Use of Molecular Sieves for Promotion of Diastereoselectivity in Palladium-catalysed Oxidative Cyclisation. Reversal of Diastereofacial Selectivity

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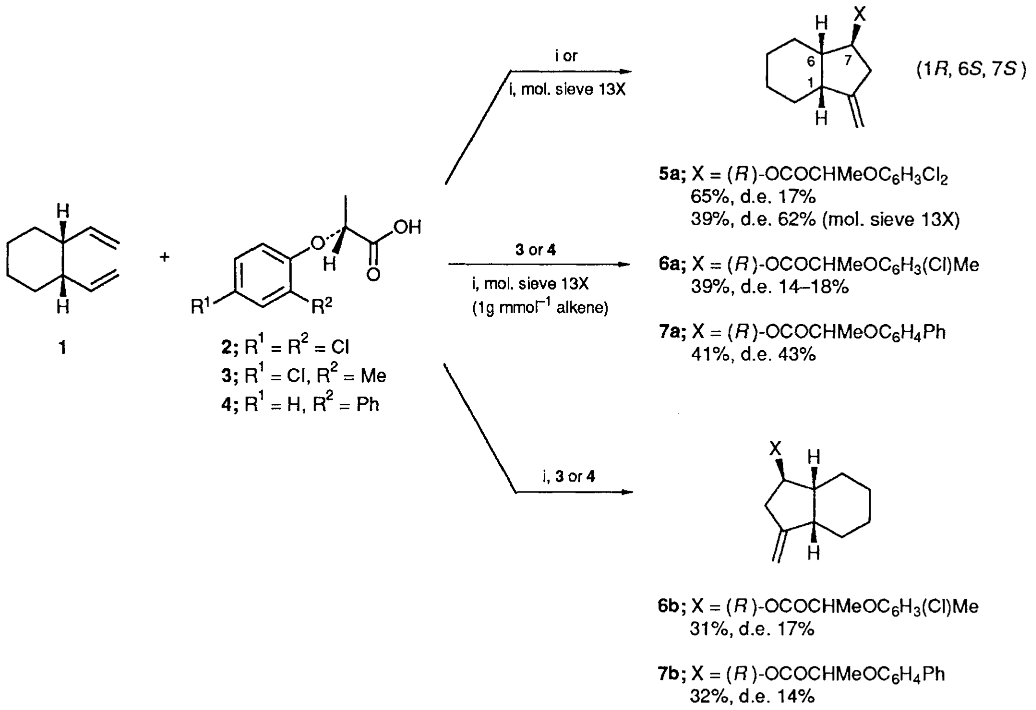
Molecular sieves have a decisive influence on the oxidative cyclisation of *cis*-1,2-divinylcyclohexane, resulting in enhanced diastereoselectivity (17–62%) as well as, occasionally, in opposite absolute configuration of the newly created chiral centres.

The catalytic oxidative cyclisation of 1,5-dienes[1] constitutes a versatile method for preparing mono- or bi-cyclic five-membered ring sysems.[2,3] The widespread occurrence of these carbocycles in natural and biologically active compounds, mainly in monochiral form (prostaglandins, pheromones and terpenes), makes the enantioselective synthesis of such molecules a challenging target in organic synthesis.

We have recently shown that *cis*-1,2-divinylcyclohexane **1** can be oxidatively cyclised with moderate diastereoselectivities to bicyclic indanol esters when chiral acids are employed as nucleophiles instead of acetic acid.[4] We have now found that the chiral induction can be not only dramatically improved by the addition of powdered molecular sieves, but actually reversed in some cases.

cis-1,2-Divinylcyclohexane **1** was treated with the *O*-aryl substituted propionic acids **2**–**4**[5] in the presence of $Pd(OAc)_2$, *p*-benzoquinone and MnO_2 in acetone to yield the *exo*-*cis*-hydrindane derivatives **5**–**7** as mixtures of two diastereoiso-



Scheme 1 *Reagents and conditions*: i, Pd(OAc)$_2$ (0.045 equiv.), *p*-benzoquinone (0.2 equiv.), MnO$_2$ (1.1 equiv.), acetone, 20 °C, 3–5 days, chiral acid (4–5 equiv.)

mers,[6] but with complete control of the relative configuration of the three chiral centres in the bicyclononane ring. It should be noted that, despite the relatively large distance to the chiral centre, substituents in the aromatic ring are found to influence strongly the stereoselectivity of the transformation. Thus, reaction of (*R*)-2-(2,4-dichlorophenoxy)propionic acid **2** with **1** afforded (1*R*,6*S*,7*S*)-7-[*R*-2-(2,4-dichlorophenoxy)]propoxy-9-methylenebicyclo[4.3.0]nonane **5a**† with a diastereoisomeric excess (d.e.) of 17%,‡ while (*R*)-2-(4-chloro-2-methylphenoxy)propionic acid **3** mainly led to the opposite (1*S*,6*R*,7*R*,11*R*) isomer **6b** [X = (*R*)-OCOCH(Me)-OC$_6$H$_3$(Cl)Me, d.e. 17%]. The addition of molecular sieves Lancaster 13X to an otherwise identical reaction mixture resulted in a considerable increase in selectivity. In the case of chiral acid **2**, the optical induction in the cyclic ester **5a** was raised to 62% d.e.† (39% yield).

Particularly interesting behaviour was observed with chiral carboxylic acids that normally lead to (··7*R*) isomers, *e.g.* the *ortho* methyl substituted propionic acid **3** (formation of **6b**). The addition of molecular sieves caused a complete inversion of configuration of the new chiral centres in the isolated diastereoisomeric mixture of cyclised esters **6a**: 39% yield, d.e. 18%. This surprising reversal of configuration of the induction was also observed with other molecular sieves (3 Å, 4 Å *etc.*) and different aryl-substituted hydroxypropionic acids. Thus, the (*R*)-*ortho*-phenyl phenoxy propionic acid **4**, which under normal conditions yielded **7b** (d.e. 14%), in the presence of Lancaster 13X gave rise to the formation of **7a** with a diastereoisomeric excess of 43% (yield 41%).

Since molecular sieves are nonchiral, the use of the same acids with opposite absolute configuration should result in the formation of enantiomeric products. This was, indeed, observed when (*S*)-2-(4-chloro-2-methylphenoxy)propionic acid **3** was used in place of the corresponding (*R*) acid **3** (14% d.e., 39% yield).

The use of zeolites is now well documented in organic chemistry.[7] However, improvement of enantioselectivity through use of molecular sieves has been reported on only rare occasions.[8–11] All these reactions are catalysed by alkoxy titanium(IV) complexes, *e.g.* the catalytic asymmetric epoxidation of allylic alcohols,[8] a Diels–Alder[9] and a glyoxylate-ene reaction,[10] and the effect has been attributed to the water scavenger properties of the molecular sieves (protection or improved formation of the metal alcoholates). In the three component catalyst Pd(OAc)$_2$–*p*-benzoquinone–MnO$_2$, water is formed during the reaction. However, when **2** was used as a nucleophile together with the molecular sieves, 1.2 equiv. of *p*-benzoquinone and no MnO$_2$, thus avoiding water formation, the same selectivity was observed as for the ordinary reoxidation composition. This suggests that the selectivity, in our case, is independent of the water trapping properties of the molecular sieves.

The origin of the molecular sieve-controlled enantioselectivity in the cyclisation of **1** is, however, not clear. As long as (*R*)-*O*-aryl propionic acids **2**–**4** are the chiral nucleophiles, a clearcut preference for the formation of one isomer with the (1*R*,6*S*,7*S*) configuration is observed independent of the original formation, without molecular sieves, of **5a**, **6b** or **7b**. A simple explanation could be that the role of the molecular sieves is to absorb the diene and/or the acid, thereby affecting the intermolecular interactions between the reactants and thus altering the energy difference between the two diastereoisomeric transition states. The fact that one diastereoisomer is, indeed, preferentially adsorbed by the molecular sieves is shown by the variable d.e. values observed when the ester **7** was isolated by simple filtration (17% d.e., 17% yield) rather than by Soxhlet extraction§ (43% d.e., 41% yield).¶

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† The absolute configuration of 9-methylenebicyclo[3.3.0]nonan-7-ol **5** (X = OH) has been determined by means of the *O*-methoxy mandelic esters, *cf.* ref. 4.

‡ Determined by capillary GLC on SE-30 type columns.

§ In order to isolate quantitative amounts of cyclised esters **5**–**7**, Soxhlet extraction of the reaction mixture with hexane–EtOAc (7 : 3) or pure EtOAc for 1.5 h was employed for all reactions run with molecular sieves.

¶ The moderate yield in all molecular sieve-promoted reactions is the consequence of the enhanced (non Pd-catalysed) reactivity of the alkene under these conditions. In the absence of the nucleophile, **1** is consumed slowly (46% after 3–5 days, GLC analysis).

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