

# Metathesis Catalysed by the Platinum Group Metals

A NEW STRATEGY FOR THE SYNTHESIS OF ORGANIC COMPOUNDS AND POLYMERS  
PART II: APPLICATIONS OF PLATINUM METALS METATHESIS CATALYSTS IN RING-CLOSING REACTIONS

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*In the first part of this review, published in the April issue of this Journal, the main catalyst systems used for metathesis catalysis were examined, and followed by a short report on metathesis activity and selectivity. In this second part, attention is now drawn to specific applications of platinum group metals metathesis catalysts, in particular, to a variety of ring-closing metathesis reactions. The last part of this review will be published in the October issue of this Journal.*

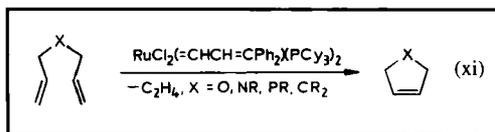
The rapid development of platinum group metals metathesis catalysts, tolerant of functional groups and aqueous media, has enabled a range of applications in organic and polymer chemistry to emerge. A selection of these will now be reviewed.

## Ring-Closing Metathesis

Ring-closing metathesis (RCM), has been shown to be a powerful tool for the synthesis of cyclic compounds in organic chemistry (7). The reaction can be applied in two variations, one to functionalised dienes forming carbocyclic compounds (38) and the other to heteroatom-containing dienes leading to heterocyclic compounds (1(d), 24, 39, 40). While the former process is also promoted by some classical (1(a), 1(b)) and well-defined carbene initiators (4(a), 4(b), 41), the latter can be induced only by catalysts that are tolerant of functional groups (24).

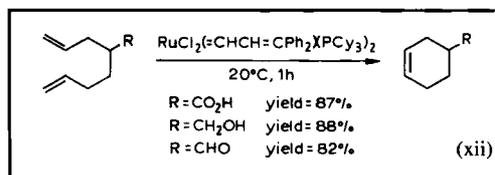
In addition to the general class of molybdenum initiators of the Schrock type (4(a), 4(b), 41), the ruthenium carbene initiators, disclosed by Grubbs, are efficient catalysts, particularly for RCM of dienes which contain functional groups. Thus, oxygen- (42), nitrogen- (43) or even phosphorus-containing (44) heterocycles can be easily prepared from the corresponding heteroatom-containing

dienes using a ruthenium carbene, **2**,  $\text{RuCl}_2(=\text{CHCH}=\text{CPh}_2)(\text{PCy}_3)_2$ , (Cy = cyclohexyl), as the catalyst, Equation (xi).

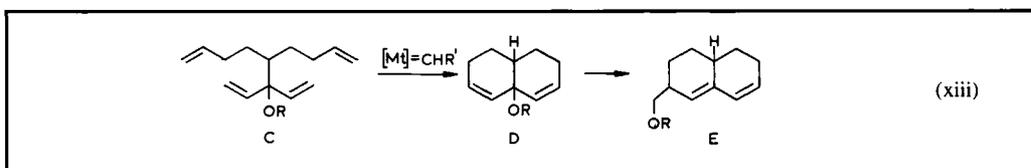


## Synthesis of Carbocycles

The ruthenium carbene initiator, **2**,  $\text{RuCl}_2(=\text{CHCH}=\text{CPh}_2)(\text{PCy}_3)_2$  was found to be extremely efficient for the synthesis of cycloalkenes bearing functional groups such as carboxylic acids, alcohols and aldehydes (38) which readily destroy the classical or well-defined tungsten and molybdenum initiators, see Equation (xii),



(4(a), 4(b), 41). The yields are substantial and such compounds can be easily handled and separated from the reaction mixture.

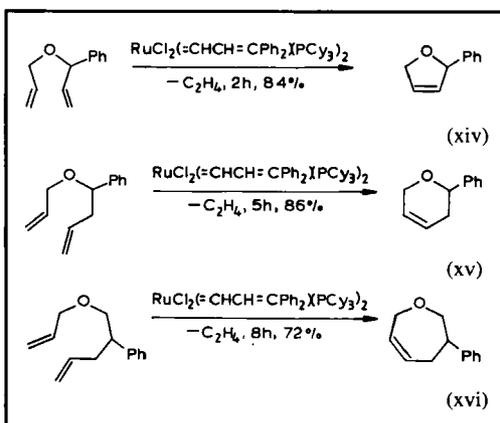


A new strategy for the diastereoselective synthesis of bicyclic derivatives such as substituted decalins makes use of readily available acyclic tetraenes, **C**, which can ring-close using the transition metal catalysed olefin metathesis approach, see Equation (xiii), (45).

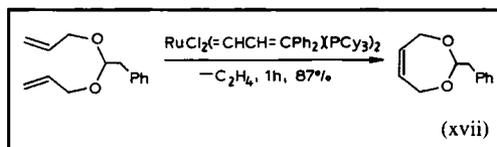
The resulting decalins, **D**, are symmetrical, affording the opportunity to perform enantioselective desymmetrisation reactions to yield non-racemic compounds. Enantioselective sigmatropic rearrangements can lead to bicyclic structures of type **E**, reminiscent of the decalin moiety of a number of reductase inhibitors used to lower cholesterol levels.

### Synthesis of Heterocycles

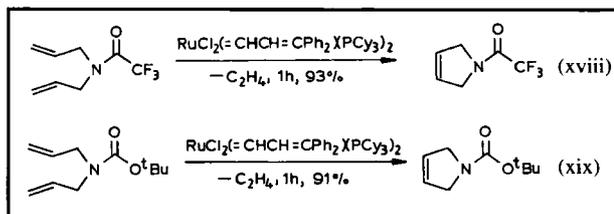
A large number of heterocycles containing endocyclic oxygen, nitrogen, phosphorus and other heteroatoms can now be prepared by using the widely tolerant ruthenium carbene initiators (42–44). A first set of such heterocycles comprises the synthesis of five-, six- and seven-membered oxygen-containing rings, and uses a ruthenium vinylidene complex **2** as a catalyst, see Equations (xiv) to (xvi), (42).



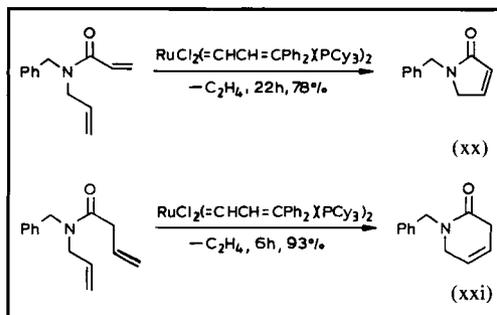
The same procedure has also been applied to the synthesis of heterocycles containing two oxygen atoms, such as seven-membered cyclic acetals, see Equation (xvii), (42).



Nitrogen-containing heterocycles have become readily available in high yield by RCM of amino dienes (43). Remarkably, the ruthenium vinylalkylidene complex **2** tolerates common protecting groups, for example, trifluoroacetyl, *tert*-butoxycarbonyl (Boc) and benzyl, see Equations (xviii) and (xix).



It is interesting to note that the cyclisation of dienes bearing benzyl groups, see Equations (xx) and (xxi), (43), cannot be effected using molybdenum-based initiators.



A large variety of nitrogen-containing compounds (heterocycles, carbocycles, alkaloids and

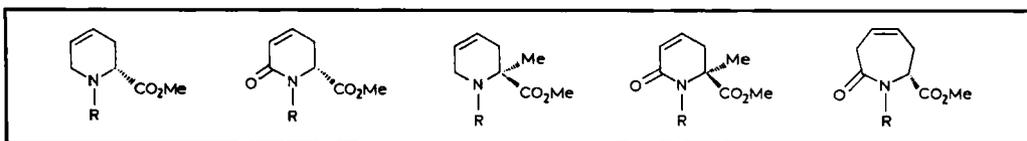


Fig. 1 Enantiomeric cyclic compounds prepared by ring-closing metathesis using benzylidene or vinylidene ruthenium complexes

peptidomimetics) obtained by RCM have recently been reviewed (46). The preparation of enantiomeric cyclic compounds, see Figure 1, through RCM by using either benzylidene or vinylidene ruthenium complexes, of basic structures 1 and 2 has recently been reported (47). It is worth mentioning the substantial enantiomeric yield which is obtained – much higher than given by the conventional methods which synthesise such compounds.

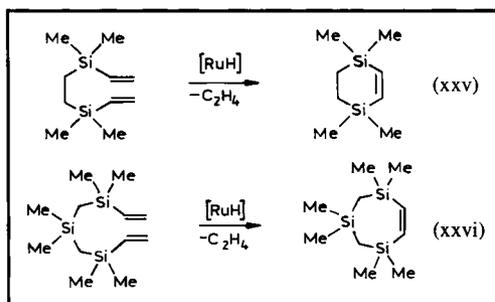
RCM of vinyl- and allylphosphonamides using the ruthenium carbene initiator,  $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$ , **1**, is an interesting method of synthesis for five- or six-membered P-heterocycles, starting from vinyl- or allylphosphonamides ( $n = 0$  or  $1$ ), see Equation (xxii), (45).

Using this same technique, when the reaction is applied to diallyl vinylphosphonates, heterocycles having both oxygen and phosphorus in the ring can be obtained, see Equations (xxiii) and (xxiv), (45).

### Synthesis of Metallacycles

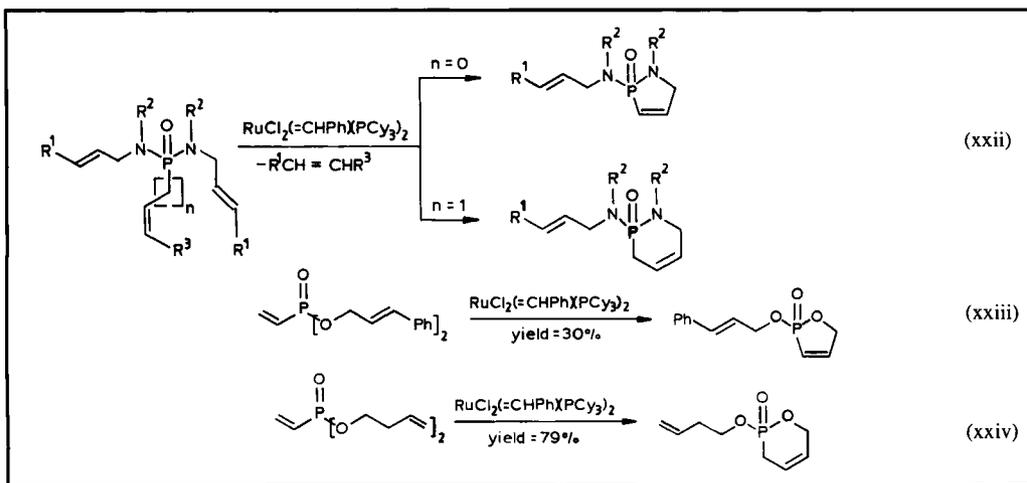
The cyclisation of divinyl derivatives containing two or three silicon atoms linked by hydrocarbon bridges, in the presence of ruthenium catalysts,

leads to the formation of six- and seven-membered unsaturated heterocycles, as can be seen from Equations (xxv) and (xxvi), (48).

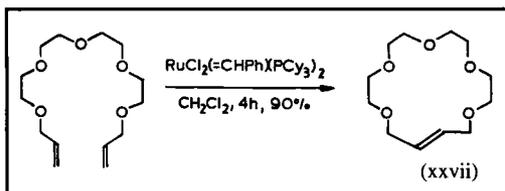


### Synthesis of Crown Ethers

A large number of compounds such as crown ethers which are important for a variety of applications have become available in high yield through the RCM of unsaturated polyethers, due to the tolerance of benzylidene ruthenium carbene complexes toward oxygen functionalities (49, 50). One interesting example is the synthesis of the unsaturated *trans*-isomer of a 17-membered crown ether in 90 per cent yield, from the corresponding



polyether diene under the influence of benzylidene ruthenium complex, 1, see Equation (xxvii).



In the same way, the synthesis of 17-, 20- and 26-membered dibenzo crown ethers has been carried out in good yield, using the above benzylidene ruthenium complex, 1, even at moderate substrate concentrations (0.35 M) at room temperature, see Equation (xxviii), (49).

### Synthesis of Polycyclic Polymers

By using the ruthenium carbene complex,  $\text{RuCl}_2(=\text{CH}_2)(\text{PCy}_3)_2$ , it has become possible to perform the highly selective and quantitative cyclisation of neighbouring vinyl groups in 1,2-polydienes, see Equation (xxix), (51).

Thus, 1,2-polybutadiene underwent cyclisation of the vinyl side-groups in the presence of the ruthenium complex with > 97 per cent yield, leading selectively to poly(cyclopentenylmethyl-

lene). Hydrogenation of this product yielded a saturated polymer with NMR spectra identical to those of atactic poly(cyclopentenylmethylene).

### Synthesis of Natural Compounds (R)-(+)-Lasiodiplodin

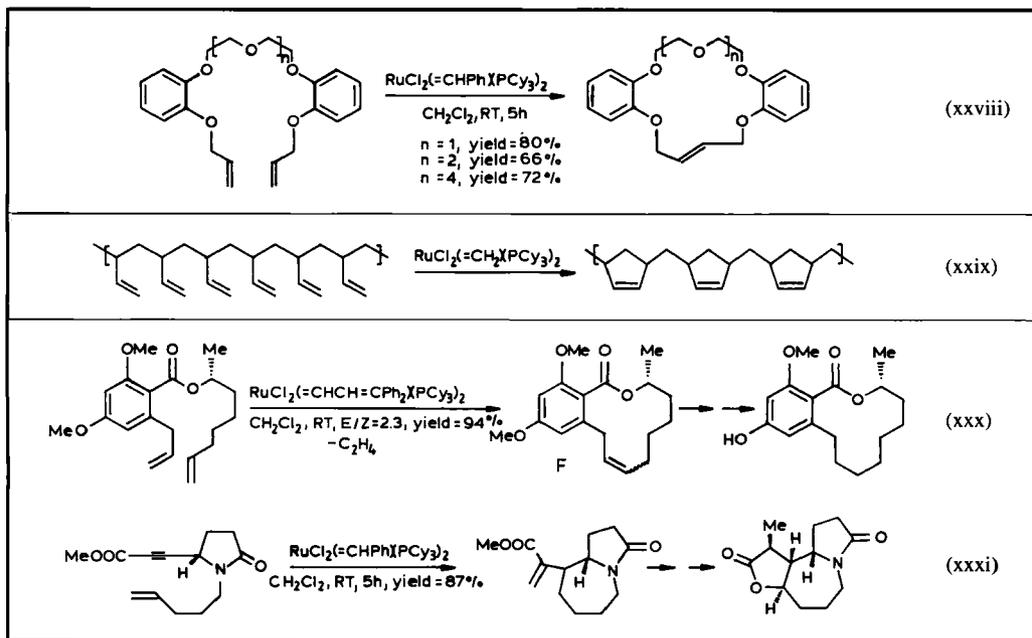
A method for the synthesis of (R)-(+)-lasiodiplodin, a natural compound that can be isolated from a culture broth of the fungus *Botryodiplodia theobromae*, which displays plant growth regulation properties, has been developed by efficiently employing RCM (90 per cent yield). The ruthenium vinylidene complex 2 induces the reaction, and produces compound F as an intermediate step, see Equation (xxx), (52).

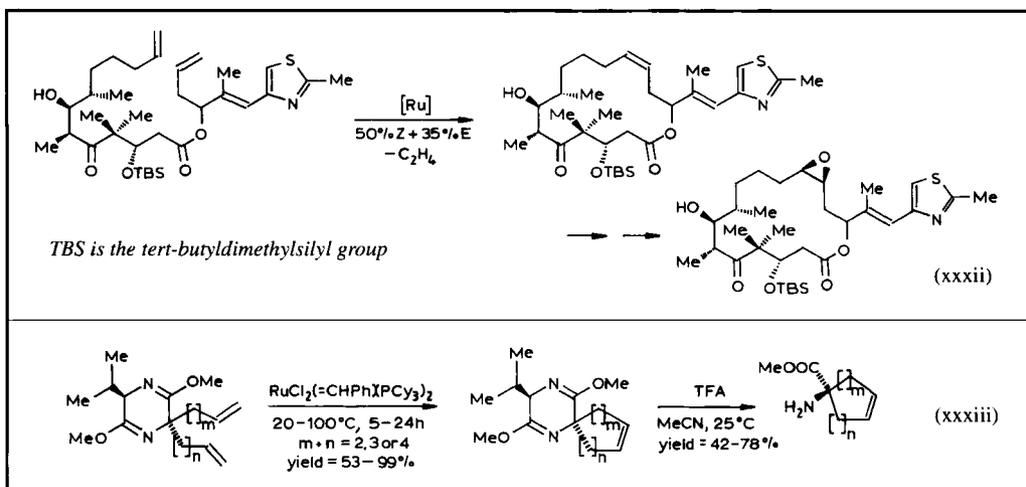
The formation of the 12-membered ring in the RCM reaction was nearly quantitative. The chiral centre bearing the methyl group was derived from that in the starting compound (S)-propene oxide.

### (-)-Stemoamide

(-)-Stemoamide, a polycyclic alkaloid with powerful insecticide properties, which can be isolated from the roots and rhizomes of stemonaceous plants, has been synthesised using the convenient RCM process, see Equation (xxxi), (53).

The formation of the 7-membered ring was





accomplished by RCM of an enyne moiety in the substrate under the influence of the ruthenium benzylidene complex  $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$ . A third ring was subsequently formed by bromolactonisation in the final stage of the reaction.

#### Epothilone A

Several procedures using a RCM reaction as an intermediate step have been reported for synthesising Epothilone A, a natural compound with great importance for cancer therapy (54). According to one of these procedures, the ruthenium benzylidene complex  $\text{RuCl}_2(=\text{CHPh})(\text{PR}_3)_2$  has been efficiently employed to give the required *cis* isomer in 50 per cent yield, see Equation (xxxii), (54a)

Nicolaou and coworkers have synthesised a library of epothilone analogs using a solid-phase RCM-cleavage approach (55).

#### Other Polycyclic Polyethers

Ciguatoxin-3C (56(a)) and hemibrevetoxin-B (56(b)) were obtained with the same ruthenium benzylidene catalyst as in the two previous reactions. Three RCMs were involved in the synthesis of the second polyether.

### Synthesis of Sub-units of Biologically Active Compounds

#### $\alpha$ -Amino Acid Esters

The stereoselective synthesis of  $\alpha$ -amino acids having the  $\alpha$ -carbon atom incorporated in a five-, six- or seven-membered ring has been effected using the ruthenium benzylidene complex

$\text{RuCl}_2(=\text{CHPh})(\text{PR}_3)_2$  as a RCM catalyst, see Equation (xxxiii), (57(a)). TFA is trifluoroacetic acid.

When  $m = n = 1$ , a better yield of final product is obtained by first hydrolysing the diene derivative of the pyrazine and then carrying out the RCM reaction. When  $m$  is different from  $n$ , the resulted amino acid ester is chiral.

#### Supramolecular Peptide Assemblies

Blackwell and Grubbs used RCM for preparing helical polypeptides (57(b)). Clark and Ghadiri linked, by a double intramolecular RCM, two cyclic octapeptides that were held parallel on top of each other by eight intermolecular hydrogen bonds (57(c)).

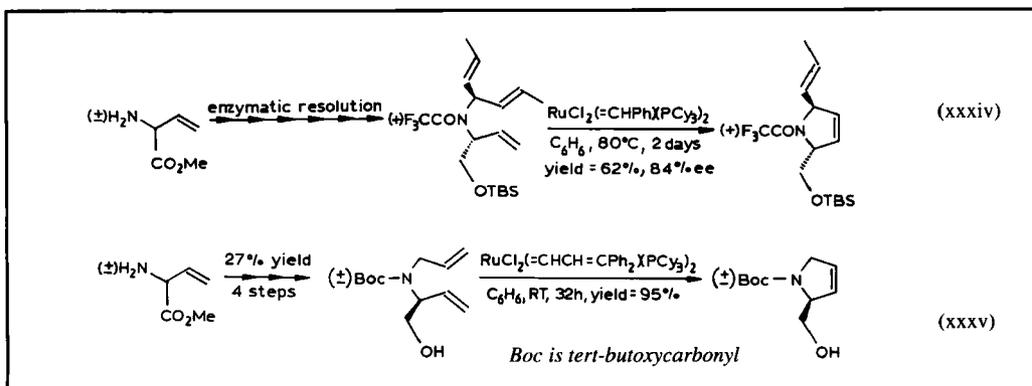
#### Azasugars

The synthesis of azasugars (polyhydroxylated pyrrolidines) has been effected starting from vinyl glycine methyl ester and using RCM in a subsequent step (58). Both ruthenium alkylidene catalysts have been efficient in forming the five-membered ring, Equations (xxxiv) and (xxxv).

These compounds have potential biological and pharmaceutical activities, based on the inhibition of glycosidases which play an important role in metabolism. Their applications include diabetes, cancer and viral diseases.

#### $\beta$ -Lactams

The RCM reaction has been successfully applied to produce a variety of new compounds with the  $\beta$ -lactam structure, see Equation (xxxvi),



(59). Such compounds are essential sub-units in some drugs, such as penicillin G, and may have important antibiotic properties.

### Chromenes

Substituted chromene units are found within a multitude of medicinally important compounds. The synthesis of a wide range of substituted chromenes has been effected from substituted dienes using ruthenium carbene initiators in the RCM step, Equation (xxxvii), (60).

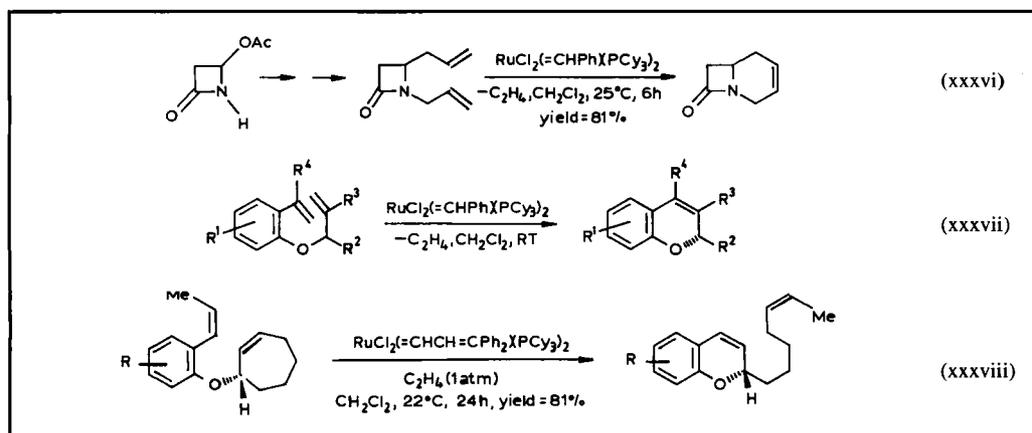
Thus, with dienes containing only R<sup>1</sup> substituents, cyclisation was nearly quantitative using only 2 mol % of the ruthenium complex RuCl<sub>2</sub>(=CHPh)(PCy<sub>3</sub>)<sub>2</sub> in methylene chloride for two hours at room temperature. Chromenes having NO<sub>2</sub>, Et<sub>3</sub>N, Br or MeO groups in the aromatic ring could be prepared efficiently by this method. On the other hand, 2-substituted chromenes have been obtained using the ruthenium vinylidene

complex RuCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>(=CHCH=CPh<sub>2</sub>) as a ring-closing catalyst, Equation (xxxviii), (61).

The net result is the opening of the seven-membered ring and the closing of the less strained six-membered ring. The function of the ethylene is to prevent the occurrence of an intermolecular metathesis reaction leading to a dimeric product. Preparation of an optically active substrate has been achieved using zirconium-catalysed kinetic resolution.

### Concluding Remarks

This concludes Part II of the paper on metathesis reactions catalysed by the platinum group metals, concerning applications of platinum metals metathesis catalysts in ring-closing reactions. The last part of this review, on acyclic diene metathesis reactions and ring opening metathesis reactions will appear in the October issue of *Platinum Metals Review*.



## References

- 38 G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, 1993, 115, 3800
- 39 M. Schuster and S. Blechert, *Angew. Chem., Int. Ed. Engl.*, 1997, 37, 2036
- 40 S. K. Armstrong, *J. Chem. Soc. Perkin Trans. I*, 1998, 371
- 41 R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare and M. O'Regan, *J. Am. Chem. Soc.*, 1992, 112, 3875
- 42 G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, 1992, 114, 5426
- 43 G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, 1992, 114, 7324
- 44 P. R. Hanson and D. S. Stoianova, *Tetrahedron Lett.*, 1999, 40, 3297
- 45 M. Lautens and G. Hughes, 13th Int. Symp. on Olefin Metathesis and Related Chemistry, Rolduc, Kerkrade, The Netherlands, July 11–15, 1999, *op. cit.*, (Ref. 5), Abstracts, p. 9
- 46 A. J. Phillips and A. D. Abell, *Aldrichim. Acta*, 1999, 32, 75
- 47 (a) S. J. Miller, H. E. Blackwell and R. H. Grubbs, *J. Am. Chem. Soc.*, 1996, 118, 9606; (b) F. P. J. T. Rutjes and H. E. Shoemaker, *Tetrahedron Lett.*, 1997, 38, 677
- 48 M. J. Morris and W. G. Stilbs, 10th Int. Symp. on Organosilicon Chemistry, Poznan, Poland, 1993, Abstracts, p. 267
- 49 B. Konig and C. Horn, *Synlett*, 1996, 1013
- 50 (a) S. J. Miller, S. H. Kim, Z. R. Chen and R. H. Grubbs, *J. Am. Chem. Soc.*, 1995, 117, 2108; (b) H. D. Maynard and R. H. Grubbs, *Polymer Prep. (ACS, Div. Polymer Chem.)*, 1998, 39, 523
- 51 G. W. Coates and R. H. Grubbs, *J. Am. Chem. Soc.*, 1996, 118, 229
- 52 A. Furstner and N. Kindler, *Tetrahedron Lett.*, 1996, 37, 7005
- 53 A. Kinoshita and M. Mori, *J. Org. Chem.*, 1996, 61, 8356
- 54 (a) Z. Yang, Y. He, D. Vourloumis, H. Vallberg and K. C. Nicolaou, *Angew. Chem., Int. Ed. Engl.*, 1997, 36, 166; (b) D. Meng, D. S. Su, A. Balog, P. Bertinato, E. J. Sorensen, S. J. Danishefsky, Y. H. Zheng, T. C. Chou, L. He and S. B. Horwitz, *J. Am. Chem. Soc.*, 1997, 119, 2733; (c) D. Schinzer, A. Limberg, A. Bauer, O. M. Böhm and M. Cordes, *Angew. Chem., Int. Ed. Engl.*, 1997, 36, 523
- 55 K. C. Nicolaou, N. Wissinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou and E. Hamel, *Nature*, 1997, 387, 268
- 56 (a) J. S. Clark and O. Hamelin, *Angew. Chem. Int. Ed.*, 2000, 39, 372; (b) J. D. Rainier, S. P. Allwein and J. M. Cox, *Org. Lett.*, 2000, 2, 231
- 57 (a) K. Hammer and K. Undheim, *Tetrahedron*, 1997, 53, 230; (b) H. E. Blackwell and R. H. Grubbs, *Angew. Chem. Int. Ed.*, 1998, 37, 3281; (c) T. D. Clark and M. R. Ghadiri, *J. Am. Chem. Soc.*, 1995, 117, 12364
- 58 C. M. Huwe and S. Blechert, *Synthesis*, 1997, 61
- 59 (a) A. G. M. Barret, S. P. D. Baugh, V. C. Gibson, M. R. Gilles, E. L. Marshall and P. A. Procopiou, *Chem. Commun.*, 1996, 2231; (b) A. G. M. Barret, S. P. D. Baugh, V. C. Gibson, M. R. Gilles, E. L. Marshall and P. A. Procopiou, *Chem. Commun.*, 1997, 155
- 60 S. Chang and R. H. Grubbs, *J. Org. Chem.*, 1998, 63, 864
- 61 J. P. A. Harrity, M. S. Visser, J. D. Gleason and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1997, 119, 1488

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## Organoplatinum(IV) Polymers

As hydrogen bonding can control the arrangement of molecules or ions in the solid state, it can be used in crystal engineering and in supramolecular synthesis. Some platinum coordination complexes contain hydrogen bonds, but little has been done with hydrogen bonding in organometallic platinum complexes.

Now, researchers at the University of Western Ontario in Canada have produced a series of organoplatinum(IV) complexes containing a range of functional groups which can take part in hydrogen bonding (C. S. A. Fraser, H. A. Jenkins, M. C. Jennings and R. J. Puddephatt, *Organometallics*, 2000, 19, (9), 1635–1642). The organoplatinum(IV) complexes were prepared by *trans*-oxidative addition of alkyl halide reagents  $RCH_2X$  ( $X = Cl$  or  $Br$ ) to  $[PtMe_2(bu_2bipy)]$ ,  $bu_2bipy = 4,4'$ -di-*tert*-butyl-2,2'-bipyridine. Dimers were formed via  $OH\cdots O$  or  $NH\cdots O$  hydrogen bonding, or polymers via  $NH\cdots Cl$  hydrogen bonding. Further derivatives could be prepared by reacting the complexes formed with  $AgBF_4$  in the presence of nicotinic acid or 4,4'-bipyridyl, and one of these, with two hydrogen-bonding groups, formed a polymer.

Extended structures can thus be designed with organoplatinum complexes via hydrogen bonding.