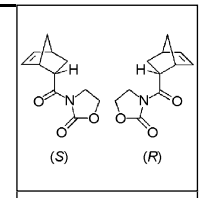
Toggling enantioselective catalysis—a promising paradigm in the development of more efficient and versatile enantioselective synthetic methodologies



Giuseppe Zanoni,* Francesca Castronovo, Maurizio Franzini†,* Giovanni Vidari and Elios Giannini

Department of Organic Chemistry, University of Pavia, Viale Taramelli, 10 – 27100 Pavia, Italy. E-mail: gzanoni@unipv.it

Received 23rd December 2002
First published as an Advance Article on the web 4th April 2003

The increasingly needed synthesis of both enantiomers of a chiral compound usually requires the use of both enantiomers of a chiral catalyst. Several of the usually employed chiral ligands are naturally available in only one enantiomeric form, the antipode often being of labor-intensive preparation. Enantiodivergent asymmetric catalysis has accrued in importance in this regard, in that it allows expeditious access to both enantiomers of a product without any direct modification on the chemical structure of the chiral promoter. Various promising examples will be discussed throughout the review. If available or envisageable, a mechanistic rationale for the observed enantioinversion will be outlined.

1 Introduction

The most effective approach for the preparation of enantiomerically enriched (scalemic) compounds relies on the multiplication of the chiral information through asymmetric catalysis

† Present address: Department of Chemistry, Stanford University, Stanford, CA, 94305-5080, USA. E-mail: franzini@stanford.edu

Giuseppe Zanoni received his BSc in chemistry at the University of Pavia, Italy, in 1991, where he completed his studies with a PhD in chemistry five years later under the supervision of G. Vidari. He also worked with B. M. Trost at Stanford University in the area of Pd-catalyzed asymmetric allylic alkylations. After two years devoted to combinatorial chemistry at SmithKline-Beecham in Milan, he moved back to the University of Pavia, where he was appointed as research associate. His scientific interests are in the area of asymmetric synthesis, organometallic chemistry, and natural products chemistry.

Giuseppe Zanoni

Francesca Castronovo received her PhD in chemistry in 2000 at Pavia, under the supervision of G. Vidari. She is currently working as a post-doc fellow in the same Department, on a project aimed at developing new agonists to the PPARγ receptor.

Maurizio Franzini received his BSc in chemistry at Pavia in 1991 under the supervision of G. Vidari. After five years as research associate at Bracco SpA, Milan, he moved to Stanford University in 1998. There he joined the group of B. M. Trost to pursue a PhD program in Organic Chemistry. He has been involved in the development of new synthetic methodologies, like organometal catalyzed asymmetric allylic alkylations.

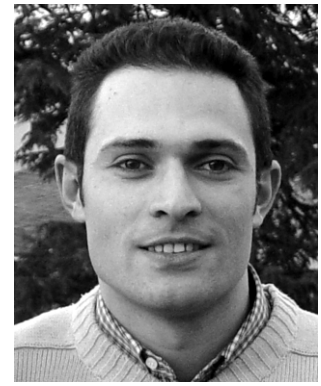
After his graduation in chemistry, Giovanni Vidari worked with P. A. Grieco at the University of Pittsburgh, PA and at Indiana University in Bloomington, IN. He began his independent research career in the Department of Chemistry of the University of Pavia, where he is now full Professor of Organic Chemistry. His interests verge on natural products, enantioselective total synthesis, and biomimetic cyclizations. He has authored about 110 research publications.

Elios Giannini received his BSc in chemistry in 1999 at Pavia under the supervision of G. Vidari. Currently he is involved as a graduate student in synthetic studies of taxane derivatives.

Francesca Castronovo

Maurizio Franzini

Giovanni Vidari



Elios Giannini

by means of complexes of transition metals and appropriately designed chiral ligands. Despite the enormous progress consolidated in the past two decades of catalytic asymmetric synthesis, the efficient preparation of both enantiomers of a chiral compound still represents a daunting task. Whether serendipitous or expected, dual enantioselective catalytic protocols undoubtedly captivate the organic chemist who wishes to probe the viability of a novel asymmetric methodology. Furthermore, in medicinal and bioorganic chemistry the demand for the immediate availability of both enantiomers of a chiral auxiliary or ligand has been soaring for the past few years.[1] Since a large swath of these chiral tools have been prepared from natural sources, like amino acids, amines, carboxylic acids, and carbohydrates, this requisite makes for a remarkable challenge. Compounds from this natural "chiral pool" most of the time are indeed readily available in only one absolute configuration. The other antipode, either the D- or L-form, can be naturally rare, or it can require resolution techniques to be isolated, or, at worst, expensive and lengthy procedures to be synthesized.

To surmount this shortcoming by large intrinsic within asymmetric catalysis, an increasing number of investigators have been exploring the possibility of transferring the chirality of a single ligand to both enantiomers of a product in an enantiodivergent fashion. This can be accomplished through a process at times dubbed in the literature as *dual* or *reversible* enantioselectivity. In other terms, by *toggling* between the diastereomeric transition states leading to the two antipodal products. Enantiodivergent asymmetric catalysis can be achieved by addition of an achiral ligand or additive, by changing the metal centre in the chiral organometallic complex, or the counter ion, or the reaction conditions, such as temperature, pressure, and solvent.

After a seminal paper in the early 1970s by Mosher, where reversal of asymmetric reduction of carbonyl compounds depended upon aging of the stoichiometric chiral alkoxyaluminiumhydride reducing agent employed,[2] a slate of intriguing examples has slowly spawned in the literature beginning in the late 1980s. But it is only with the recent publication of two reviews[3,4] related to the subject that the focus has been aimed at the specificity of this topic of increasing interest.

Hereafter only catalytic processes which rely on a clearly structurally defined chiral chemical entity as a source of asymmetric induction will be discussed. Methods based on stoichiometric chiral auxiliaries, or on even minor structural variation of the employed chiral ligand (entailing some chemical manipulations on the chiral backbone) will not be addressed, as well because they have already been covered by the above mentioned contributions.[3,4]

The selected examples illustrating this still largely under utilized methodological approach have been tentatively allotted according to three major categories, each of them presuming different general processes responsible for the observed reversal of enantioselectivity.

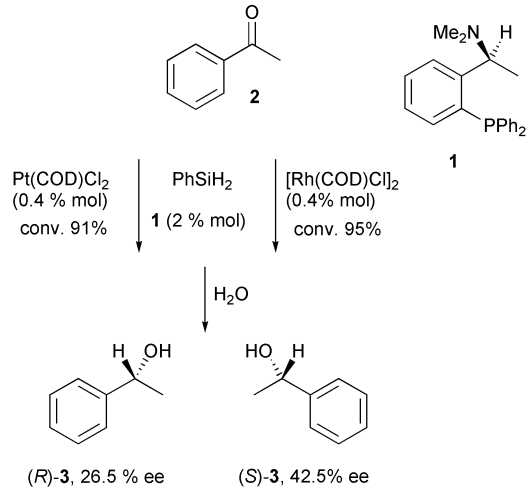
In the first one, a structural variation of a catalytically active metal complex can be invoked for the phenomenon of toggling enantioselectivity. The coordination sphere around the metal core can undergo a configurational modification, for instance by addition of an achiral additive, thus changing the structure of the transition state (TS).

In the second category, the alternate coexistence of two (or more) mechanistic pathways will warrant the stereoinduction reversal, even when no evident structural variations occur in the putative active chiral catalyst. As disclosed through particularly significant examples, the choice between competing rate determining steps dictates the fate of the catalytic process.

Finally, in the third, purely kinetic factors (differential entropy of activation for the diastereotopic pathways) adequately explain the observed overturn in the enantioselectivity.

2 Modification of the chiral complex catalyst. Change of the metal

One of the first examples of "inverse strategy" adopted to tackle the refinement of an asymmetric catalytic synthetical methodology was reported by Kreuzfeld.[5] This author chose one chiral ligand, (*S*)-amphos **1**, and tested it with several metals in the asymmetric hydrosilylation of acetophenone **2** (Scheme 1), instead of the common practice to screen a variety of ligands against a metal.



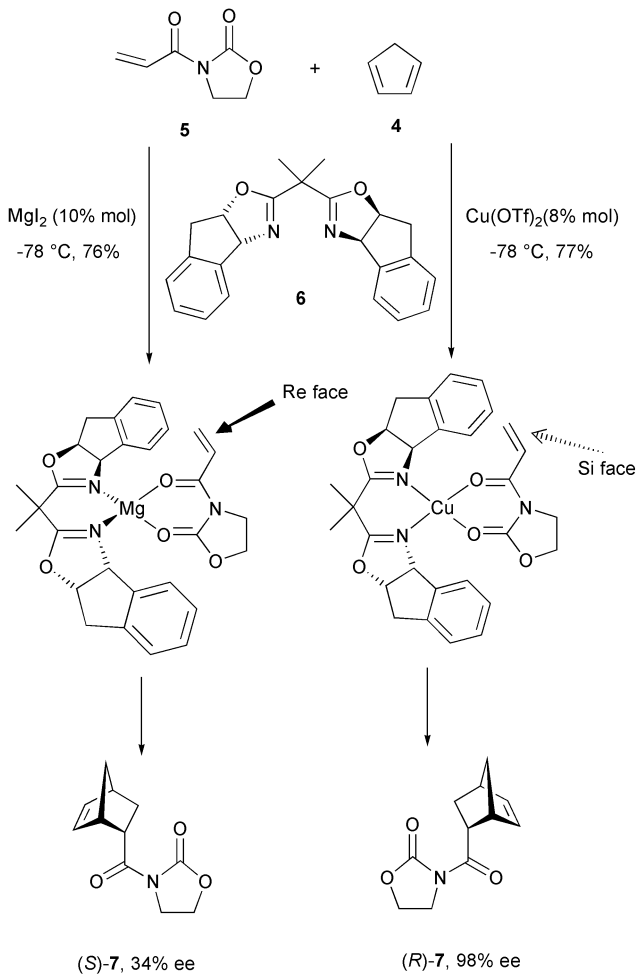
Scheme 1

Cyclooctadienerhodium(I) in combination with (*S*)-amphos gave the (*S*)-benzylic alcohol **3** in high conversion, whereas iridium, platinum and palladium induced prevalent formation of the (*R*) enantiomer. Different geometries of coordination might be deemed responsible for this reversal, but kinetic factors could play a role in the determination of the stereochemistry.

In 1996 Ghosh and coworkers observed an inversion of enantioselectivity in asymmetric Diels–Alder reactions by changing the metal centre of the chiral organometallic catalyst.[6] Cycloaddition of cyclopentadiene **4** with a variety of acryloyl-*N*-oxazolidinones (**5**) was carried out in the presence of different chiral catalysts prepared from conformationally constrained ligand **6** and a variety of transition metals (Scheme 2). The use of catalytic amounts of copper(II)-bis(oxazoline) complexes afforded cycloadduct **7** in very good yields, as well as with excellent *endo*/*exo* selectivities. The *endo*-product was obtained in high ee (up to 99%), with *R* absolute configuration at the C-2 stereogenic centre. On the other hand, in the presence of magnesium(II) the reaction proceeded with inversion of enantioselectivity, and (2*S*)-*endo*-adduct **7** was obtained in good yields although with only moderate ee (up to 55%).

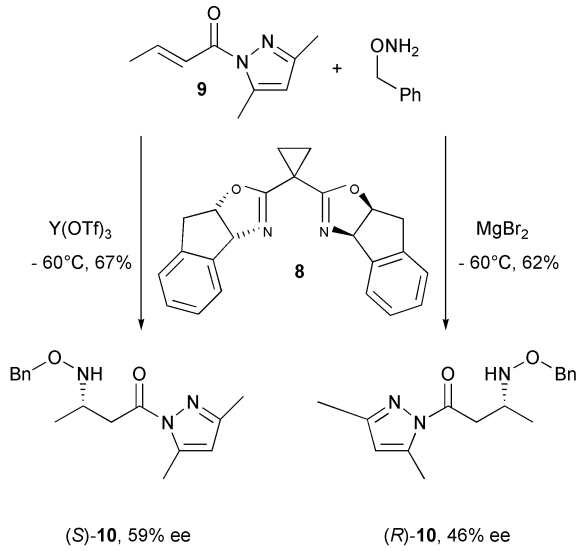
The high degree of enantiofacial selection in the presence of the chiral Cu(II)-bis(oxazoline) complex has been rationalized on the basis of transition state models proposed by Corey[7] and Evans[8] in which Cu(II) assumes a square planar coordination with the chiral bisoxazoline ligand (**6**) and the bidentate dienophile in s-*cis* conformation. Attack of cyclopentadiene preferably occurs in an *endo* fashion on the *Si*-face of the acryloyl component, leading to the observed (2*R*)-enantioselectivity. The reversal of enantiofacial selectivity with the Mg(II)-bis(oxazoline) catalyzed reaction could be explained by virtue of a Corey–Isihara type transition state model,[9] where a tetrahedral geometry now dictates preferential *endo*-attack onto the *Re*-face of the dienophile, thus providing the (2*S*)-enantiomer.

Sibi and coworkers investigated the conjugate addition of *O*-benzylhydroxylamine to α,β-unsaturated pyrazole amides, mediated by catalytic amounts of a Lewis acid, such as $MgBr_2$, $Y(OTf)_3$ or $Yb(OTf)_3$, in the presence of bis(oxazoline) **8** as a



Scheme 2

chiral ligand.[10] The magnesium complex promoted the addition of the hydroxylamine to crotonamide **9** with the formation of the (*R*)-enantiomer of the adduct **10** (Scheme 3). The opposite enantiomer was obtained by switching to lanthanide triflates as a Lewis acid, always in the presence of the same chiral bis(oxazoline) ligand.



Scheme 3

The authors proposed that in the case of $MgBr_2$ the observed (*R*)-configuration in the product was determined by a *Re*-face amine addition to an s-*cis*-substrate coordinated to the chiral complex, with a tetrahedral or a *cis*-octahedral arrangement (Fig. 1).

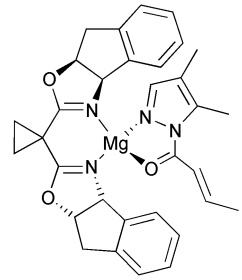
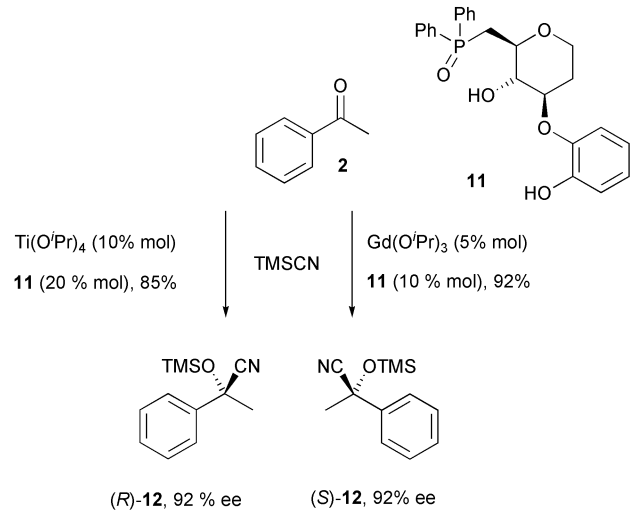


Fig. 1 Proposed structure for the reactive intermediate in the asymmetric Mg-catalyzed conjugated addition of benzylhydroxylamine to crotonamide **9**, as in Scheme 3. Reprinted with permission from ref. 10. Copyright (1998) American Chemical Society.

Although they did not try to rationalize the origin of the reversed sense of stereoinduction observed with Lewis acids yttrium and ytterbium, the higher coordination number of lanthanides must play a key role in shaping the active catalyst, thus facilitating now a *Si*-face amine addition.

In their recent efforts for the preparation of a key intermediate toward the synthesis of (20*S*)-camptothecin, Shibasaki and Curran were able to devise an expeditious catalytic system for the dual enantioselective cyanosilylation of ketones.[11] Titanium complex with ligand **11**, derived from D-glucose, was already known as catalyst of choice to accomplish (*R*)-cyanohydrins from a broad range of substrates. As for (20*S*)-camptothecin opposite selectivity was needed, a slate of other Lewis acids was screened; eventually lanthanides succeeded in giving the (*S*)-enantiomer **12**, and after some optimization work a 2 : 1 combination of $Gd(OiPr)_3$ and ligand **11** turned out as the best one (see Scheme 4).



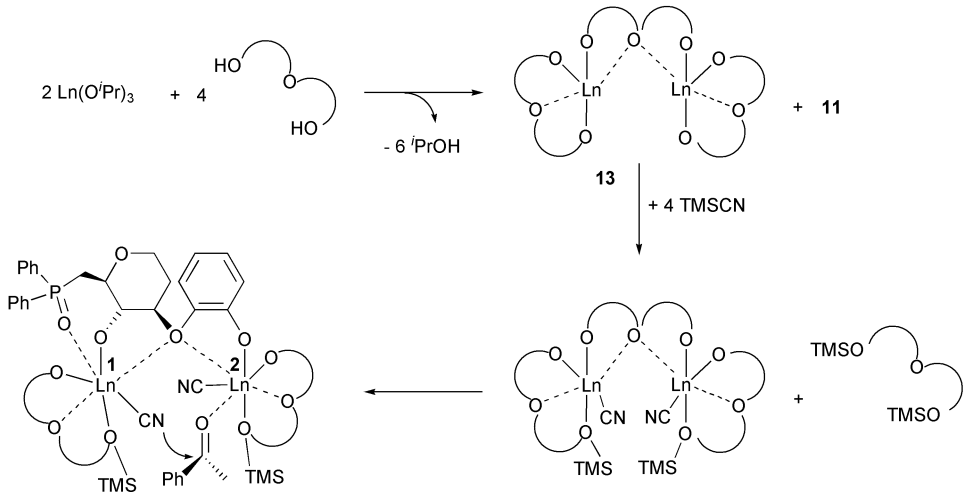
Scheme 4

The higher activity of lanthanide-**11** complexes compared to the titanium catalyst suggests that a metal-coordinated cyanide ion should be the active nucleophile within a bimetallic species **13** as sketched in Scheme 5.

The structure of the reactive 2 : 3 Ln/**11** binuclear complex **13** was inferred from ^{1}H-NMR and ESI-MS analyses. The two lanthanides have different electron density: the more electron rich Ln^1 activates cyanides for nucleophilic attack, whereas Ln^2 merely acts as a Lewis acid.

3 Modification of the chiral complex catalyst. Change of the geometry or configuration in the coordination sphere

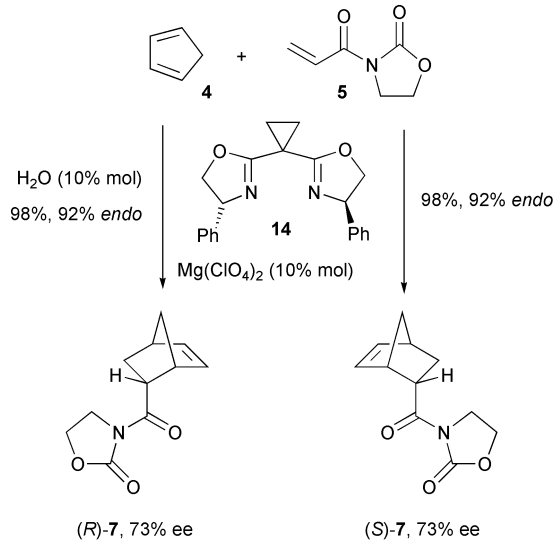
Several relevant examples in this field have been effectively summarized in the mentioned review published by Sibi.[4]



Scheme 5

Amongst them, a few cases deserve closer examination in order to highlight some recurrent underlying structural motifs.

Desimoni and others[12] reported a study about the Diels–Alder reaction of cyclopentadiene **4** and 3-acryloyl-1,2-oxazolidin-2-one **5** catalyzed by magnesium perchlorate in the presence of 4(*R*)-phenyl-substituted bis(oxazoline) **14** as ligand (Scheme 6).



Scheme 6

The *endo*-product (*S*)-**7** was obtained in ee up to 73% when the reaction was carried out for 48 h at −80 °C in dichloromethane with a catalyst loading as low as 5%. Addition of two moles of water per mole of magnesium catalyst brought about formation of enantiomer (*R*)-**7** in ee up to 73% in conditions analogous to the previous ones. With methanol as additive (*R*)-**7** was again obtained, though in lower ee (42%), while a high *endo*/*exo* selectivity was confirmed (91:9). For ethanol the preference for the (*R*) enantiomer shrank to only 16% ee in the product; but with bulkier alcohols added (*i*PrOH, *t*BuOH) the (*S*)-enantiomer became predominant, though with lower ee than in the absence of any hydroxylated additives (12% and 33%, respectively).

This peculiar trend can be rationalized by the increasing proclivity of magnesium to assume octahedral coordination geometry in the presence of oxygenated ligands of higher polarity. This geometry favourably competes with the more common tetrahedral setting, otherwise invoked to warrant for the stereoinduction observed in previous studies by Ghosh[6] and Corey.[13] The more sterically demanding the alcohol, the less is the octahedral species likely to outdo the tetrahedral one in catalyzing the reaction, due to steric overcrowding around the metal. Additionally, if only one equivalent of alcohol to the metal was used, the product was obtained with (*S*) configuration and an ee in lower figures, indicating again an unbalanced intervention of both forms of magnesium complex catalyst. Of relevance here, the absence of a measurable non-linear effect was supporting the working hypothesis of a monomeric metal species as active catalyst, an assumption otherwise too often taken for granted.

Accordingly, dienophile **5** is expected to coordinate to a tetrahedral magnesium complex giving the intermediate **A** as depicted in the calculated model of Fig. 2. The *Re* diastereoface of **A** becomes accessible to the diene due to the steric encumbrance on the *Si* face by one of the phenyl groups, predicting the overall preference for the *endo*-product (*S*)-**7**. Favourable electronic donor–acceptor interactions between the other phenyl group and the oxazolidinone moiety help predict the observed result.

In the presence of at least two equivalents of oxygenated ligands, an octahedral coordination around magnesium prevails. Amongst at least five different possible configurations, model **B** reproduced in Fig. 2 is expected to be competent to dictate the stereochemical course of the reaction. The other configurations were ruled out on basis of indirect experimental observations (for instance: the efficacy of 1,2-ethandiol as additive in giving the expected (*R*)-**7** ruled out any *trans* disposition of the added alcohol around the metal) and on ^{1}H-NMR studies, which in turn also confirmed the s-*cis* conformation of the double bond of the dienophile. With structure **B** assumed to be the most abundant and reactive, addition of cyclopentadiene is now expected to occur on the *Si* face of the acryloyl functionality resulting in (*R*)-**7** as predominant.

Further investigations into this Lewis-acid controlled Diels–Alder reaction of cyclopentadiene with acryoyloxazalidinone revealed that other additives can have the same enantioreversing effect as for water or lower alcohols; for instance, tetramethylurea fared effective.[14] Moreover, switching to triflate counterion for the magnesium complex catalyst, stereochemical results that comply with an octahedral geometry for the TS were observed. By virtue of their coordinating ability, triflate ions are now located on two of the octahedral sites, in a *trans* relationship (a reasonable model **C** is proposed in Fig. 2).

The crucial role of the counterion was further examined in a following study by the same authors on the asymmetric 1,3-dipolar cycloadditions between nitrones and monosubstituted alkenes.[15] The reaction between acryoloyloxazalidinone **5** and diphenyl nitrone **15** was catalyzed by 10 mol% of

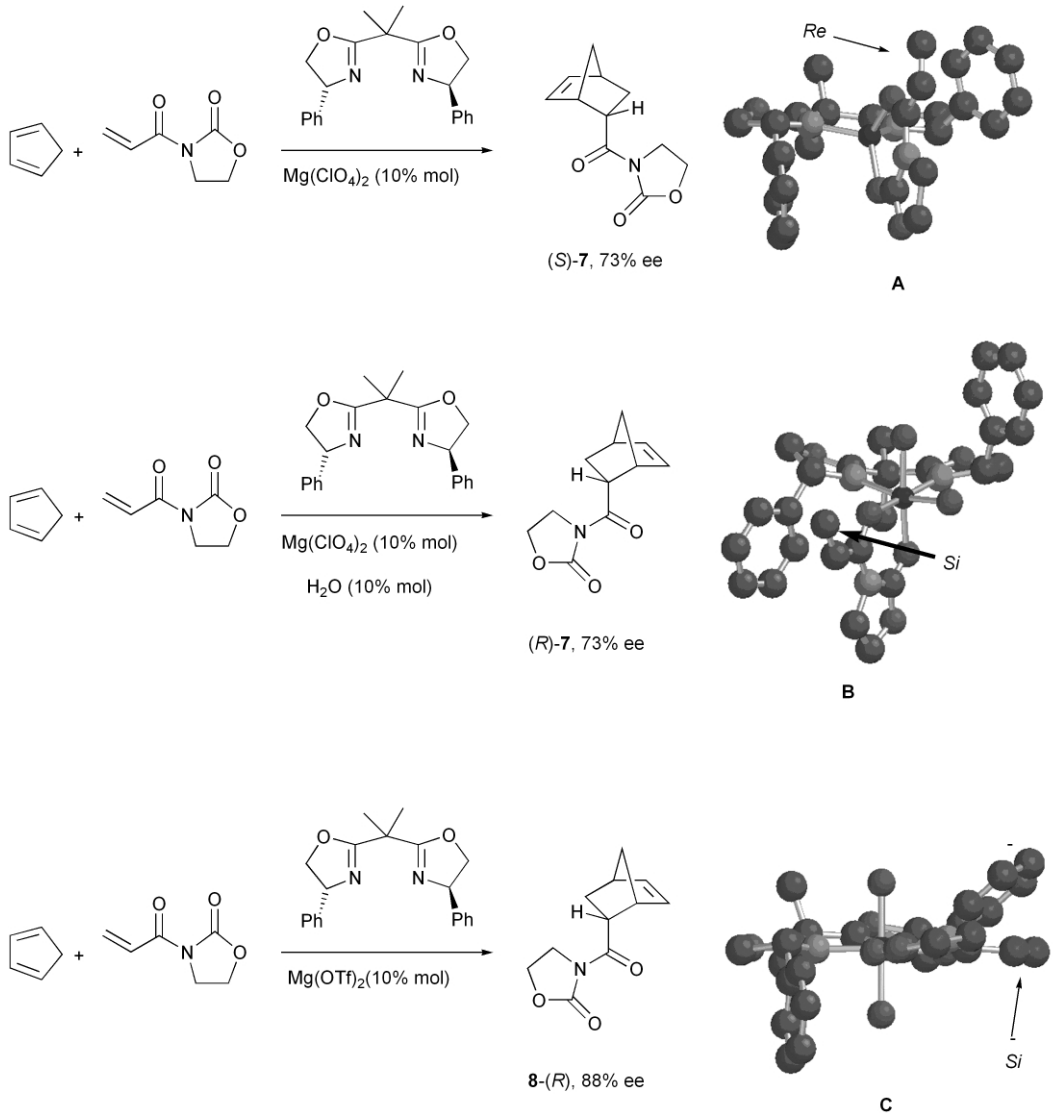
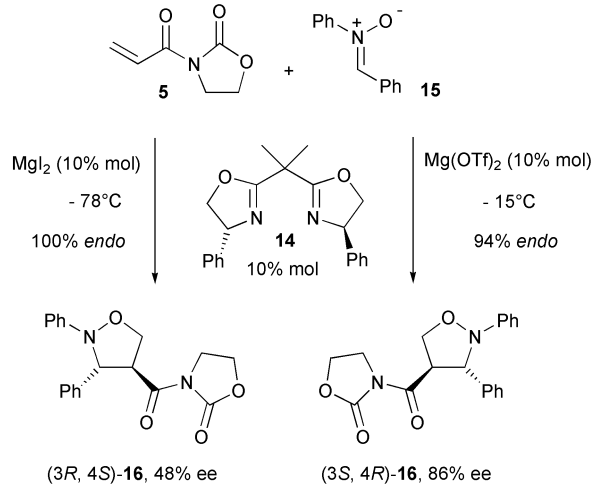


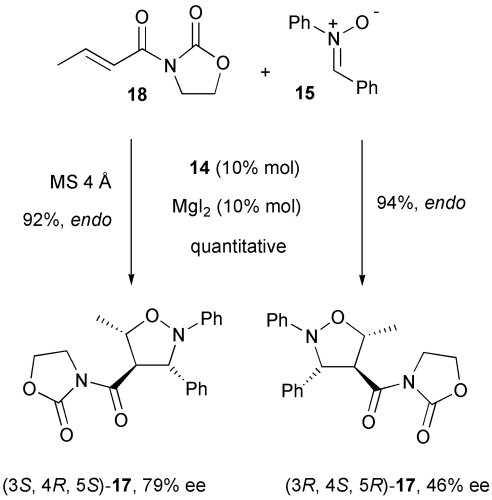
Fig. 2 Predicting models for the diastereofacial selectivity observed in the Diels–Alder reaction of cyclopentadiene with 3-acryloyl-1,2-oxazolidin-2-one **5**, catalyzed by chiral complexes of Mg with non-coordinating perchlorate counterions, in the presence of water, and with coordinating triflate counterions, as summarized in Scheme 6.

(*R*)-**14** and magnesium iodide or triflate to give either enantiomer of isoxazolidines **16** in quantitative yield and excellent *endo*/*exo* selectivity (see Scheme 7).



Scheme 7

In this study Desimoni considered the effect of molecular sieves (MS) in the reaction system, also previously independently examined by Jørgensen in the same test asymmetric catalytic 1,3-dipolar cycloaddition.[16] In the latter case, the chiral ligand was again bisphenylbisoxazoline **14** used in 10 mol% with iodine-activated magnesium (Scheme 8).



Scheme 8

The product of cycloaddition obtained in the presence of MS (*endo*-**17** as the major diastereomer, with 3*S*,4*R*,5*S* absolute

configuration and 79% ee) arose from the attack of the nitrone onto the *Re*-face of the substrate **18**, whereas in the absence of MS attack onto the *Si*-face of the alkene predominated (with opposite absolute stereochemistry in 46% ee, or 73% ee if in presence of 20 mol% H_2O). As the nitrone is a very efficient ligand for magnesium, a tetrahedral coordination like in *tet*-**19** would be disregarded (see Fig. 3). An octahedron of structure *oct*-**20,** with the two bulky nitrones *trans* to each other (hatched spheres in the drawing), would easily warrant the expected *Si*-face preference, but isomer *oct*-**21** might also be compatible with the observed stereochemical course for the reaction.

One of the more intriguing hypotheses for the role of MS stems from its plausible direct involvement in the catalytic cycles. The metal centre of the chiral complex could be bound to two oxygen atoms at the surface of the MS in a *cis*-coordination fashion, in addition to the bisoxazoline ligand and the alkenoyloxazolidinone, both bidentately coordinated to magnesium(II). The stereochemical outcome of the 1,3-dipolar cycloaddition mediated by the newly supramolecular Mg(II)-bisoxazoline-MS complex is then rationalized assuming the intermediacy of an octahedral structure *oct*-**22** in which the MS oxygens occupy *cis* positions (represented as hatched spheres). The exact structure of the binding of the magnesium(II)-box unit onto the MS oxygen atoms could not be described in detail at this stage.

At last, the same cycloaddition reaction was also studied by Kobayashi,[17] in order to survey putative reversal in enantiofacial selectivity, now with a chiral Yb(III) complex as the source of asymmetric induction. Once again, MS were responsible for a clear-cut switch in the diasterofacial selectivity, allowing the antipodal product of the 1,3-dipolar cycloaddition to be obtained with high ee (96%). Similar arguments as those advanced for the Mg(II)-catalyzed reactions may be proposed here, although the coordination number of ytterbium can be expanded beyond six, therefore other geometries are conceivable.

During their studies directed at the optimization of enantioselective Mukaiyama-aldol reactions between benzyloxyacetalde-

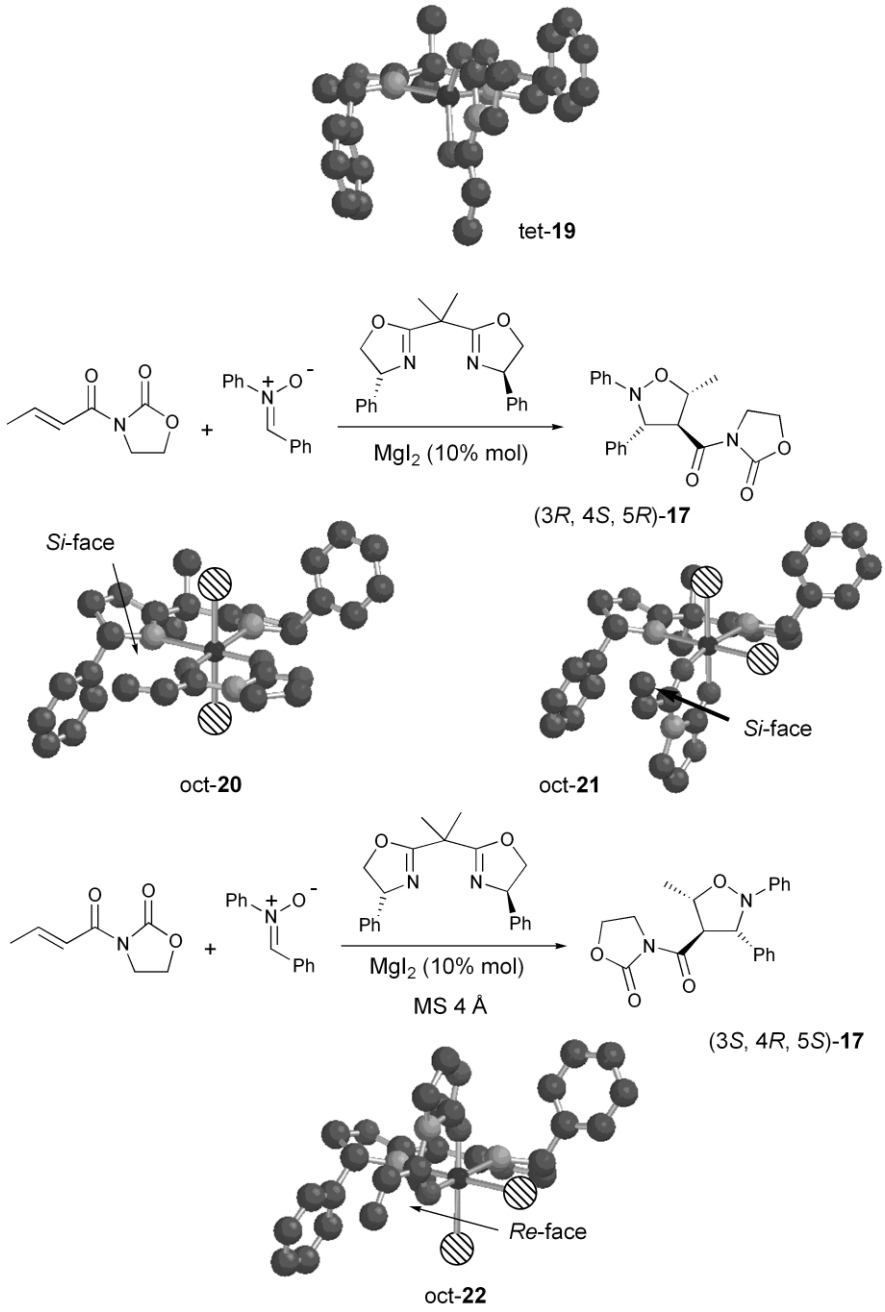
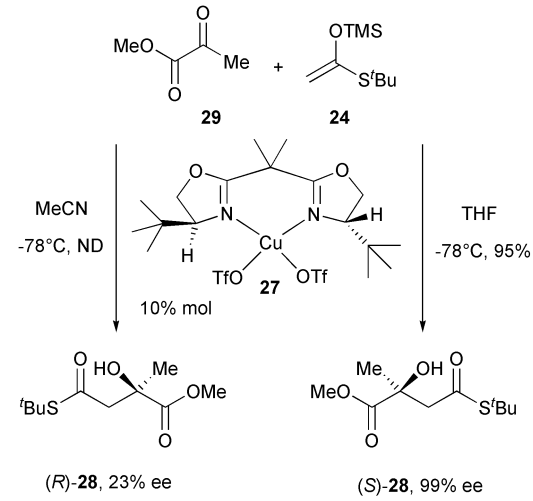


Fig. 3 Predicting models for the diastereofacial selectivity observed in the 1,3-dipolar cycloaddition of nitrone **15** with 3-acryloyl-1,2-oxazolidin-2-one **5**, catalyzed by chiral complexes of Mg in the presence or not of molecular sieves, as summarized in Scheme 8.

hyde **23** and *tert*-butyl thioacetate trimethylsilylketene acetal **24,** catalyzed by powerful Lewis acids, Evans and coworkers[18] found out that the same chiral source, ligand (*S*,*S*)-*tert*-leucine bisoxazoline **25**, [(*S*,*S*)-*tert*-Bu-box], could give rise to either enantiomer of the aldol product **26**, after acidic hydrolysis (Scheme 9).

Whereas use of $Cu(OTf)_2$ as copper source gave the (*R*)-β-hydroxy ester **26** in 91% ee, hexafluoroantimonate (SbF_6^-) as counterion for the same complex, [Cu(*S*,*S*)-*tert*-Bu-box)] (**27**), brought about the enantiomer with opposite (*S*) absolute stereochemistry, albeit in a lower 64% ee. Considering benzyloxyaldehyde bidentately chelated to the metal, in absence of counterion participation (like with non-coordinating SbF_6^-), the (*S*)-aldol product is unequivocally predicted from model **A**. With electronegative trifluoromethansulfonate (TfO^-) being instead involved in the catalytic cycle, a square pyramidal model **B** would now account for the predicted opposite stereochemical outcome. Should the two oxygens in the substrate swap coordination sites, an unproductive path would be taken on, since the electrophilic carbonyl group is subject to stronger activation when it resides in the equatorial site, in agreement with the Jahn–Teller distortion effect.

Strictly related to the previous case, an inversion of enantioselectivity was noticed during optimization studies for a Mukaiyama aldol addition of *tert*-butyl thioacetate trimethylsilylketene acetal **24** to pyruvate esters, again mediated by a [Cu(*S*,*S*)-*tert*-Bu-box](OTf)$_2$ complex (**27**/OTf^-), Scheme 10. When the reaction was carried out in CH_3CN, the (*R*)-enantiomer of the aldol adduct **28** was obtained, in reversed enantioselectivity with respect to all other trials run in a variety of solvents (ethereal, chlorinated, hydrocarburic). We can surmise that CH_3CN is now acting as a ligand. In this instance one might expect a square pyramidal Cu(II) geometry with the Box ligand, the CH_3CN and the ketone carbonyl molecules lying on the plane defined by the ligand, whereas the ester carbonyl should now occupy the weaker coordinating apical position. While there is no direct proof for this postulate, this model is based on a wealth of observations, which suggests this potential coordination geometry.



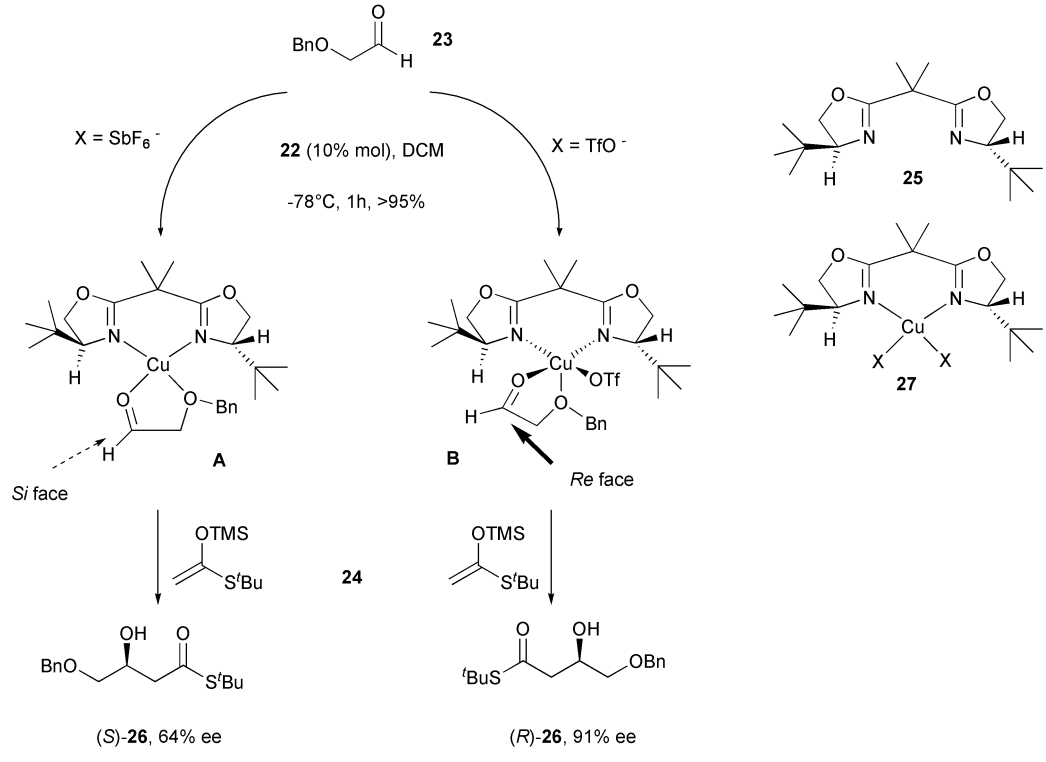
Scheme 10

4 Alternate mechanistic pathways

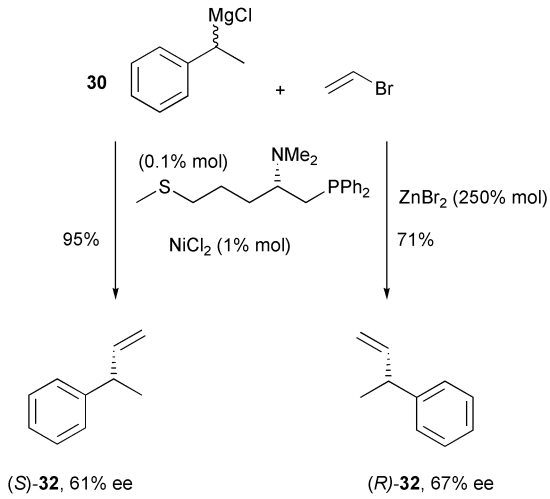
An early interesting case of switch between different enantio-discriminating mechanisms was reported by Kellogg[19] after studying the Ni(0)- or Pd(0)-catalyzed cross coupling of the Grignard reagent **30** with vinyl bromide (one example is depicted in Scheme 11).

Tridentate ligands **31** derived from amino acids with heteroatom-bearing side chain (such as those selected in Chart 1) effectively produced asymmetric induction, measured with the enantio-enrichment in the product.

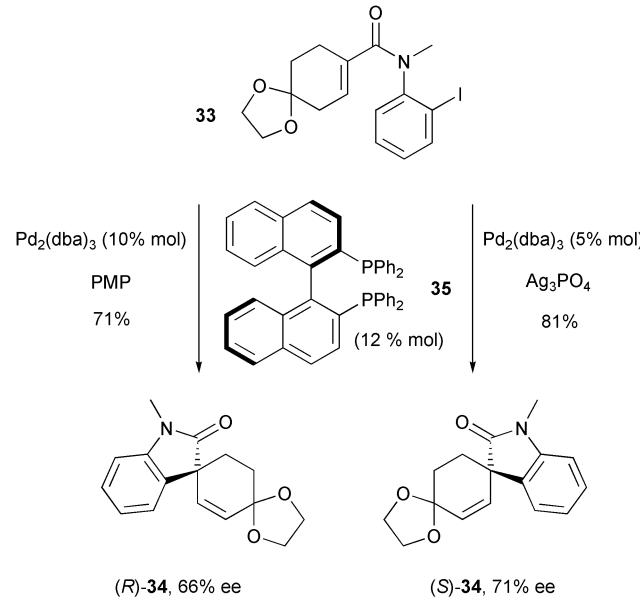
When anhydrous $ZnBr_2$ was added (2.5 equiv.), the rate of cross coupling sensibly increased and the direction of enantioselection grossly reversed. The reactions were run at 0 °C in diethyl ether, the [NiL*]/vinylbromide/Grignard reagent ratio was 1 : 100 : 250—the Grignard reagent was used in excess in order to suppress its own kinetic resolution. Yields in the product were generally 95% or higher. Similar effects were



Scheme 9



Scheme 11



Scheme 12

observed with ZnI_2, whereas $ZnCl_2$ significantly inhibited the reaction.

Ancillary experiments clearly showed that a dialkylzinc was not the reactive species and that not any particular structural feature of the β-aminophosphine ligands was affecting the role of $ZnBr_2$. Only speculative mechanistic interpretations can be proposed on basis of the body of experimental findings reported by the authors. A reversible addition of the Grignard reagent to the intermediate vinyl-Ni(II) bromide can be assumed. Selection might then occur between the two possible configurations at the scrambling benzylic carbon. Moreover, we can expect that the transmetalation step of the benzylic species with Ni would occur much faster in the presence of Zn instead of Mg, due to its closer similarity with Ni (catalyst) in terms of hardness or electronegativity. Ultimately, in the presence of Zn the enantio-discriminating event must take place at a different step of the catalytic cycle from that of the cycle plied when zinc salts are absent. The same argument would apply with Pd as metal catalyst.

The asymmetric intramolecular Heck reaction has come to the fore since the late 1980s as a powerful method for the enantioselective construction of quaternary carbon centres. Overman observed that either enantiomer of a spirocyclic chiral product could be prepared just by choosing a proper basic additive for the Pd-catalyzed reaction, a silver salt or a bulky tertiary amine.[20] The Heck intramolecular cyclization of the acryloyl-2′-iodoanilide **33** into 3,3-spirooxindole **34** in the presence of (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphtyl (BINAP) **35**, $Pd_2(dba)_3$ and Ag_3PO_4 (2 equiv.) as an iodidric acid (HI) scavenger furnished the (*S*)-enantiomer in 81% yield and 71% ee upon heating at 80 to 110 °C in DMA (Scheme 12).

Conversely, in the presence of up to five equivalents of the basic tertiary amine 1,2,2,6,6-pentamethylpiperidine (PMP), instead of Ag_3PO_4, the desired product **34** was still obtained in good yield and selectivity. This was at odds with the assumption that the migratory step in the catalytic cycle proceeded from a four-coordinate intermediate, which would accommodate a bidentate phosphine ligand only if iodide were removed from the palladium coordination sphere. Even more puzzling, the opposite enantiomer (*R*)-**34** was obtained in 77% yield and 66% ee.

This dual enantioselectivity was confirmed with a slate of different (*E*)-α,β-unsaturated 2-haloanilide derivatives when treated by prolonged heating in DMA or NMP with either catalytic system. The optimal HI acceptor for achieving highest enantiopurity strongly depended on each different substrate.

The cationic reaction manifold has been uniformly invoked to describe asymmetric Heck reactions of unsaturated triflates or halides when carried out in the presence of halide scavengers (usually Ag(I) or Tl(I) salts). Triflate dissociation, or halide scavenging, supposedly vacates a coordination site on the Pd(II) complex, thus facilitating olefin complexation (Scheme 13, **35** → **36** or **37**→ **38** → **36**). Accordingly, a chiral bidentate bisphosphine ligand can be stably bound during the migratory insertion step (**39** → **36**), conferring the rigidity needed to ensure good enantioselectivity.

On the contrary, in the absence of the halide scavenger, a chelating bisphosphine ligand would be reluctant to dissociate from (bisphosphine)(aryl)Pd(halide) complexes, which would explain the otherwise intransigence of these reactions. Moreover, once partial dissociation of a chiral bisphosphine ligand had occurred, a necessary event in order to accommodate the olefin, the resulting loss of ligand rigidity would erode the ensuing enantioselectivity.

A "neutral" Heck reaction manifold would instead justify the enantioselectivity gained in the silver-free reaction conditions (Scheme 14). This modality can also be entered from triflate substrates by carrying out the cyclization in the presence of added halide salts.

The C–C bond could now form through any of at least three pathways (insertion from a neutral tetracoordinate species **40** from partial BINAP dissociation; insertion *via* a cationic tetracoordinate species **41** from halide ionization; insertion in a

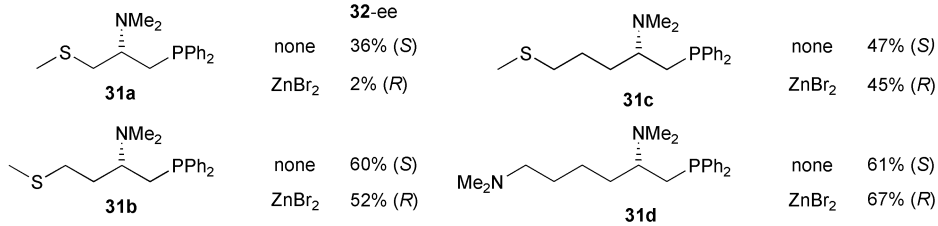
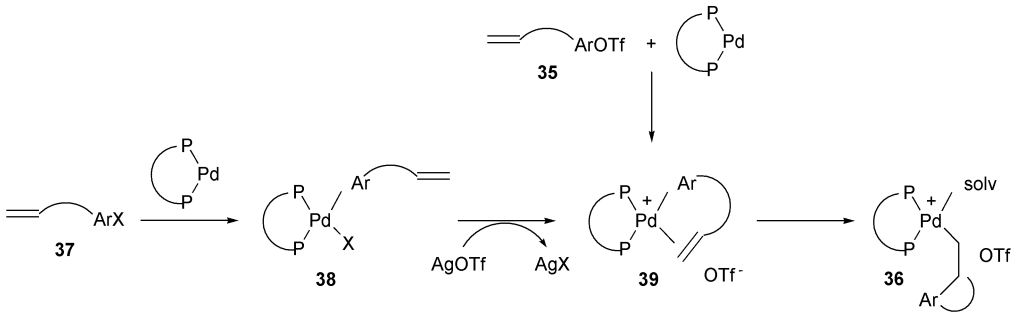
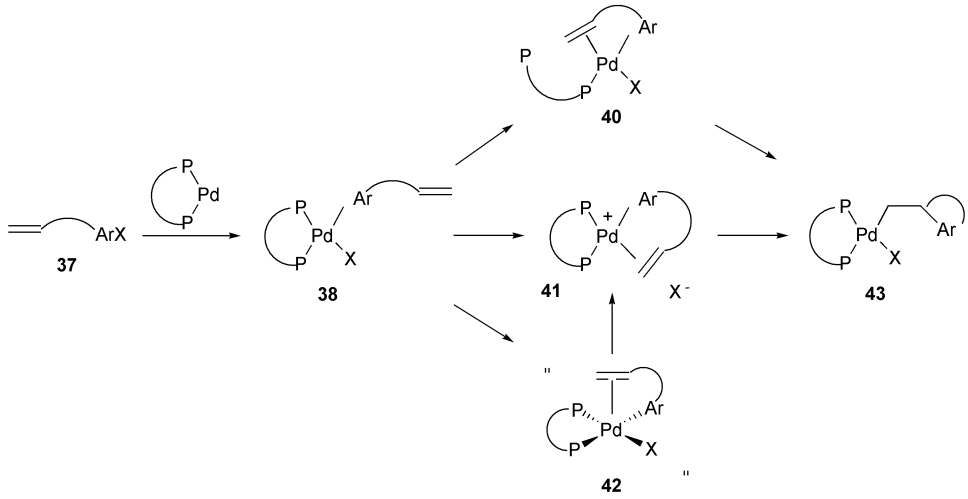


Chart 1



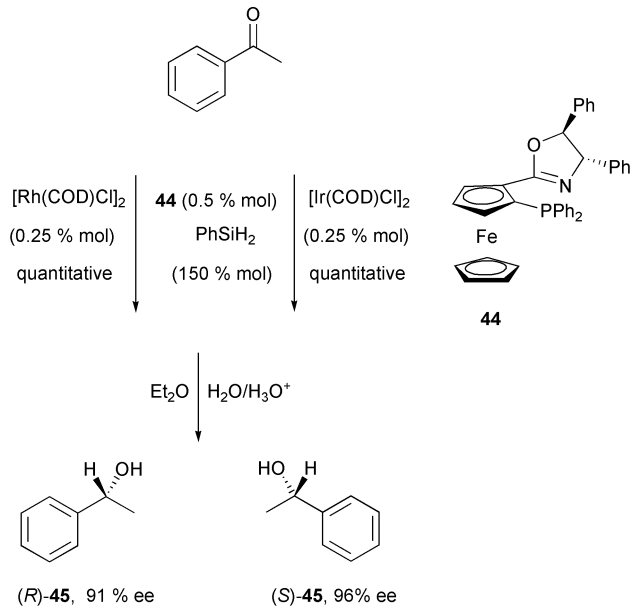
Scheme 13



Scheme 14

neutral pentacoordinate complex generically represented as **42**). The enantio-discriminating event must occur during the competent olefin coordination step, or later during the migratory insertion step. A number of studies were carried out by Overman's coworkers aimed at shedding some light on the mechanism of this neutral pathway. Amongst the key observations, the following are worth noticing. (1) The active Pd-BINAP catalyst species was shown to be monomeric on basis of not measurable non-linear effect, thence the absence of appreciable chiral amplification. (2) Trials conducted with monophosphine analogues of BINAP, which were adopted in order to mimic a monodentately coordinated BINAP, support the hypothesis that BINAP was firmly chelated throughout the catalytic cycle, and specifically at the stage of the enantioselective step. Therefore the **38** → **40**→ **43** sequence can be ruled out. (3) Previous theoretical calculations predicted that migratory insertions from five-coordinate Pd(II) complexes will have higher activation barriers than from four-coordinate complexes; this would make direct insertion **42** → **43** appear unlikely. All this suggested the stereo-regulating step of the "neutral pathway" should take place somewhere during the process where halide is displaced by the tethered alkene, that is during the oversimplified sequence **38** → **42** → **41**. Several distinct pentacoordinate intermediates are alleged to intervene between **38** and **41**. In principle, the enantioselective step could reside at the formation or breakdown of any of these intermediates. This complexity prevented the authors from advancing a three-dimensional model to rationalize the observed stereo-induction in asymmetric Heck reactions that proceed via the neutral pathway.

Another intriguing case was presented by Uemura *et al.* concerning a catalytic asymmetric hydrosilylation of ketones.[21] Oxazolinylferrocene-phosphine hybrid ligand **44**, abbreviated as (*S*,*S*,*S*)-DIPOF, was successfully employed in the Rh-catalyzed hydrosilylation of ketones, affording ee's up to the lower 90s with a variety of substrates (Scheme 15).



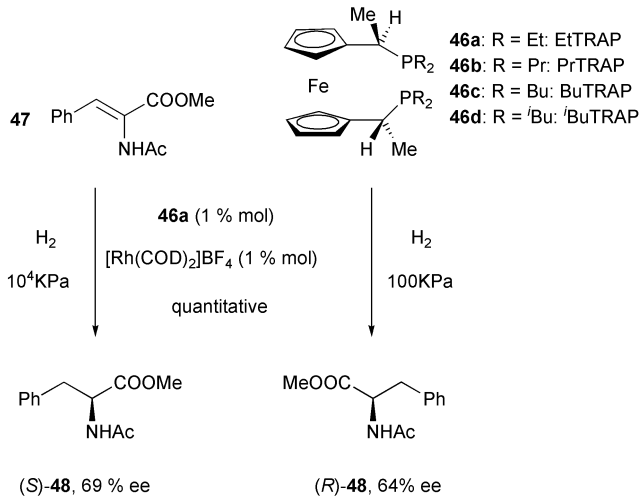
Scheme 15

Surprisingly, simple replacement of rhodium with iridium caused complete reversal in enantioselection. Once again we can surmise a kinetic factor as fundamental contribution to the observed divergent enantiodiscriminating events. With iridium, the slowest step of the catalytic cycle is the coordination of the double bond so that an enantiofacial bias must arise at this early stage. With rhodium, the H-atom transfer is known to be

generally the rate determining step, thence the site of enantiodiscrimination, whereas coordination on either face of the C = O bond would be under fast equilibration, foreshadowing Curtin–Hammett conditions.

A similar scenario can be envisioned for the catalytic asymmetric hydrogenation of α-(acetamido)acrylates with a new class of *trans*-chelating chiral bisphosphine (*R*,*R*)-(*S*,*S*)-TRAP ligands **46**, recently devised by Sawamura and Ito,[22] so that both the biferrocenyl backbone and the *P*-substituents directly contribute to the formation of the chiral environment.

Amongst the wealth of data collected by the authors for the hydrogenation of β-monosubstituted α-(acetamido)acrylate **47** as in Scheme 16, a couple of results here given are worth closer inspection.



Scheme 16

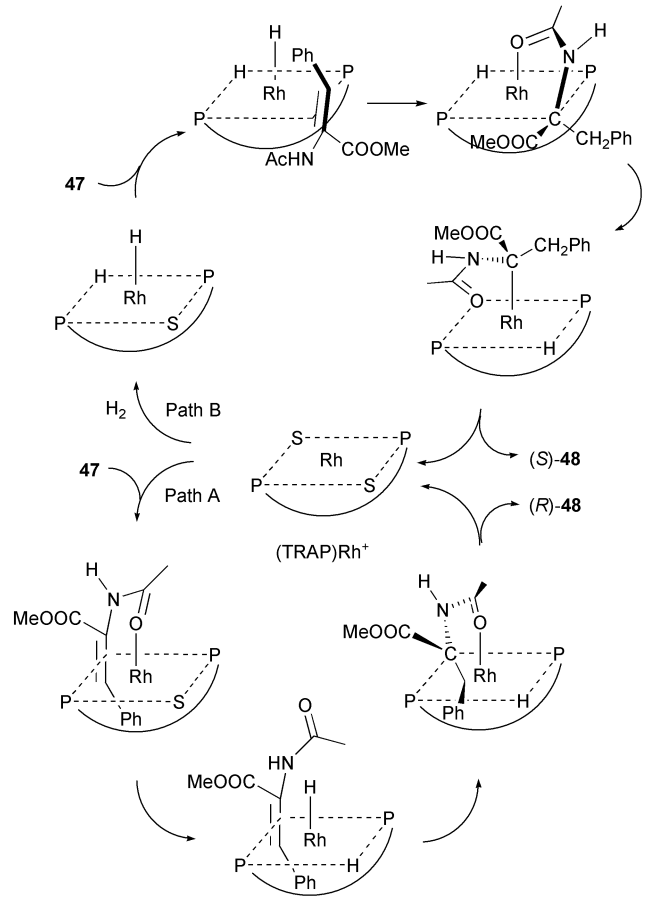
Upon increasing the H_2-pressure hundredfold, the opposite enantiomer of α-aminoacid derivative **48** was obtained under otherwise identical reaction conditions. This remarkable effect of hydrogen gas pressure can find a reasonable rationale if the coexistence of two competitive reaction pathways is assumed (see Scheme 17).

For path A, an atmospheric pressure of hydrogen allows the olefin to coordinate first to the metal, as referred to in the rhodium-catalyzed hydrogenation of enamides in the presence of *cis*-chelating biphosphines, thus leading to the (*R*)-aminoacid. When the partial pressure of hydrogen is dramatically increased, its oxidative addition to rhodium kinetically takes over. A similar event is generally accepted for the olefin hydrogenation promoted by the Wilkinson's catalyst, which is known to deliver the antipodal product, in this case the (*S*)-aminoacid.

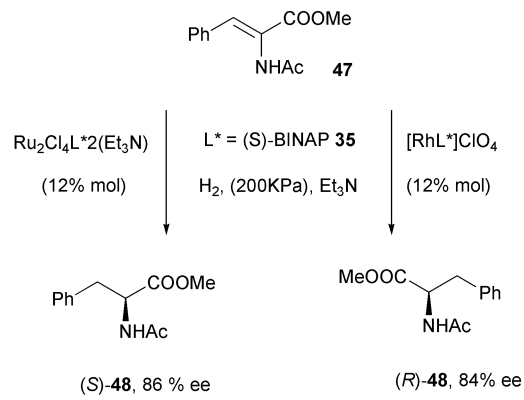
The diastereofacial discriminating event occurs at different stages in the two proposed paths, depending on the presence or not of hydride on the chirally active catalyst. Similar mechanistic dichotomy had been previously recognized by Ojima in the asymmetric hydrogenation of prochiral olefins catalyzed by rhodium complexes with chiral pyrrolidinodiphosphines.[23]

An earlier example of kindred reversal of enantioselectivity had been previously published by Ikariya *et al*.[24] The hydrogenation of α-acylaminoacrylic acid esters like **47** gave either configuration in the reduced product **48**, depending on the catalyst used, either $Ru_2Cl_4[(-)BINAP]_2$ in the presence of triethylamine, or $Rh[(-)BINAP]_2$, as illustrated in Scheme 18. Although different metals were employed in this case, once again occurrence of the enantio-discriminating step at different stages of otherwise very similar catalytic cycles can be invoked to justify the odd results.

Another interesting case of reversal of enantioselectivity observed in the product of catalytic asymmetric hydrogenation of an alkylarene was reported by the group of Burgess after



Scheme 17

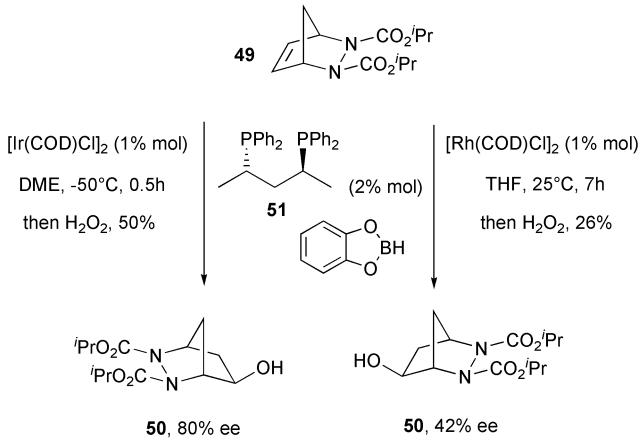


Scheme 18

submission of this review.[25] The enantioselectivity sharply switched upon variation of the temperature and pressure conditions in a hydrogenation catalyzed by a novel homochiral iridium imidazol-2-ylidene-oxazoline complex. According to the authors, and in agreement with the rationale summarized in Scheme 17 for the asymmetric hydrogenation catalyzed by TRAP-rhodium complexes as from Sawamura and Ito's work, the alternance of two mechanisms with different intermediates can be here invoked to explain the divergent enantiofacial selectivity on the alkene substrate recorded under different reaction experimental conditions.

Until recently only few examples of enantioselective transition-metal catalyzed hydroboration have been described in the literature, with rhodium as the only effective metal. Bonin and Micouin have newly reported first preliminary cases where also iridium can be adopted as metal in neutral chiral complexes capable of catalyzing an asymmetric hydroboration of *meso* hydrazines (**49**), *en route* to hydroxy diaminocyclopentanes.[26]

A relevant example is given in Scheme 19, where (*S*,*S*)-BDPP **51** was chosen as chiral ligand. The absolute configuration for diazabicyclic alcohol **50** was not definitely determined, but provisionally assigned in analogy with corresponding benzyl esters of the same structure and obtained in similar way.



Scheme 19

Most strikingly, an unprecedented reversal of enantioselectivity was recorded upon switching from rhodium to iridium, transition metals that possess the same ground state electronic configuration. This unexpected outcome was conducive to new insights in the mechanism of hydroboration. As depicted in Fig. 4, two alternative rate-determining steps can be proposed: a metal-hydrogen insertion into the transiently metal-coordinated olefin, or a metal–boron insertion.

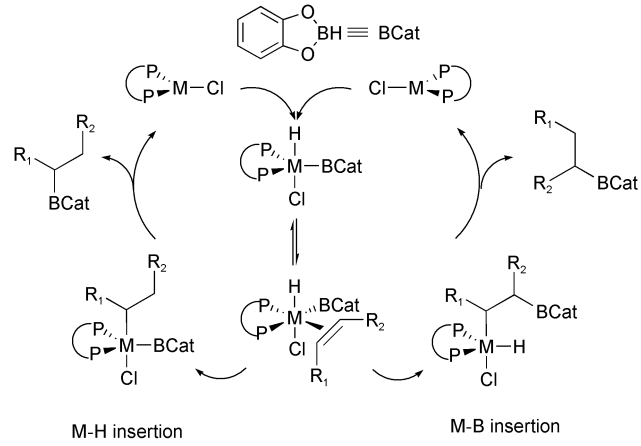
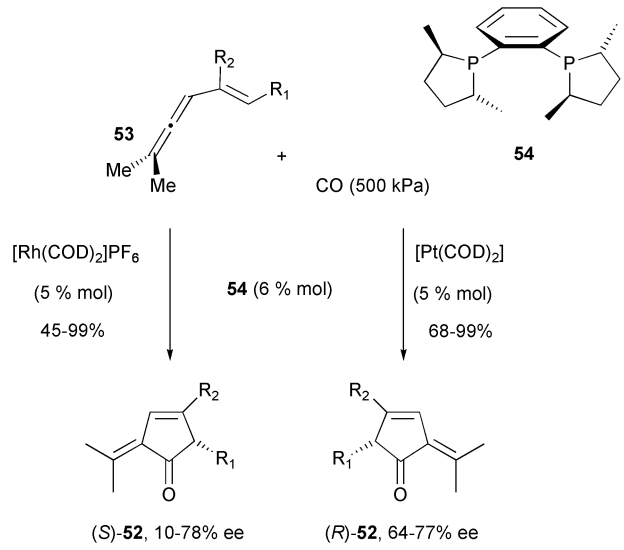


Fig. 4 Proposed alternate mechanistic cycles for the regioselective hydroboration of hydrazine **49** catalyzed by chiral complexes of Ir or Rh, as depicted in Scheme 19. Reprinted with permission from ref. 26. Copyright (2002) American Chemical Society.

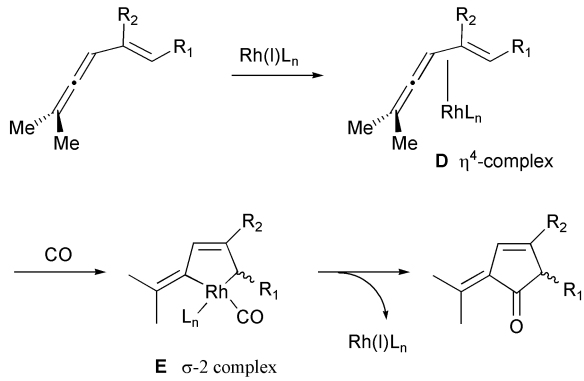
Either way leads to different regiochemistry, or, in this specific case with *meso* substrates, to opposite enantiomers, once we assume that the norbornenyl moiety undergoes reversible coordination by the chiral metal complex with some facial selectivity. Theoretical studies quoted by the authors support the working hypothesis that for iridium the insertion in the metal–boron bond would be favoured by 8 kcal mol^{-1}, whereas rhodium is known to prefer the metal–hydrogen insertion path. After changing the chiral ligand, the same authors accomplished a modest increase in chemical yield and ee in the product, a very promising improvement.

Another significant case of reversal in the induced product chirality, nominally caused by changing metal, has recently been reported by Murakami and Ito.[27] Either enantiomer of chiral 5-substituted-2-alkylidene-3-cyclopentenones **52** can be easily prepared by asymmetric carbonylative [4 + 1]-cycloaddition of vinylallenes **53**, with catalytic amounts of enantiopure chiral diphosphine (*R*,*R*)-Me-DuPHOS [1,2-bis(2,5-dimethylphosphorano)benzene] **54**, but switching from rhodium to platinum as metal centre. Best yielding reactions are summarized in Scheme 20, where reaction conditions prescribed heating in DME at 60 °C for 6 to 20 hours. The reversal of enantioselectivity occurred with all vinylallenes submitted to the carbonylative cyclization reaction conditions.



Scheme 20

Whereas with Pt observed ee values were generally over 70%, for the Rh-catalyzed carbonylative cycloaddition the product ee values varied greatly, depending on the structures of the starting vinylallenes **53**. As shown in Scheme 21, keeping



Scheme 21

with the accepted mechanism for the metal-catalyzed [4 + 1] cycloadditions, the enantio-discriminating event could reside either in a η^4-binding mode **D,** or in a planar σ^2-bound complex **E**. Carbon monoxide insertion in the metal–olefin σ-bond, followed by reductive elimination of the intermediate oxometalacyclohexene, complete the path to the final product.

In the Rh-catalyzed reaction, for which formation of reactive vinylallene-Rh-DuPHOS η^4-complex **D** found some experimental support, the stereochemistry prediction bore on model **II**, where the vinylallene better fits within the chiral pocket (Fig. 5). Conversely, in the Pt-catalyzed process the η^4-coordination reversibly leads to a planar σ^2-bonded metallacyclopentene (form **E**); the first irreversible step to dictate enantioselectivity immediately follows the constitution of this platinacyclopentene.

Two diastereomeric models are conceivable for the planar σ^2-bonded intermediate (Fig. 5, models **III**, **IV**). Model **IV** is

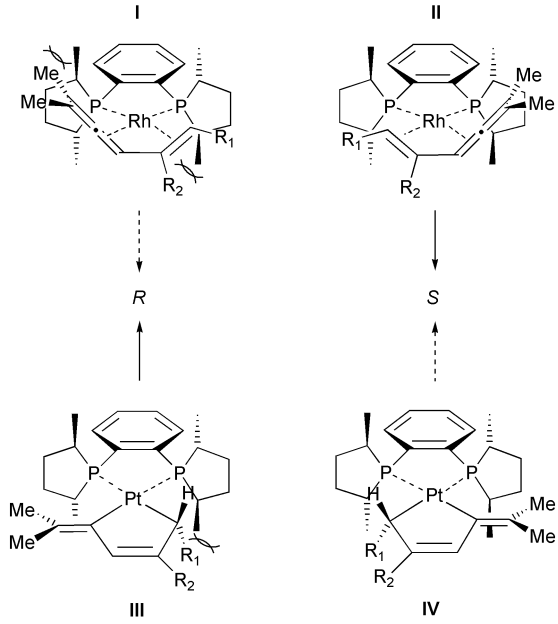
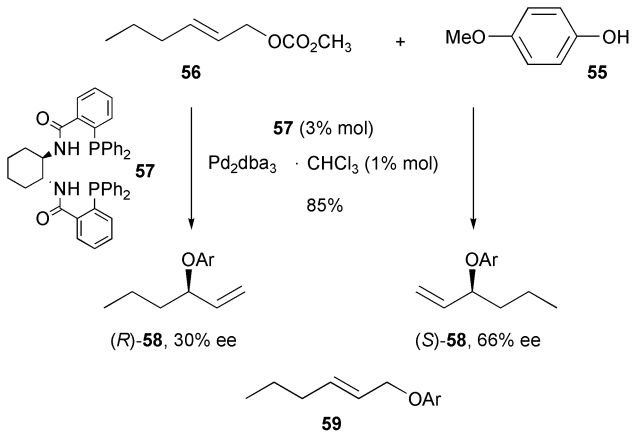


Fig. 5 Predicting models for the diastereofacial selectivity observed in the asymmetric carbonylative [4+1]-cycloaddition of vinylallene **53**, catalyzed by chiral complexes of Rh or Pt, as summarized in Scheme 20. Reprinted with permission from ref. 27. Copyright (1999) American Chemical Society.

thermodynamically more stable than model **III**. However, the predominantly obtained (*R*)-enantiomer should be derived from disfavoured model **III**, owing to a faster release of torsional strain upon incorporation of carbon monoxide, a clear case of stereoinduction determined under Curtin–Hammet control.

The asymmetric allylic alkylation (AAA) of phenols (such as **55**) has been the object of accurate and detailed study by Trost.[28] As a test case, system depicted in Scheme 22 was chosen by virtue of its versatility and of the related selectivity issues.



Solvent	E_TN(30)	**58**:**59**	**58**, ee (%)
PhMe	0.099	60:40	66 (S)
THF	0.207	48:52	51(S)
DCM	0.309	42:58	12 (S)
MeCN	0.460	23:77	30 (R)

Scheme 22

A few representative examples are here gleaned to show the effect caused by different reaction solvents on the regio- and enantioselectivity measured in the products.

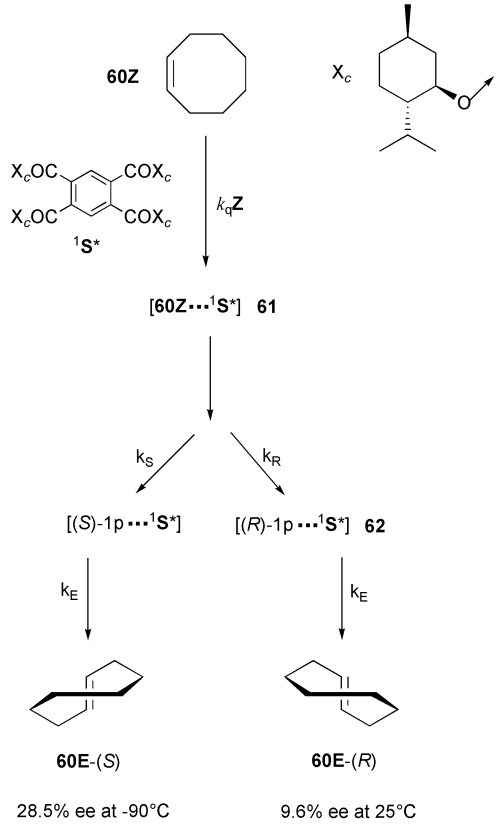
The regioselectivity figures were following a common trend along a linear correlation with the E_TN(30) solvent polarity parameters. Moreover, when the latter was increased beyond 0.30, reversal in the product absolute configuration was noticed. As a whole, more polar solvents were found to favour the formation of the more substituted product **58** with (*R*) configuration. In the case of AAA, polar solvents are supposed to better stabilize both nucleophilic phenolate and electrophilic allyl palladium, since both reactive species are charged, rather than the transition state, where opposite charges neutralize each other. This would overall slow down the rate of nucleophilic attack, which however should not be the rate-determining step in at least some of the tested solvents, because of the lack of any correlation between half-life reaction times and the solvent polarity. Conversely, in case of apolar solvents (i.e. toluene), the major enantiomer was arising from relatively fast nucleophilic attack onto the kinetic π-allyl intermediate. This is the first and easiest intermediate to be formed after palladium coordination onto the olefinic substrate, immediately followed by carbonate ionization and loss of CO_2, methoxide ion as leaving groups. In other words, the stereo-discriminating step is dictated by the electrophilic species (the more accessible π-allyl Pd complex). Whereas in more polar solvents, like acetonitrile, owing to the mentioned decreased rate of nucleophile delivery, the intermediate π-allyl–metal complex is now allowed to equilibrate via an otherwise not so fast π-σ-π isomerization that results in allyl face scrambling of the metal. The equilibration takes place between its diastereomeric forms, defined by the chirality of the ligand and the stereo-differential coordination of the metal on either allylic prochiral face. In a nutshell, these could be described as typical Curtin–Hammett conditions, where the stereoselective event descends from a nucleophile-driven discrimination between two fast-equilibrating electrophilic counterparts,[29] thus giving rise to the antipodal product. A word of caution should be given at this juncture in that the role of solvent may well extend beyond just affecting the mentioned nucleophilic attack rate, for instance it may influence the π-σ-π epimerization itself.

5 Entropy of activation in the enantio-discriminating step

In order to make predictions about the stereochemical outcome of thermal and enzymatic asymmetric reactions, organic chemists have been long relying upon expeditious models (e.g. the Felkin–Ahn modality of attack onto carbonyls), whose rationales are based on an array of factors, like charges, dipoles, chelation control, electronics, sterics, and stereoelectronics, often employed with convenient simplifications. By this way, the enthalpic contribution to the chiral discriminating process along the mechanistic pathway is exclusively accounted for, thus neglecting the entropic component related to the conformational changes and relocation of solvent molecules occurring at the stage of the transition state. The empirical mechanistic manifolds that consider only the enthalpic term usually succeed in predicting the predominant stereoisomer emerging out of an asymmetric reaction. They are however not always conducive to an explanation of less common but nonetheless relevant experimental findings, as disclosed soon thereafter. On the other hand, one of the reasons why the entropy of activation ($\Delta S^{\ddagger}$) has been disregarded by organic chemists stems from the generally narrow temperature ranges (ΔT) in which thermal reactions can be usually tested, therefore preventing a full appreciation of this factor. Moreover, the coexistence of alternate different mechanisms behind the same chemical transformation at different temperatures can hamper a straightforward and accurate analysis of energetic parameters of experimental origin.

The situation changes with many photochemical reactions, for the nature of the transition states that consist of excited states obtained after absorption of photon(s) of suitable wavelength,

per se an event not governed by the temperature. Due to its high chemical and quantum yields, Inoue and coworkers chose the enantio-differentiating geometrical photoisomerization of (*Z*)-cyclooctene (**60Z**) as benchmark to investigate this manifold, namely as a probe for the above mentioned role of $\Delta S^{\ddagger}$ in affecting photoinduced enantioselectivity. This process can be triggered through sensitization of (*Z*)-cyclooctene by the excited state S* of an optically active aromatic ester (a chromophore), proceeding through its transient complex with the substrate (so called exciplex), finally ending up in a ground-state stable product of measurable enantio-enrichment (Scheme 23).[30]



Scheme 23

Concerning this *Z–E* photoisomerization, not only has it been shown that either (*S*)-(−) or (*R*)-(+) enantiomer of (*E*)-cyclooctene **60E** can be obtained in significant predominance by simply tuning the reaction temperature within the wide range −90 to + 50 °C, but also that above the equipodal temperature (hereafter defined T_0) the ee increases with the temperature, an unusual trend, but not unheard of. Structurally diastereomeric exciplex intermediates must be conceived in the process to funnel efficient chiral transfer from the sensitizer into the product. Insofar as subtle mechanistic details involved in this process are beyond the scope of this review, suffice it here to say that enantio-differentiation occurs during the 90 degree rotational step around the breaking C = C double bond of the initial exciplex [**60Z**···^{1}S*] (**61**) into the relaxed asymmetric exciplex [(*S*)/(*R*) ^1p···^{1}S*](**62**). This in turn releases either enantiomer of a perpendicular singlet (^1p), eventually affording the final ground-state stable product **60E**.

The described process typifies a bright example of photochirogenesis, or photochemical generation of molecular chirality. According to the Arrhenius–Eyring mathematical treatment, the relative rate constant k_S/k_R for the formation of (*S*)- and (*R*)-**60E** can be expressed as

$$\ln(k_S/k_R) = -\Delta G^{\ddagger}_{S\text{-}R}/RT + \ln(A_S/A_R)$$
$$= -\Delta\Delta H^{\ddagger}_{S\text{-}R}/RT + \Delta\Delta S^{\ddagger}_{S\text{-}R}/R$$

(A_S and A_R are the frequency factors).

Values for $\ln(k_S/k_R)$ were plotted against the reciprocal of *T*, for enantio-differentiating photosensitizations carried out within the −90 to + 50 °C temperature range with a variety of optically pure alkylbenzenecarboxylates as sensitizers. Some representative results are depicted in Fig. 6, which highlights

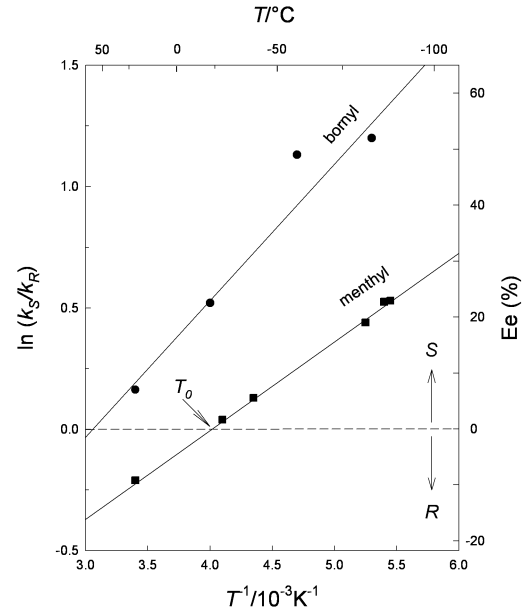


Fig. 6 Arrhenius–Eyring type diagram for the logarithm of measured relative rate constant for the formation of (*S*)- and (*R*)-**60E**, in the presence of menthyl- or bornyl-benzenecarboxylates as chiral sensitizers, *vs*. the reciprocal of temperature. The equipodal temperature is highlighted for one of the photoisomerizations. Reprinted from *Chem. Commun*., 2000, 251.

the linearity of the best fitting curve obtained throughout the entire surveyed temperature range. Such a linearity rules out the emergence of an inversion temperature,[31] hence the possibility of a shift in the rate- and stereochemical determining step within the multistep process.

More interestingly, the sense of chirality in the product was shown to switch at the mentioned equipodal temperature T_0, where no enantiodifferentiation occurs since $\Delta G^{\ddagger}_{S\text{-}R} = 0$, upon sensitization with some of the selected chiral catalysts (mostly the *ortho*-substituted benzenecarboxylates). The observed behaviour was attributed to the non-zero differential entropy of activation ($\Delta\Delta S^{\ddagger}_{S\text{-}R} \neq 0$) associated with the different conformations around the sensitizer *ortho*-alkoxycarbonyl groups. These conformations arise from the dynamic changes occurring during the rotational relaxation in the diastereomeric exciplex. Below T_0, the enthalpy factor ($\Delta\Delta H^{\ddagger}_{S\text{-}R}$) determines the enantiomeric excess, whereas above T_0 the entropic term ($\Delta\Delta S^{\ddagger}_{S\text{-}R}$) outweighs the former. In case both terms have the same sign, the switch in controlling the enantio-differentiation from one to the other bears out the reversal in the final absolute configuration.

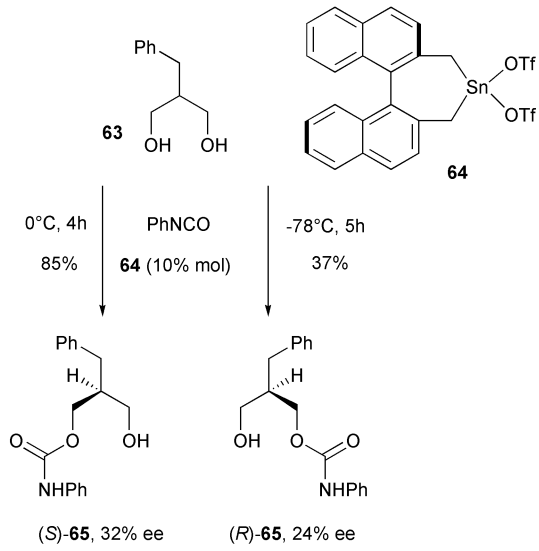
For the cyclooctene photoisomerization there are also examples of reversal of the product (**60E**) chirality caused by alteration in the reaction solvent[32*a*] or pressure,[32*b*] another two environmental factors with direct bearing on the entropic term. In the latter case, the dependence of the relative rate of two enantio-discriminating paths can be expressed at constant temperature as a function of the differential activation volume ($\Delta\Delta V^{\ddagger}$):

$$\ln(k_S/k_R) = -(\Delta\Delta V^{\ddagger}_{S\text{-}R}/RT)p + [\ln(k_S/k_R)]_{p\,=\,0}$$

Similarly to the previous scenario, variations of the reaction pressure within a few orders of magnitude can bring about reversal in the absolute configuration of the final product upon switching around the equipodal pressure (p_0). Since *T* and *p* are

independent variables, there are no consistent relationships between the signs and values for the enthalpic, entropic and volumic activation parameters of a photoisomerization reaction promoted by a particular chiral sensitizer. When the signs of $\Delta\Delta H^{\ddagger}_{S\text{-}R}$, $\Delta\Delta S^{\ddagger}_{S\text{-}R}$, and $\Delta\Delta V^{\ddagger}_{S\text{-}R}$ are all the same, chirality inversion occurs upon both *T* and *p* variation. Three-dimensional diagrams can now be drawn from experimental data (not reproduced herein),[30] where the ee figures are correlated with *T* and *p* and an equipodal line at the intersection of two enantiodifferentiating planes defines the passage from one enantiomer to the other. Therefore a combination of *p,T* that gives the highest ee can be conceivably extrapolated, an example of multidimensional control.

The entropic paradigm should be in principle applicable to any reaction (photochemical, thermal or biochemical) where weak interactions play a decisive role in driving the competing stereo-determining processes. Otera has recently described an intriguing and rare example outside photochemistry.[33] His group found a linear relationship between the reciprocal of temperature and the ee in the product (**65**) of desymmetrization of 2-substituted 1,3-propanediol **63** via monocarbamoylation catalyzed by chiral organotin **64** (Scheme 24).



Scheme 24

Carefully controlled experiments confirmed that the desymmetrization event only originated from discrimination between the two enantiotopic hydroxy groups, and dispelled alternate mechanisms (transcarbamoylation, disproportionation, multi-step process[31]) from inducing the observed temperature-dependent enantioselectivity trend.

More controversial would be the explanation given by Hanson and co-authors in their report about the influence of temperature on the enantio-selection in the styrene hydroformylation catalyzed by chiral platinum complexes.[34] With catalysts obtained from $PtCl(SnCl_3)$ and (2*S*,4*S*)-2,4-bis[bis(*p*-(dimethylamino)phenyl)phosphino]pentane (**66**) and (2*S*,3*S*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis[bis(*p*-(dimethylamino)phenyl)phosphino]butane (**67**, Chart 2) a reversal in the predominant absolute configuration in the aldehyde product **68** occurred at relatively low temperatures (T_0) of 53 and 72 °C, respectively (Scheme 25).

For instance, with complex **66** hydroformylation product **68** of *R* configuration was obtained in 41% enantiopurity at 100 °C, whereas the enantiomer *S* was obtained with 60% ee at 30 °C. Other data garnered by Hanson turned out to comply with a linear Eyring plot, at least up to 100 °C, a temperature beyond which racemization side-reactions started taking over. The authors suggested different explanations for the described behaviour of the reaction system at different temperatures.

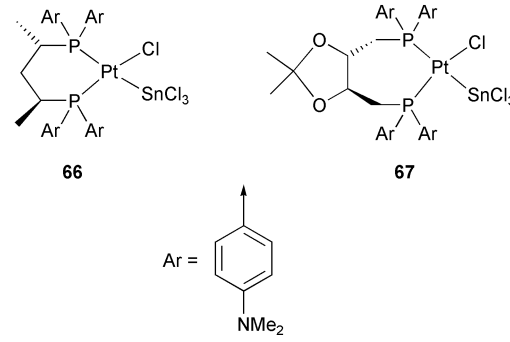
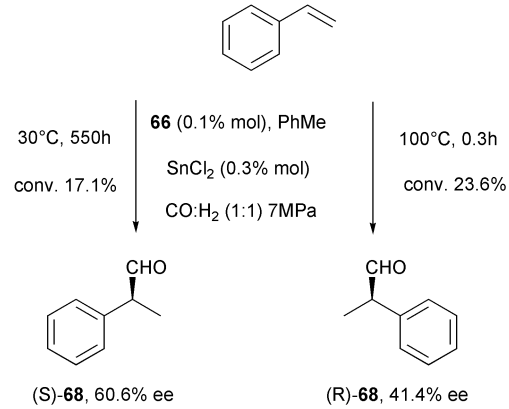


Chart 2



Scheme 25

They resorted to a change in the chelate ring conformation from δ- to a less stable λ-skew, or, more likely, to a not clearly disclosed kinetic effect, ascribed to competing reaction pathways of different activation energies. At this juncture, the hindsight coming from Inoue's experimental work and theoretical elaboration allow us to invoke the differential in activation entropy ($\Delta\Delta S^{\ddagger}_{S\text{-}R}$) as a major factor here at play.

6 Conclusion and outlook

Owing to space limitations, the thriving field of research about polymer-supported catalysts could not be dealt with in this account. Suffice it to mention the recent achievements by the group of Luis,[35] where for the first time the absolute sign of stereochemical outcome of a sample catalyzed Diels–Alder reaction depended upon the morphology of the polystyrene backbone (e.g., copolymerization *vs.* grafting) containing the catalyst (Ti-TADDOLates).

How many cases of reversing enantioselectivity have been reported somewhere in the literature, but not included in our analysis, nor in the review by Sibi[4] mentioned at the beginning of this account? Sorting them out has been no mean feat, especially where the aim of the experimental work was focused on other aspects of the asymmetric synthesis and the ee figures related to switching absolute configurations embedded amongst legion of other data.

The discussion of the hitherto selected examples of *toggling enantioselectivity* raises a fundamental question. Are all these cases a consequence of serendipitous findings, or can a design component be envisaged at least in some of them? Moreover, with this account, we hope to have given a valid contribution to the debate in the field. By virtue of the attempted rationalization and categorization, the application of the currently available mechanistic tools should allow chemists to take a leap towards the prediction of further cases of toggling enantioselectivity. Ultimately, as anticipated in the introduction, the goal is to

facilitate scientists in proposing asymmetric synthetic projects that verge on a single valuable chiral source for the preparation of both enantiomers of a given compound.

7 Acknowledgements

We thank Marcella Bovolenta, Giovanni Desimoni, David A. Evans, Giuseppe Faita, Lucio Toma, Barry M. Trost, and Jennifer Vance for their supply of additional material and their valuable suggestions.

8 References

1 *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 2000.
2 S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, 1973, **38**, 1870.
3 Y. H. Kim, *Acc. Chem. Res.*, 2001, **34**, 955.
4 M. Sibi, *Curr. Org. Chem.*, 2001, **5**, 719.
5 A. Kinting, H.-J. Kreuzfeld and H.-P. Abicht, *J. Organomet. Chem.*, 1989, **370**, 343.
6 A. K. Ghosh, P. Mathivanan and J. Cappiello, *Tetrahedron Lett.*, 1996, **37**, 3815.
7 E. J. Corey, N. Imai and H.-Y. Zhang, *J. Am. Chem. Soc.*, 1991, **113**, 728.
8 D. A. Evans, S. J. Miller and T. Y. Leckta, *J. Am. Chem. Soc.*, 1993, **115**, 6460.
9 E. J. Corey and K. Isihara, *Tetrahedron Lett.*, 1992, **33**, 6807.
10 M. P. Sibi, J. J. Shay, M. Liu and C. P. Jasperse, *J. Am. Chem. Soc.*, 1998, **120**, 6615.
11 K. Yabu, S. Masumoto, S. Yamasaki, Y. Hamashima, M. Kanai, W. Du, D. Curran and M. Shibasaki, *J. Am. Chem. Soc.*, 2001, **123**, 9908.
12 G. Desimoni, G. Faita, A. Gamba Invernizzi and P. Righetti, *Tetrahedron*, 1997, **53**, 7671.
13 E. J. Corey, N. Imai and H.-Y. Zhang, *J. Am. Chem. Soc.*, 1991, **113**, 728.
14 P. Carbone, G. Desimoni, G. Faita, S. Filippone and P. Righetti, *Tetrahedron*, 1998, **54**, 6099.
15 G. Desimoni, G. Faita, A. Mortoni and P. Righetti, *Tetrahedron Lett.*, 1999, **40**, 2001.
16 K. V. Gothelf, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 1998, **63**, 5483.
17 M. Kawamura and S. Kobayashi, *Tetrahedron Letters*, 1999, **40**, 3213.
18 D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell and R. J. Staples, *J. Am. Chem. Soc.*, 1999, **121**, 669 and following report.
19 G. Cross, B. K. Vriesema, G. Boven, R. M. Kellogg and F. van Bolhuis, *J. Organomet. Chem.*, 1989, **370**, 357.
20 A. Ashimori, B. Bachand, M. A. Calter, S. P. Govek, L. E. Overman and D. J. Poon, *J. Am. Chem. Soc.*, 1998, **120**, 6488 and references therein cited.
21 Y. Nishibayashi, K. Segawa, K. Ohe and S. Uemura, *Organometallics*, 1995, **14**, 5486.
22 R. Kuwano, M. Sawamura and Y. Ito, *Bull. Chem. Soc. Jpn.*, 2000, **73**, 2571.
23 See the seminal report by I. Ojima, T. Kogure and N. Yoda, *J. Org. Chem.*, 1980, **45**, 4728.
24 T. Ikariya, Y. Ishii, H. Kawano, T. Arai, M. Saburi, S. Yoshikawa and S. Akutagawa, *J. Chem. Soc., Chem. Commun.*, 1985, 922.
25 M. Perry, X. Cui, M. T. Powell, D.-R. Hou, J. H. Reibenspies and K. Burgess, *J. Am. Chem. Soc.*, 2003, **125**, 113.
26 A. Pérez Luna, M. Bonin, L. Micouin and H.-P. Husson, *J. Am. Chem. Soc.*, 2002, **124**, 12098.
27 M. Murakami, K. Itami and Y. Ito, *J. Am. Chem. Soc.*, 1999, **121**, 4130.
28 B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.*, 1999, **121**, 4545.
29 These conditions can also be described under the Dynamic Thermodynamic Resolution paradigm, (as opposed to the Dynamic Kinetic Resolution associated with the electrophile-controlled enantioselectivity here described), concepts covered in depth in P. Beak, *Acc. Chem. Res.*, 2000, **33**, 715.
30 Y. Inoue, N. Sugahara and T. Wada, *Pure Appl. Chem.*, 2001, **73**, 475–480 and references cited therein.
31 H. Buschmann, H.-D. Scharf, N. Hoffmann and P. Esser, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 477.
32 (*a*) Y. Inoue, H. Ikeda, M. Kaneda, T. Sumimura, S. R. L. Everitt and T. Wada, *J. Am. Chem. Soc.*, 2000, **122**, 40; (*b*) Y. Inoue, E. Matsushima and T. Wada, *J. Am. Chem. Soc.*, 1998, **120**, 10687.
33 J. Otera, K. Sakamoto, T. Tsukamoto and A. Orita, *Tetrahedron Lett.*, 1998, **39**, 3201.
34 I. Tóth, I. Guo and B. E. Hanson, *Organomet.*, 1993, **12**, 848.
35 B. Altava, M. I. Burguete, J. M. Fraile, J. I. García, S. V. Luis, J. A. Mayoral and M. J. Vicent, *Angew. Chem., Int. Ed.*, 2000, **39**, 1503.