Selective activation of carbon–carbon bonds next to a carbonyl group

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ORGANOMETALLIC complexes are used to effect a wide range of catalytic transformations in organic synthesis, such as the activation of C–H bonds[1,2]. Carbon–carbon bonds, however, are generally unreactive towards transition metals under homogeneous conditions. C–C bond activation by a process of oxidative addition to soluble transition-metal complexes has been limited mostly to stoichiometric (not catalytic) reactions[1,3–7,18], to highly strained substrates such as cyclopropane and cubane[1,8–11] or to chelating ketones[19]. Here we present a synthetically useful process of selective C–C bond activation in which the C–C bond adjacent to a carbonyl group is opened by insertion of a soluble rhodium(I) complex. The resulting organometallic intermediate can be transformed to a variety of products in a way that regenerates the rhodium complex. We anticipate that this catalytic scheme will have considerable utility in organic synthesis.

We have found that Rh(I) can be inserted into a variety of C–C bonds next to a carbonyl group. In some cases this can lead to decarbonylation—removal of the carbonyl group—whereas in others a catalytic transformation can be effected. As an example of the former, cyclobutanone (**1** in Fig. 1) was treated with an equimolar amount of $((C_6H_5)_3P)_3RhCl$ under reflux for 41 h in toluene. Decarbonylation took place, giving quantitatively the corresponding cyclopropane **4**. The formation of **4** suggests that Rh(I) undergoes an insertion into the bond between carbonyl carbon and the α-carbon, giving the five-membered acylrhodium **2** in the initial step. Extrusion of the carbonyl group from the five-membered ring then occurs with migration onto rhodium to furnish the contracted rhodacycle **3**. Subsequent reductive elimination gives rise to the cyclopropane **4** together with the rhodium carbonyl complex. Other strain-free cycloalkanones like cyclopentanone **5** and cyclododecanone **7** (Fig. 1), also underwent the rhodium-mediated decarbonylation, although less efficiently, disclosing the general ability of Rh(I) to insert into the C–C bond α to a carbonyl group. Because a stoichiometric amount of $((C_6H_5)_3P)_3RhCl$ was required for the decarbonylation reaction, it is likely that the resulting rhodium carbonyl complex[12] fails to activate the C–C bond again. The formation of the stable rhodium carbonyl complex analogous to Vaska's complex may provide the driving force for the present decarbonylation reaction.

Next, the Rh-mediated selective activation of the C–C bond α to a carbonyl group was combined with a process of hydrogenolysis, thus leading to a catalytic reaction. When cyclobutanone **1** was treated under a hydrogen atmosphere (50 atm) with Rh(I) catalyst (10 mol%), prepared *in situ* from $[(cod)RhCl]_2$ and dppe, (cod is 1,5-cyclooctadiene, dppe is 1,2-bis(diphenylphosphino)ethane), alcohol **10** (Fig. 2) was produced in 87% isolated yield. It is likely that the aldehyde **9** is formed first by the addition of dihydrogen to **2′**. The following addition of dihydrogen to **9** gives the alcohol **10**. Actually, the use of 5 mol% of the rhodium catalyst afforded a mixture of **9** and **10** (~1:1) in 81% total yield. The formation of cyclobutanol **11** was not observed, indicating that oxidative addition of the C–C bond proceeds faster than direct hydrogenation of the carbonyl group under

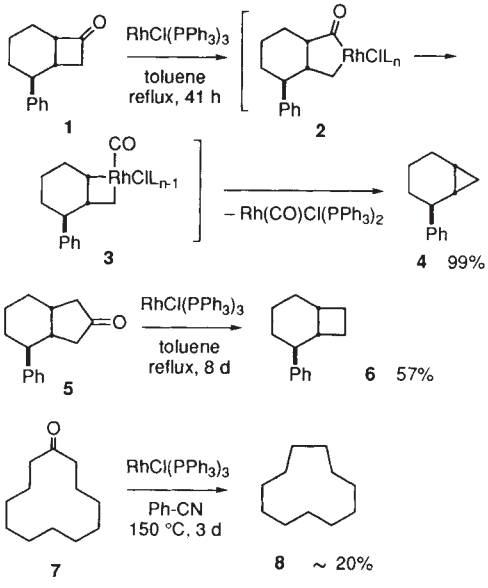

FIG. 1 The Rh-mediated decarbonylation of ketones.

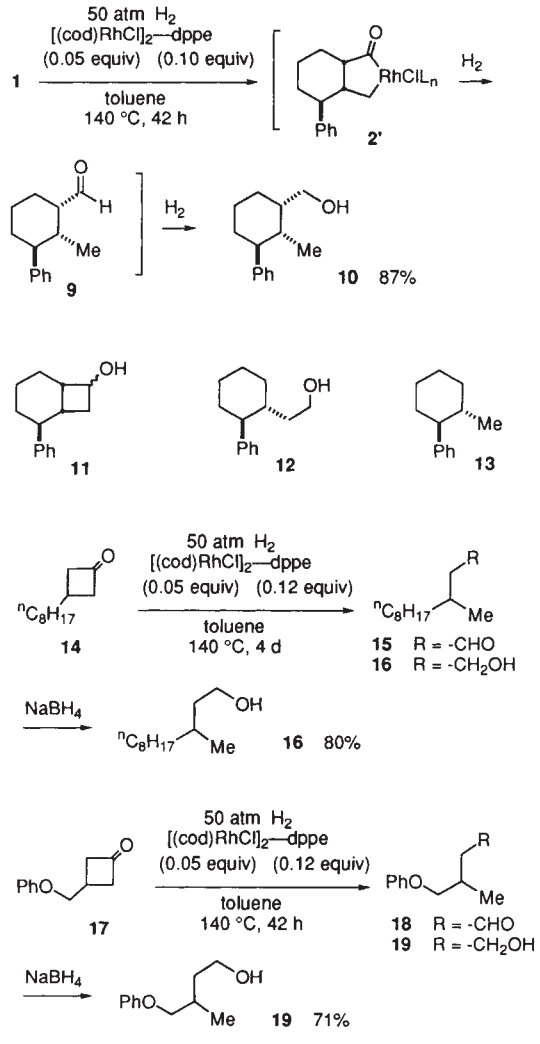

FIG. 2 The Rh-catalysed hydrogenolysis of the C–C bond α to a carbonyl group. (Abbreviations: cod, 1,5-cyclooctadiene; dppe, 1,2-bis(diphenylphosphino)ethane.)

these conditions. Moreover, alcohol **12** was not produced. This result shows that the insertion of Rh(I) took place selectively into the less-substituted C–C bond. The choice of the phosphine ligand is important for the product selectivity; when $((C_6H_5)_3P)_3RhCl$ was used, decarbonylation products (cyclopropane **4** (35%) and 1-methyl-2-phenylcyclohexane **13** (15%)) were obtained together with alcohol **10** (47%). Presumably 1-methyl-2-phenylcyclohexane **13** is formed by hydrogenation of the rhodacycle **3**. Other bidentate ligands like 1,3-bis-(diphenylphosphino)methane and 1,4-bis(diphenylphosphino)-butane also afforded a mixture of **10**, **4** and/or **13**.

Cyclobutanones **14** and **17** (Fig. 2) also underwent Rh(I)-catalysed cleavage of the α C–C single bond to afford mixtures of aldehydes and alcohols. After reduction with $NaBH_4$, 3-methylundecanol **16** (a building block in the synthesis of an insect pheromone)[13] and 2-methyl-1,4-butanediol derivative **19** (a bifunctional isoprenoid building block)[14] were isolated, respectively, in good yields (Fig. 2). Thus catalytic hydrogenolysis of C–C single bonds is accomplished via Rh(I)-mediated activation of C–C bond under a hydrogen atmosphere. The addition of dihydrogen together with relief of the structural strain of the cyclobutanone skeleton may make a large contribution to the driving force of this catalytic reaction.

A number of excellent methods are currently available for the synthesis of cyclobutanones[15–17]. In particular, [2+2] cycloaddition reaction of alkenes with ketene derivatives provides a simple

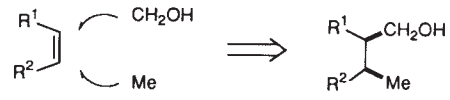

FIG. 3 *Syn* addition of methyl and hydroxymethyl groups to a C–C double bond.

and general approach to those compounds, often with control of the regio- and stereochemistry of ring substituents. Therefore, the present hydrogenolysis, coupled with preparation of cyclobutanones, achieves regio- and stereoselective *syn* 1,2-addition of methyl and hydroxymethyl groups to C–C double bonds (Fig. 3).

Although we have no experimental or theoretical result to provide a basis for argument about the mechanism of the insertion of Rh(I) into the α C–C bond, the reactions described here present the first example of practical synthetic transformations involving selective activation of C–C bonds by transition-metal complexes under homogeneous conditions, and demonstrate that the insertion of a transition metal into the C–C bond α to a carbonyl group may be a kinetically feasible fundamental process. Fine-tuning of the ligand set, the most favourable feature of homogeneous catalysts, and designing a reaction to gain a thermodynamic driving force would lead to the development of various kinds of transformations including those which can be applied to natural-product syntheses. Enantioselective hydrogenolysis of symmetrical cyclobutanones like **14** (Fig. 2) is one of the subjects worthy of further investigation. □

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SUPPLEMENTARY INFORMATION. Further details of experimental procedures for the reactions described, and of product characterization by ^1H and ^{13}C NMR and elemental analysis, are available from Mary Sheenan at the London editorial office of *Nature*.

An efficient mimic of cytochrome P-450 from a zeolite-encaged iron complex in a polymer membrane

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MANY attempts have been made to mimic the catalytic oxidative properties of the enzyme cytochrome P-450. For homogeneous systems[1] the mechanisms of oxidation can be readily determined but proper mimicry of the protein environment is difficult to achieve. Heterogeneous mimics have been designed that use organometallic complexes encapsulated in the supercages of zeolites[2,3], which enables control of selectivity and inhibition of auto-oxidation. But these systems do not show any mechanistic analogy with the enzymatic process, and the oxidation rates tend to be low. Here we report a composite catalytic system that achieves realistic mimicry of cytochrome P-450 as well as catalytic turnover rates that make the system industrially viable. Our catalyst incorporates iron phthalocyanine complexes encapsulated in crystals of zeolite Y, which are in turn embedded in a polydimethylsiloxane membrane. The polymer acts as a mimic of the phospholipid membrane in which cytochrome P-450 resides[4], acting as an interface between two immiscible phases and avoiding the need for solvents or phase-transfer agents. This system oxidizes alkanes at room temperature at rates comparable to those of the enzyme[5]. The observation of a large kinetic isotope effect and the preferential oxidation of tertiary C–H bonds suggest close mechanistic similarities to the enzymatic process.

Previously reported turnovers for the room-temperature oxidation of alkanes with iodosobenzene as oxygen atom donor and zeolite-encapsulated iron phthalocyanine (FePc)[6,7], iron-tetramethylporphyrine[8] or Mn-salen[9] as catalysts, were below 10. With *t*-butylhydroperoxide (*t*-BHP), *n*-octane turnovers of 6,000 could only be obtained at low rates (0.2 turnovers min^{-1})[10]. Membrane-embedded metallo-porphyrins[11] showed up to 20 turnovers.

Our present catalyst, comprising iron phthalocyanine in zeolite Y (FePcY), was synthesized according to an optimized version of the metallocene method[10] and was encapsulated in a polydimethylsiloxane (PDMS) membrane chosen for its high permeability and good affinity for the substrates used in the present catalytic reactions[12]. The catalyst shows a 300-fold enhanced activity in alkane oxygenations compared to traditionally[6,7] prepared zeolite-enclosed complexes. The composition of the FePcY–PDMS membrane is schematically represen-

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