Pure Appl. Chem., Vol. 76, No. 3, pp. 477–494, 2004.

Synthetic applications of planar chiral cationic η^3-allylmolybdenum complexes*

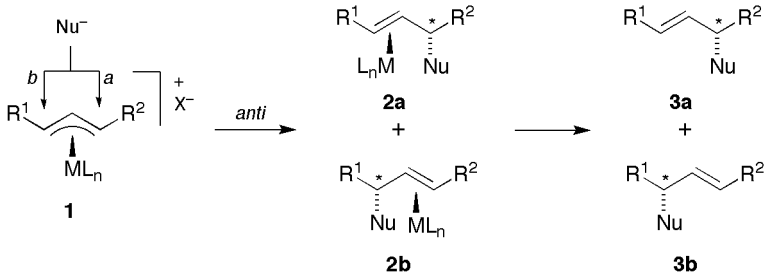
Philip Kocienski[1,2,‡], Richard Bell[3], Elyse Bourque[1], John A. Christopher[2,3], John Cooksey[1], Andrew Gunn[1,2], Alexander Kuhl[2], Yingfa Li[1], Sukhjinder Uppal[1], and Josephine Yuen[1]

[1]Department of Chemistry, Leeds University, Leeds LS2 9JT, UK; [2]Department of Chemistry, Glasgow University, Glasgow G12 8QQ, UK; [3]GlaxoSmithKline Research and Development, Medicines Research Centre, Stevenage, Hertfordshire SG1 2NY, UK

Abstract: The synthesis of planar chiral η^3-allylmolybdenum complexes is described together with some examples of the nucleophilic addition of organocopper(I) reagents.

INTRODUCTION

Planar chiral cationic π-allylmetal complexes such as **1** (Scheme 1) are potent electrophiles. Their value in asymmetric synthesis depends on: (a) easy synthesis from readily accessible enantiomerically pure precursors; (b) nucleophilic attack at the allyl ligand rather than the metal; (c) metal-controlled enantioface discrimination; (d) broad scope in the nature of the nucleophiles (soft vs. hard); (e) regioselectivity (*a* vs. *b*); and (f) mild and efficient demetallation of the intermediate alkene complexes **2a,b**. The following account shows how these aims can be satisfied by the use of planar chiral cationic η^3-allylmolybdenum complexes based on the CpMo(CO)(NO) fragment.



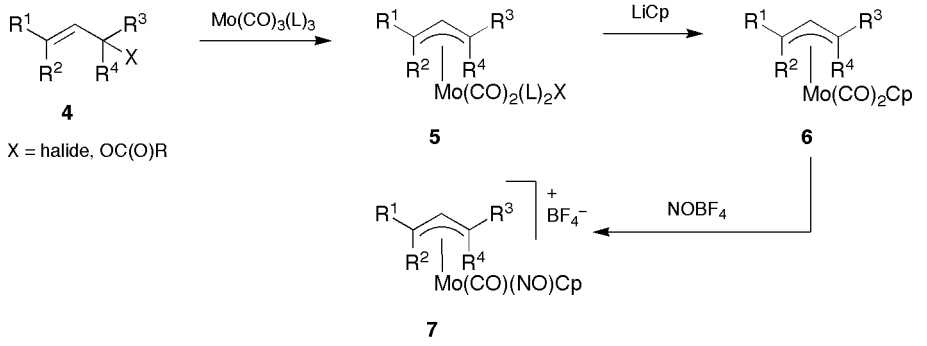
Scheme 1

PREPARATION OF CATIONIC η^3-ALLYLMOLYBDENUM COMPLEXES

Cationic η^3-allylmolybdenum complexes are typically prepared by the 3-step sequence shown in Scheme 2. Oxidative addition of a reagent $Mo(CO)_3(L)_3$ with an allylic halide or ester affords an adduct **5** which reacts with LiCp to give the neutral complexes **6**. Neutral complexes **6** are stable 18-electron species and unreactive toward nucleophiles. Activation to the highly electrophilic cationic tetrafluoro-

*Plenary and invited lectures presented at the 12th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-12), Toronto, Ontario, Canada, 6–10 July 2003. Other presentations are published in this issue, pp. 453–695.

‡Corresponding author

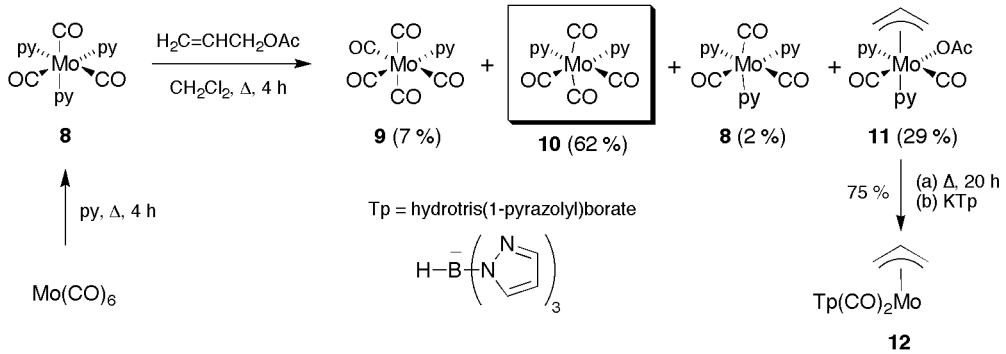


4 **5** **6** **7**

Scheme 2

borate or hexafluorophosphate complex **7** is readily achieved by treatment of neutral complex **6** with nitrosonium tetrafluoroborate or hexafluorophosphate.

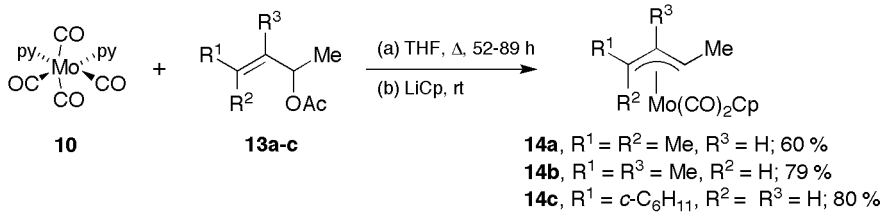
Success with the chemistry depicted in Scheme 2 depends on several variables including the leaving group X, the degree of substitution in **4** (more highly substituted systems react very slowly), the nature of the ligand L, and the presence of heteroatom substituents in the substrate. The rate of the oxidative addition is fast when X = halide, whereas esters react much slower. Liebeskind used diphenylphosphinate esters in the preparation of neutral (η^3-allyl)$Mo(CO)_2Cp$ complexes [1,2]. The ligands L on the molybdenum reagent also have a strong effect on the rate of the first step. Whereas $Mo(CO)_3(MeCN)_3$ [3,4] is the most common Mo(0) source, other variants include $Mo(CO)_3(DMF)_3$ [5], $Mo(CO)_3(PhMe)$ [6], $Mo(CO)_3$(diglyme), and $(DME)_2Mo_2(CO)_6$ [2]. A detailed evaluation of the reaction of allyl acetate with $Mo(CO)_3(py)_3$ [7,8] using ^{95}Mo NMR spectroscopy [9] elucidated the reaction pathways involved (Scheme 3) [10]. After 4 h, the major component of the reaction mixture was *cis*-$[Mo(CO)_4(py)_2]$ (**10**, 62 %) together with only 2 % of **8**, $Mo(CO)_5(py)$ (**9**, 7 %) and the expected η^3-allylmolybdenum complex **11** (29 %). A gradual increase in the concentration of **11** was mirrored by a decrease in **10**, and after a further 20 h, neutral complex **12** was isolated in 75 % yield following ligand exchange with potassium hydrotris(1-pyrazolyl)borate, an isoelectronic equivalent of the Cp ligand [11,12].



8 **9** (7 %) **10** (62 %) **8** (2 %) **11** (29 %) **12**

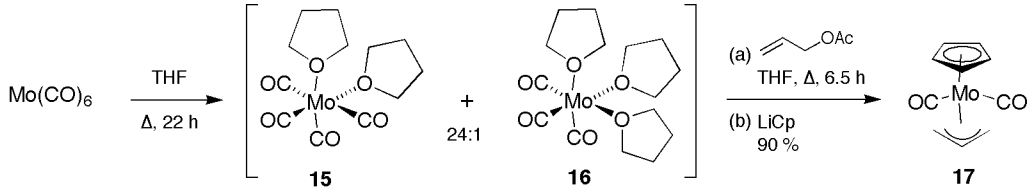
Scheme 3

$Mo(CO)_4(py)_2$ (**10**), the reagent apparently responsible for the oxidative addition, was quantitatively prepared in refluxing THF from $Mo(CO)_6$ and 2 equiv of pyridine. In situ reaction with allylic acetates **13a–c** (Scheme 4) followed by displacement of the remaining pyridine and acetate ligands with LiCp yielded a variety of neutral η^3-allylmolybdenum complexes in excellent yield and purity, including hindered complexes **14a–c** which could not be obtained with $Mo(CO)_3(MeCN)_3$.



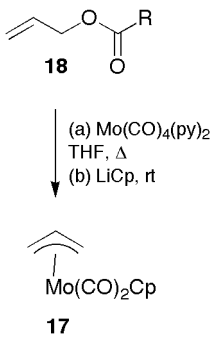
Scheme 4

Refluxing $Mo(CO)_6$ in THF for 22 h in the absence of light generates *cis*-$Mo(CO)_4(THF)_2$ (**15**, Scheme 5), which is stable in THF in the absence of light and oxygen and can be precipitated in pentane at –100 °C. Although a full characterization was precluded by instability, IR and ^{95}Mo NMR spectroscopy established the formation of *cis*-$Mo(CO)_4(THF)_2$ (^{95}Mo NMR: –927 ppm, $\Delta\omega_{1/2}$ = 120 Hz) which is in equilibrium with $Mo(CO)_3(THF)_3$ (**16**, ^{95}Mo NMR: –750 ppm, $\Delta\omega_{1/2}$ = 65 Hz). *cis*-$Mo(CO)_4(THF)_2$ reacted with pyridine (2 equiv) to give *cis*-$Mo(CO)_4(py)_2$, and it reacted with allyl acetate in 6.5 h to yield complex **17** (90 %). The increased reaction rate and higher yield in comparison with $Mo(CO)_4(py)_2$ suggests that $Mo(CO)_4(THF)_2$ provides the Mo(0) reagent of choice for the oxidative addition to allylic esters [13].



Scheme 5

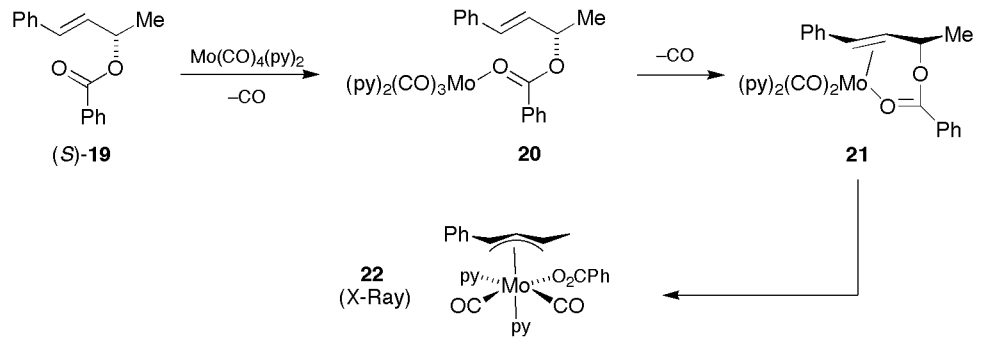
We also investigated the influence of the leaving group on the oxidative addition of *cis*-$Mo(CO)_4(py)_2$ using a series of allyl esters **18** (Scheme 6). A dependence on the donor capacity of the leaving group was established. Optimal yield of allyl complex **17** and reaction time was obtained with the benzoate leaving group. Reaction time continued to decrease as the donor capacity increased (R = Ph → *p*-MeOPh → *p*-Me_2NPh), but a detrimental effect upon yield was observed [10].



R	Time (h)	17 (%)
CF_3	25	70
CH_3	10	75
C_6H_4-*p*-F	8	82
C_6H_4-*p*-Cl	7	88
C_6H_5	6.5	94
C_6H_4-*p*-OMe	5.5	80
C_6H_4-*p*-NMe_2	4	47

Scheme 6

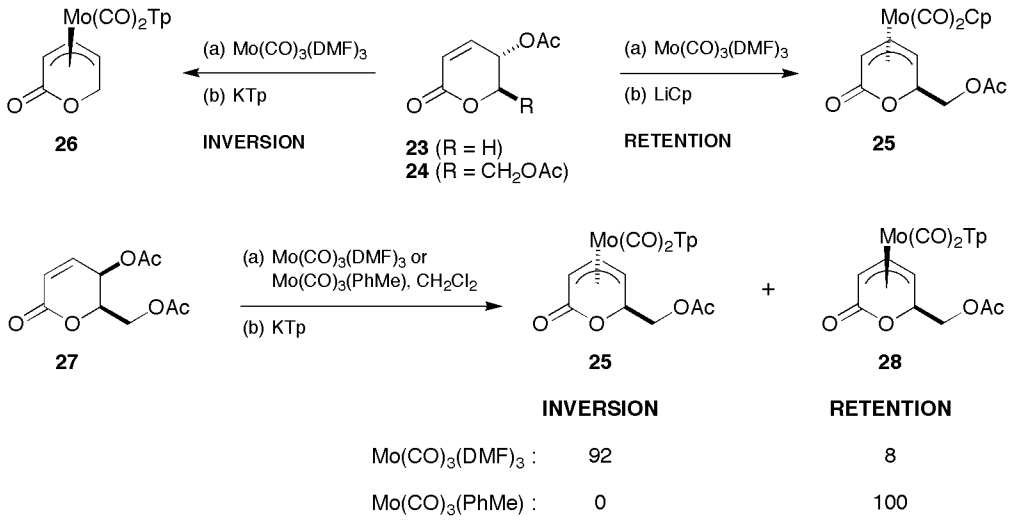
A recent investigation of the reaction of the enantiomerically pure benzoate (*S*)-**19** with $Mo(CO)_4(py)_2$ suggested a mechanism for the oxidative addition (Scheme 7). Decarbonylation of $Mo(CO)_4(py)_2$ is followed by coordination of the transient 16-electron species with the carbonyl group of the benzoate to give **20**. Following the loss of a further carbonyl ligand from **20**, and coordination of



Scheme 7

molybdenum to the olefin, intermediate **21** collapses to give molybdenum(II) complex **22**. An X-ray structure of **22** was obtained [14,15] and revealed that: (a) the carboxylate and allyl ligands were *cis* and (b) Mo(II) complex **22** had been formed with overall retention of configuration from benzoate **19**. The faster rates and cleaner reactions observed with aromatic esters accord with a mechanism in which the molybdenum serves as a Lewis acid in the first step, an idea promulgated earlier by Liebeskind and coworkers [16].

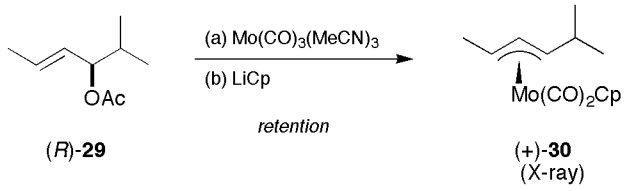
The stereochemistry of the oxidative addition of various Mo(0) species depends on the conditions (e.g., concentration), the structure of the substrate and the nature of the associated ligands [16]. Thus, the allylic acetate **23** (Scheme 8) reacted with $Mo(CO)_3(DMF)_3$ in CH_2Cl_2 with inversion of configuration to give **26**, whereas the analogous allylic acetate **24** gave the neutral complex **25** with retention of configuration. By contrast, diastereoisomeric allylic acetate **27** gave a 92:8 mixture of inversion (**25**) and retention (**28**) products with $Mo(CO)_3(DMF)_3$, whereas retentive product **28** could be prepared independently using $Mo(CO)_3(PhMe)$ as the Mo(0) source. Thus, $Mo(CO)_3(MeCN)_3$, $Mo(CO)_3(PhMe)$, $Mo(CO)_4(THF)_2$, and $Mo(CO)_4(py)_2$ appear to be unambiguous sources of Mo(0) for retentive oxidative addition pathways, with $Mo(CO)_3(DMF)_3$ giving inversion under appropriate conditions.



Scheme 8

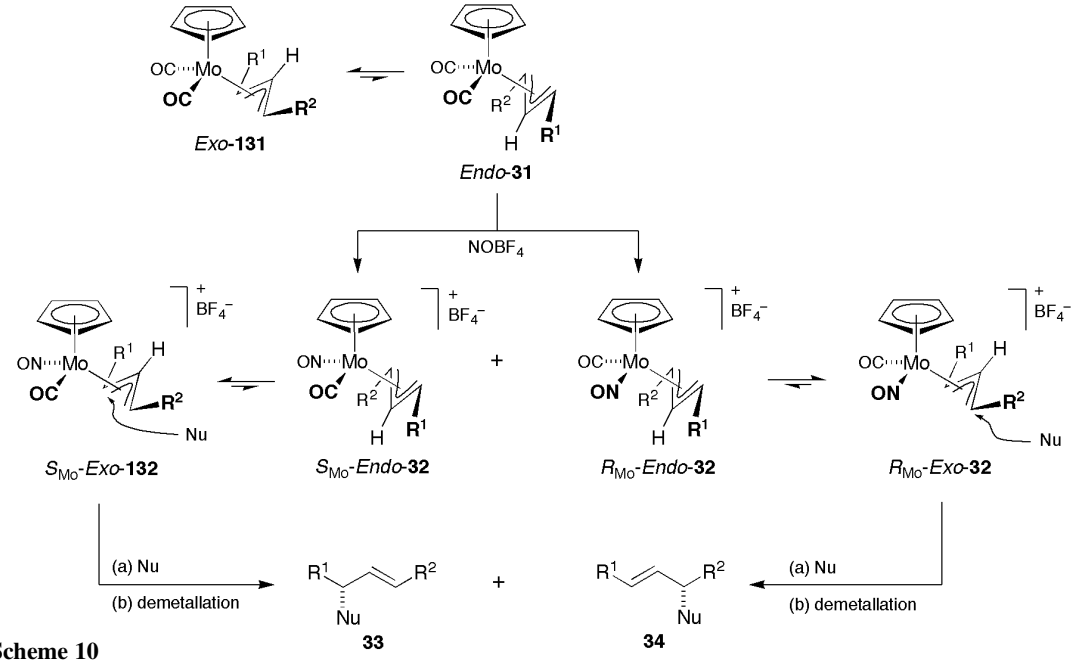
NUCLEOPHILIC ADDITION TO CATIONIC η^3-ALLYLMOLYBDENUM COMPLEXES

The first practical synthesis of enantiomerically pure η^3-allylmolybdenum complexes was reported in 1988 by Faller and Linebarrier (Scheme 9) [17]. They showed that oxidative addition of $Mo(CO)_3(MeCN)_3$ to the enantiomerically pure allylic acetate (*R*)-**29** followed by ligand exchange with LiCp gave the neutral planar chiral complex **30** with retention of configuration.



Scheme 9

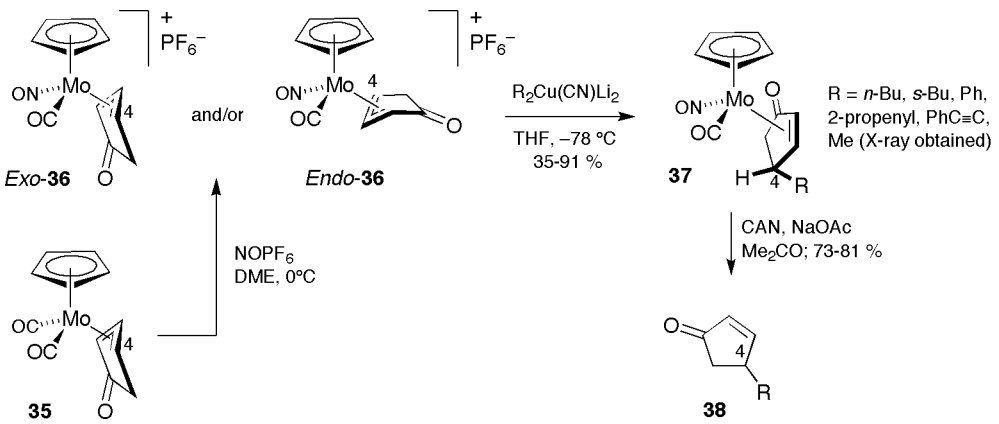
The neutral η^3-allyl complexes are inert toward nucleophiles but their cationic counterparts obtained by ligand exchange with nitrosonium tetrafluoroborate or hexafluorophosphate (Scheme 10) are highly electrophilic. Stringent precautions are needed to exclude moisture and air from the solid cationic complexes. Tetrafluoroborate salts such as **32** are very sensitive to moisture owing to decarbonylation promoted by fluoride ion liberated from hydrolysis of the tetrafluoroborate or hexafluorophosphate anions [18,19]. Unfortunately, the exchange is stereorandom [17], and, therefore, the enantiomerically pure neutral complex (**31**, planar chirality only) is converted to a diastereoisomeric mixture of 4 complexes **32** owing to (a) the creation of *central* chirality at the metal center and (b) the existence of *exo–endo* isomerism in both the neutral [20,21] and cationic complexes [22]. The isomeric composition of the cationic complexes is time-dependent. Complex **32** initially appears as a mixture of 2 *endo*-isomers in an approximately equimolar ratio owing to faster ligand exchange on the *endo*-isomers of the neutral complex [22,23]. The mixture gradually equilibrates to favor the *exo*-isomer. The *exo*- and *endo*-isomers are easily distinguished by ^1H and ^{95}Mo NMR spectroscopy [23].



Scheme 10

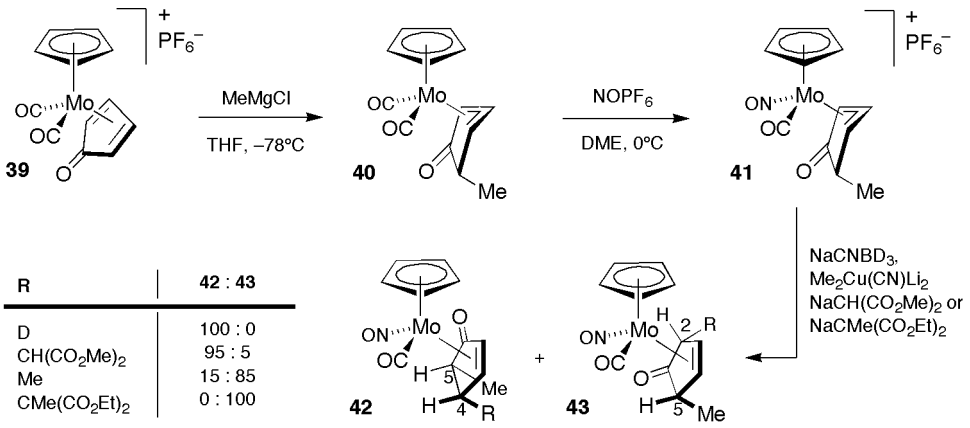
The reaction of the mixture of cationic complexes **32** with relatively soft nucleophiles such as enamines, enolates, hydride, thiophenoxide, and malonate derivatives established that the planar chirality of the complexes governs the facial selectivity of nucleophilic attack to the allylic ligand *anti* to the metal to give the two isomeric alkylation products **33** and **34** after oxidative demetallation [24]. The regiochemistry of attack is governed by the central chirality at molybdenum: addition occurs *cis* to the nitrosyl group, in accordance with attack at the point of lowest electron density on the allyl ligand. The selectivity is rationalized by a consideration of the different electronegativities and back bonding properties of the CO and NO ligands. The electronic distribution at the metal is distorted, leading in turn to a polarization of the allyl ligand [25,26]. *Exo–endo* isomerism plays no significant role in the course of the reaction because the *exo*-isomers react faster than the *endo*-isomers. The *exo*- and *endo*-isomers are in rapid equilibrium under the reaction conditions, and kinetic selection for the *exo*-isomer occurs [25,27,28]. The isomerization is generally catalyzed by the nucleophile [29]. *Exo–endo* isomerization does not involve η^3-η^1-η^3 interconversion; rather, the mechanism of rotamer interconversion for the Cp-based complexes is one of "pseudorotation" about the Mo-allyl axis [25,30–32], and, therefore, the stereochemistry of the substituents on the allyl ligand and the face of the ligand bound to the metal remain intact during the isomerization.

The foregoing discussion would suggest that the stereorandom nature of the nitrosyl ligand exchange and the powerful electronic effect of the nitrosyl group on subsequent nucleophilic addition reactions render the planar chiral cationic η^3-allylmolybdenum complexes useless in asymmetric synthesis. However, recent work suggests that the regiochemistry of nucleophilic addition depends on a wide range of factors including temperature, solvent, steric effects in the cationic complex, and the nature of the nucleophile. Liebeskind described the addition of higher-order cyanocuprates to functionalized complex **36** (Scheme 11) [33], giving olefinic complexes **37** and ultimately α,β-unsaturated ketones **38** with a high degree of regioselectivity. ^{1}H NMR spectroscopic data for olefinic complexes **37** indicated in each case the presence of predominantly a single diastereoisomer, leading Liebeskind to infer that the CO → NO+ exchange (**35** → **36**) was highly diastereoselective. Spectroscopic analysis (including the estimation of *endo–exo* rotamer composition) of cationic η^3-complex **36** was precluded by instability, but a crystal structure of intermediate **37** (R = Me) was obtained. The X-ray structure indicated that the observed products had arisen from nucleophilic addition either *trans* to the nitrosyl ligand in *exo*-**36** or *cis* to the nitrosyl in *endo*-**36**, in stark contrast to Faller's predictions. Liebeskind was unable to rationalize the apparent diastereoselectivity of the ligand exchange process. Similarly, the precise rationale for the failure of the nitrosyl to control nucleophilic attack was unclear, although a product-like transition state favoring conjugated products **38** arising from attack at C4 was suggested.



Scheme 11

Liebeskind also examined the formation of disubstituted cyclopentenone products **42** and **43** (Scheme 12) [33]. Nucleophilic addition to (η^4-cyclopentadiene)(η^5-cyclopentadiene)dicarbonyl molybdenum cation **39** yielded substituted neutral dicarbonyl complex **40**. Subsequent activation by ligand exchange yielded electrophile **41**, to which a second nucleophilic attack could be performed, more hindered nucleophiles [$Me_2Cu(CN)Li_2$ or $NaC(Me)(CO_2Et)_2$] attacking predominantly the less sterically demanding 2-position.



Scheme 12

The chemistry depicted in Schemes 11 and 12 is noteworthy because it showed that (a) comparatively hard organocuprate nucleophiles participate in the addition; (b) nitrosyl ligand exchange can be diastereoselective in some cases; (c) both electronic and steric demands of the allylic ligand play a role in determining regioselectivity, overriding the nitrosyl directing effect; (d) the enantiofacial control afforded by the metal can be exploited in a series of sequential additions to the same substrate and (e) functionalized cationic η^3-allylmolybdenum complexes (e.g., **36** and **41**) can be prepared.

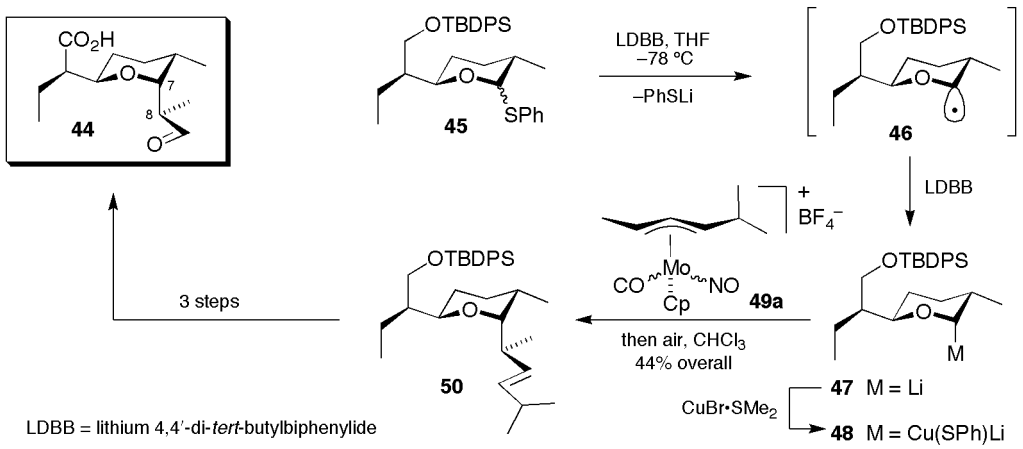
METHODS FOR DEMETALLATION FOLLOWING NUCLEOPHILIC ATTACK

The initial products of the nucleophilic addition step are η^2-alkene complexes which can be isolated in some circumstances and are usually seen as yellow spots on thin-layer chromatography. Release of the product from the η^2-complexes is usually achieved by exposing a chloroform solution of the crude material to air [29]. The procedure is mild, but slow, reaction times of a day or more generally being required. Bubbling gaseous oxygen through the crude solution is faster. Oxidation by ammonium cerium(IV) nitrate (CAN) buffered by NaOAc is a useful alternative [34]. Other methods include treatment with high-pressure CO releasing $CpMo(CO)_2(NO)$ and use of strong base [29].

SYNTHETIC APPLICATIONS: REGIOSELECTIVITY IN THE ALKYLATION OF UNSYMMETRICALLY SUBSTITUTED COMPLEXES

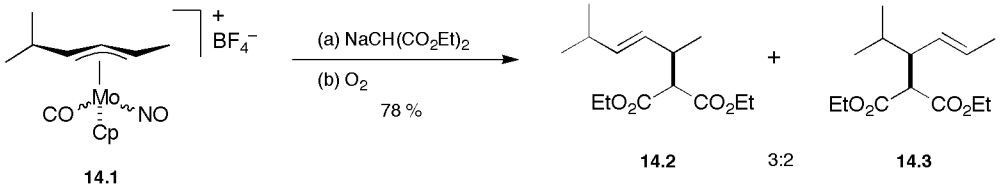
In 1996, we reported the first significant application of planar chiral cationic η^3-allylmolybdenum complexes to natural product synthesis [35,36]. The impetus for this work was the difficulty of creating the axial C7-C8 bond *cis* the equatorial methyl group at C6 stereoselectively in the intermediate **44** of the polyether antibiotic Salinomycin (Scheme 13). After a sustained bout of failure, the method depicted in Scheme 13 was employed. Reductive lithiation of the mixture of phenylthioacetals **45** with lithium 4,4′-di-*tert*-butylbiphenylide (LDBB) [37] gave the axial oxanyllithium reagent **47** as a single diastereoisomer [38,39]. The preference for the axial lithium reflects the stabilization available to the axial rad-

ical **46** (radical anomeric effect [40–42]) generated in the first step of the reductive lithiation. Attempts to alkylate the oxanyllithium reagent **47** with the η^3-allyl cationic complex **49a** were not fruitful, but the corresponding cuprate **48** alkylated with high regio- and facial-selectivity to provide the desired adduct **50** in 44 % overall yield from **45**.



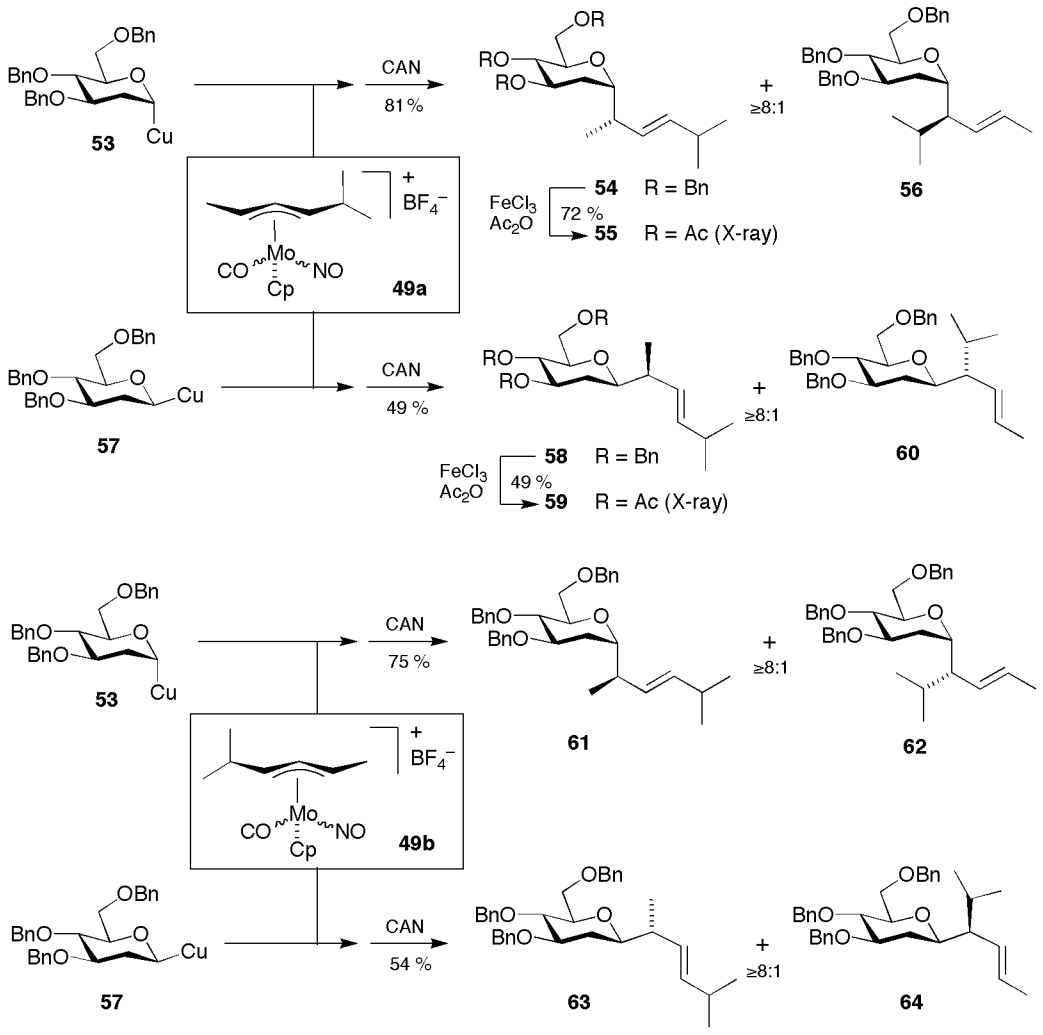
Scheme 13

The formation of **50** as a single regio- and diastereoisomer was not expected based on the extensive precedent described above; therefore, we repeated the alkylation of the complex **49b** with sodium diethyl malonate previously described by Faller and Linebarrier [17]. A mixture of the enantiomerically pure regioisomers **51** and **52** (3:2, respectively) was obtained in 78 % yield (Scheme 14).



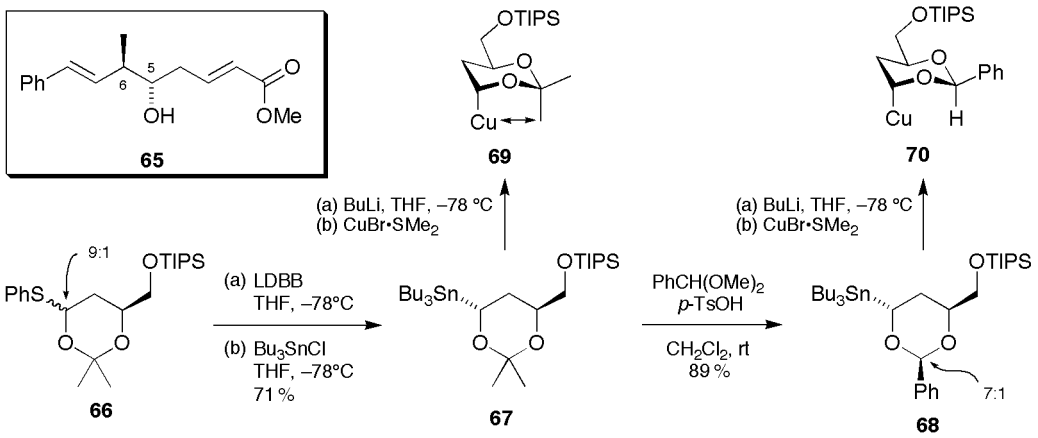
Scheme 14

In order to establish that the regio- and stereochemical observations depicted in Scheme 13 were general, we examined the alkylation of the configurationally stable organocopper(I) nucleophiles **53** and **57** [43] derived from the corresponding stannanes [44,45] at –78 °C with the Faller complexes **49a,b** (Scheme 15) [46]. In each of the 4 cases, the nucleophilic addition occurred preferentially at the less hindered terminus of the allylic unit (regioselectivity ≥ 8:1). X-ray structures of olefins **55** and **59** established that (a) the configuration of the 2-deoxy-α-glucosylcopper(I) reagent was retained in the alkylation; (b) nucleophilic addition occurred *anti* to the metal; and (c) the regiochemistry of addition is not invariably controlled by the central chirality at molybdenum.



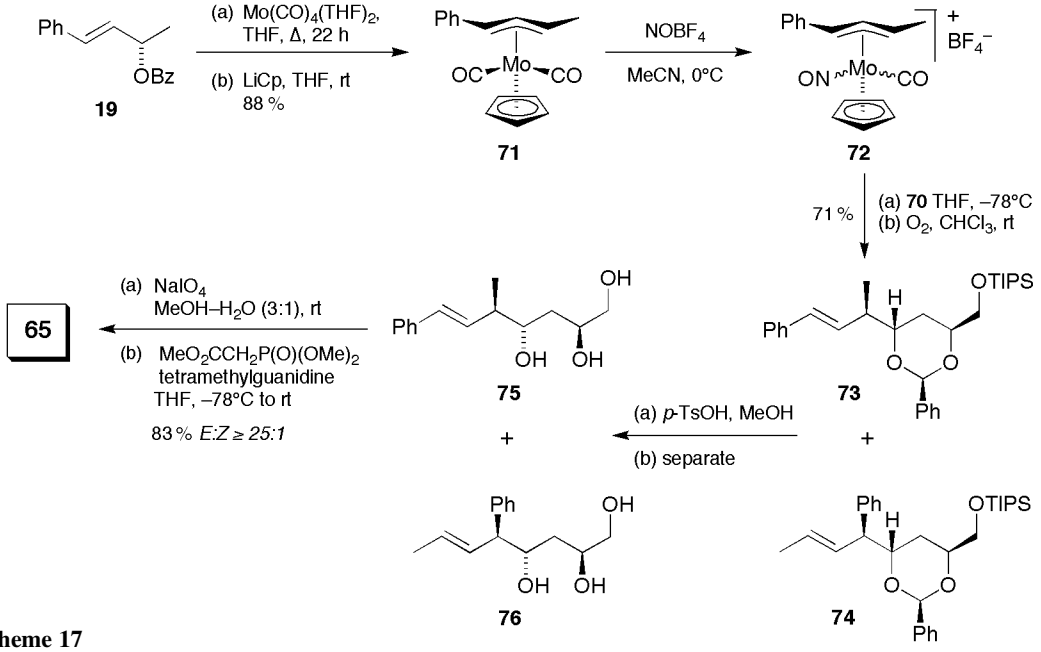
Scheme 15

A synthesis of carboxylic acid **65** (Scheme 16), a key component of the antitumor agent Cryptophycin 4, was used as a vehicle for exploring the addition of α-metallated-1,3-dioxane derivatives to cationic η^3-allylmolybdenum complexes [47]. Reductive lithiation of the *O*,*S*-acetal **66** followed by stannylation gave **67** as a single isomer in 71 % yield, with the tributylstannyl moiety in the desired axial orientation. Transacetalization of the acetonide to a benzylidene acetal proceeded smoothly to yield stannane **68** as a mixture of diastereoisomers (dr 7:1) at the acetal center, which was easily separable by column chromatography. The transacetalization reaction was required because the organocopper(I) species **69** derived from stannane **67** was not configurationally stable even at low temperature owing to a 1,3-diaxial interaction, whereas organocopper(I) reagent **70** was configurationally stable at low temperature.



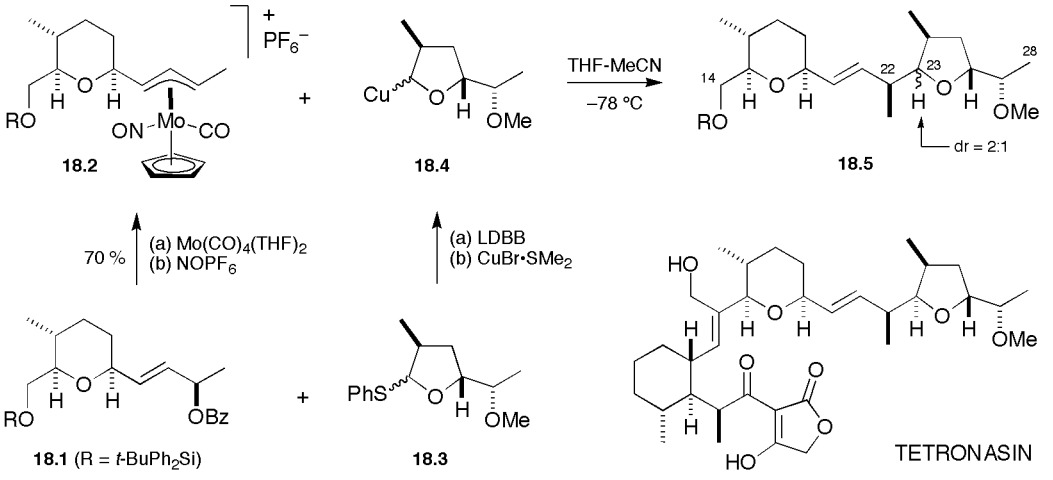
Scheme 16

Benzoate ester **19** underwent oxidative addition with retention of stereochemistry on reaction with $Mo(CO)_4(THF)_2$ complex followed by treatment with lithium cyclopentadienide to give the stable, yellow neutral complex **71** (Scheme 17) as a mixture of *exo* and *endo* rotamers (*exo*:*endo* = 13:1, δ*exo* –1617, δ*endo* –1412) according to ^{95}Mo NMR spectroscopy in C_6D_6. Nitrosyl–carbonyl exchange occurred on treatment of **71** with $NOBF_4$ to give the cationic complex **72**, which was added immediately to a solution of the organocopper(I) reagent **70** at –78 °C. After oxidative decomplexation of the metal, the addition product was obtained as an inseparable mixture of regioisomeric 1,3-dioxanes **73** and **74** in 71 % overall yield from **19**. Thus, the stereochemistry of the axial C–Cu bond in **70** had been conserved and the enantiofacial control was excellent, but the regioselectivity was poor: **73**:**74** = 1.2:1. Acidic cleavage of the silyl and acetal protecting groups yielded separable triols **75** and **76**. The desired triol **75** was subjected to periodate cleavage of the vicinal diol and the resulting crude aldehyde elongated to hydroxy ester **65** in excellent yield and stereoselectivity using a Horner–Wadsworth–Emmons reaction.



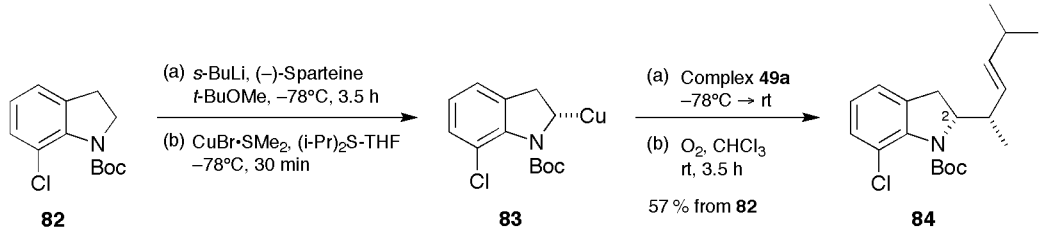
Scheme 17

A key step in our synthesis of the C14–C28 fragment **81** of the antibiotic Tetronasin (Scheme 18) entails construction of the C22–C23 bond by alkylation of the metallated tetrahydrofuran **80** by the cationic molybdenum complex **78**. In our preliminary studies [48], the organocopper(I) reagent was generated by reductive cleavage of the *O*,*S*-acetal **79**, and hence the product **81** was obtained as a mixture of diastereoisomers (2:1). There are two noteworthy features of the synthesis. First, the high reactivity of the cationic molybdenum complex enabled the alkylation reaction to occur without fragmentation of the organocopper reagent **80**. Secondly, the isolation of the complex **78** with an intact tetrahydropyran ring shows that leaving groups adjacent to the η^3-allyl moiety are tolerated.



Scheme 18

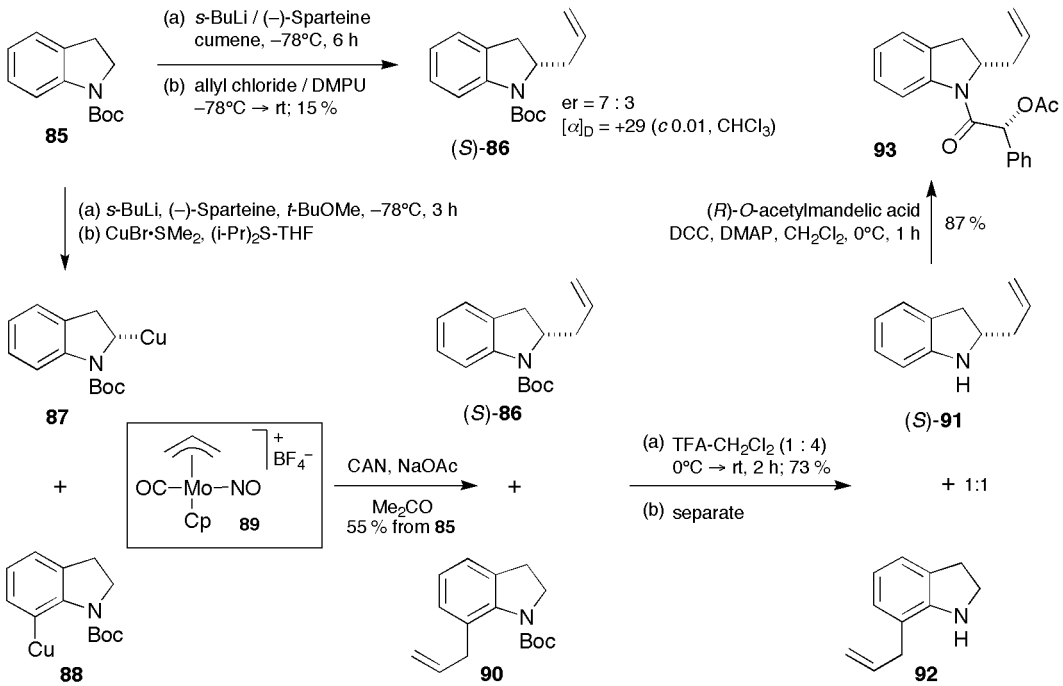
All our previous examples had exploited cyclic α-metallated ethers as nucleophiles. Our next example (Scheme 19) shows that α-metallated amine derivatives also participate in the reaction [49]. Asymmetric lithiation of the *N*-Boc derivative **82** of 7-chloroindoline under conditions developed by Beak [50] followed by transmetallation to copper using $CuBr{\cdot}SMe_2$ led to the organocopper(I) reagent **83**. Reaction with cationic complex **49a** gave a mixture of olefins in 57 % overall yield after oxidative decomplexation (O_2, $CHCl_3$ or CAN, Me_2CO). Analysis of the mixture by GCMS revealed the presence of 4 isomers, in the approximate ratio 4:9:81:6. The major product was assigned the absolute stereochemistry depicted in **84** based on three key assumptions: (a) transmetallation of the lithium reagent to the organocopper(I) reagent occurred with retention of configuration; (b) the organocopper(I) reagent reacted with the cationic molybdenum complex with retention of configuration; and (c) nucleophilic addition to the complex occurred *anti* to the molybdenum.



Scheme 19

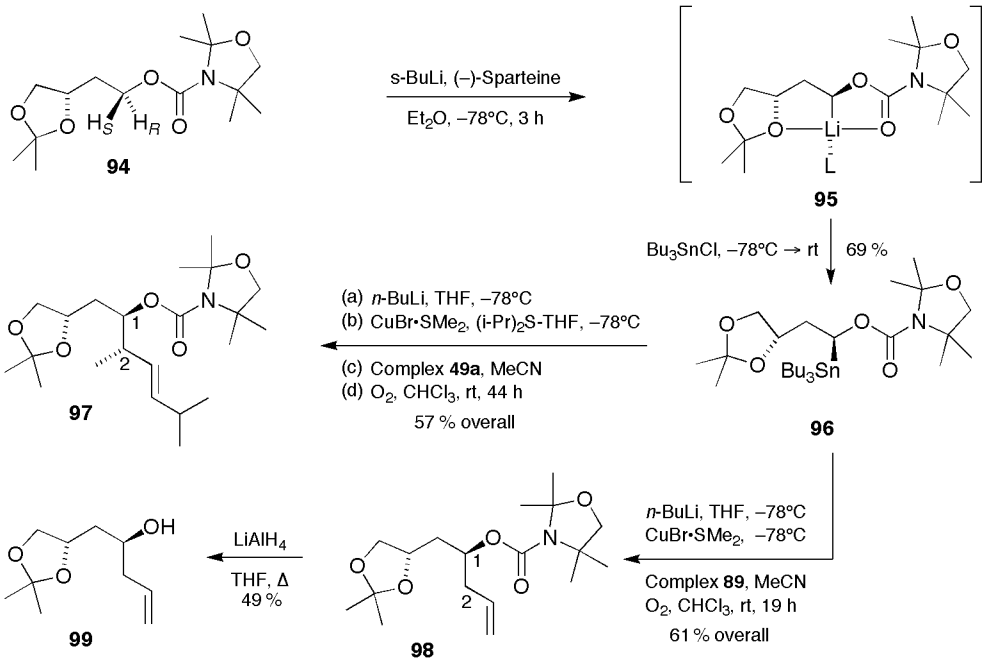
In order to prove that the organocopper(I) reagent **83** alkylated with retention of configuration, we turned to a simpler system whose stereochemistry had been established. Beak and coworkers [50] had performed an asymmetric metallation-alkylation sequence on *N*-Boc indoline (**85**) to give 2-allyl-

indoline (**86**) in 15 % yield (*S*:*R* = 7:3) as shown in Scheme 20. Lithiation with *s*-BuLi/(–)-sparteine, transmetallation to copper, and reaction with cationic complex **89** yielded an inseparable equimolar mixture of 2- and 7-substituted indolines **86** and **90** (55 %) together with 9 % of recovered indoline **85**. Comparison of the sign of optical rotation of the mixture **86** and **90** [+44.2, (*c* 0.55, $CHCl_3$)] to that reported by Beak [+29 (*c* 0.01, $CHCl_3$), 36 % ee] indicated that the lithiation, transmetallation, and allylation sequence returned material with the (2*S*)-configuration. Protonolysis allowed the separation of the regioisomeric amines **91** and **92**. The 2-allyl derivative **91** was converted into the (*R*)-*O*-acetylmandelamide **93** to give a single diastereoisomer according to ^1H and ^{13}C NMR spectroscopy and GCMS. These experiments show that the reaction of the organocopper(I) reagent **87** with the cationic molybdenum complex **89** occurred with clean retention of stereochemistry as predicted.



Scheme 20

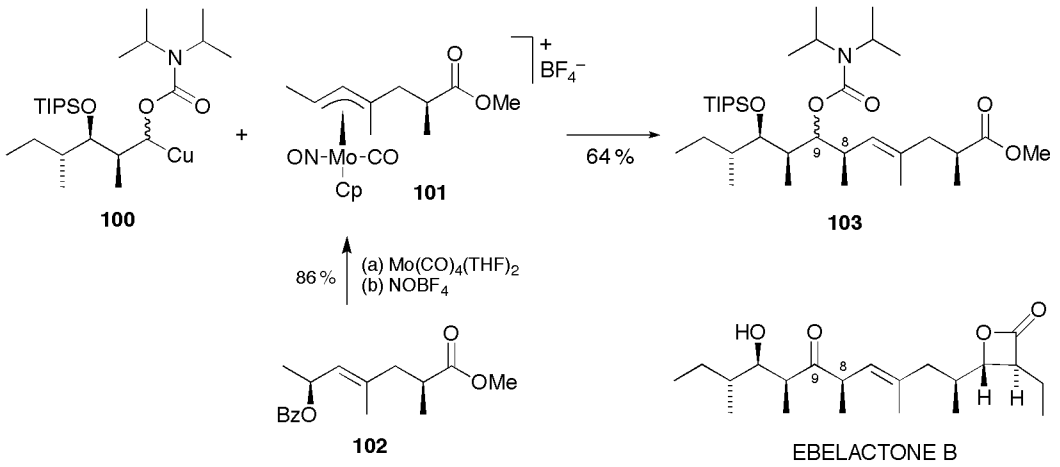
Our next example illustrates the use of an acyclic α-heteroalkylcopper(I) reagent as the nucleophile. Hoppe described the asymmetric deprotonation of achiral carbamates with *s*-butyllithium and (–)-sparteine, the carbamate serving to stabilize the α-lithio derivatives by chelation [51–54]. In the case of enantiopure acetonide **94** (Scheme 21), the ligand-directed asymmetric deprotonation of the *pro-S*-proton was reinforced by the inherent substrate-directed selectivity leading to the highly ordered intermediate **95** [55]. Stannylation occurred with retention to give the stannane **96** in 69 % yield as a single diastereoisomer. Tin-lithium exchange of stannane **96** using *n*-BuLi followed by transmetallation with $CuBr{\cdot}SMe_2$ generated the required α-heteroalkylcopper(I) nucleophile. Addition of complex **49a** in MeCN gave olefin **97** in 57 % overall yield from stannane **96** after oxidative decomplexation. ^1H NMR spectroscopy and GCMS of the crude reaction mixture revealed a mixture of 4 isomers in the approximate ratio 95:2:2:1. The absolute stereochemistry of the major isomer **97** was assigned on the basis of the same assumptions used to assign the stereochemistry of the indoline derivative **84** (see above) [49].



Scheme 21

In order to prove that the alkylation reaction proceeds with retention of configuration in the nucleophile, the α-heteroalkylcopper(I) intermediate derived from stannane **96** was treated with the simple allylmolybdenum complex **89**. A mixture of diastereoisomeric olefins (dr = 98:2, major isomer **98**) was obtained in 61 % overall yield from **96**. Reductive cleavage of the carbamate group [56] gave the (*S*)-alcohol **99** (49 %) by comparison of its optical rotation and ^{1}H and ^{13}C NMR spectroscopic data with literature values [57,58].

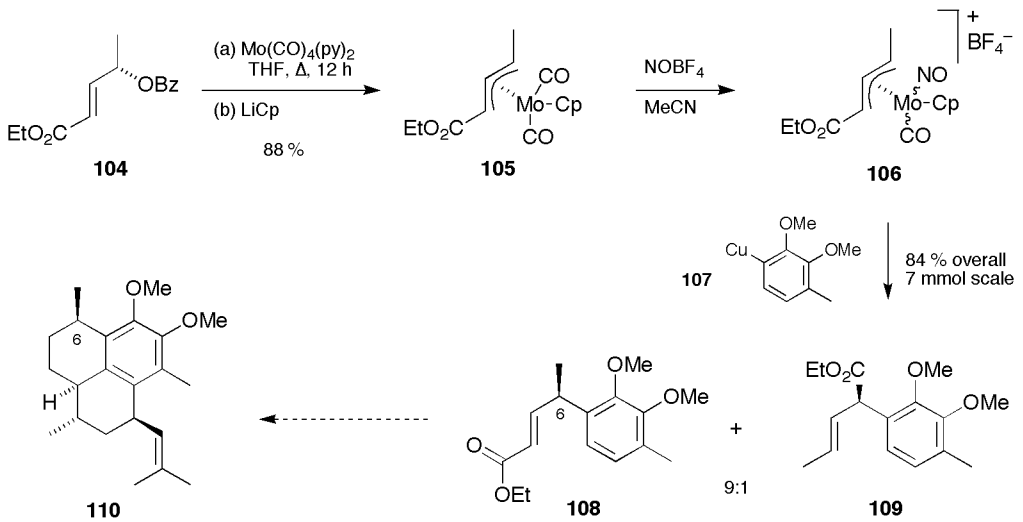
An example of the use of functionalized cationic η^3-allylmolybdenum complexes in asymmetric synthesis entails the construction of the C8–C9 bond of Ebelactone B (Scheme 22) using a trisubstituted complex **101** [59]. The organocopper(I) reagent **100** was prepared by direct metallation of the corresponding carbamate as described in the foregoing examples. The stereochemistry of the organo-



Scheme 22

copper(I) reagent is irrelevant since C9 harbors a carbonyl group in the target. The efficient synthesis of the trisubstituted complex **101** is one of the triumphs of the $Mo(CO)_4(THF)_2$ reagent. Union of **100** and **101** gave the fragment **103** in 64 % yield.

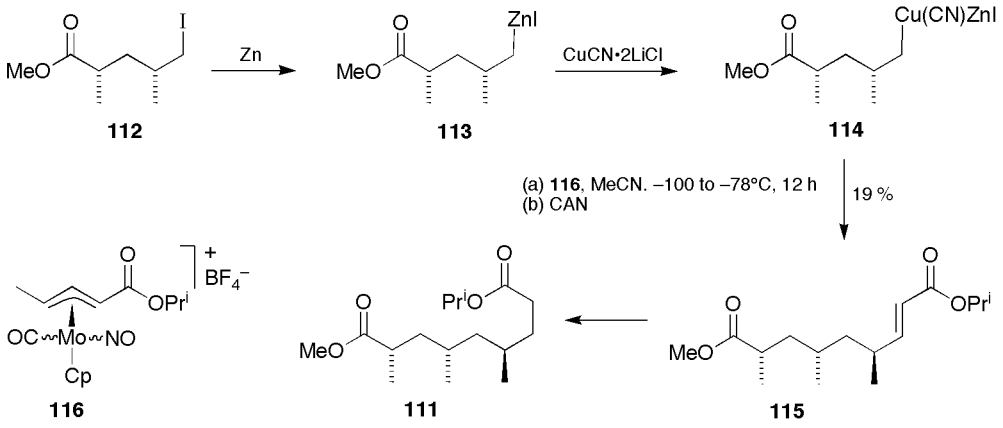
A second illustration of the use of functionalized complexes is shown in Scheme 23. The benzoate ester **104** was converted to the neutral complex **105** using $Mo(CO)_4(py)_2$ in 88 % yield as a 6:1 mixture of *exo*- and *endo*-isomers.[60] Unlike the majority of the simple alkyl-substituted complexes we have prepared, complex **105** was unstable and decomposed on standing. The cationic complex **106** was also rather labile, but freshly prepared batches reacted with the arylcopper(I) reagent **107** to give a mixture of the regioisomeric adducts **108** and **109** (6–9:1, respectively) in 84 % yield on a 7 mmol scale after oxidative decomplexation with CAN. Adduct **108** was used as the starting material for the synthesis of one of the diastereoisomeric Pseudopterosin aglycones (**110**). The regiochemistry of the addition could be improved to 95:5 by using the corresponding isopropyl esters, but then oxidative decomplexation of the η^2-alkene adducts was very slow.



Scheme 23

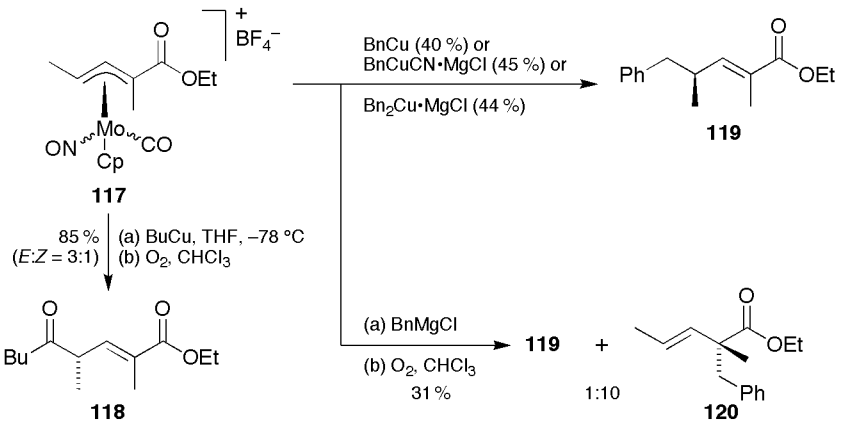
ALL THAT GLITTERS IS NOT GOLD

The reaction of η^3-allylmolybdenum complexes with nucleophiles—especially simple nucleophiles—occasionally suffers from poor yields and messy reactions. A case in point comes from our synthesis of the C1–C9 fragment **111** of the ionophore antibiotic Ionomycin (Scheme 24). Reaction of the zinc cuprate **114** with the functionalized complex **116** gave at best a 19 % yield of the adduct **115**. Isolation of the pure product was tedious, and protracted toil failed to improve the yield [61].



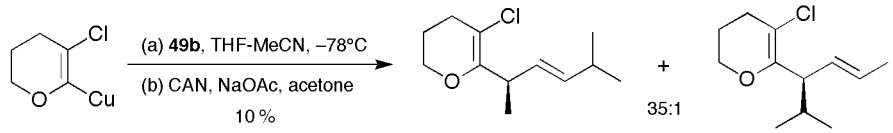
Scheme 24

The reactions of the trisubstituted functionalized complex **117** with some simple nucleophiles illustrate the influence of the nucleophile on the course and regiochemistry of the reaction (Scheme 25). In the case of BuCu, the reaction took a different and unexpected course: nucleophilic attack occurred at the carbonyl group, whereupon reductive elimination generated the vinylogous β-keto ester **118** in 85 % yield (presumably with retention of configuration) [59]. However, reaction of **117** with BnCu, BnCuCN·MgCl, or Bn_2Cu·MgCl gave the adduct **119** (40–45 %) resulting from attack at the allyl ligand at the least hindered position. By contrast, BnMgCl reacted preferentially at the more hindered position to give **119** and **120** (1:10) in 31 % yield [62].



Scheme 25

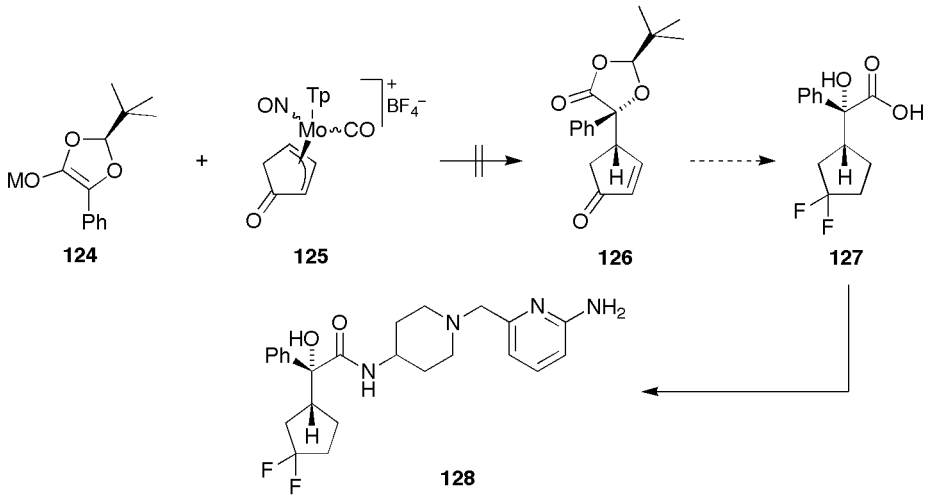
Attempts to add α-metallated dihydrofurans and pyrans to the Faller complex **49b** were fruitless. A single exception is illustrated in Scheme 26. The organocopper(I) reagent **121** gave a meager 10 % yield of the regioisomeric adducts **122** and **123** (35:1) with the predominant product resulting from attack at the less hindered carbon.



121 122 123

Scheme 26

A projected synthesis of the muscarinic M_3 receptor antagonist **128** (Scheme 27) was thwarted by the failure of the lithium or potassium enolates **124** (M = K or Li) or the corresponding enol silane (M = Me_3Si) to add to the cationic complex **125**, whose Cp variant had been previously described by Liebeskind and coworkers [33]. Despite extensive variation of the reaction conditions, no data could be adduced for the formation of the cyclopentenone adduct **126** [63].



124 125 126 127 128

Scheme 27

CONCLUSION

A wide range of planar chiral η^3-allylMo(CO)$_2$Cp complexes are now readily available by the reaction of allyl benzoates with either Mo(CO)$_4$(py)$_2$ or Mo(CO)$_4$(THF)$_2$ in refluxing THF. This combination of reagents has been successful in the synthesis of trisubstituted and functionalized complexes previously inaccessible with the standard reagents. We have shown that chiral α-heteroalkylcopper(I) reagents are especially effective nucleophilic partners that react with cationic η^3-allylmolybdenum complexes with clean retention of configuration. The reactions can be used to forge bonds with excellent stereocontrol in hindered environments. Finally we have shown that the regiochemistry of the addition is governed by many factors including steric and electronic effects in the cationic η^3-allylmolybdenum complexes, the nature of the nucleophile, temperature, and solvent.

ACKNOWLEDGMENTS

We would like to thank the Engineering and Physical Sciences Research Council, the Deutsche Forschungsgemeinschaft, FCAR (Quebec), Merck Sharp & Dohme, Pfizer Central Research, and GlaxoSmithKline for generous financial support.

REFERENCES

1. J. S. McCallum and L. S. Liebeskind. *Synthesis* 819 (1993).
2. J. S. McCallum, J. T. Sterbenz, L. S. Liebeskind. *Organometallics* **12**, 927 (1993).
3. D. P. Tate, W. R. Knipple, J. M. Augl. *Inorg. Chem.* **1**, 433 (1962).
4. R. G. Hayter. *J. Organomet. Chem.* **13**, P1 (1968).
5. M. Pasquali, P. Leoni, P. Sabatino, D. Braga. *Gazz. Chim. Ital.* **122**, 275 (1992).
6. A. N. Nesmeyanov, V. V. Krivykh, V. S. Kaganovich, M. I. Rybinskaya. *J. Organomet. Chem.* **102**, 185 (1975).
7. W. Hieber and F. Mühlbauer. *Z. Anorg. Allg. Chem.* **221**, 337 (1935).
8. A. J. Pearson and E. Schoffers. *Organometallics* **16**, 5365 (1997).
9. D. Rehder. In *Multinuclear NMR Spectroscopy*, J. Mason (Ed.), p. 479, Plenum, New York (1987).
10. A. Kuhl, J. A. Christopher, L. J. Farrugia, P. J. Kocienski. *Synlett* 1765 (2000).
11. Y. D. Ward, L. A. Villanueva, G. D. Allred, S. C. Payne, M. A. Semones, L. S. Liebeskind. *Organometallics* **14**, 4132 (1995).
12. S. Trofimenko. *J. Am. Chem. Soc.* **91**, 588 (1969).
13. A. Kuhl. Glasgow University (1999). Unpublished results.
14. A. Kuhl, L. J. Farrugia, P. J. Kocienski. *Acta Crystallogr., Sect. C* **55**, 2041 (1999).
15. A. Kuhl, L. J. Farrugia, P. J. Kocienski. *Acta Crystallogr., Sect. C* **56**, 510 (2000).
16. Y. D. Ward, L. A. Villanueva, G. D. Allred, L. S. Liebeskind. *J. Am. Chem. Soc.* **118**, 897 (1996).
17. J. W. Faller, D. Linebarrier. *Organometallics* **7**, 1670 (1988).
18. R. F. Jordan, W. E. Dasher, S. F. Echols. *J. Am. Chem. Soc.* **108**, 1718 (1986).
19. L. A. Villanueva, Y. D. Ward, R. Lachicotte, L. S. Liebeskind. *Organometallics* **15**, 4190 (1996).
20. R. B. King. *Inorg. Chem.* **5**, 2242 (1966).
21. A. Davison and W. C. Rode. *Inorg. Chem.* **6**, 2124 (1967).
22. J. W. Faller and A. M. Rosan. *J. Am. Chem. Soc.* **98**, 3388 (1976).
23. J. W. Faller and B. C. Whitmore. *Organometallics* **5**, 752 (1986).
24. R. D. Adams, D. F. Chodosh, J. W. Faller, A. M. Rosan. *J. Am. Chem. Soc.* **101**, 2570 (1979).
25. J. W. Faller, C. Lambert, M. R. Mazzieri. *J. Organomet. Chem.* **383**, 161 (1990).
26. B. E. R. Schilling, R. Hoffmann, J. W. Faller. *J. Am. Chem. Soc.* **101**, 592 (1979).
27. J. W. Faller and K.-H. Chao. *J. Am. Chem. Soc.* **105**, 3893 (1983).
28. W. E. VanArsdale, R. E. K. Winter, J. K. Kochi. *Organometallics* **5**, 645 (1986).
29. J. W. Faller and C. Lambert. *Tetrahedron* **41**, 5755 (1985).
30. J. W. Faller and M. J. Incorvia. *Inorg. Chem.* **7**, 840 (1968).
31. J. W. Faller, Y. Shvo, K. Chao, H. H. Murray. *J. Organomet. Chem.* **226**, 251 (1982).
32. J. W. Faller, C.-C. Chen, M. J. Mattina, A. Jakubowski. *J. Organomet. Chem.* **52**, 361 (1973).
33. R. H. Yu, J. S. McCallum, L. S. Liebeskind. *Organometallics* **13**, 1476 (1994).
34. A. J. Pearson, P. Bruhn, I. C. Richards. *Tetrahedron Lett.* **25**, 387 (1984).
35. M. J. Procter. Ph.D. thesis, University of Southampton (1996).
36. P. J. Kocienski, R. C. D. Brown, A. Pommier, M. Procter, B. Schmidt. *J. Chem. Soc., Perkin Trans. 1* 9 (1998).
37. P. K. Freeman and L. L. Hutchinson. *J. Org. Chem.* **45**, 1924 (1980).
38. T. Cohen and J. R. Matz. *J. Am. Chem. Soc.* **102**, 6900 (1980).
39. T. Cohen and M.-T. Lin. *J. Am. Chem. Soc.* **106**, 1130 (1984).
40. J.-P. Praly. *Tetrahedron Lett.* **24**, 3075 (1983).
41. B. Giese and J. Dupuis. *Tetrahedron Lett.* **25**, 1349 (1984).
42. G. Descotes. In *Carbohydrates*, H. Ogura, A. Hasegawa, T. Suami (Eds.), p. 89, Kodansha Ltd., Tokyo (1992).
43. D. K. Hutchinson and P. L. Fuchs. *J. Am. Chem. Soc.* **109**, 4930 (1987).

44. P. Lesimple, J.-M. Beau, P. Sinaÿ. *J. Chem. Soc., Chem. Commun.* 894 (1985).
45. P. Lesimple, J.-M. Beau, P. Sinaÿ. *Carbohydrate Res.* **171**, 289 (1987).
46. J. A. Christopher, P. J. Kocienski, M. J. Procter. *Synlett* 425 (1998).
47. J. A. Christopher, P. J. Kocienski, A. Kuhl, R. Bell. *Synlett* 463 (2000).
48. E. Bourque and J. Yuen. Leeds University (2003). Unpublished results.
49. J. A. Christopher. Ph.D. thesis, Glasgow University (2000).
50. K. M. B. Gross, Y. M. Jun, P. Beak. *J. Org. Chem.* **62**, 7679 (1997).
51. M. Marsch, K. Harms, O. Zschage, D. Hoppe, G. Boche. *Angew. Chem., Int. Ed. Engl.* **30**, 321 (1991).
52. F. Hintze and D. Hoppe. *Synthesis* 1216 (1992).
53. D. Hoppe, F. Hintze, P. Tebben. *Angew. Chem., Int. Ed. Engl.* **29**, 1422 (1990).
54. D. Hoppe and T. Hense. *Angew. Chem., Int. Ed. Engl.* **36**, 2282 (1997).
55. H. Helmke and D. Hoppe. *Synlett* 978 (1995).
56. B. Weber, S. Kolczewski, R. Fröhlich, D. Hoppe. *Synthesis* 1593 (1999).
57. T. Ishikawa, S. Ikeda, M. Ibe, S. Saito. *Tetrahedron* **54**, 5869 (1998).
58. P. J. Kocienski, C. Yeates, S. D. A. Street, S. F. Campbell. *J. Chem. Soc., Perkin Trans. 1* 2183 (1987).
59. A. Gunn. Leeds University (2002). Unpublished results.
60. R. Chow, P. J. Kocienski, A. Kuhl, J.-Y. LeBrazidec, K. Muir, P. Fish. *J. Chem. Soc., Perkin Trans. 1* 2344 (2001).
61. Y. Li. Ph.D. thesis, Leeds University (2002).
62. J. Cooksey. M. Chem. thesis, Leeds University (2003).
63. S. Uppal. Ph.D. thesis, Leeds University (2003).