Recent advances in the semi-pinacol rearrangement of α-hydroxy epoxides and related compounds

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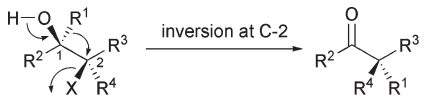
The semi-pinacol rearrangement is fast becoming an extremely reliable reaction in organic synthesis allowing the rapid construction of relatively complex stereodefined products in high yield. Recent advances in asymmetric synthesis have also enabled enantiopure precursors to partake in the rearrangement showing that extremely high levels of stereospecificity are observed. In this *critical review* recent advances in the semi-pinacol rearrangement over the past 15 years are examined which demonstrate the extremely high utility of this reaction towards the development of structurally diverse organic building blocks (74 references).

1 Introduction – historical perspective

This review is written as a continuation of the classic work on the semi-pinacol rearrangement by D. L. Coveney[1] and is intended to cover selected highlights from the literature since its publication in 1991. Emphasis will be on the observed increase in synthetic utility of the semi-pinacol rearrangement, both in terms of the nature of the migrating group, the leaving group as well as the incorporation of asymmetry to the rearrangement. It is hoped therefore that this review will act more as an overview to the period rather than comprehensively catalogue all semi-pinacol reactions from the literature; however, in order to appreciate the more recent aspects to this rearrangement, a brief historical perspective will be provided.

The term "semi-pinacol" was originally defined by Tiffeneau to describe a rearrangement involving migration toward the secondary centre of a tertiary, secondary 1,2-diol.[1] However, it has more recently been refined to denote variants of the rearrangement which employ leaving groups other than –OH (Scheme 1).[2] Such leaving groups traditionally include: the halogens (Cl, Br); activated primary amines; sulfides (–SR) and selenides (–SeR); however, a growing number of semi-pinacol rearrangements utilise an epoxide opening to facilitate migration of an adjacent group. In this way, the "leaving group" is not extruded from the molecule during the rearrangement, but remains as a source of functionality in the product; the stereospecific rearrangement therefore allows control over this newly formed chiral centre, with a high degree of fidelity. During the reaction, a C=O double bond is formed at C-1 with concomitant migration of a group from C-1 to C-2, along with loss of a leaving group from C-2 with inversion of stereochemistry at the migration terminus (C-2).

In 1968, Cheer and Johnson described this rearrangement on conformationally mobile epoxides, which resulted in ring-expanded products, *e.g.* indane-1-ols **2** and **3** gave 1- and 2-tetralones **4** and **5** respectively, using either homogeneous boron trifluoride ($BF_3{\cdot}OEt_2$) or heterogeneous alumina (Al_2O_3) to promote the reaction. During this study it was revealed that alumina catalyses the rearrangement in a stereoselective manner, whilst the Lewis-acid catalysed reaction lacks any stereoselectivity, lending support to the notion that these reactions proceed through conformationally immobile, surface-absorbed transitions states. Epoxy alcohols **2** and **3** were chosen as representative compounds since they are



X=leaving group, when X=OH reaction termed pinacol rearr^t
Migratory aptitude: $R^1 > R^2$

Scheme 1

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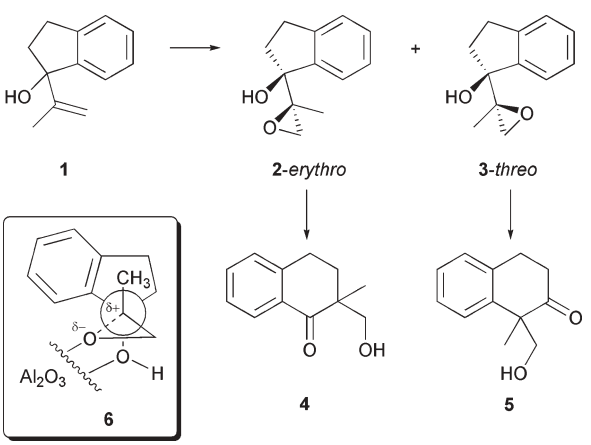
particularly suited to demonstrate the stereochemical implications derived from a rigid transition state, in which both oxygen atoms of the epoxy alcohol attach to the surface of the catalyst.[3]

The investigators set out to reveal the mechanism, and in doing so postulated that if *both* oxygen atoms are adsorbed onto the catalyst surface (*i.e.* they are *almost* mutually eclipsed, see **6**) then the migrating group in the rearrangement should be held *anti* to the epoxide oxygen (Scheme 2). In contrast, it was predicted that in the case of epoxide-oxygen adsorption alone (*e.g.* with $BF_3{\cdot}OEt_2$), stereochemical predictions would be less clear. In this case, it was expected that aryl migration would dominate in the rearrangement of either diastereomer, **2** and **3**. To test this hypothesis, the synthesis of epoxy alcohols **2** and **3** were prepared by epoxidation of allylic alcohol **1**. Under the rearrangement conditions catalysed by alumina (*via* a conformationally rigid transition state) a high degree of stereoselectivity was observed, thus the *erythro* isomer **2** gave **4** whilst the *threo* isomer **3** gave **5**. In contrast, rearrangement of either diastereomer with $BF_3{\cdot}OEt_2$ resulted in a mixture of isomers being formed, in which **5** predominated; this was explained by the increased relative migratory aptitude of the phenyl ring over the alkyl substituent, and is a reflection of conformational effects.[3]

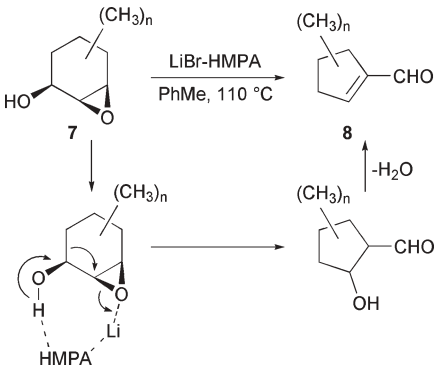
These early investigations into the semi-pinacol rearrangement also demonstrated that the *erythro* isomer **2** rearranges faster then the *threo* isomer **3** with alumina. Moreover, the stereochemical outcome of this reaction coupled with the lack of stereoselectivity in the Lewis acid catalysed rearrangement, suggests that these reactions proceed through "surface-adsorbed" transition states, *e.g.* **6**.[3]

Subsequent work on the rearrangement of epoxy alcohols was carried out by Magnusson and Thoren in 1973.[4] They required substituted cyclopentene-1-carbaldehydes, such as **8**, as part of a research programme concerned with the synthesis of sesquiterpenoid degradation products. Previous work by Rickborn and Gerkin on the ring-contraction of cyclopentane carbaldehydes prompted Magnusson and Thoren to use LiBr–HMPA in refluxing toluene to induce the rearrangement of substituted cyclohexane epoxy alcohols **7** (Scheme 3).

Although significant amounts of isomeric aldehydes were formed during the rearrangement of **7** to **8**, the synthesis



Scheme 2

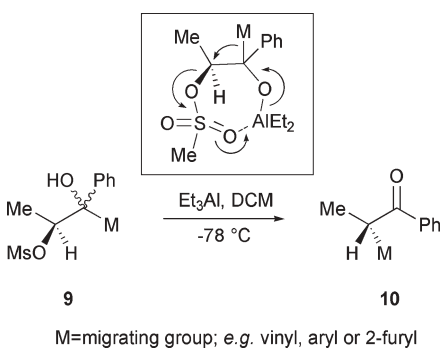


Scheme 3

offered a novel route to cyclopentene-1-carbaldehydes in high yield, *via* the ring-contraction shown in Scheme 3.[4]

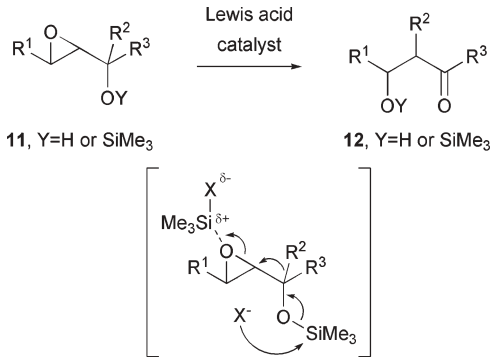
After these initial forays into the semi-pinacol rearrangement, the eighties saw an explosion of research relating to the reaction. Tsuchihashi, Suzuki and Yamamoto developed numerous variations of this process which lead to the synthesis of optically pure α-aryl and α-vinyl ketones,[5–9] the stereospecific 1,2-migration of alkyl groups,[10] a catalytic version of the rearrangement utilising epoxy silyl ethers (the so-called epoxy silyl ether rearrangement),[6,7] the stereoselective construction of quaternary carbon centres,[11] including the first asymmetric synthesis of Mycinolide IV[9] and the construction of up to four contiguous stereocentres.[12] During this period, they were able to lay the foundation for a large majority of reactions related to the semi-pinacol rearrangement seen in today's literature. For example, the extremely facile rearrangement of α-hydroxy methane sulfonates, *e.g.* **9**, promoted by triethylaluminium (1.2 eq.) to generate optically pure ketones, such as **10** (Scheme 4).[5]

The mode of migration was proven to be stereospecific due to the resulting inversion of a pre-existing chiral centre in the rearrangement precursor. In order to examine the scope of the reaction, various chiral 1,2-diols were prepared and tested; of the substrates studied, all were obtained in good to excellent yield (75–96%) and excellent enantiomeric excess (>99%). The level of activation of the α-hydroxy mesylates was found to be high enough to permit the successful migration of vinyl (75%) and 2-furyl (75%) groups. Also, under these mild rearrangement conditions the α-vinyl ketone did not undergo further isomerisation to the conjugated ketone product.[5] The reaction



M=migrating group; *e.g.* vinyl, aryl or 2-furyl

Scheme 4



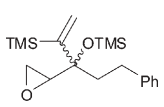
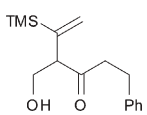
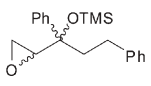
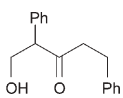
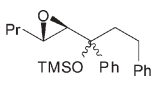
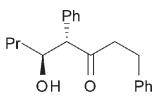
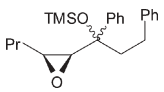
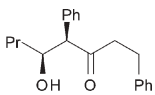
Scheme 5

was believed to proceed *via* a cyclic intermediate (see box, Scheme 4), where the hard–hard interaction between the Al–OMs groups and the pushing effect of the aluminium oxide ensured the concerted nature of the process and thus allowed for complete chirality transfer to the new stereogenic centre.[5]

Suzuki and Tsuchihashi went on to expand the process by exploiting an epoxy silyl ether semi-pinacol rearrangement to create an effective route to stereodefined aldol adducts.[6,7,11] Here they found that TMSX was capable of promoting the rearrangement and therefore could be reduced to catalytic amounts in the process (Scheme 5).[6]

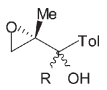
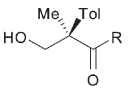
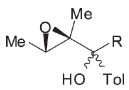
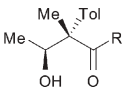
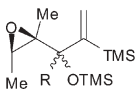
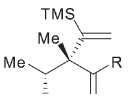
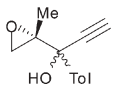
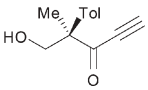
The scope and limitation of the reaction was probed and good to excellent yields were obtained with both TMSI and TMSOTf. Incorporating an α-trimethylsilylalkenyl group resulted in single isomers as the sole detectable products (Table 1).[6] However, in the case of phenyl (a group of weaker migratory aptitude than the α-trimethylsilylalkenyl) the efficiency of the reaction was inferior in terms of rate and turnover (entries 1 and 2). It was also shown that *cis*-epoxides were more problematic than the *trans*-analogues (entries 3 and 4); indeed the *cis*-epoxide (entry 4) returned only starting material with TMSI, whilst using TMSOTf resulted in 65% yield of the rearranged product, contaminated with 5% of the

Table 1 Selected examples of Suzuki's and Tsuchihashi's epoxy silyl ether semi-pinacol rearrangement

Entry	Starting material	Product	Me_3SiOTf^a (%)	Me_3SiI^a (%)
1			99[b]	91
2			72	12
3			76	62
4			65	—

[a] 5 mol% catalyst. [b] Isolated yields of purified material.

Table 2 The use of the semi-pinacol rearrangement for the stereoselective construction of quaternary carbon centres

Entry	Epoxy alcohol	Product	Yield[a] (%)	Isomeric purity (%)
1			100[b]	—[c]
2			85	>99
3			89	>99
4			97	—[c]

[a] Isolated yields. [b] 2 eq. $BF_3{\cdot}OEt_2$, DCM, −78 °C. [c] 87 ± 1% ee.

threo-isomer, which suggests that these types of compound present a limitation to the method. Overall, it was found that terminal epoxides are best catalysed with TMSOTf (less nucleophilic TfO^- cf. I^-), whilst non-terminal epoxides TMSI is the catalyst of choice.[6] Further advances of the protocol also saw the stereoselective formation of quaternary carbon centres (Table 2).[11] Rearrangement of the epoxy alcohols was smoothly effected by their treatment with $BF_3{\cdot}OEt_2$ (2 eq.) in DCM at −78 °C, giving rise to the corresponding aldol adducts in excellent yields. No racemisation was observed under these conditions and the reaction also worked well with non-terminal *trans*-epoxy alcohols (entry 2). However, again *cis*-epoxides (entry 3) caused problems, where some loss of stereospecificity was seen, suggesting a limitation to the procedure. A possible explanation for this outcome is given, Fig. 1;[11] severe steric interaction between the γ-methyl group and the α-substituent prevent the molecule from adopting the anti-periplanar conformation requisite for the rearrangement. Interestingly, in the case of the alkynyl derivative (entry 4), exclusive migration of the *p*-tolyl group was observed, confirming the very low migratory aptitude of the alkynyl group in this type of rearrangement, *vide infra*.[11]

2 Natural product syntheses

2.1 Fasicularin, avenaciolide and isoavenaciolide

The use of the semi-pinacol rearrangement in the context of total synthesis has become increasingly more important, particularly as enantiomerically enriched starting materials are becoming more widely available. In fact, early applications

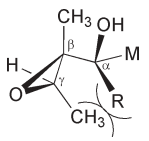
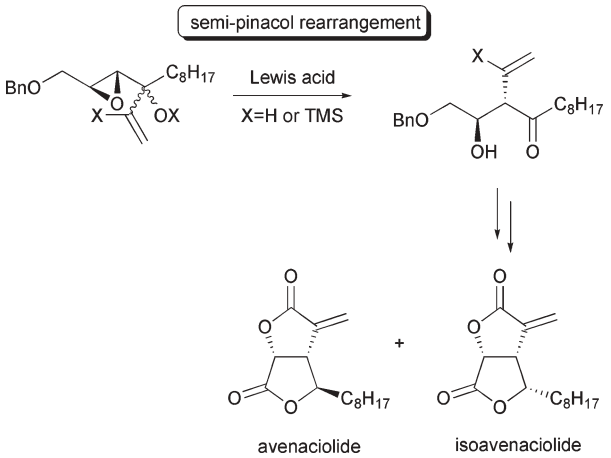


Fig. 1



Scheme 6

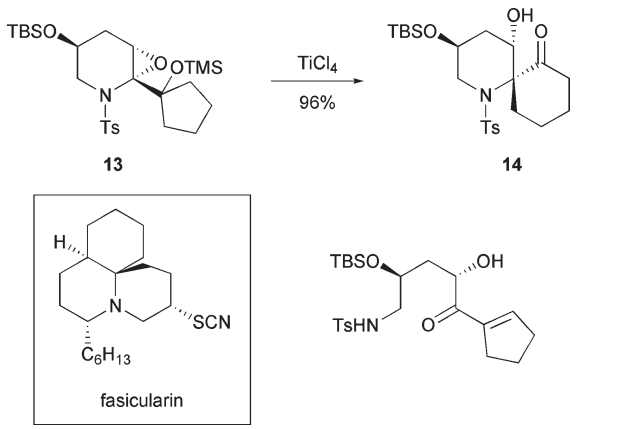
of the rearrangement by Tsuchihashi and Suzuki led to an elegant synthesis of a pair of isomeric lactones, avenaciolide and isoavenaciolide, utilising a silicon group to affect the outcome of a subsequent reduction of the rearrangement product (Scheme 6).[8,13]

More recently, an asymmetric formal total synthesis of fasicularin was reported, whereby the semi-pinacol rearrangement was successfully integrated into the synthetic plan to generate a critical spirocyclic ketone, and concomitantly incorporate the requisite stereogenic centre of fasicularin which lies adjacent to the nitrogen atom (**13** to **14**).[14]

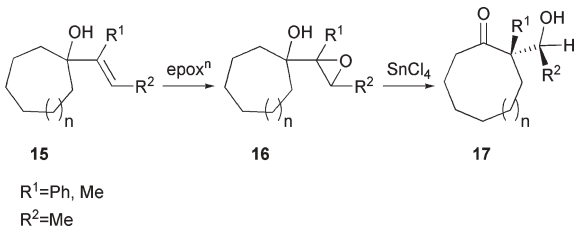
A number of features of the reaction were found to be of interest: (a) the overall efficiency of the ring-expansion, especially the clean stereochemical outcome in the formation of the spiro-ring junction, which had been dictated by the epoxide; and (b) the requirement of the trimethylsilyl ether for an effective process (the corresponding alcohol give rise to a complex mixture of products under the same conditions, from which the desired product **14** and the acyclic ketone (Scheme 7) were recovered in a disappointing 1.4 : 1 ratio and 55% yield).

2.2 Carbon macrocycles

Further use of the semi-pinacol rearrangement towards ring expansion reactions for the potential of synthesising



Scheme 7



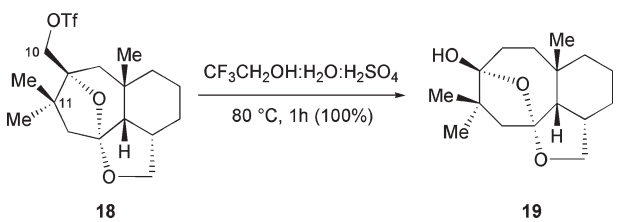
Scheme 8

macrocyclic natural products has also been demonstrated by Marson and co-workers with its application to the preparation of medium-ring aldol adducts from 2,3-epoxy alcohols of a lower homologue.[15] They utilised the semi-pinacol rearrangement as an alternative to the Tiffeneau–Demjanov[16] ring expansion, which precluded the need to handle aliphatic diazoalkanes, whilst allowing the introduction of new stereocentres of defined configuration into the products (Scheme 8).[15]

2.3 Taxane diterpenes

Other applications of the semi-pinacol rearrangement to ring-expansions in natural product synthesis can be found in their approaches towards the Taxol™ framework by Magnus *et al.*[17,18] In their efforts to secure a suitable method for the construction of the eight-membered B-ring of the taxanes, a semi-pinacol rearrangement was proposed. In the event, activation of the C-10 alcohol of **18**, by formation of a triflate, followed by treatment with aqueous acidic trifluoroethanol resulted in a rapid and clean conversion to the spiro-hemiketal **19**, in an impressive 100% yield (Scheme 9).[17]

Subsequent studies by the same group showed that the semi-pinacol rearrangement can also be effective towards the synthesis of other ring-expanded products of the taxane diterpene core and an excellent report on this subject has been published.[18] In the above example, it should be noted that the less substituted of the two possible migrating partners migrates; in general, in acyclic systems, the migratory aptitude of a *tert*-butyl group is 240 times greater than that of an ethyl group,[19] and thus the more substituted C-11 in **18** might be expected to migrate preferentially. However, in cyclic systems, such as **18**, these rearrangements are often controlled by powerful stereoelectronic effects whereby the observed migration is governed by the relative alignment of the molecular orbitals involved.[18] In such cases, when one hopes to predict the outcome of a planned 1,2-alkyl shift, careful thought must be given to the orientation of the bonds involved. The orientation of the donating electron pair should



Scheme 9

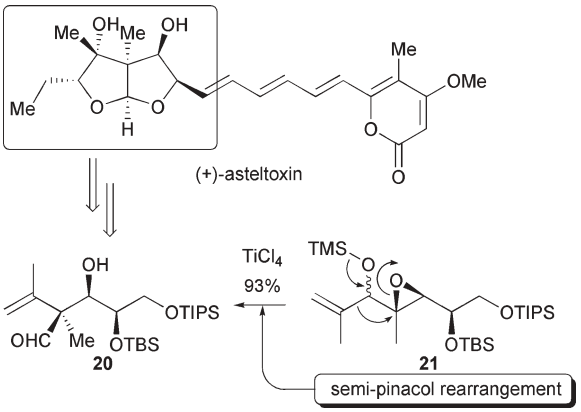
be anti-periplanar to the bond that is migrating and that this migrating bond is also anti-periplanar to the leaving group. Not only that, but it is possible that in a given case, the group which does *not* migrate remains, not because it has a lower inherent migratory aptitude, but because it is much better at stabilising the carbocation which forms (albeit transiently). In addition to this, the tendency for a group to migrate is also related to its ability to partake in anchimeric assistance, and on the nature of the departing nucleofuge.[20] With this in mind however, the rearrangement **18** to **19** only occurred with migration of the C–9 bond (pathway a, Fig. 2), exemplifying not only the subtleties involved in these systems, but also the large structural changes that can be implemented by the semi-pinacol rearrangement.

Further studies by the same research group went on to apply second, third and fourth semi-pinacol rearrangement-based approaches to related substrates in the hope of securing the rearranged product at the correct oxidation level for subsequent manipulations.[18] In summary, it was found that the eight-membered B-ring of the taxanes could be isolated in very high yield and regiospecificity, albeit by having to activate the alcohol, by the formation of the extremely reactive triflate, to force the rearrangement.

2.4 Total synthesis of (+)-asteltoxin

(+)-Asteltoxin was isolated by Steyn, Vleggaar and co-workers from the toxic maize cultures of *aspergillus stellatus* Curzi,[21] and through extensive ^{13}C and ^{18}O labelling experiments, Vleggaar was able to propose an epoxide-mediated 1,2-alkyl shift (semi-pinacol rearrangement) as part of its biosynthesis.[21] Inspired by this postulate, Cha and co-workers set about the synthesis of (+)-asteltoxin hoping to incorporate the epoxide-mediated semi-pinacol rearrangement into their biomimetic approach.[22] Among the known repertoire of stereoselective 1,2-rearrangement reactions of epoxides and their derivatives, the Tsuchihashi–Suzuki[5–12] and Yamamoto[7,23] procedures seemed particularly well suited for the enantioselective synthesis of the chosen precursors, in close parallel with the proposed biosynthesis (Scheme 10).

The requisite substrate **21** for the projected Tsuchihashi–Suzuki reaction was readily prepared by a sequence of well precedented transformations, whilst the precursor to the Yamamoto rearrangement was deemed to be more challenging, and may have brought about further difficulties in subsequent steps. As such, the epoxy silyl ether rearrangement, using the method of Tsuchihashi and Suzuki, was investigated. Having synthesised the pivotal epoxy silyl ether **21**, the scene was set to carry out the crucial rearrangement to afford **20**. Thus, exposing the epoxy silyl ether to $TiCl_4$ resulted in the desired rearrangement and production of aldehyde **20** in 93% yield. Since both epimers smoothly underwent the acid-catalysed semi-pinacol rearrangement, further investigation to secure a single isomer was not warranted. Interestingly, rearrangement of the corresponding acetonide of **21** (rather than the silicon protecting groups) using either $TiCl_4$ or $SnCl_4$ gave only poor (40–45%) yields of the desired product; conformationally restricting the rotational degrees of freedom in this way may be the cause of these low yields.



Scheme 10

A second-generation approach by Cha and co-workers to an advanced intermediate of asteltoxin also included a semi-pinacol rearrangement.[22] This time the extended alkenyl side-chain was incorporated (see **22**, Scheme 11) which acted to streamline the synthesis by eliminating several transformations which had previously been necessary to incorporate it. Not surprisingly, the rearrangement of the related epoxy silyl ether **22** progressed well in 96% yield to give aldehyde **23**, in parallel with the route from **21** (Scheme 11).

The work outlined above illustrates the powerful synthetic utility of the stereoselective 1,2-rearrangement of readily available enantiopure 2,3-epoxy alcohols and their silyl ethers. The remarkably efficient construction of a new quaternary centre embedded in a challenging array of multiple stereocentres in an easily predictable and well-defined configuration was also demonstrated. Compared to the innovation and advances in methodology as a whole, applications of these powerful epoxide rearrangements in natural product synthesis lag behind. This is surprising in view of the impressive advances in enantioselective epoxidation reactions over the years which allows direct access to the epoxy alcohol precursors in high enantiomeric purity.

2.5 Synthetic approaches to ingenol

Based on their successes at employing the semi-pinacol rearrangement towards the synthesis of asteltoxin,[22] the Cha research group also utilised the reaction to rapidly assemble

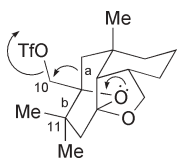
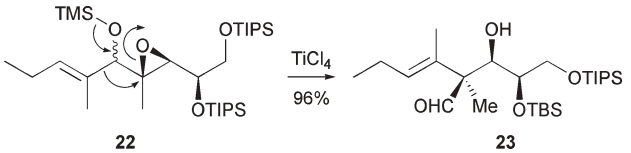
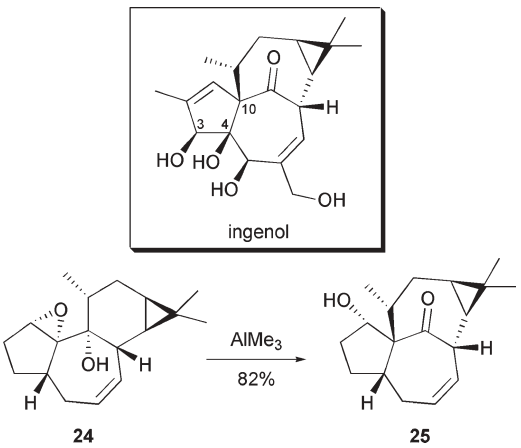


Fig. 2



Scheme 11

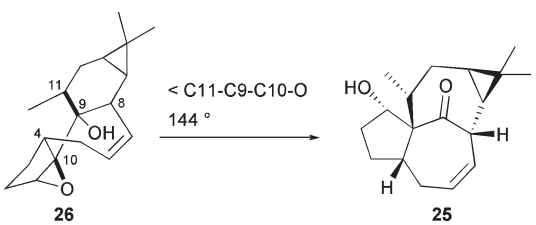


Scheme 12

the carbocyclic core of ingenol (Scheme 12).[24,25] The C-3 monoester of ingenol is known to be amongst the most potent tumour promoters, and it is believed that this activity is associated with binding to protein kinase C and with mimicking the function of the endogenous ligand 1,2-diacylglycerol.[24] Contrary to this, some esters of ingenol have been reported to possess anti-leukemic and anti-HIV activity. The highly strained ''inside–outside'' intrabridgehead stereochemistry of the BC ring system presents a particularly taxing synthetic challenge, and as such several attempts, some successful, have been made at its synthesis.

However, an efficient, convergent approach to ingenol remains to be seen. To this end, Cha and co-workers have exploited the semi-pinacol rearrangement, once again, to rapidly assemble the carbocyclic core of this interesting molecule. Their key strategy for addressing the inside-outside *trans* stereochemistry of ingenol, along with concomitant, diastereoselective construction of the quaternary C-10 centre, relied on the 1,2-alkyl shift **24** to **25**, based on a Tsuchihashi–Suzuki semi-pinacol rearrangement of a 2,3-epoxy alcohol or silyl ether. Molecular modeling allowed predictions to be made relating to the stereochemistry about C-4, and its importance to the pivotal Lewis acid catalysed rearrangement of **24**, with respect to the anti-periplanar stereoelectronic requirements necessary to ensure the desired migration of the C-9–C-11 (ingenol numbering) bond (Scheme 13). In the natural configuration at C-4 (*e.g.* **26**), the epoxide C-10–O bond is anti-periplanar to the C-9–C-11 bond, as required for its conversion to **25**, whereas the C-8–C-9 bond is nearly orthogonal.

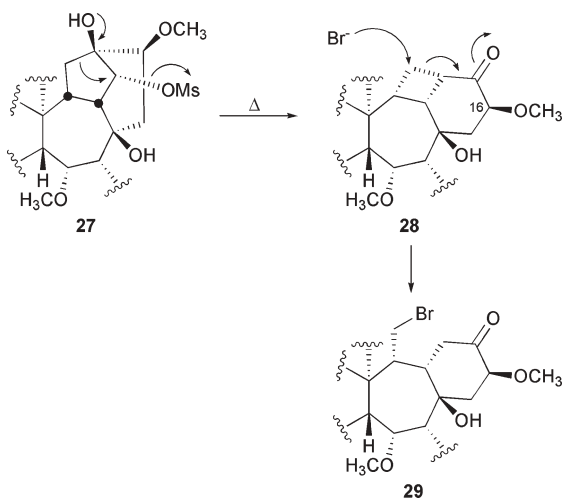
However, in the case of the opposite configuration at C-4 (not shown), migration of only the undesired C-8–C-9 bond, that now occupies the anti-periplanar position, could occur. To this end, racemic material was used in one of the coupling partners to generate separable diastereomers so that the stereochemical outcomes of both C-4 epimers could be assessed simultaneously. Once access to the desired epoxy alcohol **24** was secured, its exposure to $AlMe_3$ allowed the key semi-pinacol rearrangement to proceed cleanly, affording the desired ingenane **25** as the sole isomer in 82% yield, which now contained the entire ingenol carbon framework and stereochemistry; epoxidation of the other diastereomer resulted in the oxidation of the wrong double bond. In short, the semi-pinacol rearrangement had been utilised to construct the demanding ''inside–outside'' stereochemistry of ingenol along with the formation of the quaternary centre at C-10 in a convergent manner. The investigators projected that the utility of this method could also be extended to the synthesis of a unified approach to the ingenane, tigliane and daphnane diterpenes.



Scheme 13

2.6 Novel synthesis of 12,13-*seco* norditerpenoid alkaloids *via* ring contraction

The semi-pinacol rearrangement is very useful for the cleavage and formation of C–C bonds, and it is gradually becoming increasingly utilised in natural product synthesis, particularly with respect to ring expansion protocols (*vide supra*). However, interest in the rearrangement in the regard of ring contraction has also been examined.[26] In 2001, Wang applied this procedure to the synthesis of 12,13-*seco* norditerpenoid alkaloids. In the event, treatment of a triol precursor with methanesulfonyl chloride in pyridine, at room temperature, gave reasonable yields (77%) of the desired mesylate **27** (Scheme 14). After optimisation of the reaction conditions, it was found that reaction of the mesylate with NaOH in DMF under rather harsh conditions (150 °C, 10 h) afforded the desired rearranged products, namely, the 12,13-*seco* norditerpenoid alkaloid **28** (70%) and its C-16 epimer (15%). It was envisioned that, after ring contraction, the cyclobutane ring **28** could be opened up to generate the desired product **29**. Although the authors were unable to achieve the desired



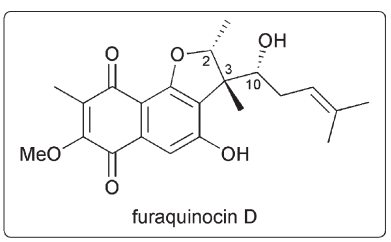
Scheme 14

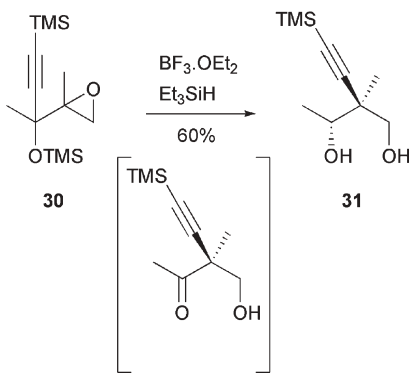
ring-opened products **29**, other novel 12,13-*seco* norditerpenoid alkaloids were obtained which, it was noted, should prove helpful for similar modifications to other norditerpenoid alkaloids. The relatively high yield (70%) for the rearrangement of this complex and activated substrate is a testament to the synthetic utility of the semi-pinacol rearrangement.

2.7 The synthesis of furaquinocin D

The furaquinocins constitute a novel class of cytocidal antibiotics and their relative and absolute stereochemistry was established by the collaboration of Smith and Ōmura.[27] The structure of these compounds comprises two biosynthetically distinct moieties, *i.e.* the polyketide-derived naphthoquinone and an isoprenoid side-chain, both of which pose significant synthetic challenges, not to mention the stereocontrol over three contiguous stereogenic centres at C-2, C-3 and C-10 (Scheme 15). In Suzuki's total synthesis of furaquinocin D, it was anticipated that these stereogenic centres could be incorporated by utilising a reductive semi-pinacol rearrangement.[28]

The synthesis began with the pivotal rearrangement by treating epoxy silyl ether **30** with $BF_3{\cdot}OEt_2$ (3 eq.) in the presence of Et_3SiH (5 eq., CH_2Cl_2, −78 °C to 20 °C, 3 h), which effected the migration of the alkynyl group to give **31** (Scheme 15); despite the known low migratory aptitude of this functional group,[29] a clean 1,2-shift was observed, transiently forming the keto alcohol, and the desired reduced 1,3-diol **31** was formed as the sole detectable product, in 60% overall yield. Note the *in situ* reduction proceeded with high stereoselectivity thereby establishing the desired C-2–C-3 stereochemical relationship.[28] Deprotection of the TMS–alkynyl group, followed by selective silylation of the primary hydroxyl, gave an alcohol ready for coupling with the aromatic component and the successful elaboration into furaquinocin D.[28]



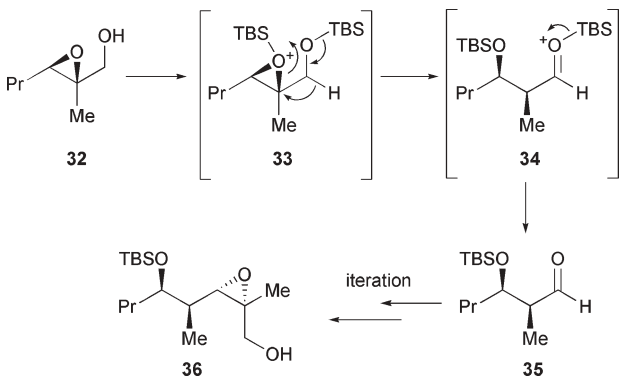


Scheme 15

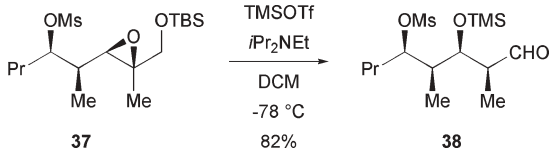
3 Hydride migrations

The migration of hydride in the semi-pinacol rearrangement has also been exploited. In particular, Jung *et al.* have made use of the reaction to generate a range of so-called non-aldol aldol reactions.[30–40] For example, in the seminal paper in this area, Jung and D'Amico reported a novel method for synthesising aldol products using non-aldol chemistry. They were able to show that all four diastereomers of 2-methyl-3-alkoxy-alkanals **35** could be prepared in high enantiomeric purity by a unique non-aldol route (Scheme 16).[30]

The absolute stereochemistry for both stereogenic centres was introduced by way of a Sharpless asymmetric epoxidation reaction, providing **32**,[41] followed by a semi-pinacol rearrangement which, incorporated an intramolecular transfer of hydride to open the epoxide regiospecifically (**33** to **34**, with inversion of stereochemistry), thus generating the desired alkanals **35**. Following the preparation of optically pure **32**, treatment of the alcohol with TBSOTf at low temperature generated the optically active aldehyde **35** in excellent yield, the proposed mechanism can be seen in Scheme 16. The best conditions found were the direct treatment of the epoxy alcohol **32** with 1.3 eq. of TBSOTf and 1.35 eq. of Hünig's base in the presence of molecular sieves at −42 °C, to afford the rearranged product **35**, in 87% crude yield. The diastereomeric purity showed that the product was a >50 : 1 mixture at the centre α to the aldehyde and following chromatography a 94 : 4 mixture was obtained in 78% yield. Simply by employing the opposite enantiomer of diisopropyl tartrate in the Sharpless epoxidation strategy resulted in the enantiomeric aldehyde of **35** in a similar yield, diastereo- and enantiomeric purity. Access to the *anti*-diastereomers was also achieved simply by utilising the (*Z*)-allylic alcohols as precursors to **32**. Applying the (*Z*)-allylic alcohols to the epoxidation/rearrangement procedure resulted in the desired *anti*-aldol products in comparable yield and stereochemical purity to the *syn*-compounds. In summary, following a three step process of Wittig/reduction, epoxidation and rearrangement all four diastereomers of the 2-methyl-3-(silyloxy)alkanals **35** could be obtained in high yield and excellent enantioselectivity; the (*E*)-allylic alcohols ultimately giving the *syn*-aldol adducts and the (*Z*)-allylic alcohols giving the *anti*-aldol adducts.[30] This procedure represents the first example of a hydride migration adjacent to the epoxide carbon in the preparation of



Scheme 16



37 38

Scheme 17

aldehydes. A second advantage of this approach, particularly for the preparation of polypropionates (Scheme 17), is that the product of the rearrangement contains an alcohol in a protected form, thus iterative reactions can be performed without the need for a subsequent protection, usually necessary in traditional aldol chemistry. The investigators went on to demonstrate this iterative process, which was exemplified by the synthesis of bis(propionate) **38**.[30,31]

Over the last fifteen years Jung *et al*. have continued to expand and develop the scope of hydride migration in the non-aldol aldol reaction, and it is now established both experimentally and mechanistically.[30,32–34] For instance, this variant of the semi-pinacol rearrangement has been studied, comprehensively, towards securing a novel synthesis of the tedanolides.[31,35–38] During the course of the research into the C-1–C-11 hemisphere of the tedanolides, a fragment was decided upon, **41**, which contained all the necessary functionality of the C-5–C-11 fragment (Scheme 18). The epoxide precursor to **41** contained a novel feature compared to all other substrates that had previously been subjected to the rearrangement; notably, an epoxide having both allylic and tertiary (or secondary) centres, thus creating the unique circumstance whereby two relatively stable carbocations are possible. A test reaction was implemented to ensure that the chosen rearrangement strategy could be utilised and extended to complete a synthesis of the tedanolides. Thus, exposure of the desmethyl compound **39** to the usual rearrangement conditions (TBSOTf, Hünig's base), unfortunately, afforded the undesired product, ketone **40**, in excellent yield (85–90%). This demonstrated that the preferred reaction pathway proceeds *via* migration of the silyloxymethyl group to an allylic carbocation, rather than the normal desired internal hydride shift to a tertiary carbocation, as shown in A (Scheme 18). Accordingly, the route to the desired target, **41**, was changed to account for this difference in carbocation stabilities. Thus, cyclisation of the homoallylic benzyl ether **39** with NBS gave rise to the bromotetrahydrofuran **42** in 75% yield as a single diastereoisomer (Scheme 19).

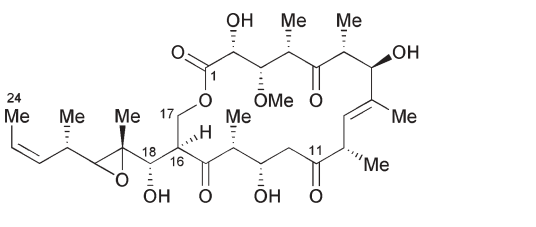
Rearrangement of this substrate (under slightly more forceful conditions: *e.g.* TfOH, HBr or TsOH) promoted a rapid rearrangement to the hydroxy aldehydes **43** and **44** ($\sim$1 : 1) in good yield (80–90%). The desired diastereomer **44** could then easily be taken forward in a straightforward manner. In this example, the bromotetrahydrofuran served to act as alkene protecting group, since its removal to reveal the homoallylic alcohol could be achieved with *t*-BuLi. Overall, the desired non-aldol aldol was made to occur in this system by using a novel reversible protection of the alkene as a bromo ether.[35,36]

Jung and Marquez also managed to utilise the undesired 1,2-rearrangement **39** to **40** for the preparation of the lower hemisphere of tedanolide.[35]

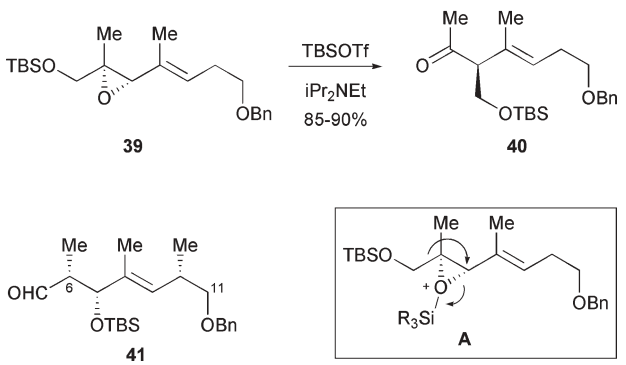
Other, more sensitive substrates can also partake in the reaction in a clean and efficient manner. For example, it has been shown that substrates containing mesylates, such as **45**, can undergo rearrangement to the desired aldehydes (**46**) in excellent chemical and diastereochemical yields.[39] Moreover, the mesylates can then either be removed with methylmagnesium bromide,[31] or perhaps more synthetically useful, can be displaced by various nucleophiles (Scheme 20).

Jung and Sun went on to demonstrate this concept using nitrogen, oxygen and sulfur nucleophiles which served to extend the non-aldol aldol process by allowing access to the formation of β-amino and β-thioacyl alcohols **50** and **51** (X = S or O) respectively (Scheme 20).[39]

Continued further work by this group, exploiting their non-aldol aldol, has led to successive approaches to the synthesis of the C-1–C-11 fragment of the tedanolides,[36–38] in particular the use of lactol ethers in place of the bromotetrahydrofurans have shown reduced by-products,[37] and the formation of a fully functionalised protected synthesis of the C-1–C-11 fragment using several rearrangement processes are of note.[38]

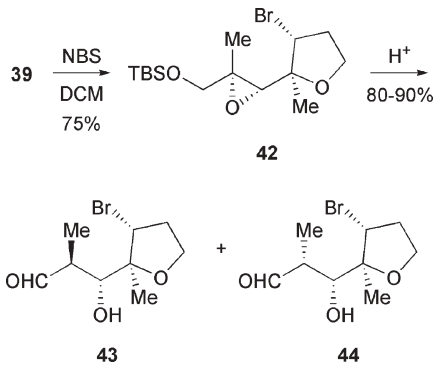


tedanolide



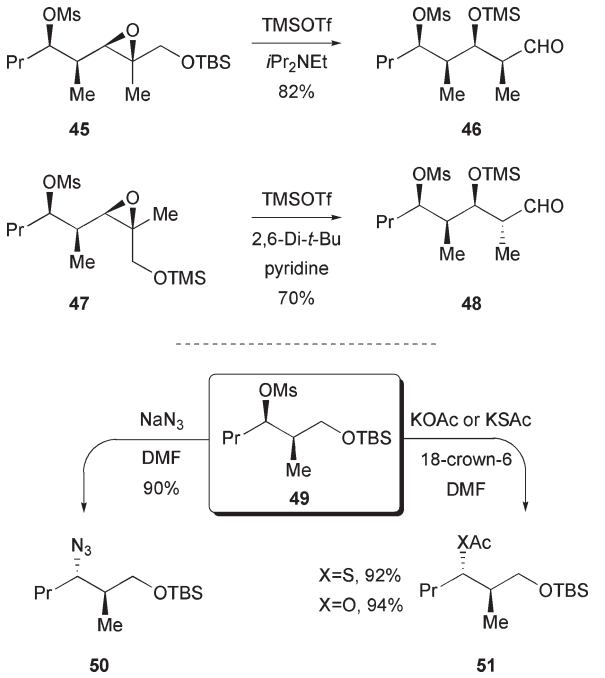
39 40 41

Scheme 18



42 43 44

Scheme 19



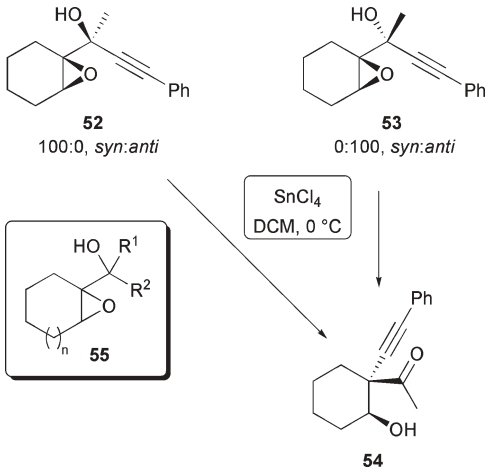
Scheme 20

4 Formation of quaternary carbon centres

The asymmetric construction of molecules with quaternary carbon stereocentres, that is, carbon centres with four different non-hydrogen substituents, represents a very challenging and dynamic area in organic synthesis. The preparation of compounds of this type with catalytic enantioselective reactions is particularly demanding.[42] The creation of quaternary carbon centres is a crucial aspect of several areas in total synthesis but is often difficult to accomplish; few general and efficient methods of constructing a quaternary centre are available, and even fewer proceed with stereocontrol.[43] In this regard, the enantiospecific rearrangement of enantiomerically pure epoxides and their derivatives has been thoroughly studied with respect to the preparation of compounds containing quaternary carbon centres, and the semi-pinacol rearrangement is able to achieve this goal.

Early efforts towards the stereoselective construction of quaternary centres was achieved by Marson *et al*. by utilising a highly stereocontrolled migration of groups containing sp-, sp^2- and sp^3-hybridised carbon atoms.[2] A highly diastereoselective semi-pinacol rearrangement of 2,3-epoxy alcohols was induced by $SnCl_4$ and was shown to be applicable to a wide variety of migrating groups including methyl, *t*-butyl, cyclopropyl, vinyl, alkynyl, phenyl and 2-furyl (**55**, Scheme 21).[2] A synthetically valuable feature of the rearrangement was that either *syn*- or *anti*-epoxy alcohols (*e.g.* **52** and **53**) afforded the same diastereomerically pure β-hydroxy ketone **54**, thus precluding the need to separate isomers (Scheme 21).

Additionally, the reaction products contained two stereogenic centres, one being quaternary, in contrast to the traditional pinacol rearrangements whereby one chiral centre is lost during the reaction.[2] It was also noted that the



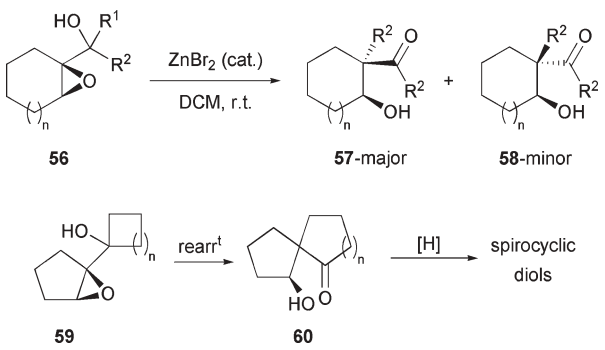
Scheme 21

semi-pinacol rearrangements described lack any competing side-reactions, such as attack by chloride and the rearrangement to give aldehydes or 1,2-hydride shifts giving cycloalkanones.[2]

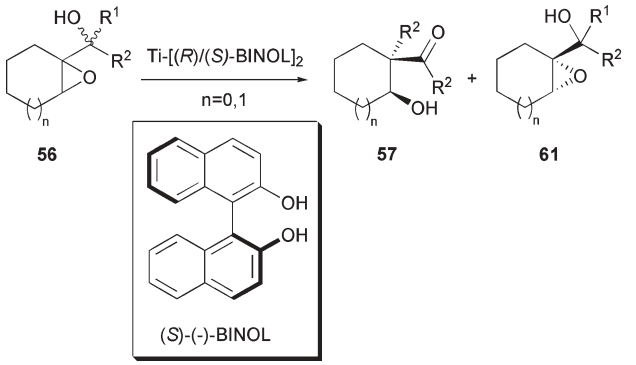
Similarly, work by Tu *et al*. revealed zinc bromide to be an efficient catalyst for the stereoselective semi-pinacol rearrangement of α-hydroxy epoxides, thus generating quaternary carbon centres (Scheme 22).[44] This method also provided an improved synthesis of diastereomerically enriched spirocyclic diols.[44] Of note in this example is the stereoselective creation of an all-carbon spirocyclic centre, for example, **59** to **60** (Scheme 22). The investigators elegantly further developed this semi-pinacol rearrangement for the enantioselective preparation of β-hydroxy ketones and tertiary α-hydroxy epoxides by utilising a kinetic resolution of racemic tertiary α-hydroxy epoxides using the chiral catalyst Ti[(*R*)/(*S*)-BINOL]$_2$ (Scheme 23).[45]

Previous work developed by the group,[44] prompted the suggestion that certain chiral Lewis acids which could be used to catalyse the rearrangement could also be employed to effect a kinetic resolution of the racemic substrates (Scheme 23 and Table 3).[45]

The (*S*)-BINOL–Ti(O*i*Pr)$_4$ system was found to be the most promising catalyst for the resolution, and to optimise the reaction, the ratio of the chiral ligand to Ti was studied along with the choice of solvent and temperature. It was found hat the enantioselectivity is highly dependant on



Scheme 22



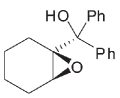
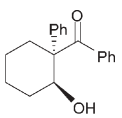
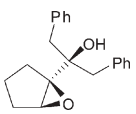
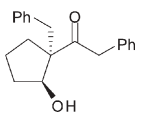
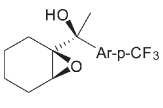
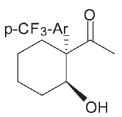
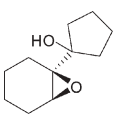
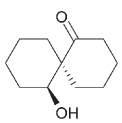
Scheme 23

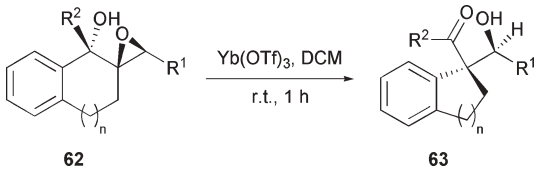
the ratio of ligand to metal, with two or more equivalents of (*S*)-BINOL inducing the highest ee's for both the rearranged product and the unreacted α-hydroxy epoxide starting material, in toluene at room temperature.[45] A selected range of substrates can be seen in Table 3. It appears as though the *S* value is highly dependant on the migrating group, with alkyl groups giving rise to the lowest *S* value; this is consistent with previous results which report that alkyl groups appear to be a limitation to this type of protocol.[46] Although the enantiomeric excesses are modest in many cases (24–94% ee), it is important to note that one or two recrystallisations of many of the recovered α-hydroxy epoxides raised the enantiomeric purity to ⩾99% ee.

Roberts and co-workers have also shown that the products resulting from the Juliá-Colonna polyamino acid-catalysed epoxidation of α,β-unsaturated ketones can be transformed into ring-contracted products containing quaternary chiral centres *via* a semi-pinacol rearrangement (Scheme 24).[47]

Further contributions towards the synthesis of quaternary carbon centres has come from the research labs of Walsh.[48] In 2003 they developed a protocol for the asymmetric

Table 3 Selected examples of the kinetic resolution/semi-pinacol rearrangement

Substrate	Product	Conv. (%)	Recov. SM ee (%)	Product ee (%)	*S*
		63	94	60	11.5
		69	70	32	3.7
		67	77	41	4.8
		69	51	24	2.5

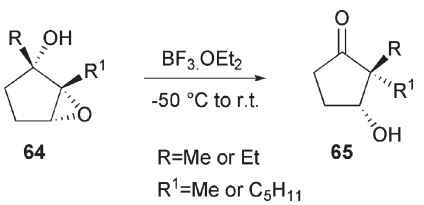


Scheme 24

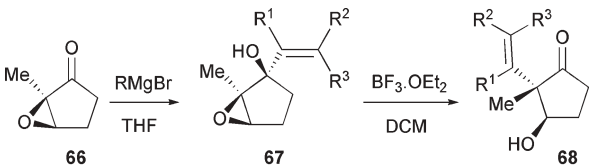
1,2-addition of alkylzinc reagents to cyclic α,β-unsaturated ketones and a tandem diastereoselective epoxidation with dioxygen.[48] It was shown, with a select few of the resulting enantiopure epoxy alcohols *e.g.* **64**, that these could cleanly undergo a semi-pinacol rearrangement, resulting in quaternary-centre containing aldol adducts, *e.g.* **65**, in good yield (70–89%) and excellent enantiomeric excess (97–99%) (Scheme 25).[48]

Following on from this work, we recently reported an extension to the procedure by incorporating alkenyl substituents into the newly formed quaternary carbon centre, thereby allowing for more heavily functionalised products to be obtained (Scheme 26, Table 4).[49]

This extension was found to be complementary to the α-vinylation of ketones using vinyl cation synthons[50] or the methodology developed by Piers and Marais for the intramolecular palladium-mediated direct α-vinylation of enolates.[51] Interestingly, during the course of this research we found that extending the method to six-membered ring analogues was not trivial. For example, the attempted rearrangement of **74**, under the same conditions established in the five-membered ring



Scheme 25



R=alkenyl
R^1, R^2, R^3=H or Me (see Table 4)

Scheme 26

Table 4 Rearrangement of alcohols **67** to **68**[a]

Entry	R^1	R^2	R^3	Product	Yield[b] (%)
1	H	H	H	**69**	78
2	Me	H	H	**70**	70
3	H	Me	Me	**71**	56
4	H	Me	H	(*E*)-**72**	83
5	H	H	Me	(*Z*)-**73**	90

[a] $BF_3{\cdot}OEt_2$ (2.0 eq.), DCM, 0 °C. [b] Isolated yield

series, resulted in the formation of the conjugated product **76**, regardless of the diastereomer of epoxy alcohol **74** used; a carbocation induced, enolate formation is the explanation for this unexpected outcome (Scheme 27).[49]

5 Tandem processes

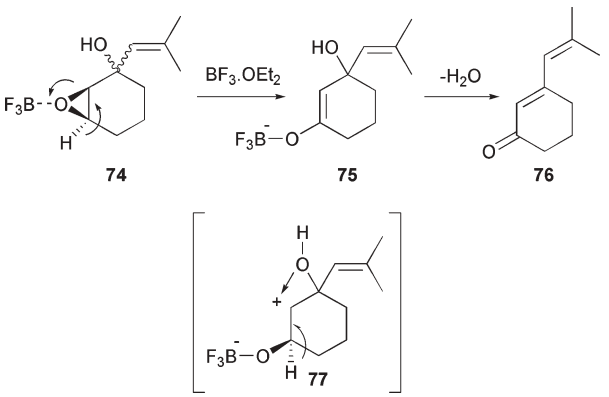
5.1 Tandem semi-pinacol rearrangement/Mukaiyama aldol reaction

Tandem processes often allow complex molecular frameworks to be constructed in a highly stereoselective manner by combining more than one reaction into a single synthetic step, whilst they also serve to shorten the corresponding multi-step synthesis. The semi-pinacol rearrangement has been exploited in tandem reaction processes where the reaction has been carried out in conjunction with various other known reactions. For example, Jung has employed his non-aldol aldol in tandem with a Mukaiyama aldol reaction.[40] This has been exemplified by the synthesis of **80** from **78**; a proposed mechanism is also presented (Scheme 28).[40] Rahn and Kalesse have also extended this protocol by utilising an aldehyde, generated from the epoxy-alcohol rearrangement of **83**, developed by Jung, and exposing it, in a one-pot fashion, to a vinylogous Mukaiyama aldol reaction with **85** to provide rapid and efficient access to polyketide frameworks (Scheme 28).[52]

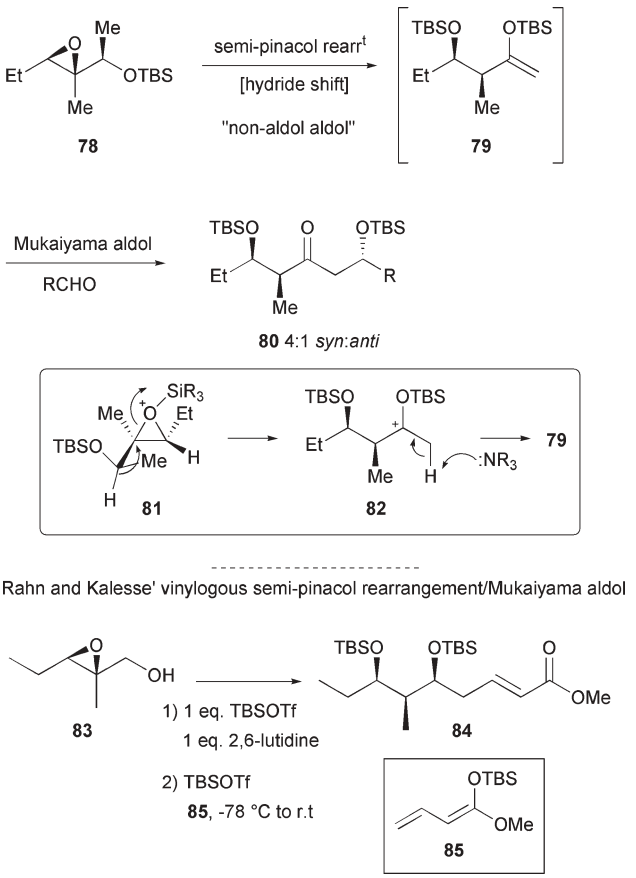
5.2 Nucleophilic alkene induced rearrangement

The reaction of a nucleophilic π-system with a 2,3-epoxy alcohol is a powerful means of creating a new C–C bond.[53] In doing so, a transient carbocation is formed (**89** in Scheme 29) which is able to react further, with other nucleophilic species, in a tandem process. Marson *et al*. have shown that such a carbocation can be successfully trapped by the migrating group in a tandem semi-pinacol (acyloin) rearrangement.[54]

For example, it was shown that attack of an alkene unit onto a chelated 2,3-epoxy alcohol leads to the stereoselective formation of a cyclopropane ring **87**, followed by ring expansion, by way of a semi-pinacol rearrangement mechanism (Scheme 29).[54] Exposure of the epoxy-alcohol **86** to $SnBr_4$ (DCM, 0 °C) afforded the cyclopropyl α-ketol **87** (in 65% isolated yield) as a single diastereomer. The mechanism of the transformation is outlined in Scheme 29 and is rationalised as follows: chelation-controlled conversion of the epoxide **88** to



Scheme 27

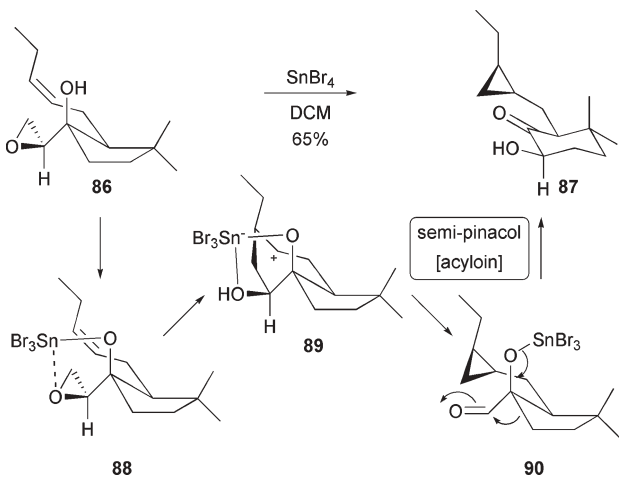


Scheme 28

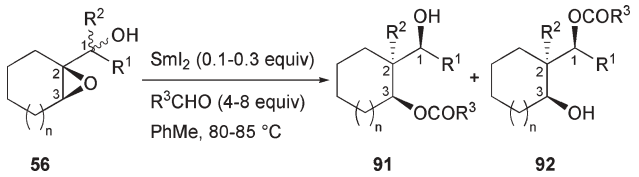
the seven-membered ring diol **89**, followed by its collapse to the cyclopropyl derivative **90**. The resulting aldehyde then undergoes a ring-expansion reaction, by way of migration of the *less*-substituted group, to generate the α-ketol product **87**.[54]

5.3 Tandem semi-pinacol rearrangement/Tishchenko reaction

The importance of 1,3-diol units possessing a quaternary stereogenic centre at C-2 is exemplified by being present in



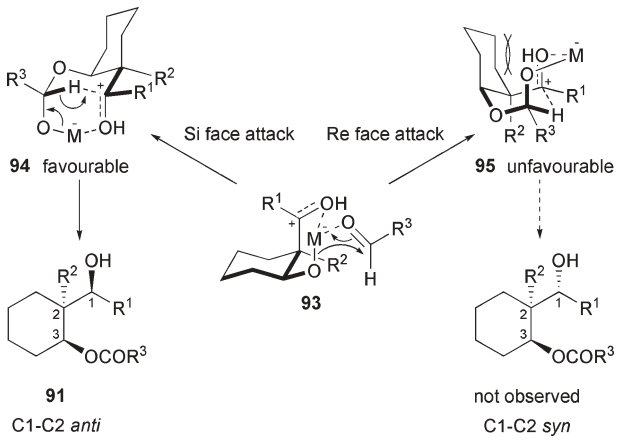
Scheme 29



Scheme 30

many biologically significant molecules and chiral ligands and several procedures based on the semi-pinacol rearrangement of α-hydroxy epoxides have been developed to prepare this motif. However, they generally require one equivalent, or an excess, of a promoter and produce only the β-hydroxyketone.[46] Additionally, a reductive step is required to achieve the diol oxidation level. Tu and others has previously reported upon a one-step procedure based on a tandem semi-pinacol/Meerwein–Ponndorf–Verley reduction of α-hydroxy epoxides, but they too required at least one equivalent of Lewis acid.[55] In the last few years, Tu and co-workers have also described examples of a tandem semi-pinacol rearrangement, this time in concert with the Tishchenko reaction[46] and alkylation reactions.[56] Further work has shown that catalytic amounts of SmI_2 (0.1–0.3 eq.) can promote the semi-pinacol/Tishchenko reaction of α-hydroxy epoxides to form 2-quaternary 1,3-diol monoesters efficiently and with high diastereoselectivity (Scheme 30).[46,57]

Several features were found to be of interest to the authors: (1) the construction of three contiguous stereocentres, one of which is quaternary, in one-step; (2) C-1 epimers form a single diastereomeric product, where the products have the same 2-quaternary 1,3-diol core; (3) it is effective with catalytic amounts of SmI_2; and (4) the newly formed secondary C-1–OH group has the β-configuration, which is not readily accessible by their previous procedure. As such, this new method can be utilised to generate 2-quaternary 1,3-diols with a C-1,C-2-*anti* configuration.[46] Numerous tertiary α-hydroxy epoxides were examined, the results of which are summarised in Table 5. It was found that the configuration of the products at C-1 is independent to that of the substrates. The diastereocontrol of the reaction was very high; indeed, the *syn*-diastereomer was not able to be isolated in the current study. It is also noteworthy that the opposite stereochemistry at C-1 is observed when compared to the products of the reaction mediated by $Al(iPrO)_3$.[55] It appears as though the reaction is partially dependant on the electronics and



Scheme 31

stoichiometry of the aldehyde, but this is useful since it implies that the scope of the reaction can be explored by screening various different aldehydes.

Solvent effects were also noted, and it was found that non-polar solvents work best, and an indication that alkyl migrating groups cannot be used in the reaction is implied as the reactions only real limitation. A mechanistic overview is also given (Scheme 31) as is a proposed catalytic cycle.[46]

It is believed that when the *Si* face of the aldehyde is attacked, a favourable transition state **94** is formed, which leads to the formation of **91** with C-1,C-2-*anti* configuration. In contrast, attack at the *Re* face results in transition state **95**, which is unfavourable due to steric hindrance between the cyclohexane ring and the 1,3-dioxo heterocycle.[46]

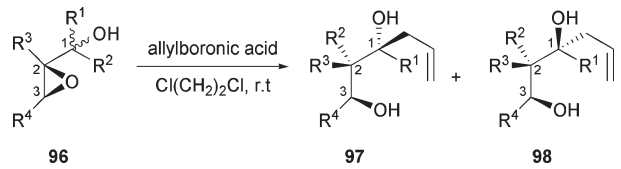
5.4 Semi-pinacol rearrangement/alkylation reactions

Continuing on from this work, Tu has also demonstrated that the semi-pinacol rearrangement can be used in tandem with alkylation reactions.[56] In this instance, a boron mediated tandem process occurs, whereby a smooth stereospecific semi-pinacol rearrangement of an α-epoxy alcohol and the subsequent allylation or propargylation of the intermediate β-hydroxy ketone is achieved (Scheme 32).

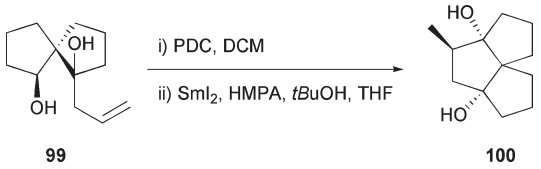
Here, the pivotal dual roles of $RB(OH)_2$, namely, Lewis acidity and alkylating agent, are mandatory. Interestingly, the relative stereochemistry of C-1 in the 1,3-diol product **97/98**, which is independent of the relative configuration of C-1 in the substrate **96**, can be tuned by the substituent R^4. Various

Table 5 SmI_2 catalysed semi-pinacol rearrangement/Tishchenko reaction

Entry	*n*	*syn* : *anti*	R^1	R^2	R^3	SmI_2 (eq.)	Yield (%)	**91** : **92**	*t*/h
1	1	—	Ph	Ph	Ph	0.1	95	100 : 0	4
2	1	70 : 30	Me	Ph	Ph	0.15	96	100 : 0	4
3	1	61 : 39	Et	Ph	Ph	0.15	92	100 : 0	4
4	1	87 : 13	*i*Pr	Ph	Ph	0.2	92	100 : 0	6
5	1	56 : 44	Allyl	Ph	Ph	0.3	70	100 : 0	8
6	1	100 : 0	Bn	Ph	Ph	0.3	95	0 : 100	2
7	1	79 : 21	*n*Bu	Ph	Ph	0.3	78	100 : 0	6
8	0	70 : 30	Bn	Ph	Ph	0.3	88	44 : 56	6
9	0	80 : 20	Me	Ph	*p*-C_6H_4Cl	0.3	85	74 : 26	7
10	1	60 : 40	Me	2-Thiophenyl	*p*-C_6H_4Cl	0.25	83	0 : 100	4
11	1	91 : 9	Me	Cyclopropyl	*p*-C_6H_4Cl	0.3	78	93 : 7	4



Scheme 32

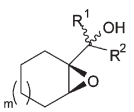
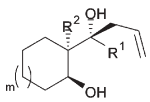
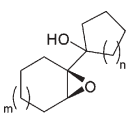
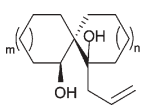
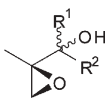
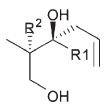


Scheme 33

substrates are amenable to the reaction and the migrating group R^2 can be aryl or alkyl, demonstrating the broad scope of the reaction (Scheme 32 and Table 6).[56]

It was found that when R^3 and R^4 formed a linked unit or R^4 was an alkyl group (entries 1–6, Table 6), the two adjacent stereocentres C-2 and C-3 had a *trans* relationship (*i.e.* C-2–R^2 was *trans* to C-3–OH) and the C-1–OH group had predominantly the α-configuration;[56] the relative stereochemistry being derived from the highly stereospecific boron-promoted semi-pinacol rearrangement as well as the subsequent diastereoselective intramolecular allylation. Epimers at C-1 gave rise to only a single diastereomeric product, indicating that the migration of R^2 is highly stereoselective irrespective of the relative configuration of C–1 in **96**. In the spirocyclic systems (entries 4–6, Table 6), *cis-trans*-spirocyclo-1,3-diols were obtained as the major products. However, conversely, when the substrate possessed non-linked R^3 and R^4 groups, and/or R^4 was hydrogen, an inversion of the configuration was found on the C-1–OH. For example, in entries 7 and 8, the major product was obtained in good yield in the β-configuration.

Table 6 Tandem semi-pinacol rearrangement/allylation

Entry	Substrate	Erythro : threo[a]	Major product **97** : **98**[b]	Yield[c] (%)
				
1	*m* = 1, R^1 = Me, R^2 = Ph	70 : 30	>99 : <1	75
2	*m* = 0, R^1, R^2 = Ph		>99 : <1	81
3	*m* = 0, R^1 = Me, R^2 = 2-thienyl	88 : 12	>99 : <1	69
				
4	*m* = 0, *n* = 0		71 : 29	>99
5	*m* = 1, *n* = 0		85 : 15	80
6	*m* = 1, *n* = 1		>99 : <1	91
				
7	R^1 = Me, R^2 = *cy*Propyl	78 : 22	31 : 69	71
8	R^1 = Me, R^2 = Ph	69 : 31	<1 : >99	61

[a] The ratio of two C-1 epimers in **96**. [b] Ratios determined by NMR. [c] Isolated yields.

It was shown that the nature of the migrating group had a significant influence on the tandem reaction. For example, when R^2 was *n*-butyl or benzyl, the expected rearrangement/allylation did not readily take place.[56] As a demonstration of the utility of this reaction, Tu and co-workers carried out a very short synthesis of the tricycle[6.3.0.0] framework **100** of the natural products pentalenene and isocomene in two steps and 50% yield from the semi-pinacol rearrangement/alkylation product **99** (Scheme 33).[56]

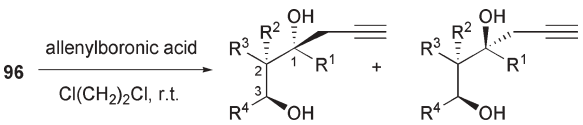
The scope of the reaction was further expanded with the incorporation of a propargylic group. These results can are summarised in Table 7. The propargylic products were obtained in moderate yields, and the diastereoselectivity observed matched that as seen in the allyl case. A mechanistic explanation for this selectivity is given.[56]

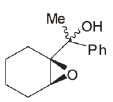
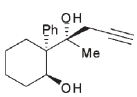
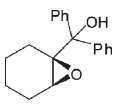
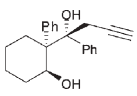
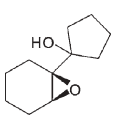
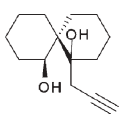
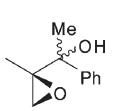
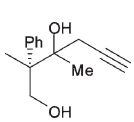
6 Miscellaneous reactions

6.1 The cyclic aldol problem

Baldwin *et al.* have exploited the semi-pinacol rearrangement to provide a solution to the cyclic aldol problem.[58] Over the last 20–25 years a great deal of work has been carried out to

Table 7 Tandem semi-pinacol rearrangement/propargylation.



Entry	Substrate	Erythro : threo[a]	Major product	**101** : **102**[b]	Yield[c] (%)
1		70 : 30		>99 : <1	55
2				>99 : <1	40
3				>99 : <1	74
4		69 : 31		1 : 1	48

[a] The ratio of two C-1 epimers in **96**. [b] Ratios determined by NMR. [c] Isolated yields.

detail the stereochemical outcome of the aldol and related reactions. Such work has revealed that the acyclic aldol condensation adheres to the mechanistic rules previously established, whereby the relative stereochemistry of the β-hydroxyl carbonyl product (*syn*/*anti*) is usually the result of a closed Zimmerman–Traxler transition state, in which the enolate geometry is transferred to the product by minimising non-bonding interactions.[59] The absolute stereochemistry in acyclic aldol reactions can then often be controlled by incorporating chiral auxiliaries.[60]

In contrast to the regularity and predictability associated with the acyclic aldol reaction, cyclic ketones have often proved more capricious. In general, cyclic aldol reactions run under equilibrating conditions and favour the *anti*-diastereomer.

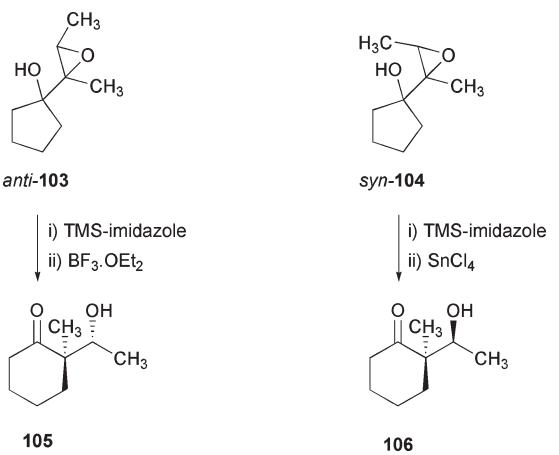
As would be expected for an enolate constrained to an (*E*)-configuration, one would predict these aldol condensations run under kinetic conditions to favour the formation of the *anti*-products. In general, this is true, although the diastereomeric ratios are often sensitive to the nature of the counter ion and reaction conditions and even to the carbonyl components themselves, and results become even more unpredictable when the cyclic enolate is fully substituted (leading to products which contain a quaternary chiral centre).

It became clear to the investigators that epoxides such as **103** and **104** (Scheme 34) possess all the stereochemical information of the target aldol products, which could be accessed provided that a Lewis acid-mediated semi-pinacol rearrangement/ring-expansion could be effected under controlled conditions.[58] It was envisioned that the relative stereochemistry in the aldol products could be established by starting from epoxy alcohol precursors **103** and **104** possessing the correct relative stereochemistry. These starting materials could be easily accessed using known procedures for the stereospecific epoxidation of substituted alkenes; the process could then be expanded to control the absolute stereochemistry by employing known methods for the enantioselective epoxidation of prochiral allylic alcohols. In general, it was found that the epoxy alcohols were not as reliable substrates for the rearrangement compared with their TMS ethers, for example, the unprotected alcohol suffered in terms of yield and diastereomeric ratios.[58] Nevertheless, the TMS ethers proved to undergo the rearrangement successfully, with a number of Lewis acids, generating the desired aldol adducts in high yield. The TMS epoxy ether derived from the (*E*)-alkene **103** gave rise to the *anti*-keto alcohol **105** in 81% isolated yield, the *anti*/*syn* ratio of the crude material being 94 : 6 in favour of the *anti*-diastereomer, whilst the rearrangement precursor derived from the (*Z*)-alkene **104** yielded the same two products in a <1 : 99 ratio in favour of the *syn*-isomer **106**, which was isolated in 89% yield after chromatography. Similar results were obtained for substrates **107** to **110** (Scheme 35).

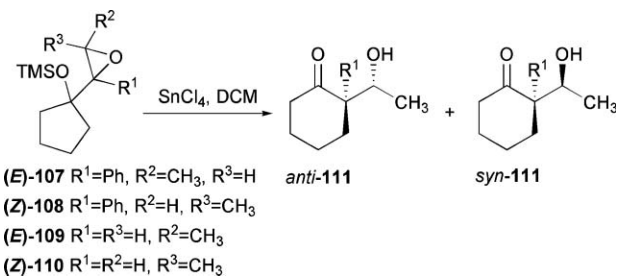
To determine the importance of the nature of the substituent at the migration terminus, two additional substrate types (**107–110**) were studied (Scheme 35). Rearrangement of phenyl-substituted epoxide **107** resulted in the expected product **111** (87% yield, *anti*/*syn*, 98 : <2, R^1 = Ph), similarly, epoxide **108** gave **111** (88% yield, *anti*/*syn*, 5 : 95). However, overall yields for the *anti*/*syn*-isomers suffered when the migration terminus was unsubstituted (R^1 = H). For example, **109** afforded the cyclohexanone products in a ratio of *anti*/*syn*, 3 : 97 in 50–60% yield and **110** afforded the products in a ratio of *anti* : *syn*, 99 : 1 also in 50–60% yield. In summary, the semi-pinacol rearrangement provides a reasonable method for achieving β-hydroxy cycloalkanones in good yields and with high levels of diastereoselectivity, particularly when the α-carbon is fully substituted.[58]

6.2 Azaspirocyclic ketones

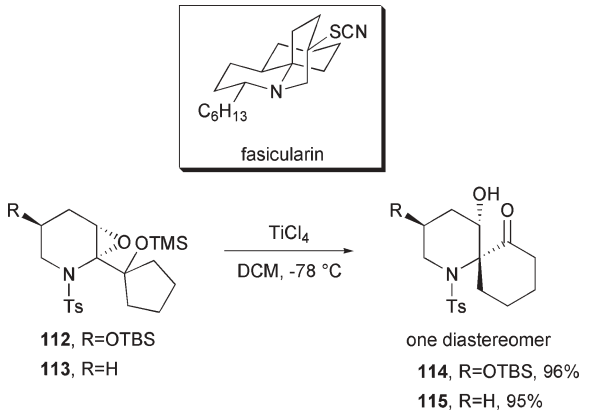
During synthetic studies into the synthesis of the azaspirocyclic ring systems present in alkaloids, such as fasicularin (Scheme 36), Dake and others have shown that the synthesis of 1-azaspirocyclic ketones (*e.g.* **114** and **115**) can be achieved using a semi-pinacol rearrangement with concomitant ring expansion (Schemes 36 and 37).[61] They were able to reveal that the predictability and stereochemical outcome of the reaction differs simply by making structural variations to the substrates, which is in contrast to the analogous rearrangement performed on carbocyclic frameworks (compare **117–119/121** to **122–123**, Scheme 37). They also found out that cyclopentanol silyl ethers (**112** and **113**) expand to form cyclohexanones (**114** and **115**) in a 1,2-*anti*-fashion, whereas cyclobutanol silyl ethers (**116** and **117**) expand *via* either a 1,2-*anti*-shift or a 1,2-*syn*-shift, depending on the substituents and reaction conditions, providing products **118–121**. A brief explanation as to the reason for this difference in behaviour was suggested as being due to the greater propensity for the cyclobutane ring to expand compared to the cyclopentane ring as a way to reduce



Scheme 34



Scheme 35

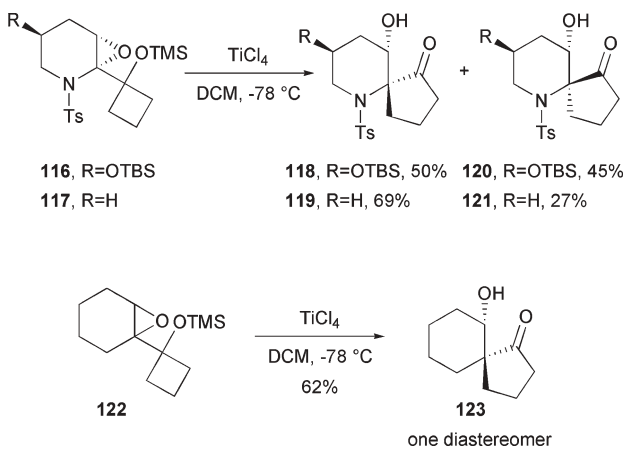


Scheme 36

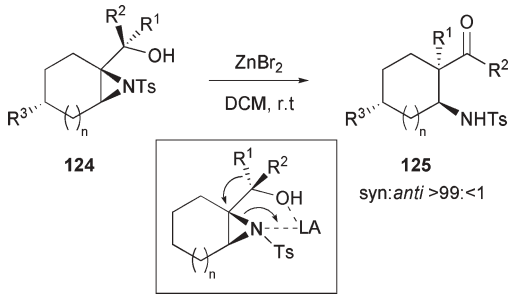
ring strain.[61] In short, a new method for the formation of diastereomeric 1-azaspiro[5.4]-decanones was uncovered, whereby spiro-fused heterocyclic ring systems containing two contiguous stereocentres can be fashioned in a single operation.

6.3 Tosylaziridine ring-opening

Most of the work described herein is related to the chemistry of epoxy alcohols, whereby the epoxide opening promotes the migration of an adjacent group; the chemistry of epoxy alcohols has recently been reviewed.[62] However, in keeping with the description of the semi-pinacol rearrangement outlined in Coveney's original review of the reaction, "*…the term 'semi-pinacol' is now used generally to describe all such rearrangements which are related to, or reminiscent of, the pinacol rearrangement*,"[1] Tu has revolutionised the entire range of semi-pinacol rearrangements accessible by elaborating the nature of the leaving group. For example, a new rearrangement of 2,3-aziridino alcohols has been reported,[63,64] which incorporates the ring opening of tosyl aziridines (Scheme 38 and Table 8). This new protocol involves the highly stereoselective construction of a quaternary carbon centre resulting in the efficient formation of β-amino carbonyl compounds in excellent yields.[63]



Scheme 37



Scheme 38

As can be seen in Table 8, all reactions were complete in less than one hour with the exclusive formation of a single diastereomer. In contrast to the epoxide series of related semi-pinacol rearrangements, a separable pair of diastereomeric alcohols (entries 4 and 5, Table 8) afforded methyl and ethyl migration respectively. This suggests that the migratory aptitude of $R^1$and R^2 depends heavily on the configuration of the carbon bearing the hydroxyl group but not on the migratory ability.[63] This interesting and unusual phenomenon suggested a mechanism in which the Lewis acid first coordinates to the aziridine nitrogen and the hydroxyl oxygen, and cleavage of the activated C–N bond of the aziridine occurs concomitantly with 1,2-shift of the migrating group (Scheme 38). The five-membered ring structure resulting from coordination of the Lewis acid to nitrogen and oxygen prevent the free rotation of the C-1–C-2 bond and thus it is the group R^1, that is *anti* to the C–N bond, that migrates.[63]

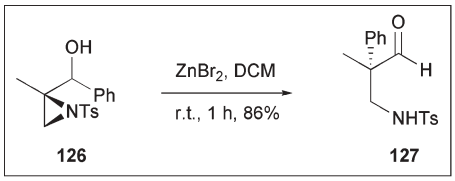
Various Lewis acids (*e.g.* $AlCl_3$, $ZnCl_2$, $Sn(OTf)_2$, $BF_3{\cdot}OEt_2$, $SnCl_4$ *etc.*) were demonstrated to promote the reaction, and other successful rearrangement substrates included the acyclic substrate **126**. Tu and co-workers have also shown that this variant of the rearrangement can be applied to the synthesis of the core of *cis*-3a-aryloctahydroindole alkaloids present in, for example, mesembrine (Scheme 39).[65]

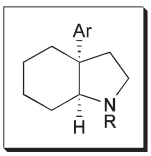
6.4 Halo-cation induced semi-pinacol rearrangements

Tu has further expanded the nature of the leaving group by successfully demonstrating that halogen cations can induce the semi-pinacol rearrangement.[66] The combination of chloramine-T/ZnX_2 provided the source of the halogen cation, which generated a highly efficient and stereoselective method for the preparation of α-quaternary-β-haloketo compounds (Scheme 40).[66]

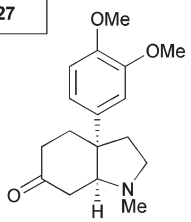
Table 8 Tosylaziridine ring opening

Entry	*n*	R^1	R^2	R^3	Yield (%)	*t*/min
1	1	Me	Me	H	88	30
2	0	Me	Me	H	85	30
3	1	Me	Me	Me	78	60
4	1	Me	Et	H	90	30
5	1	Et	Me	H	89	30
6	0	Me	Ph	H	85	30
7	1	Ph	H	H	85	40
8	0	Ph	H	H	83	40
9	0	H	*o*-ClC_6H_4	H	85	40



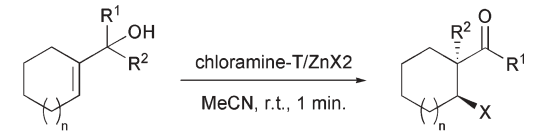


cis-3a-aryloctahydroindole nucleus



mesembrine

Scheme 39



128

R^1, R^2=H, Aryl, Alkyl

n=0, 1

129

syn:*anti* >99:<1

X=Cl, Br, I

Scheme 40

See Table 9 for selected examples; all reactions were complete in one minute at room temperature resulting in a single diastereomer of the β-halo ketone. A possible mechanism is also mooted.[66]

Of note in Table 9 is the successful rearrangement of both tertiary and secondary alcohols. It was found that in the case of secondary alcohols an electron rich aromatic group was necessary for the rearrangement to occur. The reaction also works well for both five- and six-membered rings (compare entries 1 and 3). Spirocyclic products can also be obtained (entries 4 and 5), and the reaction also works well in acyclic systems (entry 6). Chlorine, bromine and iodine also work well as the source of "X^+" (entries 2, 7 and 8).

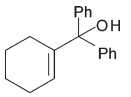
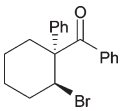
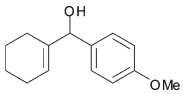
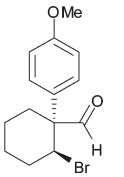
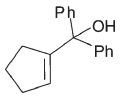
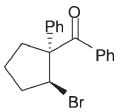
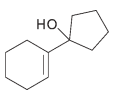
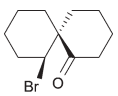
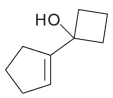
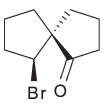
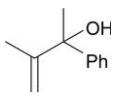
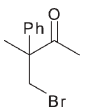
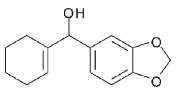
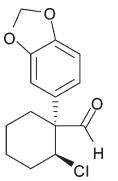
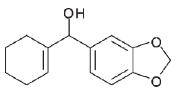
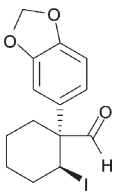
Finally, the asymmetric construction of α-quaternary-β-fluoro aldehydes has been developed by Tu and co-workers, which utilises a quinine/Selectfluor® system to induce an enantioselective semi-pinacol rearrangement (Scheme 41).[67] Moderate ee's (54–82%) were achieved on a range of substrates consisting of aryl-alkenyl secondary alcohols.[67]

6.5 Synthesis of cyclobutanones

Further examples of ring expansion reactions, integrating mesylates as the leaving group, have been explored by Cha and colleagues.[68] They have developed an enantioselective synthesis of 2-substituted cyclobutanones by applying a semi-pinacol rearrangement to α-hydroxycyclopropylcarbinols **132** (Scheme 42).

Despite the utility of cyclobutanes in organic synthesis,[69] very few general procedures exist for preparing enantiomerically pure derivatives, as such, Cha's efforts to address this shortfall are reported.[68] The key synthetic step to the substituted cyclobutanes is depicted in Scheme 42. Access to

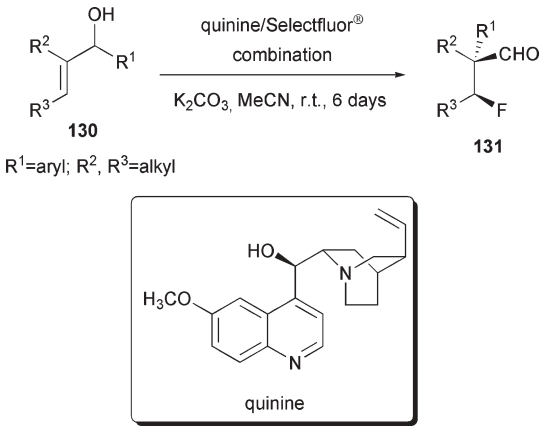
Table 9 Halogen cation induced rearrangement

Entry	Substrate	Product	Yield[a] (%)
1			94
2			85
3			92
4			75
5			94
6			88
7			90
8			75

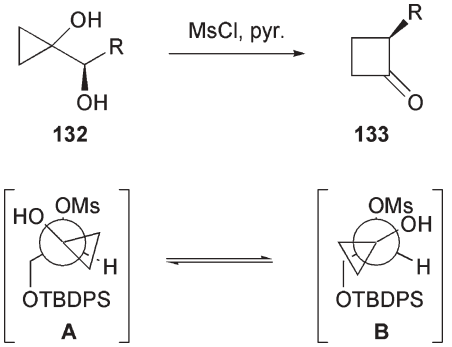
[a] Isolated yields.

various enantiomerically pure rearrangement precursor's, *e.g.* **132**, was achieved following established literature procedures, after which it was anticipated that the preferential migration of a single diastereotopic C–C bond, followed by inversion of configuration at the stereocentre, would occur, allowing access to 2-substituted cyclobutanones with high enantiocontrol. In the event, treatment of **132** (R = CH_2OTBS) with mesyl chloride in pyridine resulted in the facile 1,2-rearrangement, with concomitant ring expansion, to afford **133** (R = CH_2OTBS) in an unoptimised 58% yield; see Table 10 for other selected examples.

The key rearrangement took place with a high (>90%) level of chirality transfer, and it is believed that the (*S*)-configuration of the 2-substituted cyclobutanone product can be



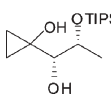
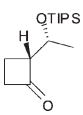
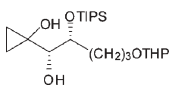
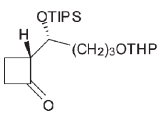
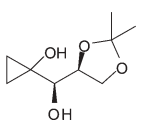
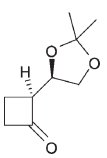
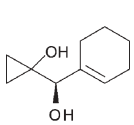
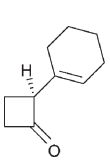
Scheme 41



Scheme 42

rationalised by the anti-periplanar requirement in the preferred transition state arising from conformer **A** (Scheme 42). Nonbonding interactions, between the cyclopropyl ring protons and the $-CH_2OTBDPS$ group, are thought to destabilise the alternate transition state, conformer **B**. In short, a sequential cyclopropanation/semi-pinacol ring expansion protocol has been developed which provides convenient access to enantiomerically pure 2-substituted cyclobutanones.[68]

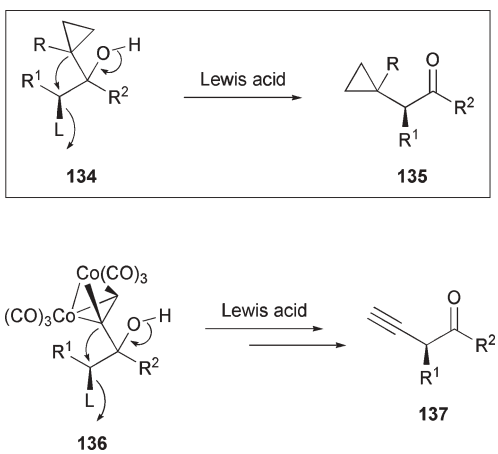
Table 10 Selected examples of cyclopropyl alcohol to cyclobutanone ring-expansion reactions *via* the semi-pinacol rearrangement

Entry	Substrate	Product	Yield (%)
1			57
2			57
3			71
4			72

6.6 Novel migrating groups

In 1996 a communication by Suzuki and co-workers successfully demonstrated an improved procedure for enhancing the migratory aptitude of alkynyl groups by complexing the triple bond to cobalt, and demonstrated the ease with which it underwent a 1,2-shift, in contrast to the free alkynes which are known not to migrate readily.[70] The poor migratory aptitude of the alkynyl group is thought to derive from the higher activation energy associated with its migration compared to alkenyl (and other) group(s) migration. The large difference in activation energies seems to derive from the stability of the two-electron three-centred system formed when it migrates. Compared to the alkenyl system, the alkynyl group needs more energy to form a two-electron three-centred system due to its larger contribution of s-character from sp-hybridisation.[71] As a result of this poor migratory aptitude, Suzuki postulated that (by analogy to the cyclopropyl group, see box, Scheme 43)[72] the corresponding Co-complex would migrate; compare **134** with **136**. Their findings show that cobalt complexation does indeed facilitate the 1,2-shift of alkynyl groups.[70]

They were able to demonstrate this phenomenon by successfully rearranging **138** (R = *n*-Bu) in a clean 61% yield (55 °C, benzene, EtMgBr); the un-complexed analogue does not undergo the 1,2-shift under these conditions.[29] The reaction was also shown to proceed at lower temperatures (−20 to 20 °C) in the presence of Me_3Al. Notably, these Lewis acidic conditions did not induce any Nicholas-type alkylation. The screening of a number a different alkynyl groups demonstrated that the migratory aptitudes of the complexes varied depending on the substituent, see Table 11 in conjunction with Scheme 44. For example, a silyl or methoxymethyl group enhances the migratory aptitude, while a propenyl group makes the complex less prone to migrate (entries 2–4, Table 11); the investigators postulate that this trend may be due to the ability of the substituent to stabilise the positive charge that would develop at the migrating cluster

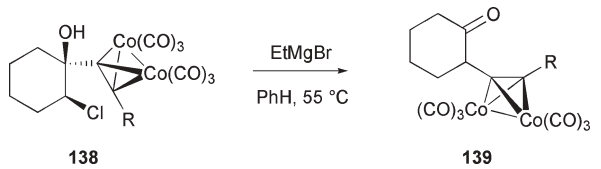


Scheme 43

Table 11 Migration of cobalt complexes[a]

Entry	R	*T*/°C	Yield (%)
1	*n*Bu	20	78
2	Me_3Si	0	84
3	$MeOCH_2$	−20	80
4	H_2C=CMe	20	58

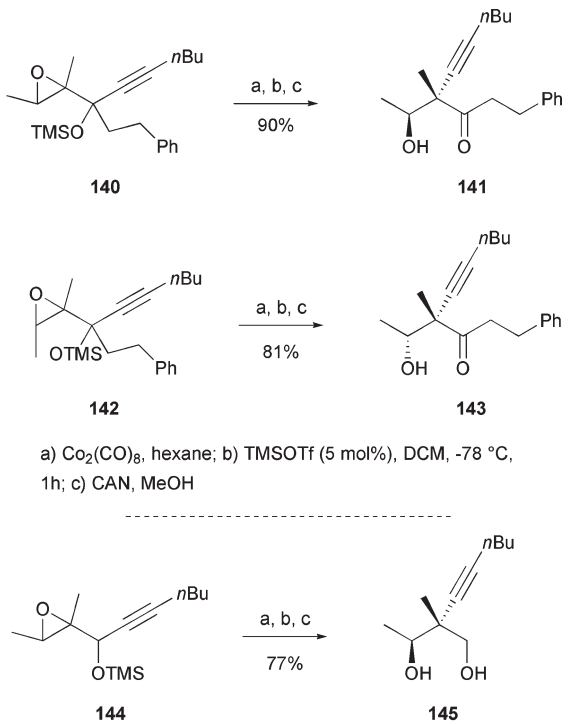
[a] Me_3Al, DCM, 2 h.



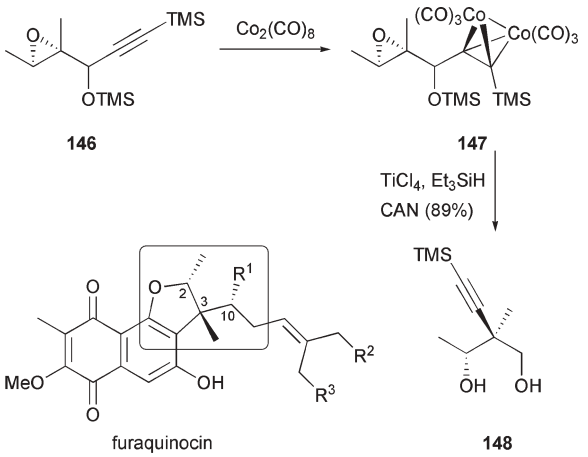
138 **139**

Scheme 44

during the 1,2-shift.[70] It appears as though the migratory aptitude of the complex is much larger than anticipated, and in competition experiments the complexed triple bond migrated in preference to both alkyl and aryl groups, even in the case of a *p*-methoxyphenyl group. Only in the example incorporating a TMS-substituted vinyl group (one of the best migrating groups known)[73] does the Co-complex suffer by not being the sole migrating group. In further studies the group also demonstrated the use of the technique towards the synthesis of quaternary carbon centres (**141** and **143**) and a reductive version of the reaction which allowed access to a fragment of the furaquinocin antibiotic core, **144** to **145**, which is outlined in Scheme 45.[70]



Scheme 45



Scheme 46

Suzuki has since applied this elegant strategy, for improving alkyne migration, to the synthesis of the furaquinocins. Also, in doing so, Suzuki was able to secure a flexible route to the natural products which is general enough to allow the synthesis of many congeners. Amongst some of the improvements made on their preliminary studies (*vide supra*, Scheme 15) was the incorporation of enantioselectivity into the process (Scheme 46).

The retrosynthetic plan suggested two simplified precursors one of which was **148**. Synthesis of the 1,3-diol fragment *via* a semi-pinacol rearrangement was the key to its success. With the poor migratory aptitude of the alkynyl group alluded to above, Suzuki employed their newly developed Co-complex strategy to find a way around this problem. Upon conversion of alkyne **146** to the corresponding cobalt complex **147**, the alkynyl group became an efficient migrator in the subsequent 1,2-anionotropic reaction. Following the 1,2-shift and *in situ* reduction, oxidative decomplexation using CAN readily regenerated the alkynyl group (**147–148**) in 89% yield (97% ee), an improvement upon earlier attempts in the absence of cobalt.

6.7 Catalysis by rare earth triflates

Work by Roberts and co-workers in 2001 demonstrated that the enantiopure epoxides generated by the Juliá-Colonna epoxidation, *e.g.* **149**, can undergo a facile semi-pinacol rearrangement, catalysed by rare earth triflates ($Sc(OTf)_3$, $La(OTf)_3$ or $Yb(OTf)_3$) (Scheme 47 and Table 12).[74] The enantiopure epoxyketones were converted into aldol adducts by Grignard addition followed by rearrangement catalysed by the rare earth triflates. It was found that the rearrangement conditions constitute an efficient, convenient and mild alternative to previously reported procedures.[74]

149 R^1=Me, OCH_2Ph, Ph **150**
R^2=Me, Ph

Scheme 47

Table 12 $R^1 = R^2 = Me$

Catalyst	Mol% cat.	*t*	Yield (%)
$Sc(OTf)_3$	20	6 h	90
$La(OTf)_3$	20	10 h	90
$Yb(OTf)_3$	20	3 h	99
$Yb(OTf)_3$	15	15 h	97
$Yb(OTf)_3$	10	3 days	87
$Yb(OTf)_3$	5	6 days	87

7 Conclusion and outlook

The semi-pinacol rearrangement is well established as part of the synthetic chemists toolbox and its use towards the synthesis of stereodefined mono- and di-substituted aldol adducts, diols, ketones, ring-expanded and ring-contracted products, β-amino ketones, β-halo ketones as well its use in tandem reactions is well precedented, as shown herein. With the number of methods for generating enantiopure compounds on the increase, the highly stereospecific semi-pinacol rearrangement is an ideal reaction to be exploited by the conversion of these substrates into novel and highly complex structures with full transfer of chirality. The reaction offers unique opportunities to perform both stereoselective and stereospecific rearrangements which are capable of generating products which are not accessible by other synthetic methods. With this in mind the semi-pinacol rearrangement should feature more heavily in asymmetric synthesis in the future.

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