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Asymmetric functionalisation of tricarbonylchromium(0) complexes of arenes by non-racemic chiral bases

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Non-racemic chiral bases have been proven to be of significant use in the synthesis of a wide range of enantiomerically enriched *organic* molecules. Their use in the synthesis of *organometallic* reagents and catalysts, however, is still in its infancy. This article reviews one of the first areas of organometallic chemistry to be examined in this context, *i.e.* asymmetric functionalisation of tricarbonylchromium(0) complexes of arenes using non-racemic chiral bases.

Introduction

The use of chiral lithium amide bases[1] and alkyllithiums in conjunction with chiral ligands[2] to desymmetrise organic molecules began in earnest in the late 1980s and early 1990s. In view of the excitement generated by the pioneering studies in this area, it was clear that this approach to the synthesis of non-racemic chiral molecules would have applications in organometallic chemistry and, in particular, the study of organometallic complexes used in organic synthesis. Tricarbonylchromium(0) complexes of aromatic compounds have received much attention as building blocks for organic synthesis, partly because of the intriguing changes in reactivity that occur on complexation of an aromatic compound to the tricarbonylchromium(0) unit, and partly because of the inherent stereochemical properties of complexes of polysubstituted arenes. Two major changes that occur when an arene ring is complexed to a tricarbonylchromium(0) unit are: (i) an increase in the acidity of the hydrogens attached to the aromatic ring,[3] and (ii) an increase in the acidity of any benzylic hydrogens associated with the arene.[4] Thus, it is not too surprising that some of the first attempts to exploit chiral bases in organometallic chemistry focused on the introduction of chirality into tricarbonylchromium(0) complexes of arenes. This article reviews progress to date on the application of chiral bases to aromatic functionalisation and benzylic functionalisation of tricarbonylchromium(0) complexes of arenes.

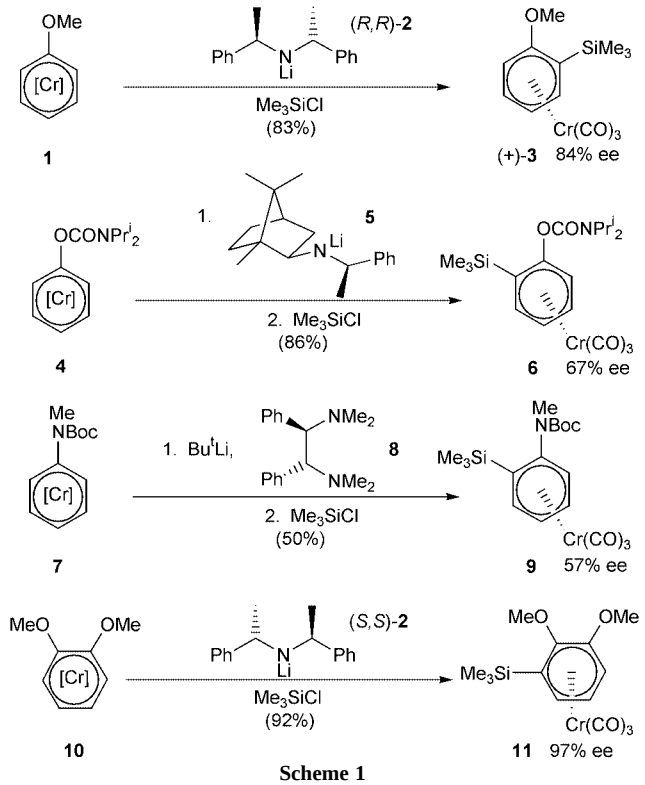
Sue Gibson did her first degree in Cambridge and her D. Phil. in Oxford under the supervision of Professor Steve Davies. She was then awarded a Royal Society European Fellowship to study at the ETH, Zürich with Professor Albert Eschenmoser. In 1985, she returned to the UK to a lectureship in organic chemistry at the University of Warwick, in 1990 she was appointed to a lectureship at Imperial College, London, and last year, she took up the Daniell Chair of Chemistry at King's College London. Her research interests revolve around the application of transition metals in organic synthesis. Current projects include the immobilisation of transition metal catalysts on solid supports, the biological and catalytic applications of conformationally constrained amino acids, and the application of chiral base chemistry and tricarbonylchromium(0) complexes of arenes to natural product synthesis and catalyst design.

Ellie Reddington attended school in North America, Asia and Europe. In 1996, she received her B.Sc. Hons. in Chemistry from Imperial College, London. She then started her Ph.D. on 'Chiral base-mediated asymmetric functionalisation of organometallic complexes' under the supervision of Sue Gibson. In 1999, she moved to King's College London with Professor Gibson where she completed her Ph.D.

Aromatic functionalisation

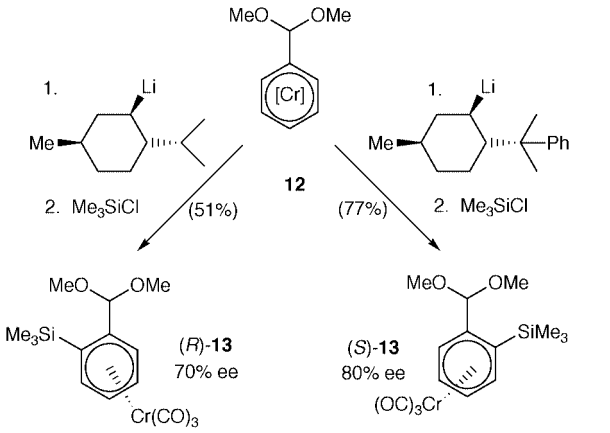
Aromatic functionalisation of tricarbonylchromium(0) complexes of arenes using a chiral amide base or an alkyllithium/chiral ligand combination was first reported in 1994. Indeed, there was a flurry of publications in this year from three groups, all of whom had identified and realised the potential of chiral bases in this area. Although the overall goal was the same, *i.e.* selective functionalisation of one of the *ortho* positions of a monofunctionalised arene complex, the methods of achieving this goal differed. Each group obtained success with a different directing group and a different chiral base or alkyllithium/chiral ligand combination. The introduction of a trimethylsilyl substituent was examined by each group and the result obtained was either typical or optimal. The Simpkins group successfully desymmetrised the tricarbonylchromium(0) complex of anisole **1** ([Cr] = tricarbonylchromium(0)) using chiral base (*R,R*)-**2** to give the planar chiral complex **3** in very good yield and enantiomeric excess,[5] the Kündig group successfully desymmetrised the prochiral carbamate complex **4** using chiral base **5** to give the trimethylsilyl derivative **6**,[6] and the Uemura group successfully desymmetrised the Boc-protected amine complex **7** using diamine **8** in conjunction with Bu^{t}Li to yield **9** (Scheme 1).[7] These results, and the many others described in these papers, demonstrated for the first time that planar chirality in (arene)tricarbonylchromium(0) complexes could be created using chiral bases. In parallel, the Schmalz group had been considering the possibility of using enantioselective *ortho*-deprotonation/silylation of 1,2-dimethoxyarene complexes in connection with their work on the synthesis of calamenen, pseudopterosin and helioporin. They discovered they were able to desymmetrise the disubstituted complex **10** using (*S,S*)-**2** to give the trisubstituted planar chiral complex **11** in excellent yield and enantiomeric excess.[8]

In the course of the studies described above, a problem was encountered with arguably one of the most synthetically useful classes of (arene)tricarbonylchromium(0) complexes, *i.e.* benzaldehyde acetal complexes; benzylic deprotonation often competed effectively with *ortho*-lithiation. This problem was addressed by the Green group using organolithium reagents derived from (1*R*)-menthyl chloride and (1*R*)-8-phenylmenthyl chloride. Reaction of these two reagents with the acetal complex **12** followed by addition of chlorotrimethylsilane afforded enantiomers (*R*)-**13** and (*S*)-**13**, respectively, in acceptable yield



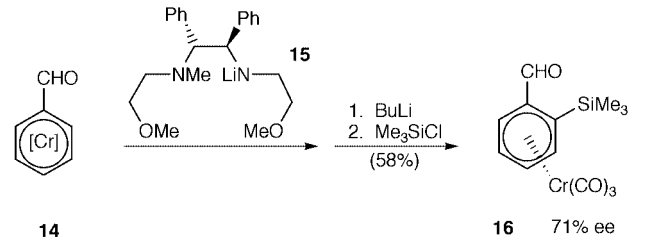
Scheme 1

and enantiomeric excess (Scheme 2).[9] A solution to the enantioselective functionalisation of (benzaldehyde)tricarbonylchromium(0) itself was provided by the Alexakis group,



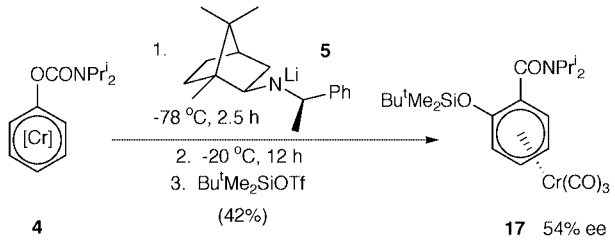
Scheme 2

which although strictly outside the scope of this review is nevertheless of interest in this context. In a typical example of their approach, reaction of complex **14** with **15** gave an amino alcoholate with an appended tertiary amine; subsequent addition of *n*-butyllithium followed by chlorotrimethylsilane gave complex **16** in notable enantiomeric excess (Scheme 3).[10]



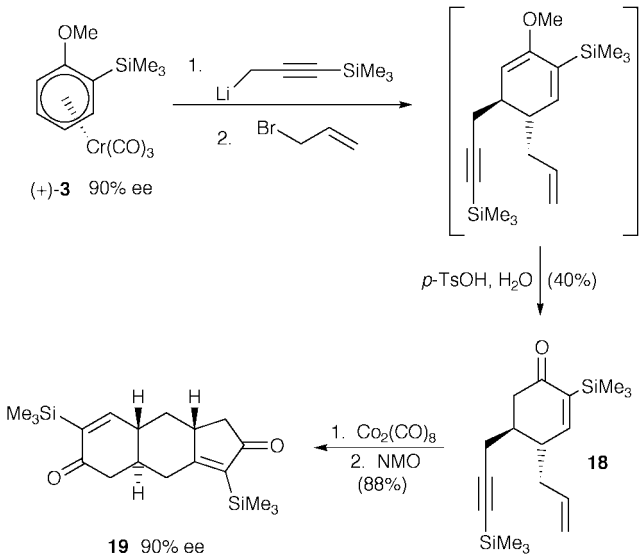
Scheme 3

Recently, the reaction of complex **4** with lithium amide **5** has been used to initiate an anionic *ortho*-Fries rearrangement. Warming the anion generated to −20 °C and stirring for 12 h induced the rearrangement; after quenching, product **17** was isolated and shown to be enantiomerically enriched (Scheme 4).[11]



Scheme 4

The chiral base approach to enantiomerically enriched (arene)tricarbonylchromium(0) complexes is starting to be applied in the synthetic arena. Thus complex **3**, made using the Simpkins method, has been used at the start of two synthetic studies. Kündig used a nucleophilic addition to (+)-**3** followed by an electrophilic quench and *in situ* hydrolysis to form the substituted cyclohexenone **18**. A subsequent Pauson–Khand reaction gave diastereomerically pure tricycle **19** in enantiomeric excess equal to that of (+)-**3** (Scheme 5).[12] Elaboration of



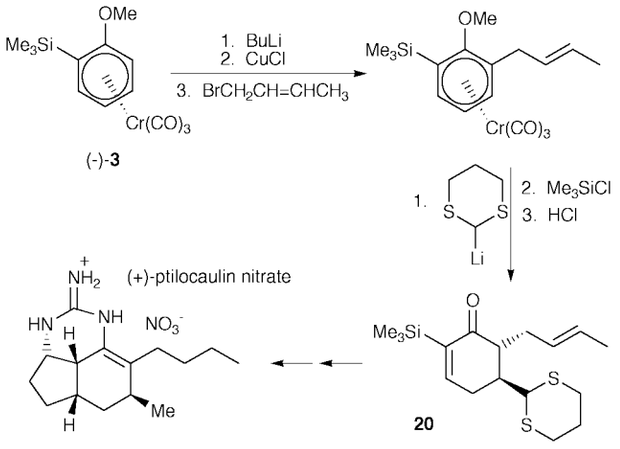
Scheme 5

(−)-**3** by the Schmalz group followed by nucleophilic addition and work-up gave substituted cyclohexenone **20**.[13] This was subsequently converted into (+)-ptilocaulin nitrate, an antimicrobial and cytotoxic metabolite of a Caribbean sponge (Scheme 6).[14] In both of these studies, the stereochemical information introduced using the chiral base is relayed first of all across the complexed arene ring to the chiral centre constructed on addition of the nucleophile. The stereochemistry of this chiral centre subsequently controls the formation of the remaining chiral centres in the product.

Benzylic functionalisation

Ethers: simple functionalisation

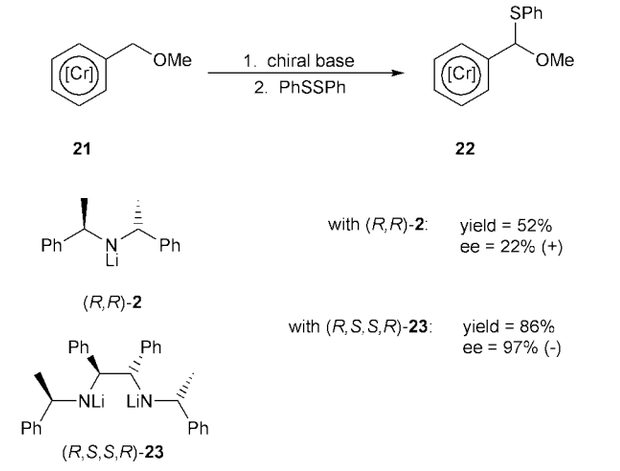
In 1996, we decided to examine the possibility of using chiral base methodology to asymmetrically functionalise the benzylic position of (arene)tricarbonylchromium(0) complexes. We selected the tricarbonylchromium(0) complex of benzyl methyl ether **21** as our test substrate as: (i) it was readily available and (ii) it had been demonstrated previously that it could be alkylated in good yield using *n*-butyllithium followed by quenching with a range of alkylating reagents.[15] That said, we



Scheme 6

were somewhat concerned that the high degree of conformational flexibility of complex **21**, compared to other substrates that had been successfully desymmetrised by chiral base technology, would render discrimination between its two benzylic sites difficult.

In an initial exploratory experiment, the well-established chiral base (*R*,*R*)-**2** was used to deprotonate **21** and diphenyl disulfide was used to quench the reaction. Workup provided the novel complex (+)-**22** in 52% yield. Complex **22** proved easy to analyse by chiral HPLC and its ee was found to be a moderate 22% (Scheme 7). In view of our reservations about the

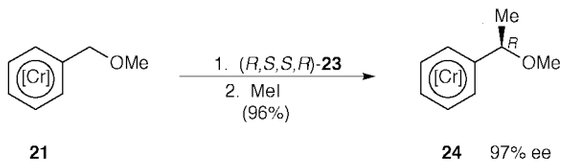


Scheme 7

conformational flexibility of **21**, we were highly encouraged by this seemingly modest result and decided to undertake further experiments with different bases. The next base used was the C_2-symmetric vicinal diamide **23**. A straightforward two-step synthesis of this base had been reported in 1994,[16] but its potential as a chiral base had not been explored in any detail. Using this base, the reaction of complex **21** to give the α-phenylsulfenyl derivative (−)-**22** proceeded in 86% yield and, to our delight, the ee of the product was found to be 97% (Scheme 7).[17]

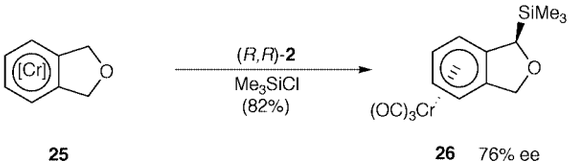
In order to glean information about the absolute stereochemistry of the products of this highly enantioselective system, the reaction between ether complex **21** and chiral base (*R*,*S*,*S*,*R*)-**23** was next quenched with iodomethane. This gave the α-methylbenzyl methyl ether complex **24** in 96% yield and 97% ee (Scheme 8). Comparison of the $[\alpha]_D$ of this material with literature data[18] revealed that the absolute configuration of **24** was *R*.

In parallel to our benzylic deprotonation studies on the acyclic ether **21**, the Simpkins group had been examining the effect of chiral bases on the cyclic ether complex **25**.[19] In a



Scheme 8

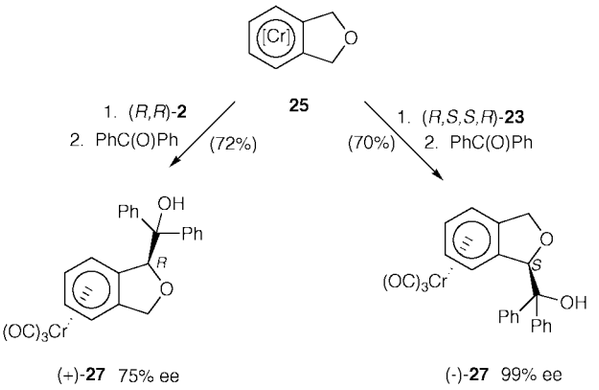
typical example from their work, (1,3-dihydroisobenzofuran)-tricarbonylchromium(0) **25** was treated with the monoamide base (*R*,*R*)-**2** in the presence of chlorotrimethylsilane. The product of benzylic functionalisation **26** was isolated in 82% yield and 76% ee (Scheme 9). Thus, in this case, in contrast to



Scheme 9

the acyclic ether case, the well-established monoamide base (*R*,*R*)-**2** led to good enantioselectivity. The absolute configuration of **26** was assigned by analogy with the product of methylation, the stereochemistry of which was rigorously determined by chemical correlation.

A little later, the reactions of the cyclic ether complex **25** with monoamide base (*R*,*R*)-**2** and the diamide base (*R*,*S*,*S*,*R*)-**23** followed by a benzophenone quench were reported by Simpkins.[20] Interestingly, switching from the monoamide base to the diamide base raised the enantioselectivity of this reaction from 75% to 99% (Scheme 10). Moreover, the absolute configuration



Scheme 10

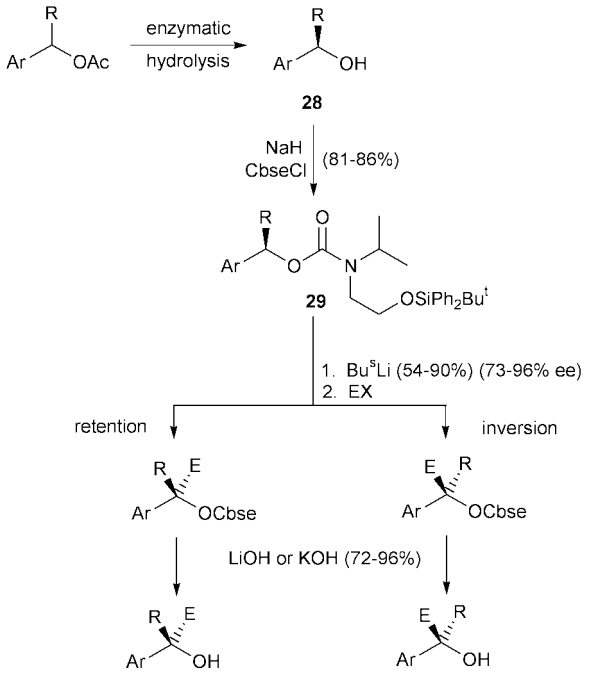
of the product **27** changed from *R* to *S* with the change of base, an observation reminiscent of the change from (+) to (−) observed with acyclic ether complex **21** in the production of sulfur derivative **22**.

Ethers: further elaboration

As a result of the studies described above, it was clear that asymmetric functionalisation of the benzylic position of ether complexes using the diamide base (*R*,*S*,*S*,*R*)-**23** was a high-yielding and highly enantioselective reaction. At this point, we decided to examine whether or not the reactivity discovered could be used as a basis for further elaboration of ether complexes and the generation of enantiomerically enriched products.

Synthesis of tertiary ethers. The synthesis of enantiomerically enriched tertiary alcohols is more challenging than their secondary counterparts, which are now readily available by a

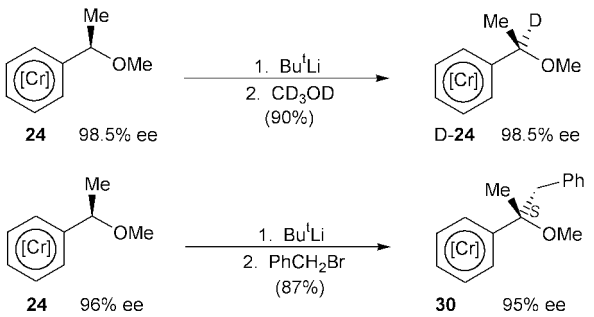
variety of reliable and versatile routes. In 1996, Hoppe and Dewing reported that enantiomerically enriched secondary alcohols **28**, derived from racemic mixtures by enzymatic hydrolysis, could be converted into enantiomerically enriched tertiary alcohols *via* deprotonation/electrophilic quench sequences on carbamate derivatives **29** (Scheme 11).[21] Some of



Scheme 11

the electrophilic quenches proceeded with retention of configuration, others with inversion. We thus decided to probe whether or not optically active complexes of secondary benzyl ethers. such as **24**, could be converted into optically active complexes of tertiary benzyl ethers by a deprotonation/electrophilic quench protocol. If so, it would be of interest to determine whether the reaction proceeded with retention or inversion of configuration.

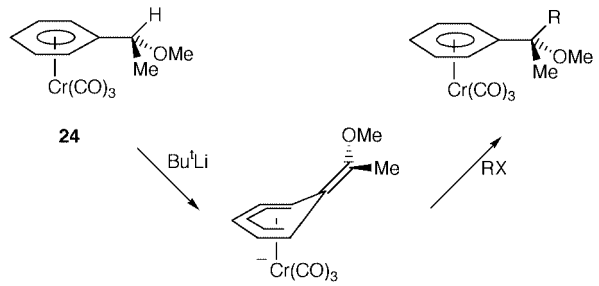
Complex **24** (98.5% ee and *R* configuration) was deprotonated with *tert*-butyllithium in THF at −78 °C, and, after 90 min at this temperature, the anion was quenched with deuteriomethanol. Work-up gave a 90% yield of complex D-**24** (91% D incorporation) which HPLC analysis revealed had an ee of 98.5% and was also of *R* configuration (Scheme 12). Thus the



Scheme 12

deprotonation/quench sequence had clearly proceeded with overall retention of configuration, presumably *via* a configurationally stable anion.[22]

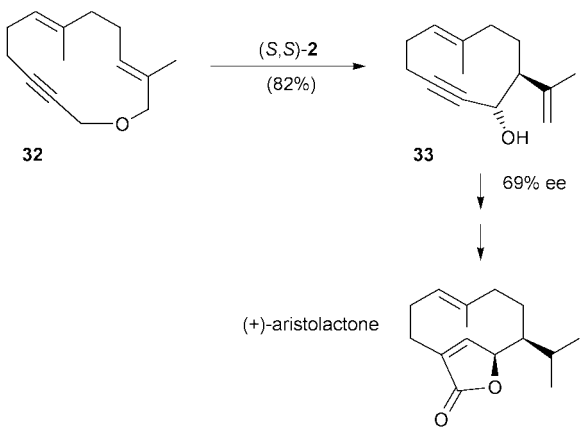
Having ascertained that the lithium anion of **24** is configurationally stable at −78 °C, our attention turned to synthetically more interesting electrophiles. Whilst deprotonation of (±)-**24** followed by quenching with iodomethane and chlorotrimethylsilane has been shown to proceed in yields of 93 and 53%, respectively, indicating that the formation of carbon–carbon and carbon–heteroatom bonds in this system is chemically feasible,[23] the stereochemical consequences and the synthetic scope of this type of process needed to be determined. We examined several systems varying both the benzylic substituent on the secondary ether and the electrophile used in the quench. In a typical example, complex **24** was deprotonated and quenched with benzyl bromide. Work-up led to the isolation of the novel complex **30** of essentially the same enantiomeric purity as its precursor in 87% yield (Scheme 12). An X-ray crystallographic analysis of this product revealed that its absolute configuration was *S*. Thus the deprotonation/benzylation of **24** proceeds with overall retention of configuration. This may be rationalised as follows: abstraction of the benzylic proton of **24** from a conformation that places it antiperiplanar to the tricarbonylchromium(0) unit gives the chromium-centred and configurationally-locked anion **31** (Scheme 13). The



Scheme 13

incoming electrophile then approaches the sterically less-hindered *exo*-face of the intermediate to give the observed product under excellent stereochemical control.

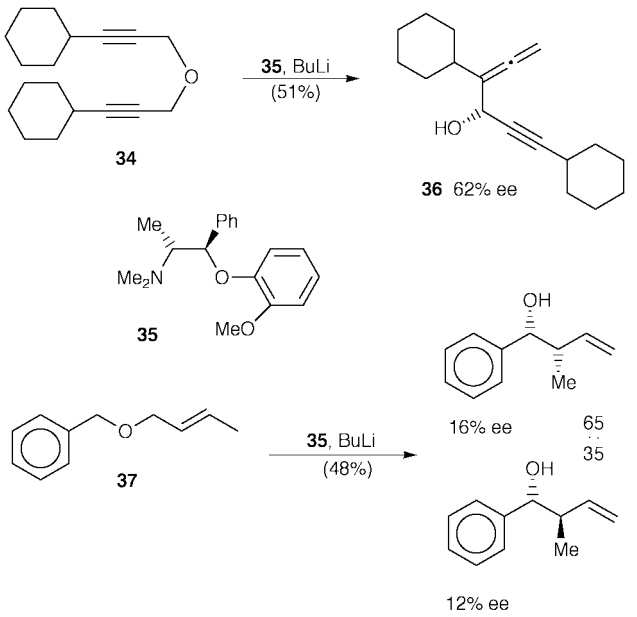
[2,3]-Wittig rearrangement. Our attention turned next to stereochemical control of the [2,3]-Wittig rearrangement. This is a useful carbon–carbon bond-forming reaction[24] and, as such, asymmetric versions of it are a desirable goal.[25] Research in recent years has produced several approaches, the greatest success being achieved using chiral auxiliaries.[26] Enantioselective versions of the [2,3]-Wittig rearrangement involving an achiral substrate and a chiral non-racemic base are synthetically more attractive, but this approach has been much less successful. The best result to date for a *cyclic* system is the conversion of the 13-membered ether **32** into the 10-membered alcohol **33** in 69% ee and 82% yield using (*S*,*S*)-**2** (Scheme 14).



Scheme 14

This success was attributed to special conformational effects as the same base gave a poorer result with a 17-membered homologue, and racemic products when applied to acyclic α-(allyloxy)acetic acids and amides.[27] Typical results to date for

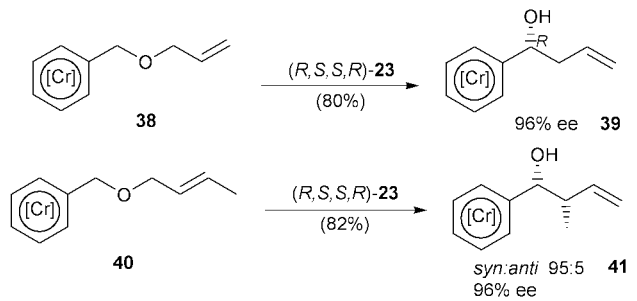
linear systems are exemplified by reactions carried out using a norpseudoephedrine/BuLi combination.[28] Thus Wittig rearrangement of dialkyne **34**, under the influence of **35**, produced alcohol **36** in moderate yield and ee, whilst rearrangement of unsaturated ether **37** gave a moderate yield of a diastereomeric mixture of alcohols each of poor optical purity (Scheme 15).



Scheme 15

In view of the high enantioselectivities and yields obtained for the asymmetric functionalisation of tricarbonylchromium(0) complexes of alkyl benzyl ethers, and earlier reports that tricarbonylchromium(0) complexes of allyl benzyl ethers undergo [2,3]-Wittig rearrangements,[29] we decided that it would be of interest to determine whether or not such Wittig rearrangements could be performed under good enantiomeric control using non-racemic chiral bases.

The first reaction to be examined was that of parent allyl benzyl ether complex **38** with diamide base (*R,S,S,R*)-**23**. This was found to proceed in good yield (80%) and excellent ee (96%) (Scheme 16).[30] In order to determine the absolute



Scheme 16

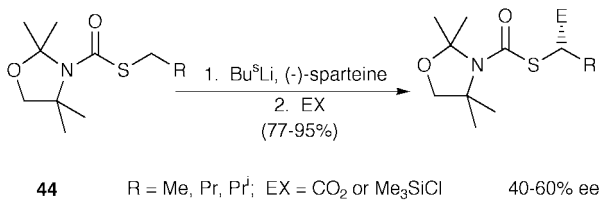
configuration of the product **39**, the tricarbonylchromium(0) unit was removed by photolysis and the $[\alpha]_D$ of the resulting alcohol compared with literature values.[31] This revealed that the absolute configuration of **39** was *R*, a result consistent with the sense of asymmetric induction observed for the functionalisation of complex **21** with external electrophiles.

A series of rearrangements were examined in order to determine the effect of substituents on chemical yields and enantioselectivities. In the first series of experiments, substituent patterns were chosen which would lead to products containing just one chiral centre. These experiments gave products of very good optical purity (84–94%), but the chemical yields ranged from good to poor (82–25%). Next the rearrangement of complex **40** was examined, as this gives rise to two chiral centres, raising the issue of diastereoselectivity. Pleasingly, the but-2-enyl complex **40** rearranged smoothly to give a good yield (82%) of alcohol **41** (Scheme 16). The diastereomeric ratio of the product complex was found to be 95 : 5 and the relative stereochemistry of the major isomer was identified as *syn* by comparison of its spectroscopic data and the data of its decomplexation product with literature values obtained from a racemic sample. HPLC analysis of **41** revealed that its ee was 96%. Thus the yield, diastereoselectivity and enantioselectivity observed for the rearrangement of **40** to **41** under the influence of base (*R,S,S,R*)-**23** compare well with the rearrangement of the non-complexed material **37** under the influence of the norpseudoephedrine/BuLi combination.

Thioethers

The configurational instability of α-sulfur substituted alkyllithium compounds **42**[32] and benzyllithium compounds **43**[33] is

well documented and attempts to use these species in asymmetric synthesis have met with little success to date. Indeed, the first examples of enantiomerically enriched α-sulfur substituted alkyllithium compounds, whose chirality is determined solely by the stereogenic carbon centre, were prepared only quite recently. Thus, generation of α-sulfur substituted alkyllithiums by deprotonation of **44** with Bu^{s}Li/(−)-sparteine and subsequent quenching with carbon dioxide or chlorotrimethylsilane gave products in 77–95% yield and 40–60% ee (Scheme 17).[32]

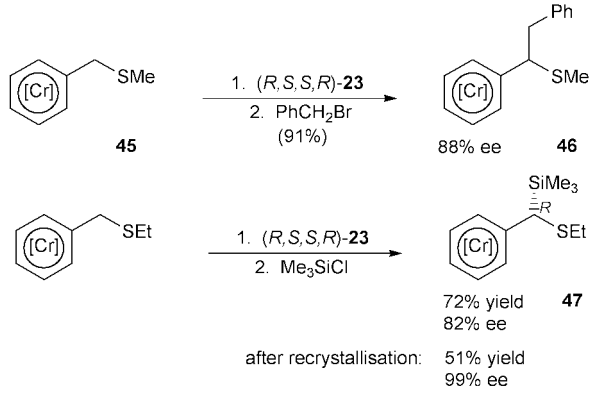


Scheme 17

In view of (i) the recognised instability of α-sulfur substituted lithium compounds, and (ii) the emerging potential of chiral sulfides as ligands in asymmetric synthesis,[34] we wanted to determine whether or not anions of tricarbonylchromium(0) complexes of alkyl/aryl benzyl sulfides would be sufficiently configurationally stable to undergo bond-forming reactions and produce enantiomerically enriched products.

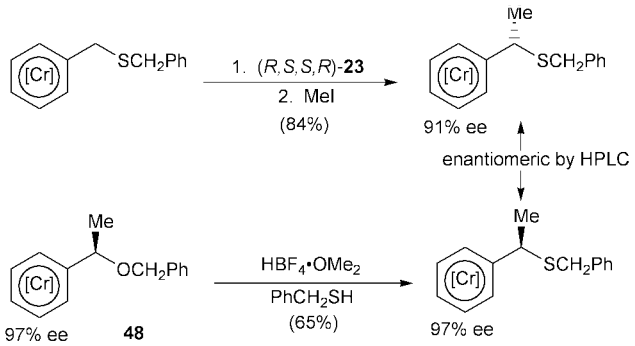
A series of thioether complexes was easily and efficiently prepared by reacting (benzyl alcohol)tricarbonylchromium(0) with a range of thiols in the presence of tetrafluoroboric acid.[15] After some experimentation, it emerged that enantioselectivity was a function of the thioether substituent and that methyl and benzyl substituents gave the best results. In a typical experiment, thioether complex **45** was reacted with (*R,S,S,R*)-**23** and quenched with benzyl bromide to give the benzylic substitution product **46** in 91% yield and 88% ee (Scheme 18).[35] In order to determine the absolute stereochemistry of the chiral sulfides generated by this new approach, we subjected the silyl substituted complex **47** (Scheme 18) to X-ray crystallographic analysis. To our surprise, this revealed that **47** was the opposite enantiomer to the one we had predicted based on the results obtained with the analogous ether complexes.

In order to probe this change in stereochemical outcome further, the ether complex **48** (97% ee) was reacted with benzyl



Scheme 18

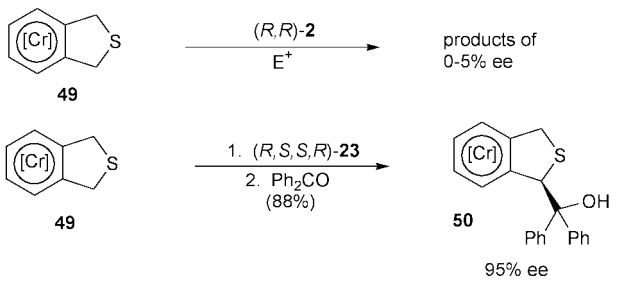
thiol in the presence of acid. Work-up gave a thioether complex in 65% yield and HPLC analysis of this material revealed that it was the opposite enantiomer to that obtained by the deprotonation/quench route (Scheme 19). As acid catalysed substitutions



Scheme 19

of this type are known to proceed with retention of configuration,[36] this result is stereochemically consistent with the X-ray crystallographic analysis of **47**. It thus appears that deprotonation of tricarbonylchromium(0) complexes of benzyl sulfides with the chiral base (*R*,*S*,*S*,*R*)-**23** proceeds in the opposite stereochemical sense to deprotonation of the corresponding ethers.

The Simpkins group also examined the effect of chiral bases on tricarbonylchromium(0) complexes of thioethers, but their focus was on the cyclic system **49**. Initially, **49** was reacted with the monoamide base (*R*,*R*)-**2** and subjected to a range of quenches, but these reactions gave products of very low ee (*ca.* 5%) (Scheme 20).[19] On re-examining the system with the



Scheme 20

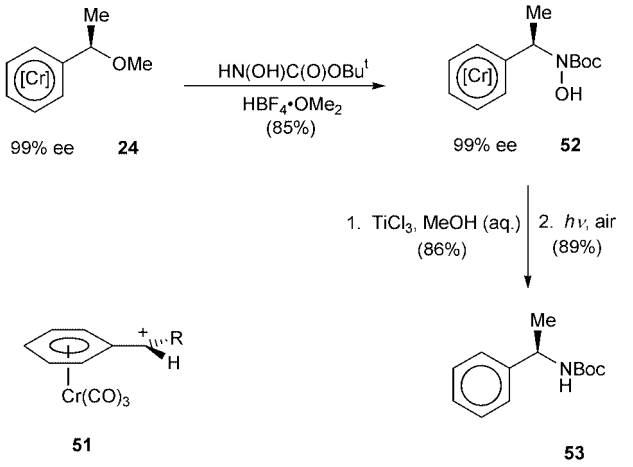
diamide base (*R*,*S*,*S*,*R*)-**23**, however, they were able to generate products in excellent yield and ee.[37] Addition of benzophenone to **49** using (*R*,*S*,*S*,*R*)-**23**, for example, generated **50** in 88% yield and 95% ee (Scheme 20). Interestingly, comparison of **50** with (−)-**27** obtained from the cyclic ether **25** indicates that the change in stereochemistry observed in the acyclic systems is not repeated here. This may be a function of the increased rigidity of the cyclic system.

In summary, diamide base (*R*,*S*,*S*,*R*)-**23** can be used to asymmetrically functionalise complexes of benzylic sulfides. Although the enantiomeric excesses observed in the acyclic system are slightly lower than those observed in the corresponding oxygen ether system, the relatively high selectivity compared to other α-sulfur substituted lithium systems suggests that the anion involved possesses unusually high stereochemical stability. This is attributed to the delocalisation of the negative charge onto chromium (and beyond onto the carbonyl ligands) which raises the energy barrier to rotation about the *ipso* carbon–benzylic carbon bond.

Amines

The efforts of our group and the Simpkins group to use chiral bases to asymmetrically functionalise tricarbonylchromium(0) complexes of benzylic amines, or their derivatives, have, to date, proved unsuccessful. Nevertheless, we have demonstrated that it is possible to access this important class of compounds using the reliable and robust ether chemistry.

Initial experiments were carried out using complex **24** of 99% ee. It was hoped that nucleophilic substitution of this complex using a nitrogen nucleophile would give us access to enantiomerically enriched amines. Literature precedent, however, was not encouraging: although substitution of α-oxygenated (arene)tricarbonylchromium(0) complexes with acid/nucleophile combinations *via* a chromium-stabilised carbocation intermediate **51** (Scheme 21) is well-established for carbon,

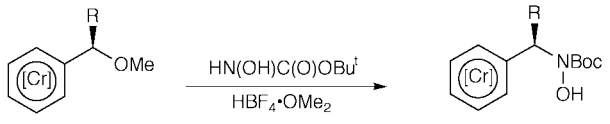


Scheme 21

hydrogen, and oxygen nucleophiles, the use of nitrogen nucleophiles is rare and inefficient. Thus, reactions of ammonia and primary and secondary amines with benzyl alcohol complexes in the presence of hexafluorophosphoric acid gives low yields of substitution products.[38] Indeed our initial reactions of complex **24** with a wide range of amines in the presence of tetrafluoroboric acid were disappointing, providing only very low levels of nitrogen incorporation and complex mixtures of products. In contrast, protonation of **24** at −40 °C with tetrafluoroboric acid followed by addition of commercially available *tert*-butyl-*N*-hydroxycarbamate gave the nitrogen substitution product **52** in 85% yield (Scheme 21). Moreover the ee of the novel complex **52** was measured by chiral HPLC and found to be 99%.[39]

The absolute configuration of the nitrogen substitution product **52** was determined by chemical correlation. Reduction of the nitrogen–oxygen bond using titanium trichloride in aqueous methanol proceeded smoothly. Subsequent oxidative removal of the tricarbonylchromium(0) unit gave carbamate **53** (Scheme 21), the optical rotation of which was essentially identical to a sample prepared from authentic (*R*)-α-methylbenzylamine. Thus the absolute configuration of **52** is *R* and the conversion of **24** to **52** proceeds with retention of configuration, presumably *via* a chromium stabilised carbocation **51**.

In order to probe the effect of increasing steric hindrance around the benzylic position on the nitrogen substitution reaction, complexes **54** and **55** bearing ethyl and *iso*-propyl groups, respectively, were prepared and reacted with *tert*-butyl-*N*-hydroxycarbamate. The reactions gave products **56** and **57** in moderate yield and 96 and 91% ee respectively (Scheme 22).



R	educt	ee (%)	product	ee (%)	yield (%)
Me	**24**	99	**52**	99	85
Et	**54**	96	**56**	96	53
i-Pr	**55**	98	**57**	91	43

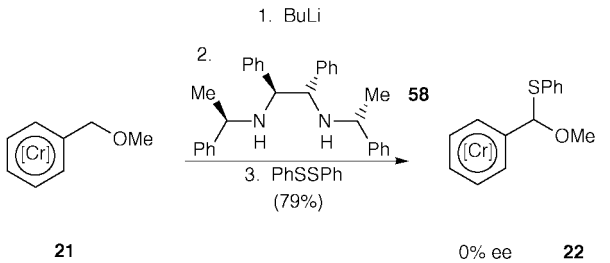
Scheme 22

Thus, increasing steric hindrance on going from methyl to *iso*-propyl leads to notable yield reduction and a small but significant stereochemical leakage. These effects are attributed to a reduced rate of addition of the nitrogen nucleophile to the intermediate carbocation, the increased lifetime of which leads to byproducts and rotation about the *ipso* carbon–benzylic carbon bond.

Mechanistic probes

Several studies have been carried out in order to probe the mechanism of the highly selective reactions described above.

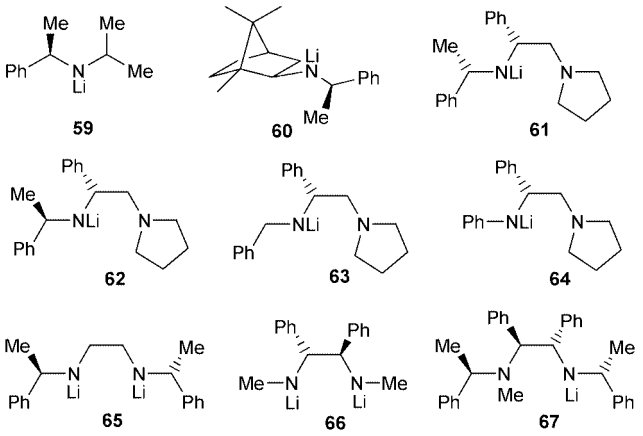
Addition of diamine after BuLi. In order to test whether the benzylic asymmetric functionalisations described in previous sections were due to asymmetric deprotonations or to asymmetric electrophilic quenches, we performed an experiment in which the substrate was deprotonated with the achiral base *n*-butyllithium and the chiral diamine was added afterwards.[40] Thus methyl ether complex **21** was treated with 1.1 equiv. of butylithium followed by 1.1 equiv. of diamine **58** (and 1 equiv. of lithium chloride). The reaction was subsequently quenched with 2 equiv. of diphenyl disulfide to give the expected product **22** in 79% yield (Scheme 23). The ee of **22** was measured and



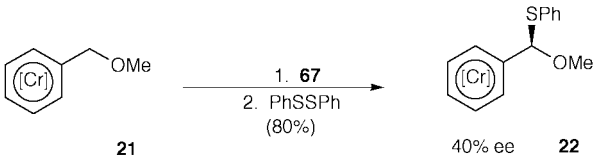
Scheme 23

found to be zero. Thus the racemic anion generated in this experiment did not undergo an asymmetric electrophilic quench under the control of the chiral diamine present in the reaction mixture. This result is consistent with the asymmetric control observed in the benzylic functionalisations originating in the deprotonation step rather than the quench step.

Effect of base structure. As diamide base (*R*,*S*,*S*,*R*)-**23** was only the second base we had examined in our initial studies on the functionalisation of oxygen ether **21**, we thought it prudent to screen other chiral bases to establish whether or not the high yields and ees obtained with (*R*,*S*,*S*,*R*)-**23** were unique to this structure. Amides **59**–**64** were used in the conversion of ether **21** to sulfur derivative **22** and found to give only moderate yields and enantioselectivities compared to (*R*,*S*,*S*,*R*)-**23**.[41] We also synthesised and tested bases **65** and **66** to probe whether all the features of (*R*,*S*,*S*,*R*)-**23** were essential to the high yields and



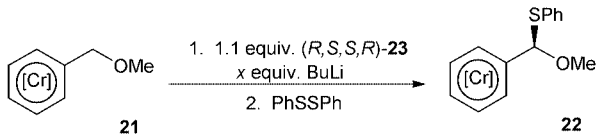
selectivities. These studies revealed that both the backbone and the side chain chirality were necessary for optimum results.[41] Finally, in order to ascertain whether the second lithium amide was necessary for success, base **67** was synthesised[42] and tested on substrate **21** (Scheme 24). This gave a good yield (80%) and



Scheme 24

moderate ee (40%) of the *R* enantiomer of **22**, a finding which was later used to explain results obtained by varying the equivalents of BuLi used in the reaction (*vide infra*).

Effect of BuLi stoichiometry. All the reactions described above were carried out using 2.2 equiv. of BuLi and 1.1 equiv. of diamine. In an effort to minimise the amount of BuLi required in these experiments, **21** was converted to **22** using 1.1 equiv. of BuLi and the effect on yield and ee determined. In order to determine the effect on ee of reducing the equivalents of BuLi used still further, reactions using 0.55 and 0.275 equiv. of BuLi were also performed (Scheme 25). Pleasingly, use of



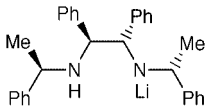
BuLi (equiv.) (*x*)	yield (%)	ee (%)	recovered substrate (%)
2.2	95	98	0
1.1	96	95	0
0.55	60	92	40
0.275	21	96	67

Scheme 25

1.1 equiv. of BuLi had negligible detrimental effect on yield and ee, producing **22** in 96% yield and 95% ee. It was interesting to note that although reduction of the equivalents of BuLi to 0.55 and 0.275 gave the expected drop in yield (60 and 21% respectively; an experimental error of ±5% in BuLi measurement accounts for the unreasonably high yield in the first case), the enantioselectivity of the reaction remained very high (92 and 96% respectively).

The results obtained by varying the equivalents of BuLi may be explained as follows. The dilithiated species (*R*,*S*,*S*,*R*)-**23** (or an aggregate thereof) is clearly a highly enantioselective

reagent. If we assume that the monolithiated species **68** is relatively unselective, a hypothesis supported to a degree by the low ee (40%) obtained with **67**, then it follows from the results obtained on reducing the number of BuLi equivalents that (i) there is a ready exchange of lithium cations between all the nitrogen sites in the system, and (ii) (*R*,*S*,*S*,*R*)-**23** is more reactive than **68** with respect to complex **21**. In conclusion, it



68

appears that all the deprotonation power of the BuLi is channelled through the highly selective diamide species rather than the relatively unselective monoamide species.

Conclusion

Studies carried out in the last five years have demonstrated that chiral bases provide an excellent entry into enantioenriched tricarbonylchromium(0) complexes of arenes. Moreover, the products of these studies are starting to be used in synthetic endeavours. It is anticipated that in the next few years, chiral bases will be used to generate a wide variety of enantioenriched organometallic complexes which will find uses both in synthesis and catalysis. Whilst the selectivities that can be achieved are impressive and useful, discovery of the origin of this selectivity in both the organometallic systems described here and the organic systems developed over the last fifteen years remains a significant challenge.

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