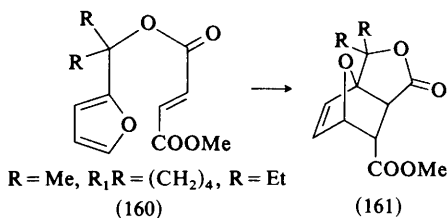
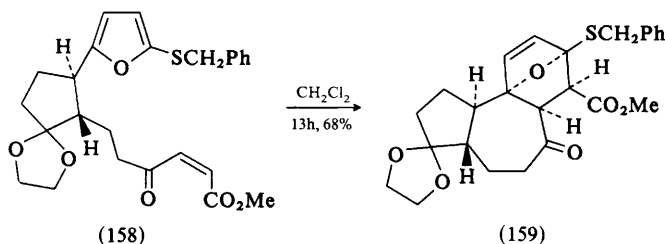
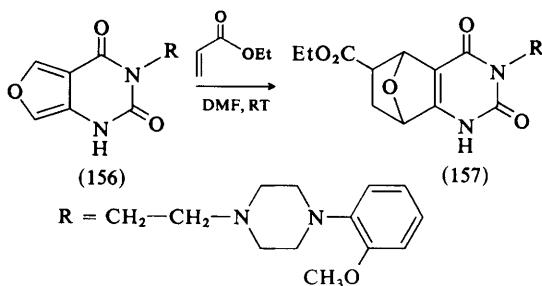
<sup>247</sup> D. L. Boger and M. Zhang, *J. Am. Chem. Soc.*, 1991, **113**, 4230.

<sup>248</sup> W. Adam, R. Albert, L. Hasemann, V. O. N. Salgado, B. Nestler, E.-M. Peters, K. Peters, F. Precht, and H. G. von Schnering, *J. Org. Chem.*, 1991, **56**, 5782.

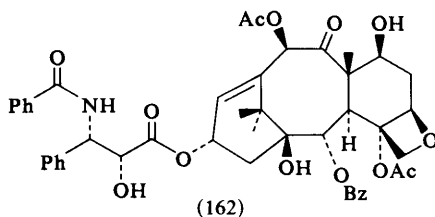
<sup>249</sup> J. J. McNally and J. B. Press, *J. Org. Chem.*, 1991, **56**, 245; K. Ando, N. Akadegawa, and H. Takayama, *J. Chem. Soc., Chem. Commun.*, 1991, 1765.

<sup>250</sup> L. M. Harwood, T. Ishikawa, H. Phillips, and D. Watkin, *J. Chem. Soc., Chem. Commun.*, 1991, 527 for other examples of high pressure Diels-Alder reactions see R. W. M. Aben, L. Minuti, H. W. Scheeren, and A. Taticchi, *Tetrahedron Lett.*, 1991, **32**, 6445; V. Branchadell, M. Sodupe, R. M. Ortuno, A. Oliva, D. Gomez-Pardo, A. Guingant, and J. d'Angelo, *J. Org. Chem.*, 1991, **56**, 4135.

<sup>251</sup> M. E. Jung and J. Gervay, *J. Am. Chem. Soc.*, 1991, **113**, 224; see also A. P. Kozikowski and W. Tuckmantel, *J. Org. Chem.*, 1991, **56**, 2826.

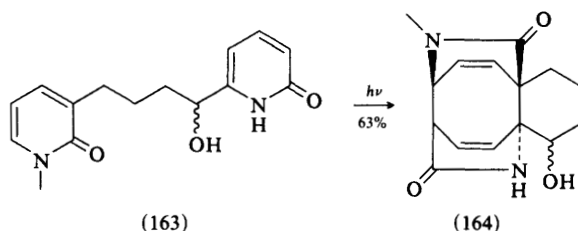


**Other Cycloadditions.**—The nature of the current frontier in organic synthesis is well illustrated by Taxol (162).<sup>252</sup> It is obtained in very small quantities from yew bark and has exciting anti-tumour and anti-leukaemic activity. There are no particularly bizarre functional groups present; it is the number of groups and their cocatination that poses the problem. Moreover, synthesis of a few milligrams has no practical value. Kilograms are required for clinical studies. An interesting approach to the fused central bicycle uses the [4 + 4] photodimerization of bis-pyridones (163), to give (164), which installs four new chiral centres.<sup>253</sup> There have

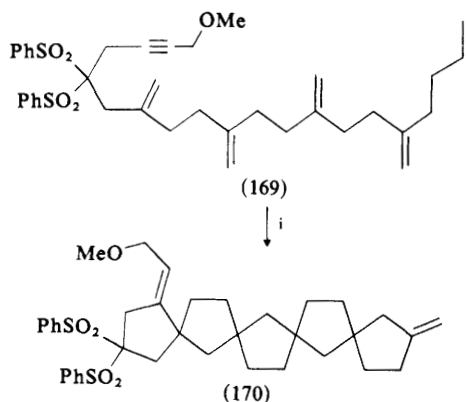
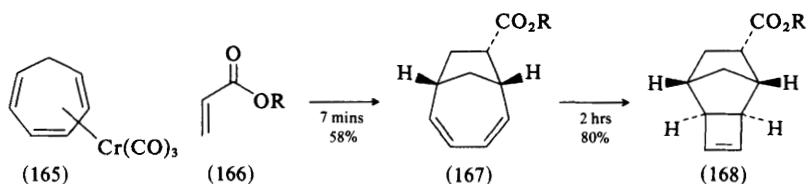


<sup>252</sup> S. Bleichert and A. Kleine-Klausning, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 412; J.-N. Denis, A. Correa, and A. E. Greene, *J. Org. Chem.*, 1991, **56**, 6939.

<sup>253</sup> S. McN. Sieburth and J. Chen, *J. Am. Chem. Soc.*, 1991, **113**, 8163.



only been sporadic reports of [6 + 2] cycloadditions, but by photolysing a chromium(o) tricarbonyl triene complex (165) in the presence of an electron deficient diene (166), good yields of the deligated adduct (167) can be obtained (36–93%) and prolonged photolysis gives the cyclobutene (168).<sup>254</sup> The two previous examples



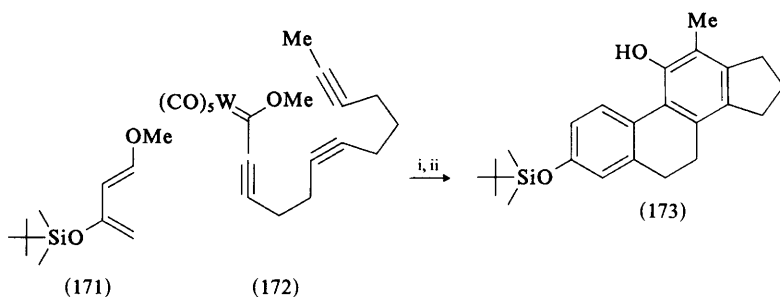
2.5 mol% (dba)<sub>3</sub>Pd<sub>2</sub>CHCl<sub>3</sub>, 10 mol% Ph<sub>3</sub>Sb, 10 mol% AcOH, 86% yield

demonstrate the rapid elaboration of complexity that can be achieved by cycloaddition. Other vivid examples are provided by Trost's synthesis of five rings (170) in a single step, from (169), by what he terms 'polyolefin polycycloisomerization' using palladium catalysis<sup>255</sup> and the construction of the entire steroid ring system (173) by Diels–Alder reaction (171), (172) (ring A), carbonylation, and electrocyclic ring closure (ring C).<sup>256</sup>

<sup>254</sup> J. H. Rigby and J. A. Henshilwood, *J. Am. Chem. Soc.*, 1991, **113**, 5122.

<sup>255</sup> B. M. Trost, *Janssen Chimica Acta*, 1991, **9**(1), 3; B. M. Trost and Y. Shi, *J. Am. Chem. Soc.*, 1991, **113**, 701.

<sup>256</sup> J. Bao, V. Dragisich, S. Wenglowky, and W. D. Wulff, *J. Am. Chem. Soc.*, 1991, **113**, 9873.

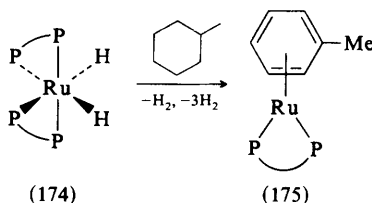


Reagents: i,  $\text{CH}_3\text{CN}$ ,  $\text{CO}$ ,  $25^\circ\text{C}$ , 16 h; ii,  $110^\circ\text{C}$ , 23 h

Scheme 2

### 3 Functional Group Manipulation

**Oxidation.—Hydroxylation.** It would be highly desirable to be able to emulate the ability of micro-organisms to introduce a functional group at a remote unfunctionalized carbon centre. Progress in this area has been slow, but practically useful methodology has been achieved. Ruthenium tetroxide selectively oxidizes<sup>257</sup> adamantane to 1-adamantanol in 62% yield with no isomeric contaminants.<sup>258</sup> Metal insertion into unactivated C–H occurs *via* a concerted C–H oxidative addition pathway<sup>259</sup> which may be followed by oxygen insertion,<sup>260</sup> C–C bond cleavage,<sup>261</sup> or by hydrogen elimination. The power of this technology is demonstrated by the elimination of 3 moles of molecular hydrogen from methylcyclohexane by the ruthenium complex (174) to give (175).<sup>262</sup>



<sup>257</sup> For general reviews of methane and hydrocarbon oxidation, H. Schwarz, *Angew. Chem., Int. Ed. Engl.*, 1991, 820; K. Eller and H. Schwarz, *Chem. Rev.*, 1991, 91, 1121; D. H. R. Barton and D. Doller, *Coll. Czech. Chem. Commun.*, 1991, 45, 984; *idem*, *Pure Appl. Chem.*, 1992, 63, 1567. A comprehensive description of Barton's work in this area was given in last years Annual Report.

<sup>258</sup> J. M. Bakke and J. E. Braenden, *Acta Chem. Scand.*, 1991, 45, 418; for a similar iodosyl benzene oxidation catalysed by a manganese complex, C.-M. Che, W.-T. Tang, K.-Y. Wong, W.-T. Wong, and T.-F. Lai, *J. Chem. Res.*, 1991, (S) 30, (M) 401; osmium trichloride, S.-I. Murahashi, T. Sato, T. Naota, H. Kumobayashi, and S. Akutagawa, *Tetrahedron Lett.*, 1991, 32, 2145; a binuclear iron complex, N. Kitajima, M. Ito, H. Fukui, and Y. Moro-oka, *J. Chem. Soc., Chem. Commun.*, 1991, 102.

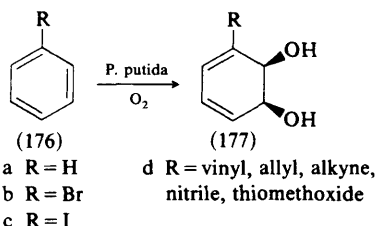
<sup>259</sup> M. R. A. Blomberg, P. E. M. Siegbahn, U. Nagashima, and J. Wennerberg, *J. Am. Chem. Soc.*, 1991, 113, 424.

<sup>260</sup> L.-C. Kao, A. C. Hutsoj, and A. Sen, *J. Am. Chem. Soc.*, 1991, 113, 700.

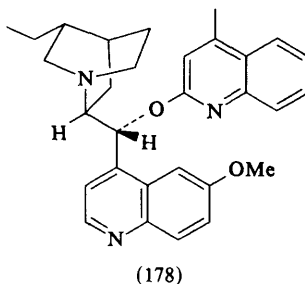
<sup>261</sup> P. A. M. van Koppen, J. Brodbelt, M. T. Bowers, D. V. Dearden, J. L. Beauchamp, E. R. Fischer, and P. B. Armentrout, *J. Am. Chem. Soc.*, 1991, 113, 2359.

<sup>262</sup> J. D. Koola and D. M. Roddick, *J. Am. Chem. Soc.*, 1991, 113, 1450.

The efficient conversion of benzene derivatives<sup>263</sup> to enantiomerically pure<sup>264</sup> cis-benzene glycols (177b-d) by *Pseudomonas putida* is still unmatched by abiotic chemical synthesis. Most functional groups are tolerated at C-1, but those that are not (177d) can be introduced by substitution of the bromo (176b) or iodo compounds (176c) using the requisite stannane under palladium catalysis.<sup>265</sup> The plane of symmetry in the meso-diol (176a) is removed by enantioselective galactosyl transfer using *E. coli*  $\beta$ -galactosidase<sup>266</sup> or by *P. cepacia* lipase catalysed hydrolysis of a tetrol derivative.<sup>267</sup>



**Dihydroxylation.** The cinchona alkaloid catalysed, osmium tetroxide dihydroxylation of alkenes can now be applied to terminal alkenes<sup>268</sup> by using a new rate enhancing ligands (e.g., 178),<sup>269</sup> which seem to be evolving towards a BINAP type structure. The increased reactivity allows as little as 0.5 mol% of osmium tetroxide (or the safer potassium osmate(vi) dihydrate) to be used with potassium ferricyanide as reoxidant.<sup>270</sup> The diene (179) undergoes diastereoselective hydroxylation to give the syn, anti tetrol (180) (94%) and the syn, syn stereoisomer (5%).<sup>271</sup>



<sup>263</sup> For applications of this micro-organism to other aromatics see D. R. Boyd, D. R. Bushman, R. J. H. Davis, M. R. J. Dorrity, L. Hamilton, D. M. Jerrina, W. Levin, J. J. McCullough, R. A. S. McMordie, J. F. Malone, and H. P. Porter, *Tetrahedron Lett.*, 1991, **32**, 2963; D. R. Boyd, N. D. Sharma, P. J. Stevenson, J. Chima, D. J. Gray, and H. Dalton, *Tetrahedron Lett.*, 1991, **32**, 3887.

<sup>264</sup> D. R. Boyd, M. R. J. Dorrity, M. V. Hand, J. F. Malone, N. D. Sharma, H. Dalton, D. J. Gray, and G. N. Sheldrake, *J. Am. Chem. Soc.*, 1991, **113**, 666.

<sup>265</sup> D. R. Boyd, M. V. Hand, N. D. Sharma, J. Chimica, H. Dalton, and G. N. Sheldrake, *J. Chem. Soc., Chem. Commun.*, 1991, 1630.

<sup>266</sup> D. H. G. Crout, D. A. MacManus, and P. Critchley, *J. Chem. Soc., Chem., Commun.*, 1991, 376.

<sup>267</sup> C. R. Johnson, P. A. Ple, and J. P. Adams, *J. Chem. Soc., Chem. Commun.*, 1991, 1006; cf. H. A. J. Carless and O. Z. Oak, *J. Chem. Soc., Chem. Commun.*, 1991, 61.

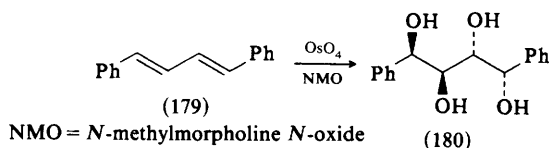
<sup>268</sup> K. B. Sharpless, W. Amberg, M. Beller, H. Chen, J. Hartung, Y. Kawanami, D. Lubben, E. Manoury, Y. Ogino, T. Shibata, and T. Ukita, *J. Org. Chem.*, 1991, **56**, 4585.

<sup>269</sup> Y. Ogino, H. Chen, E. Manoury, T. Shibata, M. Beller, D. Lubben, and K. B. Sharpless, *Tetrahedron Lett.*, 1991, **32**, 5761.

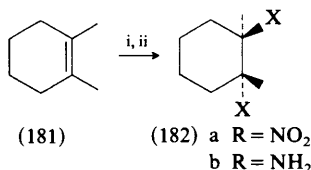
<sup>270</sup> Y. Ogino, H. Chen, J.-L. Kwong, and K. B. Sharpless, *Tetrahedron Lett.*, 1991, **32**, 3965.

<sup>271</sup> C. Y. Park, B. M. Kim, and K. B. Sharpless, *Tetrahedron Lett.*, 1991, **32**, 1003; cf. M. Burdisso, R. Gandolfi and A. Rastelli, *Tetrahedron Lett.*, 1991, **32**, 2659.





The dihydroxylation (and cleavage) of alkenes by permanganate is entirely suppressed by the addition of oxalyl chloride, and *trans* vicinal dichlorides are formed instead.<sup>272</sup> Stereospecific *trans* addition of dinitrogen tetroxide to dimethyl cyclohexene (181) gives the dinitro adduct (182a) which is readily reduced to the diamine (182b, Scheme 3).<sup>273</sup>



Reagents: i, N<sub>2</sub>O<sub>4</sub>, Et<sub>2</sub>O; ii, H<sub>2</sub>, RhCl(PPh<sub>3</sub>)<sub>3</sub>

**Scheme 3**

**Epoxidation.** A general method for the enantioselective epoxidation of unfunctionalized alkenes<sup>274</sup> continues to be elusive. The observation that cytochrome P450<sub>cam</sub> (which has an iron porphyrin prosthetic group) and related systems are capable of epoxidation of alkenes, prompted the synthesis of model systems based on manganese<sup>275</sup> and iron porphyrins.<sup>276</sup> But, unfortunately, most of the abiotic systems require aggressive regenerating reagents such as sodium hypochlorite (bleach), peroxides or ozones which damage the porphyrin<sup>277</sup> and frequently the stereochemistry of the alkene is scrambled during epoxidation. The 'natural' substrate for Cytochrome P450<sub>cam</sub> is camphor, but other substrates are accepted. For example *cis*- $\beta$ -styrene is epoxidized with retention of alkene stereochemistry in 78% enantiomeric excess<sup>278</sup> and an essentially identical result has been obtained using an abiotic tetraphenyl porphyrin with D<sub>4</sub> symmetry.<sup>279</sup> The most generally useful catalysts at present are those based on manganese(III) di-imine complexes<sup>280</sup> (183).  $\beta$ -Methyl styrene is epoxidized with good stereoselectivity (92% ee, 81% yield) and uniquely for these systems the electron deficient alkene *cis*-methyl cinnamate also gives good results (89% ee, 65% yield).<sup>281</sup> Non-metallic reagents in this area are

<sup>272</sup> I. E. Marko and P. F. Richardson, *Tetrahedron Lett.*, 1991, **32**, 1831.

<sup>273</sup> W. Zhang and E. N. Jacobsen, *Tetrahedron Lett.*, 1991, **32**, 1711; for the synthesis of vicinal diamines from diols see R. Oi and K. B. Sharpless, *Tetrahedron Lett.*, 1991, **32**, 999.

<sup>274</sup> Review; C. Bom, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 403.

<sup>275</sup> S. Campestrini, A. Robert, and B. Meunier, *J. Org. Chem.*, 1991, **56**, 3725.

<sup>276</sup> G.-X. He and T. C. Bruice, *J. Am. Chem. Soc.*, 1991, **113**, 2747.

<sup>277</sup> For the use of *t*-amine *N*-oxides in place of hydrogen peroxide see A. M. d'A. R. Gonsalves, R. A. W. Johnstone, M. M. Pereira, and J. Shaw, *J. Chem. Soc., Perkin Trans. I*, 1991, 645; R. Ire, Y. Ito, and T. Katsuki, *SYNLETT*, 1991, 266.

<sup>278</sup> P. R. Ortiz de Montellano, J. A. Fruetel, J. R. Collins, D. L. Camper, and G. H. Loew, *J. Am. Chem. Soc.*, 1991, **113**, 3195.

<sup>279</sup> R. L. Halterman and S.-T. Jan, *J. Org. Chem.*, 1991, **56**, 5253.

<sup>280</sup> Review of C2 diamines as chiral catalysts, C. Bolm, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 542.

<sup>281</sup> E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, and L. Deng, *J. Am. Chem. Soc.*, 1991, **113**, 7063; W. Zhang and E. N. Jacobsen, *J. Org. Chem.*, 1991, **56**, 2296.



The Katsuki–Sharpless rules for enantioselective epoxidation (Figure 1)<sup>283</sup> have remained essentially unbreached for the past 11 years, but an exception has now been found. The combination of allylic and homoallylic hydroxyl groups in the

b  $R = Bn$ 

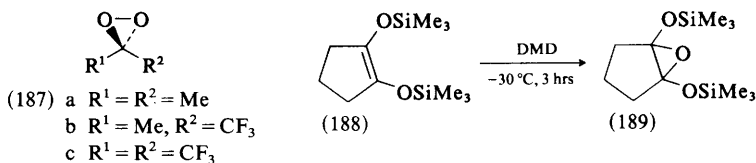
<sup>285</sup> S. Takano, Y. Iwabuchi, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1991, 820; S. Takano, Y. Iwabuchi, and K. Ogasawara, *J. Am. Chem. Soc.*, 1991, 113, 2786.

## Synthetic Methods

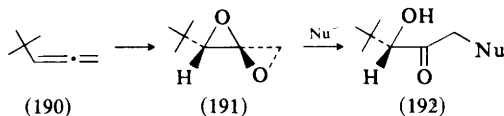
spawned a wealth of new methodology for the functionalization of epoxy alcohols<sup>286</sup> and in particular the 'parent epoxy alcohol' glycidol.<sup>287</sup>

For those rare cases where it is simply not possible to make the epoxide enantiomerically pure, Julia has developed a resolution technique in which the epoxide undergoes ring opening with dimethyl sulfide to give sulfonium salts which are resolved as dibenzoyl tartrate sulfonium salts. Base treatment regenerates the original epoxides.<sup>288</sup>

The dioxiranes (187a-c)<sup>289</sup> are the most mild, efficient, reagents available for the epoxidation of alkenes<sup>290</sup> and this has enabled the synthesis of epoxides of unprecedented reactivity. Electron donating groups and ring strain both greatly increase the reactivity of epoxides, but using DMD even two oxygen substituents (188) are



tolerated<sup>291</sup> and the previously unknown flavonoid epoxides,<sup>292</sup> benzofuran epoxides,<sup>293</sup> and fulvene endocyclic epoxides<sup>294</sup> have been isolated. Similarly, lithio enolates are converted to  $\alpha$ -hydroxy ketones<sup>295</sup> and phenols to orthoquinones.<sup>296</sup> Perhaps the most stunning application has been the stereoselective conversion of allenes (190) to crystalline spiro-epoxides (191), which undergo regioselective  $S_N2$  substitution (192).<sup>297</sup> Treatment of the cyclopropene (193a) with peracid<sup>298</sup> gives the fused epoxycyclopropane (194), which rapidly rearranges to an alkene, which in turn undergoes a further epoxidation (195), in contrast dimethyl dioxirane has



<sup>286</sup> Conversion of epoxy alcohols: to aldols, K. Maruoka, J. Sato, and H. Yamamoto, *J. Am. Chem. Soc.*, 1991, **113**, 5449; 2,3-epoxy-1,4-butanediols, Y. Aoyama, H. Urabe and F. Sato, *Tetrahedron Lett.*, 1991, **32**, 6731; triols by kinetic resolution A. Ishikawa and T. Katsuki, *Tetrahedron Lett.*, 1991, **32**, 3547; enantiomeric epoxy alcohols, V. Jager, D. Schroter, and B. Koppenhoefer, *Tetrahedron*, 1991, **47**, 2195.

<sup>287</sup> Review of applications of glycidol R. M. Hanson, *Chem. Rev.*, 1991, **91**, 437.

<sup>288</sup> B. Cimetiere, L. Jacob, and M. Julia, *Bull. Soc. Chim. Fr.*, 1991, **128**, 926.

<sup>289</sup> W. Adam, S. E. Bottle, and R. Melo, *J. Chem. Soc., Chem. Commun.*, 1991, 770; W. Adam, R. Curci, M. E. G. Nunez, and R. Mello, *J. Am. Chem. Soc.*, 1991, **113**, 7654.

<sup>290</sup> Mechanism; R. W. Murray, D. L. Shiang, and M. Singh, *J. Org. Chem.*, 1991, **56**, 3677; A. Messeguer, F. Sanchez-Baeza, J. Casas and B. D. Hammock, *Tetrahedron*, 1991, **47**, 1291.

<sup>291</sup> W. Adam, L. Hadjirapoglou, and X. Wang, *Tetrahedron Lett.*, 1991, **32**, 1295.

<sup>292</sup> W. Adam, D. Golsch, L. Hadjirapoglou, and T. Patonay, *Tetrahedron Lett.*, 1991, **32**, 1041.

<sup>293</sup> W. Adam, L. P. Hadjirapoglou, T. Mosandl, C. R. Saha-Moller, and D. Wild, *J. Am. Chem. Soc.*, 1991, **113**, 8005; furan epoxides rearrange to 1,4 enediones before isolation B. M. Adger, C. Barrett, J. Brennan, M. A. McKervery, and R. W. Murray, *J. Chem. Soc., Chem. Commun.*, 1991, 1553.

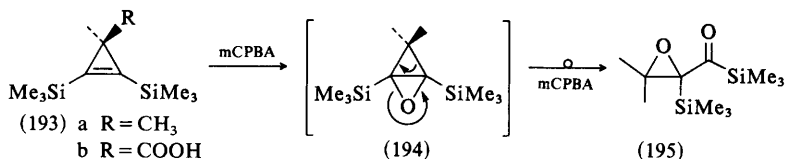
<sup>294</sup> W. Adam, L. P. Hadjirapoglou, and A. Meffert, *Tetrahedron Lett.*, 1991, **32**, 6697.

<sup>295</sup> K. R. Guertin and T.-H. Chan, *Tetrahedron Lett.*, 1991, **32**, 715.

<sup>296</sup> J. K. Crandall, M. Zucco, R. S. Kirsch, and D. M. Coppert, *Tetrahedron Lett.*, 1991, **32**, 5441.

<sup>297</sup> J. K. Crandall, D. J. Batal, D. P. Sebestra, and F. Lin, *J. Org. Chem.*, 1991, **56**, 1153.

<sup>298</sup> K. W. Wood and P. Beak, *J. Am. Chem. Soc.*, 1991, **113**, 6281; R. D. Bach, A. L. Owensby, C. Gonzalez, H. B. Schlegel, and J. J. W. McDouall, *J. Am. Chem. Soc.*, 1991, **113**, 2338.



no effect on the alkene bond and instead oxidizes a methyl group to a carboxylic acid (193b).<sup>299</sup> The oxidation of alcohols to ketones and carboxylic acids implicit in this reaction has been developed into a synthetically useful procedure using trifluoromethylmethyl dioxirane[b]<sup>300</sup> and goes by a mechanism in which oxygen is inserted directly into the  $\alpha$  C-H bond.<sup>301</sup> Dioxiranes also oxidize other heteroatom bonds. Diazoketones are converted to  $\alpha$ -ketoaldehydes,<sup>302</sup> hindered oxazolidines to hydroxyamines,<sup>303</sup> and arenes can be released from chromium tricarbonyl arene complexes.<sup>304</sup>

**Reduction.—Heterogeneous Hydrogenation.**<sup>305</sup> It is common knowledge that the reduction of alkenes on noble metal catalysts results from the *cis* addition of surface bound hydrogen to the less hindered side of the alkene,<sup>306</sup> but beyond this almost nothing else is known. Whitesides has shown that soluble platinum alkene complexes are reduced on platinum black with incorporation of deuterium with retention of configuration of the platinum alkene bonds. If metathesis of the alkene between the 'soluble' platinum and the platinum surface also proceeds with retention of configuration then the reduction must also occur with overall retention of stereochemistry.<sup>307</sup> The incorporation of excess deuterium or tritium in saturated groups during reduction of alkenes is a common problem and a new system using platinum black in deuterium oxide and THF reduces cycloalkenes to predominantly the perdeuteroalkanes, *e.g.* cyclodecene was converted to C<sub>10</sub>D<sub>20</sub> in 60% yield.<sup>308</sup> The mechanism for this process probably involves a  $\pi$ -allyl or alkyl platinum complex similar to that implicated in the montmorillonite-diphenylphosphine palladium(II)<sup>309</sup> reduction of 1,4-butyne-diol to *cis*-butene-1,4-diol and isomerization to 2-hydroxytetrahydrofuran.<sup>310</sup> Rieke zinc, prepared from zinc bromide and potassium, reduces alkynes to *cis* alkenes,<sup>311</sup> without using hydrogen!<sup>312</sup>

<sup>299</sup> G. D. Maynard and L. A. Paquette, *J. Org. Chem.*, 1991, **56**, 5480.

<sup>300</sup> R. Mello, L. Cassidei, M. Fiorentino, C. Fusco, W. Hummer, V. Jager, and R. Curci, *J. Am. Chem. Soc.*, 1991, **113**, 2205.

<sup>301</sup> B. A. Marples, J. P. Muxworthy, and K. H. Baggeley, *Tetrahedron Lett.*, 1991, **32**, 533.

<sup>302</sup> H. Ihmels, M. Maggini, M. Prato, and G. Scorrano, *Tetrahedron Lett.*, 1991, **32**, 6215.

<sup>303</sup> C. Bonvalet, F. Bouelle, D. Scholler, and A. Feigenbaum, *J. Chem. Res.*, 1991, (S) 348.

<sup>304</sup> A.-M. Lluch, F. Sanchez-Baeza, F. Camps, and A. Messegue, *Tetrahedron Lett.*, 1991, **32**, 5629.

<sup>305</sup> For a review of chiral heterogeneous catalysis H.-U. Blaser, *Tetrahedron: Asymmetry*, 1991, **2**, 843.

<sup>306</sup> N. Ravasio and M. Rossi, *J. Org. Chem.*, 1991, **56**, 4329.

<sup>307</sup> T. R. Lee and G. M. Whitesides, *J. Am. Chem. Soc.*, 1991, **113**, 368; T. R. Lee, P. E. Laibinis, J. P. Folkers and G. M. Whitesides, *Pure Appl. Chem.*, 1992, **63**, 821.

<sup>308</sup> T. R. Lee and G. M. Whitesides, *J. Am. Chem. Soc.*, 1991, **113**, 369.

<sup>309</sup> For other chiral phosphine ligands see H.-J. Zeiss, *J. Org. Chem.*, 1991, **56**, 1783; M. J. Burk, *J. Am. Chem. Soc.*, 1991, **113**, 8518.

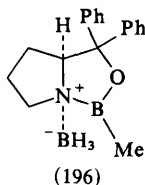
<sup>310</sup> J. S. Chickos, J. Y.-J. Uang, and T. A. Keiderling, *J. Org. Chem.*, 1991, **56**, 2594.

<sup>311</sup> W. N. Chou, D. L. Clark, and J. B. White, *Tetrahedron Lett.*, 1991, **32**, 299.

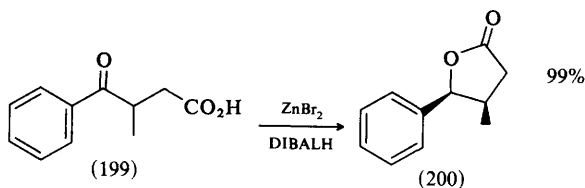
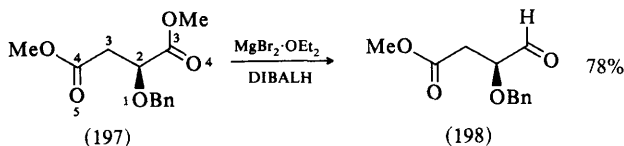
<sup>312</sup> For transfer hydrogenolysis, in which no hydrogen gas is released see H. Weiner, J. Blum, and Y. Sasson, *J. Org. Chem.*, 1991, **56**, 4481; 6145.

## Synthetic Methods

**Carbonyl Reduction.**<sup>313</sup> The oxazaborolidine (196)<sup>314</sup> is emerging as a general catalyst for the enantioselective reduction of ketones<sup>315</sup> and particularly aryl alkyl ketones.<sup>316</sup> The lithium borohydride reagent derived from the 9BBN hydroboration of nopol reduces dialkyl ketones with good to excellent enantioselectivities, but the stereoselectivity and reactivity drop if a potassium counter-ion is used. This presumably reflects the role of the lithium ion in coordination to the carbonyl group.<sup>317</sup>



Regioselectivity in the reduction of the diester (197) to the aldehyde (198) is achieved by selective formation of a five rather than a six membered chelate with magnesium bromide etherate and then reduction with di-isobutyl aluminium hydride (DIBALH),<sup>318</sup> similarly zinc bromide was used to organize the  $\gamma$ -ketoacid (199) for reduction to (200).<sup>319</sup>



**Protection.**<sup>99</sup>—The migration of acyl groups from secondary or tertiary alcohols to primary alcohols or amines is commonly observed in partially protected aminols. The reverse migration can be induced by treatment with triphenyl phosphine-carbon

<sup>313</sup> J. Seyden-Penne, 'Reductions by the Alumino- and Borohydrides in Organic Synthesis', VCH, New York, 1991; G. D. Paderes, P. Metiver, and W. L. Jorgensen, *J. Org. Chem.*, 1991, **56**, 4718.

<sup>314</sup> Preparation: D. J. Mathre, T. K. Jones, L. C. Xavier, T. J. Blacklock, R. A. Reamer, J. J. Mohan, E. T. T. Jones, K. Hoogsteen, M. W. Baum, and E. J. J. Grabowski, *J. Org. Chem.*, 1991, **56**, 751.

<sup>315</sup> T. K. Jones, J. J. Mohan, L. C. Xavier, T. J. Blacklock, D. J. Mathre, P. Sohar, E. T. T. Jones, R. A. Reamer, F. E. Roberts, and E. J. J. Grabowski, *J. Org. Chem.*, 1991, **56**, 763.

<sup>316</sup> E. J. Corey, X.-M. Cheng, K. A. Cimpich, and S. Sarshar, *Tetrahedron Lett.*, 1991, **32**, 6835; E. J. Corey and J. O. Link, *J. Org. Chem.*, 1991, **56**, 442.

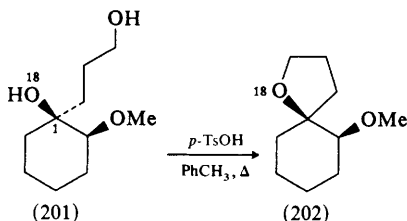
<sup>317</sup> M. M. Midland, A. Kazubski, and R. E. Woodling, *J. Org. Chem.*, 1991, **56**, 1068; for borane reagent based on aminohydroxyboranes see K. Tanaka, J. Matsui, and H. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1991, 1311; K. Soai, S. Yokoyama, and T. Hayasaki, *J. Org. Chem.*, 1991, **56**, 4264.

<sup>318</sup> G. E. Keck, M. B. Andrus, and D. R. Romer, *J. Org. Chem.*, 1991, **56**, 417; for the use of DIBALH-BuLi<sup>ate</sup> complexes see A. Anantanarayan and H. Hart, *J. Org. Chem.*, 1991, **56**, 991.

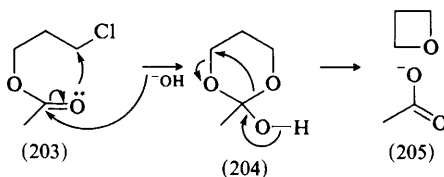
<sup>319</sup> R. Frenette, M. Monette, R. N. Young, and T. R. Verhoeven, *J. Org. Chem.*, 1991, **56**, 3083.

tetrabromide and indeed this is a convenient procedure for O-acylation in the presence of primary amines.<sup>320</sup>

**Ethers.** It is a textbook paradigm that tertiary carbonium ions are more stable than primary or secondary carbonium ions.<sup>321</sup> However, the diol (201) (and its epimer at C-1) cyclizes with retention of configuration at the tertiary centre (202). Presumably a carbonium ion at C-1 is disfavoured by the adjacent electron withdrawing methoxyl group<sup>322</sup> and retention of the <sup>18</sup>O label rules out direct neighbouring group participation.<sup>323</sup>



The Williamson synthesis of oxetanes (205) from 4-halo alcohols gives poor yields, because the intermediate alkoxide fragments; however, 3-chloropropyl acetate (203) cyclizes much more readily, by rearrangement of the ortho-ester (204).<sup>324</sup>



Homoallyl alcohols (206) and aldehydes undergo an intramolecular Prins reaction to give dihydropyrans (209),<sup>325</sup> however, if a hydroxyl group is vicinal to the carbonium ion centre pinacol ring contraction gives an acyl tetrahydrofuran (210).<sup>326</sup>

The cleavage of ethers by acyl halides is greatly improved by catalysis with cobalt(II) chloride, consequently even diethyl ether is cleaved in fair yield (49%).<sup>327</sup>

<sup>320</sup> P. K. Dutta, C. Chaudhuri, S. B. Mandal, A. K. Banerjee, S. C. Pakrashi, and B. Achari, *J. Chem. Res.*, 1991, (S) 201, (M) 2180.

<sup>321</sup> For a related cyclisation with a secondary to tertiary carbonium ion rearrangement see A. F. Mateos, C. M. Almendra, J. de P. Teresa, and R. R. Gonzalez, *Bull. Soc. Chim. Fr.*, 1991, **128**, 898.

<sup>322</sup> Review of electronegatively substituted carbocations, X. Creary, *Chem. Rev.*, 1991, **91**, 1627; M. Saunders and H. A. Jimenez-Vazquez, *Chem. Rev.*, 1991, **91**, 375.

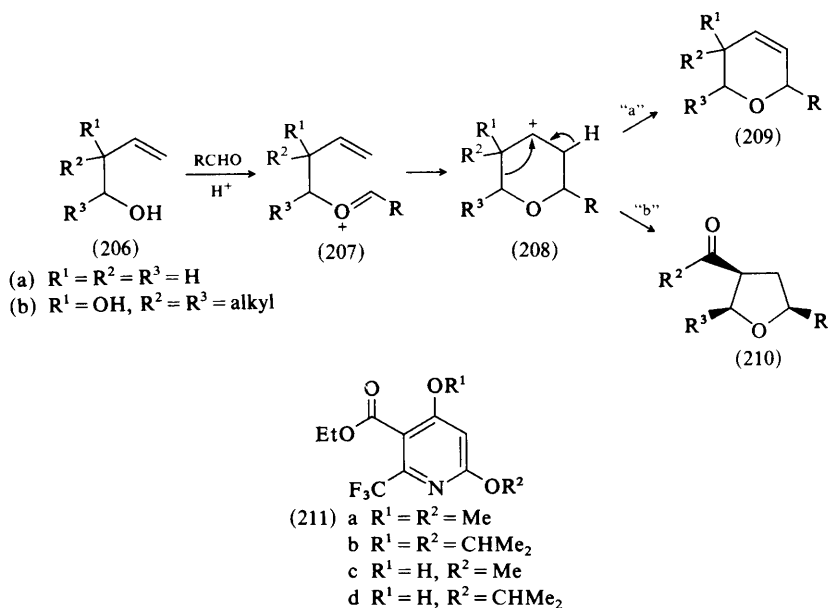
<sup>323</sup> L. A. Paquette and J. T. Negri, *J. Am. Chem. Soc.*, 1991, **113**, 5072; J. T. Negri, R. D. Rogers, and L. A. Paquette, *J. Am. Chem. Soc.*, 1991, **113**, 5073.

<sup>324</sup> J. Dale and S. B. Fredricksen, *Acta Chem. Scand.*, 1991, **45**, 82.

<sup>325</sup> A. C. Razus, M. D. Gheorgiu, and E. Bartha, *Rev. Roumaine. Chem.*, 1991, **36**, 215; F. Perron-Sierra, M. A. Promo, V. A. Martin, and K. F. Albizzati, *J. Org. Chem.*, 1991, **56**, 6188.

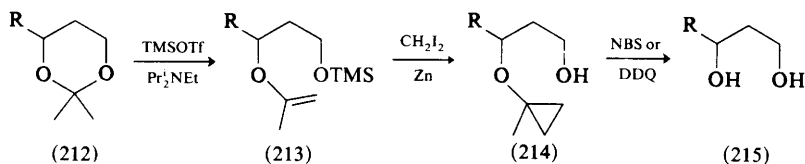
<sup>326</sup> M. H. Hopkins, L. E. Overman, and G. M. Rishton, *J. Am. Chem. Soc.*, 1991, **113**, 5354; M. J. Brown, T. Harrison, P. M. Herrington, H. H. Hopkins, K. D. Hutchinson, P. Mistra, and L. E. Overman, *J. Am. Chem. Soc.*, 1991, **113**, 5365; M. J. Brown, T. Harrison, and L. E. Overman, *J. Am. Chem. Soc.*, 1991, **113**, 5378.

<sup>327</sup> J. Iqbal and R. R. Srivastava, *Tetrahedron*, 1991, **47**, 3155.



Methyl<sup>328</sup> (211a) and isopropyl (211b) pyridine diethers are cleaved selectively at the 4-position by sodium thiomethoxide and aluminium chloride respectively.<sup>329</sup>

Terminal acetonides (212) are cleaved regioselectively to vinyl ethers (213) which are readily cyclopropanated. The 1-methyl cyclopropyl ethers (214) so formed are stable to strong base, moderate acid, and reduction but are cleaved by NBS or DDQ (Scheme 4).<sup>330</sup>



Scheme 4

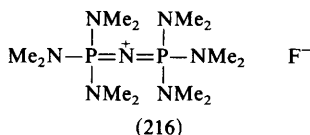
**Silyl Ethers and Fluoride Reagents.** It is a general perception that fluoride based reagents are the best choice for cleaving silyl ethers, but all the various methods have disadvantages. Tetrabutylammonium fluoride is difficult to dry, KF and CsF are not sufficiently reactive, HF is difficult to handle and  $\text{BF}_3 \cdot \text{OEt}_2$  is too acidic. Consequently, several new reagents and old reagents in new guises have been

<sup>328</sup> For the suppression of radical hydrogen abstraction by the use of trideuteriomethyl ethers see D. L. J. Clive, A. Khodabocus, M. Cantin, and Y. Tao, *J. Chem. Soc., Chem. Commun.*, 1991, 1755; D. L. J. Clive, A. Khodabocus, P. G. Vernon, A. G. Angoh, L. Bordeleau, D. S. Middleton, C. Lowe, and D. Kellner, *J. Chem. Soc. Perkin Trans. I*, 1991, 1757.

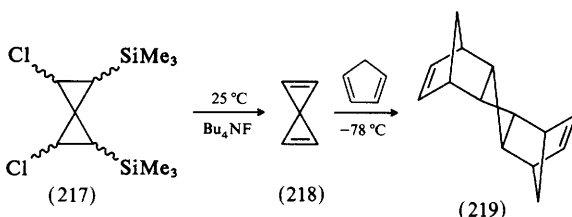
<sup>329</sup> S. G. Hedge, *J. Org. Chem.*, 1991, **56**, 5726.

<sup>330</sup> S. D. Rychnovsky and J. Kim, *Tetrahedron Lett.*, 1991, **32**, 7219, 7223.

proposed. Tetrabutylammonium difluorotriphenylstannate is non-hydroscopic and is 18 times more reactive as a nucleophile to benzyl bromide than CsF.<sup>331</sup> Another 'naked' fluoride reagent, phosphazanium fluoride (216), shows unique *E2* activity and readily gives 1-alkenes from 1-halides, however, it is sufficiently nucleophilic to effect coupling of allyl silanes and 1-iodoalkanes.<sup>332</sup> Catalytic transfer hydrogenation is selective for the cleavage of primary *t*-butyl dimethylsilyl (TBDMS) ethers<sup>333</sup>



and the acidity of  $\text{BF}_3 \cdot \text{OEt}_2$  has been used to advantage<sup>334</sup> in the elimination of tertiary silyl ethers and alcohols to alkenes,<sup>335</sup> one pot cleavage and oxidation to a ketone has been achieved by photolysis with DDQ.<sup>336</sup> Phenols and alcohols and primary alcohols are converted to TBDMS ethers upon treatment with *t*-butyldimethylsilanol under Mitsunobu conditions<sup>337</sup> and phenolic silyl ethers are selectively cleaved by potassium fluoride supported on alumina and irradiated with ultrasound.<sup>338</sup> Despite the disadvantages mentioned above, a column packed with glass helices covered in tetrabutyl ammonium fluoride sufficed to effect elimination from the silyl chloride (217) to give spiropentadiene (218) which was trapped in a Diels-Alder reaction to give (219).<sup>339</sup>



#### 4 New Reaction Conditions

If synthesis of a single natural product is a challenge then consider the possibilities of making hundreds at a time! Parallel synthesis is currently used by immunologists to prepare polypeptides as candidate antigens. The chemistry is similar to conven-

<sup>331</sup> M. Gringas, *Tetrahedron Lett.*, 1991, **32**, 7381.

<sup>332</sup> R. Schwesinger, R. Link, G. Thiele, H. Rotter, D. Honert, H.-H. Limbach, and F. Mannle, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1372; for a study of fluoride solvation see G. T. Hefter, *Pure Appl. Chem.*, 1992, **63**, 1749.

<sup>333</sup> J. F. Cormier, *Tetrahedron Lett.*, 1991, **32**, 187.

<sup>334</sup> Siloxanes and silyl ethers are appreciably less basic than dialkyl ethers, J. F. Blake and W. L. Jorgensen, *J. Org. Chem.*, 1991, **56**, 6052.

<sup>335</sup> G. H. Posner, E. M. Shulman-Roskes, C. H. Oh, J.-C. Carry, J. V. Green, A. B. Clark, H. Dai, and T. E. N. Anjeh, *Tetrahedron Lett.*, 1991, **32**, 6489.

<sup>336</sup> O. Piva, A. Amougay, and J.-P. Pete, *Tetrahedron Lett.*, 1991, **32**, 3993.

<sup>337</sup> D. L. J. Clive and D. Kellner, *Tetrahedron Lett.*, 1991, **32**, 7159.

<sup>338</sup> E. A. Schmittling and J. S. Sawyer, *Tetrahedron Lett.*, 1991, **32**, 7207.

<sup>339</sup> W. E. Billups and M. M. Haley, *J. Am. Chem. Soc.*, 1991, **113**, 5084; for other triangulanes see K. A. Lukin, S. I. Kozhushkov, A. A. Andrievsky, B. I. Ugrak, and N. S. Zefirov, *J. Org. Chem.*, 1991, **56**, 6176.



tional solid phase peptide synthesis<sup>340</sup> except that the growing chains are attached to plastic pins (typically 96) on a backboard. Each synthetic step is conducted in a new plate with an individual well for each pin containing the requisite reagent. A new variant of this technique uses light cleavable protecting groups and an optical mask to differentiate the individual areas of a glass plate. The preparation of 1024 peptides on a single slide has been demonstrated and 250 000 syntheses per square centimetre are possible, in principle, using currently available masking technology.<sup>341</sup>

Techniques such as photochemistry<sup>342</sup> have been universally adopted but there are wealth of opportunities waiting to be discovered with other forms of energy such as ultrasound, microwaves, radiolysis,<sup>343</sup> and electrochemistry.

Ultrasound promoted reactions<sup>344</sup> can be divided into two types: heterogenous systems in which the effect of the ultrasound is to increase surface area by dispersion or 'cleaning'. These typically involve metals such as lithium,<sup>345</sup> Li/TiCl<sub>3</sub>,<sup>346</sup> potassium,<sup>347</sup> iron,<sup>348</sup> magnesium, zinc,<sup>349</sup> or zinc-copper couple.<sup>350</sup> This cleaning effect was used to destroy disordered domains on the surface of Raney Nickel in preference to the more robust crystalline domains prior to modification with tartaric acid.<sup>351</sup> 'True' sonochemical reactions proceed exclusively *via* radicals or radical ions.<sup>352</sup> But it is frequently difficult to distinguish the latter possibility because ultrasound also causes localized (and unquantifiable) heating which may promote ionic reactions.<sup>353</sup> The dilemmas that this area presents are illustrated by the free radical polymerization of vinyl carbazole. The rate was studied as a function of ultrasound intensity. At the highest settings (100 Wcm<sup>-2</sup>) polymerization stopped, but recommenced when the ultrasound was turned off.<sup>354</sup> Equally, what conclusions can be drawn from the observation that the 5' acylation of adenosine by subtilisin is accelerated by ultrasound?<sup>355</sup>

<sup>340</sup> T. Weiland and M. Bodansky, 'The World of Peptides, A Brief History of Peptide Chemistry', Springer-Verlag, Heidelberg, 1991.

<sup>341</sup> S. P. A. Fodor, J. L. Read, M. C. Pirrung, L. Stryer, A. T. Lu, and D. Solas, *Science*, 1991, **251**, 767; G. von Kiederowski, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 822.

<sup>342</sup> N. Turro, 'Modern Molecular Photochemistry', University Science Books, Mill Valley, 1991.

<sup>343</sup> For homolytic aromatic hydroxylation using radiolysis see M. K. Eberhardt in *Reviews on Heteroatom Chemistry*, 4, ed. S. Oae, MYU K. K., Tokyo, 1991 and high pressure radiolysis for Co-C bond formation see R. van Eldik, H. Cohen, and D. Meyerstein, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1158.

<sup>344</sup> K. S. Suslick, *Science*, 1991, **253**, 1397; K. S. Suslick, *Proc. Natl. Acad. Sci. USA*, 1991, **88**, 7708; W. Worthing, *Chem. Eng. News*, 1991, Oct. 8th, 18.

<sup>345</sup> G. J. Price and A. A. Clifton, *Tetrahedron Lett.*, 1991, **32**, 7133.

<sup>346</sup> S. N. Nayak and A. Banerji, *J. Org. Chem.*, 1991, **56**, 1940.

<sup>347</sup> T. Chou, S.-H. Hung, M.-L. Peng, and S.-J. Lee, *Tetrahedron Lett.*, 1991, **32**, 3551.

<sup>348</sup> K. S. Suslick, S.-B. Choe, A. A. Cichowlas, and M. W. Grinstaff, *Nature*, 1991, **353**, 414.

<sup>349</sup> G. Etelman, M. Rifqui, P. Layrolle, J. Berlan, and M. Koenig, *Tetrahedron Lett.*, 1991, **32**, 5965; A. P. Marchand and G. M. Reddy, *Synthesis*, 1991, 198.

<sup>350</sup> L. A. Sarandeses, A. Mourino, and J.-L. Luche, *J. Chem. Soc., Chem. Commun.*, 1991, 818.

<sup>351</sup> A. Tai, T. Kikukawa, T. Sugimura, Y. Inoue, T. Osawa, and S. Fujii, *J. Chem. Soc., Chem. Commun.*, 1991, 795; 1324.

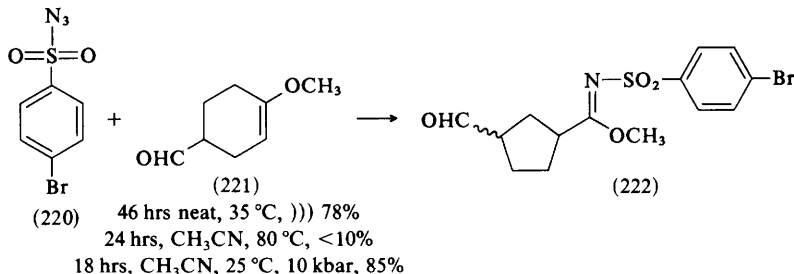
<sup>352</sup> M. J. Dickens and J.-L. Luche, *Tetrahedron Lett.*, 1991, **32**, 4709.

<sup>353</sup> T. Ando, P. Bauchat, F. Foucaud, M. Fujita, T. Kimura, and H. Sohmiya, *Tetrahedron Lett.*, 1991, **32**, 6379.

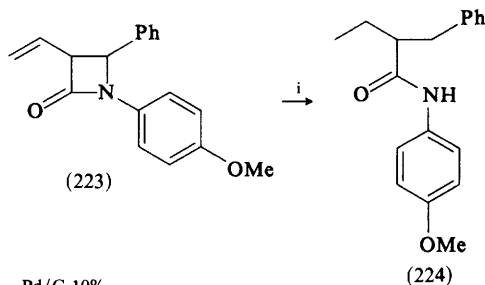
<sup>354</sup> J. P. Lorimer, T. J. Mason, and D. Kershaw, *J. Chem. Soc., Chem. Commun.*, 1991, 1217; cf. M. J. S. M. Moreno, M. L. Sa e Malo, and A. S. Campos Neves, *Tetrahedron Lett.*, 1991, **32**, 3201 (perruthenate oxidations); B. C. Ranu and M. K. Basu, *Tetrahedron Lett.*, 1991, **32**, 3243 (zinc borohydride reductions).

<sup>355</sup> M. Criton, G. Dewynther, and J.-L. Montero, *Recl. Trav. Chim. Pays-Bas*, 1991, **110**, 443.

The cycloaddition of aryl sulfonyl azides (220) to enol ethers (221) is promoted both by ultrasound<sup>356</sup> and high pressure.<sup>357</sup> It was assumed that the high pressures that result from the collapse of cavitation bubbles mimic the conditions of bulk high pressure reactions. A wide range of esters were cleaved by almost stoichiometric amounts of water and di-isopropyl ethylamine (Hunig's base) in acetonitrile at 8 Kbar.<sup>358</sup>



The use of microwave ovens<sup>359</sup> continues to attract controversy. The esterification of propan-1-ol with ethanoic acid proceeds at the same rate in a microwave oven as when heated conventionally.<sup>360</sup> In other cases the even heating that can be achieved with microwaves gives better and faster<sup>361</sup> results than can be obtained conventionally, particularly if the substrate rather than the solvent preferentially absorbs the microwaves.<sup>362</sup> For example the  $\beta$ -lactam (223) undergoes hydrogenation and hydrogenolysis in 45 secs at 110 °C (Scheme 5).<sup>363</sup>



Scheme 5

<sup>356</sup> D. Goldsmith and J. J. Soria, *Tetrahedron Lett.*, 1991, **32**, 2457.

<sup>357</sup> For general reviews of high pressure reactions see N. S. Isaacs, *Tetrahedron*, 1991, **47**, 8463; K. Matsumoto and K. M. Acheson, 'Organic Synthesis at High Pressure', Wiley, New York, 1991; M. Buback, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 641.

<sup>358</sup> Y. Yamamoto, T. Furuta, J. Matsuo, and T. Kurata, *J. Org. Chem.*, 1991, **56**, 5737; for the use of LiBr/DBU see D. Seebach, A. Thaler, D. Blaser, and S. Y. Koo, *Helv. Chim. Acta*, 1991, **74**, 1102.

<sup>359</sup> General reviews, D. M. P. Mingos and D. R. Baghurst, *Chem. Soc. Rev.*, 1991, **20**, 1; R. A. Abramovitch, *Org. Preps. Proc. Int.*, 1991, **23**, 683.

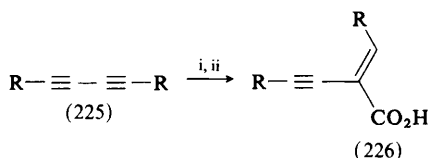
<sup>360</sup> S. D. Pollington, G. Bond, R. B. Moyes, D. A. Whan, J. P. Candlin, and J. R. Jennings, *J. Org. Chem.*, 1991, **56**, 1313.

<sup>361</sup> A. K. Bose, M. S. Manhas, M. Ghosh, V. S. Raju, K. Tabei, and Z. Urbanczyk-Lipowska, *Heterocycles*, 1990, **30**, 741.

<sup>362</sup> R. A. Abramovitch, D. A. Abramovitch, K. Iyanar, and K. Tamareselv, *Tetrahedron Lett.*, 1991, **32**, 5251.

<sup>363</sup> A. K. Bose, M. S. Manhas, M. Ghosh, M. Shah, V. S. Raju, S. S. Bari, S. N. Newaz, B. K. Banik, A. G. Chaudhary, and K. J. Barakat, *J. Org. Chem.*, 1991, **56**, 6968.

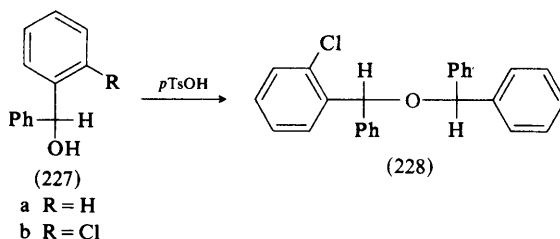
Electrochemical<sup>364</sup> carboxylation<sup>365</sup> of the diyne (225) to (226) in a single compartment cell is regio- and stereoselective (Scheme 6).<sup>366</sup>



Reagents: i,  $Ni^{II}$  (10%), Ligand, Mg anode, DMF,  $Bu_4N^+BF_4^-$ ; ii,  $H_2O$

Scheme 6

Many racemic compounds resolved spontaneously<sup>367</sup> by chance crystallization<sup>368</sup> of a single enantiomer and a recent report suggests that the enantiomeric excess may be improved by magnetically stirring the solution!<sup>369</sup> This apparently implausible observation has been attributed to fragmentation of the first seed crystal by the stirrer bar, resulting in a much faster crystallization than normal.<sup>370</sup> Solid state reactions in crystals frequently have different selectivities to the corresponding reactions in solution. Crystals of the alcohols (227a) (227b) were crushed with a mortar and pestle to give a cocrystal<sup>371</sup> which was then mixed with *p*-toluenesulfonic acid to give exclusively the 'mixed' ether (228), whereas in refluxing toluene a statistical mixture of the possible products was formed.<sup>372</sup>



<sup>364</sup> T. Shono, *Electroorganic Synthesis*, Best Synthetic Methods series Academic, London, 1991; J. S. Swenton and G. W. Morrow, 'Synthetic Applications of Anodic Oxidations, Tetrahedron Symposia-In-Print', 42, *Tetrahedron*, 1991, 47, 531.

<sup>365</sup> Review, G. Silvestri, S. Gambino, and G. Filardo, *Acta Chem. Scand.*, 1991, 45, 987.

<sup>366</sup> S. Derien, J.-C. Clinet, E. Dunach, and J. Perichon, *J. Chem. Soc., Chem. Commun.*, 1991, 549.

<sup>367</sup> For rationale crystal engineering of diastereoisomers see F. J. J. Leusen, H. J. B. Slot, J. H. Noordik, A. D. van der Haest, H. Wynberg, and A. Bruggink, *Recl. Trav. Chim. Pays-Ras.*, 1991, 110, 13; G. Coquerel, N. Mofaddel, M. N. Petit, and R. Bouaziz, *Bull. Soc. Chim. Fr.*, 1991, 128, 419, 773.

<sup>368</sup> For automated crystallization see M. Caron, C. M. Moren, J. C. Bondiou, J. P. Bourgogne, C. Porte, and A. Delacroix, *Bull. Soc. Chim. Fr.*, 1991, 128, 684.

<sup>369</sup> This should not be confused with the now discredited observation of chiral induction by spinning a reaction vertically relative to the earth's gravitational field, D. Edwards, K. Cooper, and R. C. Dougherty, *J. Am. Chem. Soc.*, 1980, 102, 381.

<sup>370</sup> J. M. McBride and R. L. Crandall, *Angew. Chem., Int. Ed. Engl.*, 1991, 30, 293.

<sup>371</sup> For the use of triphenyl phosphine oxide as a crystallization aid see A. L. Llamas-Saiz, C. Foces-Foces, J. Elguero, P. Molina, M. Alajarin, and A. Vidal, *J. Chem. Soc., Chem. Commun.*, 1991, 1694; for cholic acid inclusion complexes see K. Miki, N. Kasai, M. Shibakami, K. Takemoto, and M. Miyata, *J. Chem. Soc., Chem. Commun.*, 1991, 1757 and tartaric acid inclusion complexes F. Toda, A. Sato, L. R. Nassimbeni, and M. L. Niven, *J. Chem. Soc., Perk. Trans. II*, 1991, 1971.

<sup>372</sup> F. Toda and K. Okuda, *J. Chem. Soc., Chem. Commun.*, 1991, 1212.

## **5 Epilogue**

This is my last year on the synthetic methods review and I think my attitude to the difficulties in compiling it, can be encapsulated in another quote from Warren ‘...you have a nagging worry in the back of your mind that everything in the literature is interesting’.<sup>1</sup>