Highlights

Pd-Catalyzed Enantioselective Allylic Substitution: New Strategic Options for the Total Synthesis of Natural Products

*Timm Graening and Hans-Günther Schmalz**

*T*he enantioselective version of palladium-catalyzed allylic substitution, sometimes referred to as AAA (asymmetric allylic alkylation), has emerged as a powerful synthetic tool.[1] Since the first report of a stoichiometric AAA reaction in the 1970s,[2] it took almost 20 years of research until effective catalytic systems based on chiral ligands were developed. The major challenge in conducting such reactions enantioselectively arises from the fact that both the departure of the allylic leaving group, resulting in the formation of a cationic π-allyl–Pd complex and, in most cases, the attack of the nucleophile occur on the π face of the substrate opposite to the metal. Asymmetric induction therefore proceeds remote to the employed chiral ligands. However, some particularly successful concepts to address this issue have been devised, and over 100 catalysts have been developed.[3]

Besides high levels of asymmetric induction, advantages of the AAA methodology are a broad tolerance towards functional groups and, in contrast to many other catalytic asymmetric methods, a great flexibility in the bond type to be formed. For instance, H, O, N, S, P, and C nucleophiles can be employed. Among the many new opportunities thus arising for the synthetic
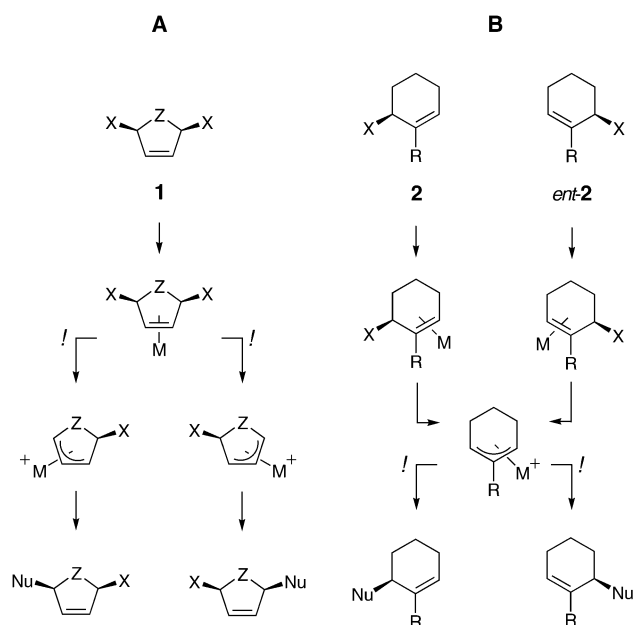
chemist,[4] AAA reactions of cyclic substrates of type **1** and **2** have recently proven to be of particular value as they

1 Z = CH$_2$CH$_2$, CH$_2$, O   *rac*-**2**
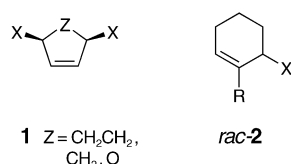
lead to novel and highly efficient strategies in the total synthesis of natural products. The abundance of the corresponding cyclic subunits in natural products together with the inherent potential in controlling the stereochemistry of cyclic scaffolds in the course of a synthesis makes these building blocks very attractive.

The reactions of *meso* compounds **1** and those of chiral cyclohexenes **2** with allylic leaving groups X differ in the nature of the enantiodiscriminating step (pathways **A** and **B**, respectively, in Scheme 1). In the substitution of *meso* compounds of type **1** (path **A**), the formation of the intermediate η³-π-allyl–metal complex (ionization) constitutes the enantiodiscriminating step. The nucleophile is then introduced at the least-hindered allyl terminus with overall retention of configuration. Following path **B**, substrates of type **2** can be employed as racemic mixtures. With

[*] Prof. Dr. H.-G. Schmalz,
Dipl.-Chem. T. Graening
Institut für Organische Chemie
Universität zu Köln
Greinstrasse 4, 50939 Köln (Germany)
Fax: (+49) 221-470-3064
E-mail: schmalz@uni-koeln.de

Scheme 1. Different reaction pathways of the Pd-catalyzed substitution of *meso*-**1** (path A) and *rac*-**2** (path B).

the formation of the π-allyl complex, the stereochemical information of the substrate is lost and in this case the attack of the nucleophile from the face opposite to the metal represents the enantiodiscriminating step. According to Trost, this deracemization process can be regarded as a DYKAT (dynamic kinetic asymmetric transformation).[4] Both pathways allow the selective induction of chirality and make up the starting point of some very efficient natural product syntheses published recently.

In a synthesis of *epi*-hygromycin A (Scheme 2) Trost et al. made use of four Pd-catalyzed allylic-substitution reactions employing versatile diphosphane bisamide ligands of type **3** in all cases.[5]
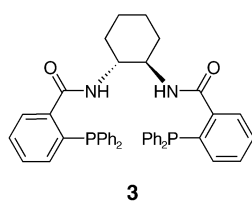

As a result of a larger bite angle of the phosphane groups, these ligands are believed to envelop the allylic system. The reaction of the *meso*-dihydrofuran **4** with the nucleophile **5** as an acyl anion equivalent afforded the monosubstitution product **6** in excellent yield and enantioselectivity (93% *ee*). The second allylic substitution was carried out with the ligand *ent*-**3**. Although a chiral ligand is not necessary in this case, a higher reactivity was observed. Moreover, the phenolic glycoside **10** was formed with perfect *cis* diastereoselectivity, in contrast to a previous synthesis in which the glycosylation step led to an anomeric mixture. The subsequent steps in the synthesis of **10** involved dihydroxylation of the double bond, Horner–Wadsworth–Emmons olefination, and attachment of the aminocyclitol moiety **9**.

The synthesis of the aminocyclitol building block **9** (Scheme 3) started from the readily available racemic conduritol tetraester *rac*-**11**. In a remarkable twofold asymmetric allylic substitution process, both enantiomers were converted into the same bisbenzoate **15** by employing the chiral ligand **3**.[5b] The ionization of the tetraesters **11** and *ent*-**11** proceeded with different reaction
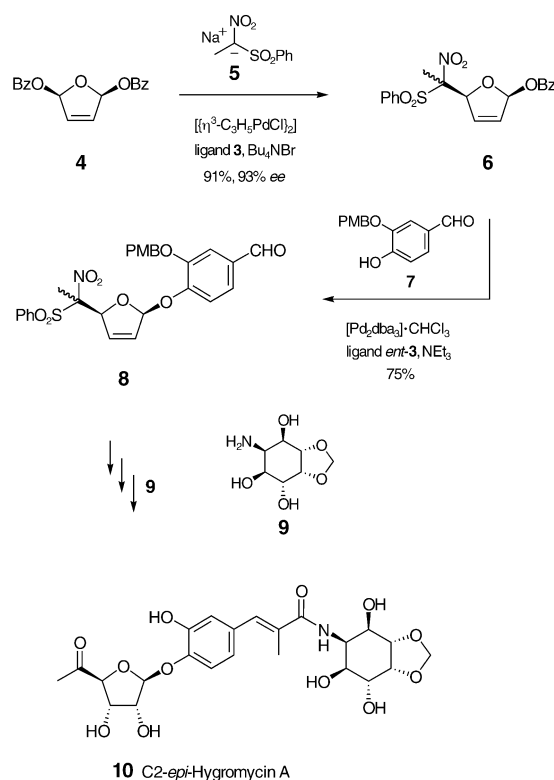
Scheme 2. Synthesis of *epi*-hygromycin A by Trost and co-workers. PMB = *para*-methoxybenzyl, dba = *trans,trans*-dibenzylideneacetone.
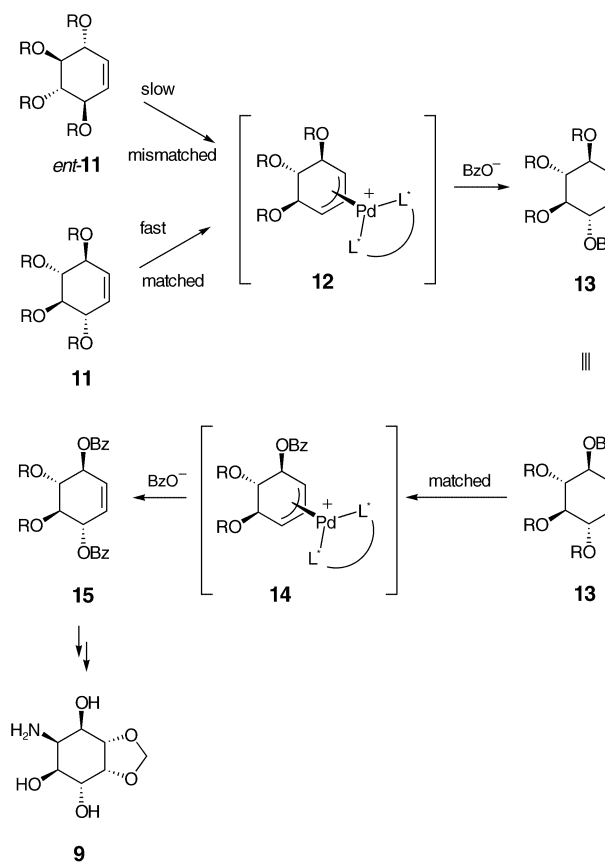

Scheme 3. Synthesis of aminocyclitol **9** by a twofold allylic substitution/deracemization strategy. Bz = benzoyl.

rates, representing matched and mismatched cases, respectively. With the tetraacetate *rac*-**11** (R = Ac) a nearly perfect kinetic resolution was observed and only 50 % (i.e. the enantiomer **11**) of the starting material was converted. When the leaving group was changed from an acetate to a more reactive alkyl carbonate, both enantiomers were rapidly converted into complex **12**. Attack of the benzoate nucleophile led initially to the enantiomerically pure monosubstitution product **13** (R = $CO_2CH_2CCl_3$), which still bears an allylic leaving group (with the same configuration as in the matched substrate **11**). A second substitution then gave rise to conduritol tetraester **15** (> 99 % *ee*). Reductive cleavage of the carbonate groups R and desymmetrization by derivatization of one of the homotopic hydroxy groups was followed by five further steps to yield the required aminocyclitol derivative **9**.

Notably, the straightforward strategy used for the synthesis of the glycoside part of *epi*-hygromycin A was not based on a sugar-derived starting material from the chiral pool. Instead, the *meso* compound **4** was used, which is not
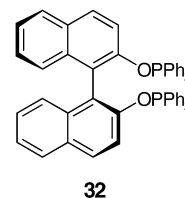
suited for common enzymatic desymmetrization methods.

AAA reactions also provide easy access to chiral nitrogen-substituted cyclopentene derivatives, which may serve as building blocks for the synthesis of alkaloids, as demonstrated by Blechert and co-workers. In a recent synthesis of (−)-swainsonine (**22**, Scheme 4) the key intermediate **17** was prepared by an intramolecular substitution of one of the enantiotopic carbamate groups of **16**.[6a] As demonstrated earlier, ligand **3** gives excellent *ee* in this transformation if NEt_3 is used as a base.[6b] The cyclization product **17** already contains the two vicinal stereocenters found in (−)-swainsonine (**22**). Upon treatment of the allyltosylamide **18** with the Grubbs catalyst under an atmosphere of ethylene, a remarkable ring-opening/ring-closing-metathesis cascade took place. In the reaction, the oxygen-bearing stereocenter was transferred to the side chain of the newly formed dihydropyrrole **19**. Only a few more steps were required to set up the indolizidine framework, and the synthesis was completed by dihydroxylation and deprotection.
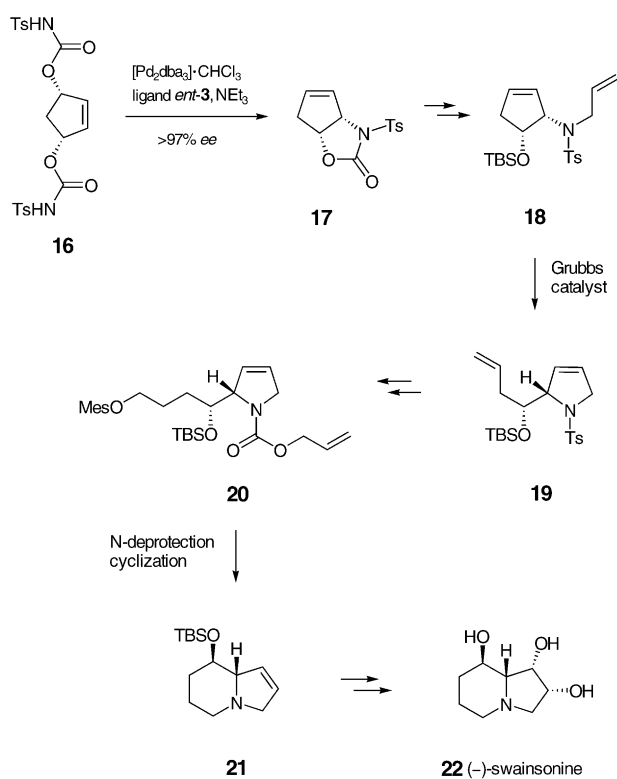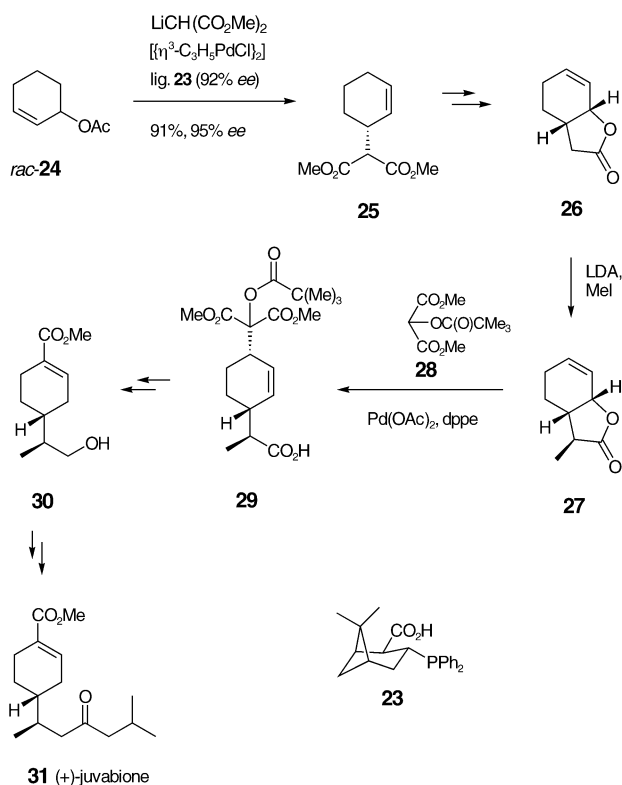
In the synthesis of (+)-juvabione (**31**) by Bergner and Helmchen (Scheme 5), two Pd-catalyzed allylic substitutions were used to attach the side chains onto the cyclohexene ring.[7] At first, asymmetric alkylation of cyclohexenylacetate (*rac*-**24**) with lithium dimethyl malonate in the presence of ligand **23** afforded **25** in 91 % yield with 95 % *ee*. After a sequence of Krapcho decarbomethoxylation, saponification, iodolactonization, and dehydrohalogenation, the enantiomerically pure key intermediate **26** was obtained, which was also used in the synthesis of (−)-wine lactone.[7b] Fully diastereoselective α-methylation afforded the lactone **27** in which the C=C bond is favorably positioned for a second allylic substitution. The 2-acyloxymalonate **28** was used as a formyl anion equivalent in the second Pd-catalyzed allylation, which proceeded with complete regio- and diastereoselectivity to give **29**. The final part of the synthesis was initiated by reduction and glycol cleavage to liberate the masked carboxy group. This was followed by methylation and isomerization of the double bond to yield **30**, which was finally converted into (+)-juvabione (**31**) in three steps.

Recently it was demonstrated by Mori et al. that the use of *N*-sulfonated *ortho*-bromoaniline as a nucleophile in an AAA process of type **B** paves the way for a simple assembly of optically active indolines by means of a Heck cyclization. On this basis, a new strategy for the synthesis of *Strychnos* alkaloids was devised and demonstrated in the synthesis of (−)-dehydrotubifoline (**42**) and (−)-tubifoline (Scheme 6).[8] In the first step, the Pd-catalyzed reaction of the cyclohexene *rac*-**34** with the anilide **33** in the presence of (*S*)-binapo (**32**) as a

Scheme 4. Synthesis of (−)-swainsonine by Blechert and co-workers. TBS = *tert*-butyldimethylsilyl, Ts = *para*-toluenesulfonyl.

chiral ligand yielded the building block **35** in 84 % *ee*. After recrystallization enantiomerically pure **35** was obtained. A nitrile group was introduced and Heck cyclization of **36** gave rise to the

Scheme 5. Synthesis of (+)-juvabione by Helmchen and Bergner. dppe = 1,2-Bis(diphenylphosphanyl)ethane.

annulated indoline **37**, in which the crucial quaternary stereocenter had been installed. This delivered the cyclohexene double bond in the correct position for the cyclization of **38** to **39** through Pd-mediated allylic oxidation. The double bond was shifted further by one position in a four-step sequence to set the stage for the final Heck cyclization.

tion. After removal of the *N*-protecting groups and alkylation of the more reactive pyrrolidine nitrogen atom with a iododalkene C_4-unit (→**41**), a Heck reaction directly afforded the target compound **42**. The synthesis is characterized by the fact that all cyclizations are performed in a fully diastereoselective manner using Pd-catalyzed reac-

tions and that the absolute stereochemical information was established in the initial AAA reaction.

In a spectacular synthesis of (−)-codeine (**53**) and (−)-morphine (**54**, Scheme 7) Trost and Tang followed a related general strategy for the stereo-controlled construction of a complex cyclic framework around a cyclohexane ring.[9] Asymmetric allylic substitution of *rac*-**44** with the functionalized phenol **43** afforded the key intermediate **46** (87% *ee*). The enantiomeric purity was enhanced to 96% *ee* by recrystallization at the stage of the homologous nitrile **47**. In an intramolecular Heck reaction, the second (quaternary) stereocenter was established with complete diastereoselectivity. The product **48** also served as an intermediate in the total synthesis of (−)-galanthamine.[9b] For the synthesis of morphine, the common intermediate **48** was first converted into the bromoalkene (*Z*)-**49** before a second Heck cyclization was used to build up the phenanthrene scaffold with a correctly placed double bond. Allylic oxidation of **50** (SeO$_2$, then Dess–Martin periodinane reagent) followed by diastereoselective reduction with DIBAH (diisobutylaluminum hydride) gave the alcohol **51**, which was then converted into the secondary amine **52**. The final cyclization by means of a photochemically induced intramolecular hydroamination yielded (−)-codeine (**53**, R = Me), from which (−)-morphine (**54**, R = H) was prepared by a known protocol. A noteworthy feature of this latest synthesis of
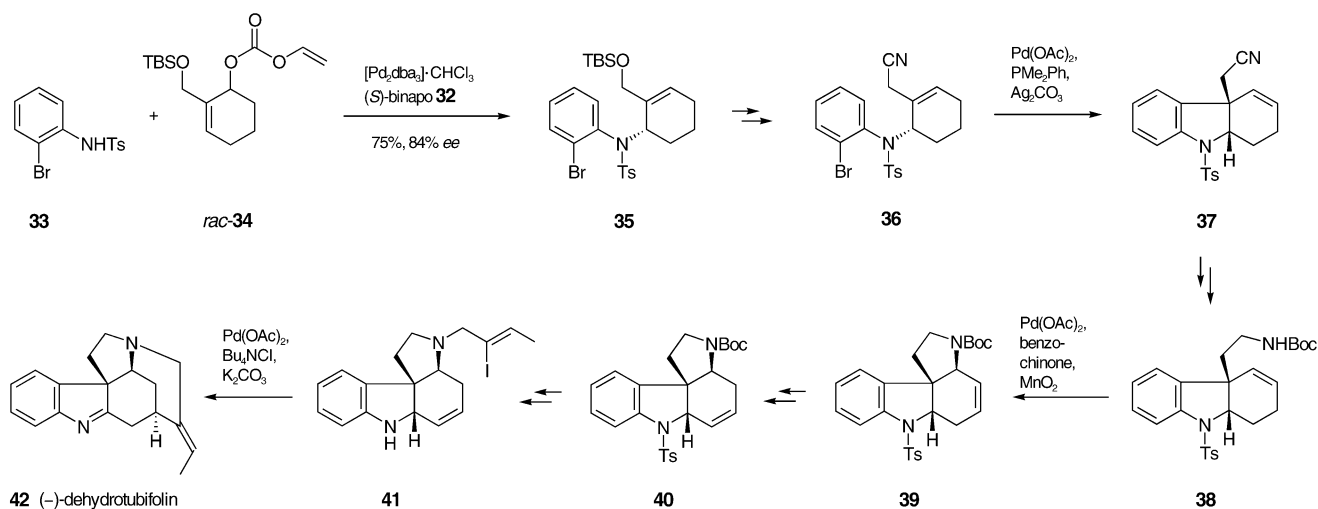
Scheme 6. Synthesis of (−)-dehydrotubifoline by Mori et al. following an AAA/Heck cyclization strategy. Boc = *tert*-butyloxycarbonyl.
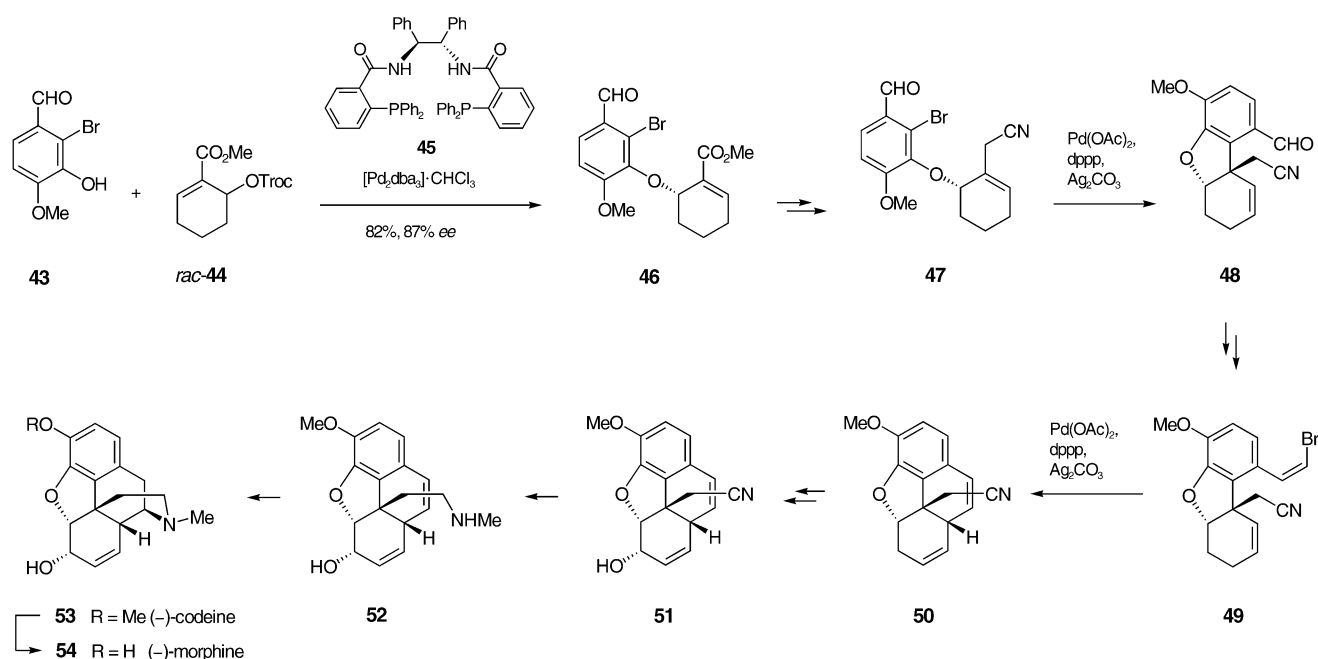
Scheme 7. Synthesis of (−)-morphine by Trost and Tang. Troc = 2,2,2,-trichloroethoxycarbonyl, dppp = bis(diphenylphosphanyl)propane.

the prominent target molecule morphine is the masterly use of the double bond in the pivotal cyclohexene ring to serve as a platform for three successive Pd-catalyzed transformations.[10]

The few selected examples discussed herein show only a facet of the synthetic scope of asymmetric allylic substitution. Besides the manifold options for further transformation of the double bond of the AAA reaction products, the true synthetic power arises from the variety of functionalized building blocks that can be enantioselectively joined in a convergent manner.

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[10] For recent reviews on morphine syntheses, see: a) B. H. Novak, T. Hudlicky, J. W. Reed, J. Mulzer, D. Trauner, *Curr. Org. Chem.* **2000**, *4*, 343; b) P. R. Blakemore, J. D. White, *Chem. Commun.* **2002**, 1159.