Unexpected Inversions in Asymmetric Reactions: Reactions with Chiral Metal Complexes, Chiral Organocatalysts, and Heterogeneous Chiral Catalysts

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1. Introduction

The recognition of the optical activity of organic compounds, followed by the detailed analysis of optical isomerism,[1] laid the foundation for the development of asymmetric syntheses, a group of reactions of fundamental significance. Asymmetric syntheses, available in great varieties, are the indispensable source of a large number of chiral compounds that have become essential for human society. Some of the most important procedures that belong to this group are asymmetric organocatalytic, asymmetric homogeneous and heterogeneous metal catalytic reactions, and enzyme-catalyzed procedures. One of the main tasks of pertinent research is the development of chiral catalysts that enable the preparation of the required product in the highest possible enantiomeric excess (ee). The value of ee depends on a number of known and yet unknown factors not only for a given reaction but also for each individual compound within a reaction type.

Experimental observations occasionally reveal unknown phenomena, too—one of these is the so-called unexpected sense of enantioselectivity, the subject of the present review. This phenomenon has been mentioned in the literature under a variety of names including "unexpected inversion of enantioselectivity", "change/dramatic change in the sense/direction of enantioselectivity", "chirality inversion", "switch of the expected chiral sense", and "unexpected reversal of the enantioselectivity/enantioselection/enantiodifferentiation/chiral induction/stereochemistry/configuration". Authors designate unexpected experimental observations in their manuscripts as "dramatic", "remarkable", "surprising", and "interesting". Of course, these expressions do not facilitate orientation in the literature.

Experimental results exhibiting a stereochemistry different from the relationships generally accepted for the sense of enantiodifferentiation (ED) will be referred to as "unexpected inversion" or simply "inversion" in this review. The detailed possible definition is as follows: the absolute configuration of a product in a reaction is

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Mihály Bartók was born and raised in Szeged, Hungary. He received his M.Sc. degree in organic chemistry from University of Szeged under the direction of Professor Gabor Fodor. In 1966 he received his candidate of chemistry degree in the Moscow State University under the supervision of Professors N. I. Shuikin and A. F. Plate in the field of heterogeneous catalytic organic reactions. He was dean of the Faculty of Science and director of Department of Organic Chemistry in University of Szeged. He is a member of the Hungarian Academy of Sciences (1987). Professor Bartók became professor emeritus at University of Szeged in 2003. His research interests are stereochemistry and mechanism of heterogeneous catalytic organic reactions and heterogeneous enantioselective catalysis.

unexpected if, in earlier reactions using a chiral catalyst of identical absolute configuration and substrates with not significantly different structures, the absolute configuration of the product was the opposite. There may be, however, further criteria depending on the reaction type, especially as more and more knowledge is accumulating. For example, in the case of chiral metal complex catalysts, metal and counterions may also play determinant roles in addition to the chiral ligand (**L***). When the roles of the individual components of the chiral system have been identified, however, the phenomenon gradually ceases to be unexpected and a new unexpected result may appear. In addition to the main components of a reaction, other factors that may play a role are the experimental parameters, namely, the temperature, the solvents, the various achiral additives, the **L***/substrate or the chiral catalyst/substrate ratio, or the concentration of the catalyst, to mention just the most common ones.

When faced with the interpretation of a new phenomenon, a scientist would first examine any antecedents in closely related fields. Such antecedents may be expected to be found among homogeneous catalytic asymmetric procedures employing the thoroughly investigated metal complex catalysts as well as among organocatalytic processes and heterogeneous catalytic enantioselective reactions; the latter two fields have been developed enormously in the past few years.

The objective of this manuscript is to draw, from the collected experimental observations, some generalized conclusions that may set further tasks. The results obtained in the course of studying unexpected inversions are important contributions to the understanding of the mechanisms of the reactions studied and, more specifically, to the identification of the origin of chiral induction. Naturally, the rapid development of and the volume of data available on various reactions prevented us from a full discussion of all fields. On the other hand, in most cases, there is no opportunity—mainly due to considerations of size—to also include details published in easily accessible journals. For the same reason, the review of other important reactions (e.g., addition of organometallic reagents, polymerizations, asymmetric autocatalysis, etc.) was also omitted from the program; these could be treated at length on another occasion. The manuscript calls attention to the antecedents of the relevant reaction by citing a few characteristic publications and reviews. Comprehensive reviews have been published mainly with the aim of highlighting the possibility of novel syntheses that enable the preparation of both enantiomers with the help of the same chiral catalyst.[2–5] Although unexpected inversion has already been discussed in two short subsections in the reviews on heterogeneous catalytic enantioselective hydrogenations,[6] to our best knowledge similar chapters/subchapters are absent from the monographs and reviews addressing asymmetric organocatalytic and heterogeneous catalytic reactions.

This review gives insight into the homogeneous catalytic asymmetric reactions, the organocatalytic reactions, and the heterogeneous catalytic asymmetric reactions. The last part attempts to give a full account of unexpected inversions observed in the course of studies on heterogeneous metal catalytic enantioselective hydrogenations. Finally, after a critical analysis of the numerous experimental observations described, the review ends with the compilation of generalizable conclusions and the designation of further tasks. Findings and interpretation of unexpected inversion have provided important data with respect to the stereochemistry. It is my hope that the present review catalyze similar research.

2. Unexpected Inversions in Metal Complex Catalyzed Asymmetric Reactions

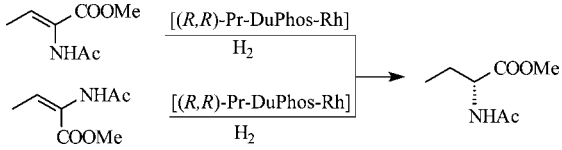
In asymmetric reactions/syntheses of this type, chiral induction is supplied by chiral molecules of natural origin (amino acids, carbohydrates, alkaloids) and their synthetic derivatives, or other synthetic chiral compounds. These chiral molecules participate in asymmetric syntheses as the ligands of metal complexes. The results obtained in the field of metal complex catalyzed reactions have been the subject of numerous monographs and reviews, which also give continuous account of the state of these highly significant syntheses (in addition to the well-known early works,[7–13] see, e.g., the reviews published in the past few years[14–16]).

As regards the stereochemical course of metal complex catalyzed reactions, experimental observations have already allowed the formulation of empirical rules for certain widely used chiral ligands. However, similar relationships have not been established for a large number of chiral ligands, since the principal aim in these instances is the optimization of the preparation of a given enantiomer in >90% ee. Perhaps the most important parameter of optimization is the input of the appropriate chiral ligand. Continuous completions and corrections of the rules of the stereochemistry are, therefore, not surprising.

2.1. Hydrogenation and Transfer Hydrogenation

Most of these methods were discovered by Kagan, Knowles, and Noyori.[17–19] Studies on the stereochemistry of homogeneous asymmetric reactions have taken their models from the hydrogenation and transfer hydrogenation of prochiral compounds with C=C bonds and prochiral ketones in the presence of Rh and Ru complexes. The large number

Scheme 1. Hydrogenation of *E* and *Z* Isomers over DuPhos-Rh Catalyst

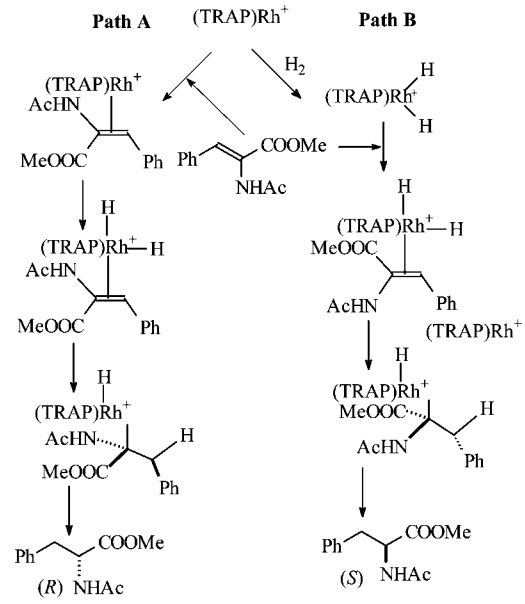


of studies allowed the establishment of certain empirical rules.[11–14] According to ref 14: (i) Remarkably, the DuPhos-Rh system provides excellent enantioselectivities for both *Z* and *E* isomeric substrates, and the hydrogenation products are formed with the same configuration (Scheme 1). (ii) An (*R,R*)-(*S,S*)-*i*-Bu-TRAP-Rh catalyst provides 96% ee for hydrogenation of a tetrahydropyrazine carboxamide derivative; interestingly, a related (*R,R*)-(*S,S*)-Me-TRAP-Rh catalyst provides the hydrogenation product with a different configuration (Scheme 2).[20b]

In the asymmetric catalytic hydrogenation of α-(acetamido) acrylates using chiral TRAP-Rh catalysts, remarkable effects of ligand P-substituent and hydrogen pressure were observed. Only a small change in the ligand P-substituent influenced the catalytic activity and enantioselectivity dramatically, indicating that a unique and efficient asymmetric environment is created around the metal center of TRAP-Rh complex. The most surprising unusual experimental observation made in studies on the hydrogenation of compounds containing prochiral C=C bonds[20,21] is the effect of hydrogen pressure on the sense of ED (Table 1).[21a]

The dramatic effect of hydrogen pressure may be explained on the basis of the assumption that the hydrogenation proceeds through two competitive pathways. Path **A** involves the coordination of olefin to complex followed by the oxidative addition of hydrogen, giving (*R*)-product preferentially. Path **B** involves the oxidative addition of hydrogen prior to the coordination of the C=C bond, favoring the formation of (*S*)-product. Decrease in the hydrogen pressure suppresses path **B**, because low hydrogen pressure is unfavorable for the oxidative addition of hydrogen (Scheme 3).[21a]

Scheme 3. Two Competitive Pathways in the Hydrogenation of Methyl 2-(Acetylamino)cinnamate Using TRAP-Rh Catalyst



In the same reaction in the presence of triethylamine, the (*S*)-BINAP-Ru complex promoted the formation of the (*S*)-product, whereas (*S*)-BINAP-Rh complex catalyzed that of the (*R*)-product in higher ee (84%).[21b] In contrast, the (*R*)-BINAP-Rh and (*R*)-BINAP-Ru complexes give the same result with the opposite product configuration (see, e.g., in ref 12, p 38). Today these results no more sound unusual, but in 1985 it could well be unexpected to obtain products of opposite configurations using the chiral ligand with the same configuration.

Burgess et al. synthesized novel iridium complexes and studied their effects in the asymmetric hydrogenation of

Scheme 2. Hydrogenation of a Tetrahydropyrazine Carboxamide Derivative

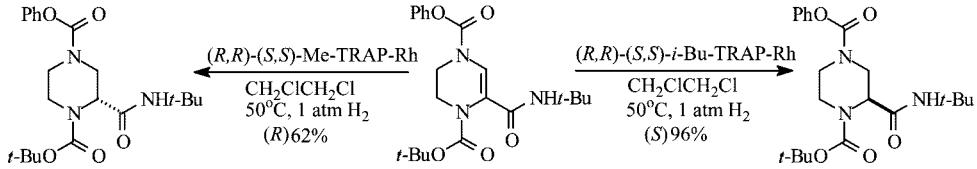
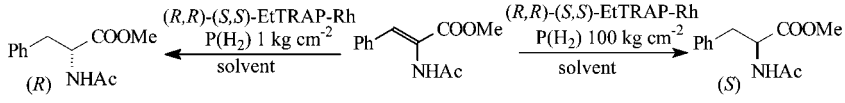
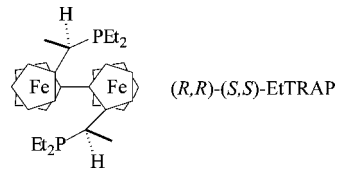


Table 1. Inversion in Hydrogenation of Dehydroamino Acid Esters



entry	ee (%)	conv. (%)	solvent	temp. (°C)	conv. (%)	ee (%)
1	36	100	DCM	15	100	77*[a]
2	64	100	DCM	30	100	69*
3	18	100	MeOH	30	100	79*



(*R,R*)-(*S,S*)-EtTRAP

[a] Unexpected inversion, marked with * in the manuscript.

Scheme 4. Inversion in Enantioselective Hydrogenation of 2-(4′-Methoxyphenyl)-but-1-ene

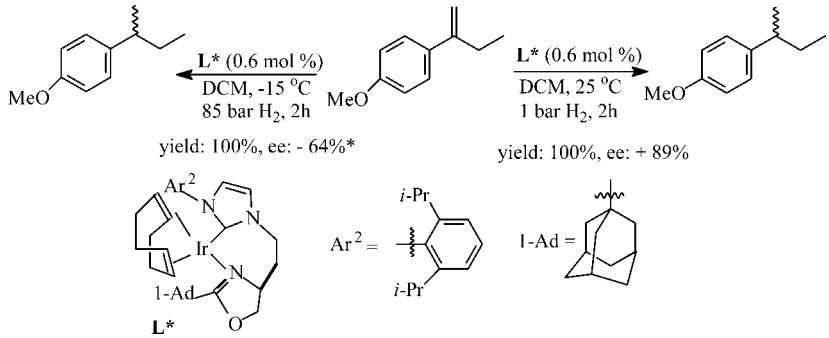
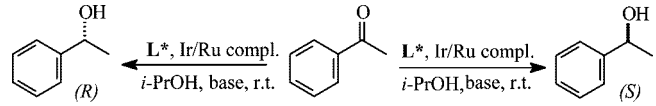
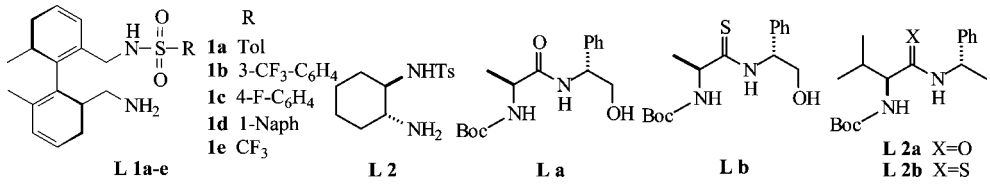


Table 2. Inversion in Transfer Hydrogenation of Acetophenone



entry	ee (%)	conv. (%)	L*	additive, Add/L	complex	L*	additive, Add/L	conv. (%)	ee (%)	ref
1	53	88	**L1a**	*i*-PrOK, 1	Ir(III)compl.	**L1a**	*i*-PrOK, 10	84	46*	22
2	65	92	**L1b**	*i*-PrOK, 1	Ir(III)compl.	**L1b**	*i*-PrOK, 10	83	48*	22
3	61	95	**L1c**	*i*-PrOK, 1	Ir(III)compl.	**L1c**	*i*-PrOK, 10	79	48*	22
4	53	93	**L1d**	*i*-PrOK, 1	Ir(III)compl.	**L1d**	*i*-PrOK, 10	86	49*	22
5	55	23	**L1e**	*i*-PrOK, 1	Ir(III)compl.	**L1e**	*i*-PrOK, 10	93	47*	22
6	95	78	**L2**	*i*-PrOK, 1	Ir(III)compl.					22
7	90	59	**L2**	*i*-PrOK, 10	Ir(III)compl.					22
8	20*	35	**Lb**	*i*-PrONa, 5	$[Ru(pcy)Cl_2]_2$	**La**	*i*-PrONa, 5	83	92	23a
9	81*	49	**L2b**	*i*-PrONa, 5	$[Ru(pcy)Cl_2]_2$	**L2a**	*i*-PrONa, 5	5	0	23a
10	92*	57	**L2b**	*i*-PrONa, 10 LiCl, 10	$[Ru(pcy)Cl_2]_2$					23a
11	95*	88	**L2b**	*i*-PrONa, 5 LiCl, 5	$[RhCl_2$ cp]					23a



arylalkenes. The most striking[21c] of the numerous experimental results obtained under high-pressure/low-temperature or high-temperature/low-pressure conditions are shown in Scheme 4.

The authors interpret their results according to ref 21a, emphasizing that this unexpected observation implies that it is of a steric, rather than an electronic, origin. Deuterium-labeling experiments provide evidence for other types of competing mechanisms that lead to D incorporation at positions that do not correspond to direct addition to the double bond.[21c]

In the field of transfer hydrogenation, experimental observations of unexpected inversion are also found in the literature, two examples of which are presented in Table 2.

Monosulfonated diamines, with an axially chiral biaryl backbone in combination with different Ir(III) complexes, were investigated in the catalytic transfer hydrogenation of acetophenone under *i*-PrOH/*i*-PrOK conditions (entries 1−5). The resulting catalysts showed an unexpected base-dependent enantioselectivity. Less base than chiral catalyst resulted in a (*R*)-secondary alcohol; excess of base gave the (*S*)-enantiomer.[22] By altering the amount of base, the authors were able to influence not only the activity but also the enantioselectivity of the reaction. With a small increase from 0.6 to 1.4 equiv, the ee changed from 82% (*R*) to 49% (*S*). This very unusual finding was observed with all ligands **1a**−**e**, but not with ligand **2** (entries 6 and 7).[22] The authors assumed that the availability of the binding sites at different pH levels may play a crucial role in this change of mechanism. However, the structures of the two catalysts at low and high base concentrations have not been published since then.

The other example for unexpected inversion (entries 8−11) is a consequence of a subtle change in the structure of the chiral ligand.[23a] A change in the ligand structure, namely, replacement of the amide oxygen in Boc-protected amino acid amides by sulfur **La** → **Lb**, **L2a** → **L2b**, and modification of the catalytic system with a lithium salt, lead to a novel and most efficient class of Ru and Rh catalysts for the asymmetric transfer hydrogenation of aromatic ketones in propan-2-ol. In addition, the replacement of the amide functionality for the corresponding thioamide resulted in a dramatic switch of the product enantioselectivity. Under optimized conditions, the secondary alcohol products were obtained in high yield and enantioselectivity (up to 97% ee) using only 0.25 mol % catalyst loading. The authors also confirmed the phenomenon in substituted acetophenones.[23]

The switch of the sign of enantioselectivity on going from amides to the appropriate thioamides may arise from

a different mode of coordination due to significant differences in the acidity of the NH functions in amides and carbamates relative to those in thioamides. In their recent reports published in this field, however, they supply no evidence supporting the interpretation of the phenomenon discovered.[23b,c]

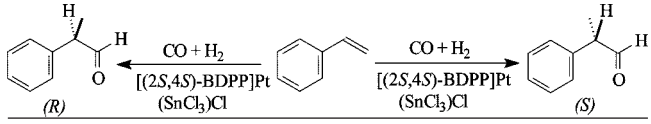
2.2. Asymmetric Hydroformylation

Although evidence on the stereochemistry of hydroformylation was already available at the beginning of the 1980s,[24] the formulation of relationships depending on the absolute configuration of the chiral ligand requires further experiments.[25] Consiglio and Pino performed asymmetric hydroformylation of butene isomers under identical experimental conditions and observed ED sense inversion depending on the structure of the butenes involved.[24] Inversion was not unexpected, since the reactions of but-1-ene, (*E*)-but-2-ene, and (*Z*)-but-2-ene exhibit different stereochemistries due to the excessive differences between the steric structures of these compounds. Table 3, however, shows unexpected inversion depending on the temperature in the presence of the same Pt complexes.[26,27]

Kollár et al. and later Hanson and co-workers reported a very interesting Pt-catalyzed hydroformylation of styrene in which a change from (*S*)- to (*R*)-enantioselectivity was seen as a function of temperature: catalysis by [(2*S*,4*S*)-BDPP]-Pt($SnCl_3$)Cl gave the branched aldehyde with 63% ee (*S*) at 40 °C but 17% ee (*R*) at 100 °C.[26]

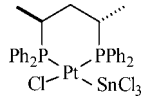
Kollár et al. proposed that the reversal of enantioselectivity might be due to a temperature-dependent change in the conformation of the catalyst's six-membered chelate ring. It is more likely, however, that the enantioselectivity-determining step changed with temperature.[27] Casey et al. have reported deuterioformylation studies and the CO and H_2 pressure dependence of ee, which show that, at low temperature, enantioselectivity is set by largely irreversible platinum hydride addition to styrene. At high temperature, in contrast, platinum hydride addition is reversible and enantioselectivity is set by a combination of partially reversible alkyl migration to CO and hydrogenolysis of the platinum acyl intermediate. The explanation as to why the selectivity-determining step changes as a function of temperature is based on a detailed analysis of reaction kinetic data obtained at various temperatures.[27]

Table 3. Inversion in Hydroformylation of Styrene



entry	ee (%)	yield (%)	temp. (°C)	CO (psi)	H_2 (psi)	n/i[a]	yield (%)	ee (%)	ref
1			50	580	580		20	63	26
2	17*	18	100	580	580				26
3			40	500	500	2.2	19	60	27
4	10*	3	100	500	500	2.4			27

[a] n/i = normal aldehyde/isoaldehyde.



2.3. Asymmetric Oxidations

2.3.1. Sharpless Asymmetric Epoxidation

Scheme 5 represents the experimentally verified basic scheme of the stereochemical course of enantioselective oxidation in the presence of (*R*,*R*)-DMT and (*S*,*S*)-DMT, in the case of the widely investigated model compound *trans*-hex-2-en-1-ol.

In 1980 Sharpless and Katsuki achieved the enantioselective epoxidation of primary allylic alcohols.[28] The details of the oxidation are also summarized in some of the pertinent reviews.[12,29] According to Scheme 5 in the case of (*R*,*R*)-DMT as ligand, the product formed in excess is the (2*S*,3*S*)-epoxide, whereas in the case of (*S*,*S*)-DMT as ligand, it is the compound with the opposite absolute configuration, (2*R*,3*R*)-epoxide.[30a]

According to experiments reported in 2002, in the presence of soluble polymer-supported tartrate ester ligands, the reaction surprisingly exhibited a stereochemistry of the opposite direction, depending on the molecular weight of the polyethylene glycol monomethyl ether (MPEG), under otherwise identical experimental conditions (Table 4, entries 2 and 3).[30b] Janda et al. investigated this fascinating effect in more detail (Table 4, entries 4−14).[31]

The results have clarified that the enantioselectivity of this reaction can be reproducibly reversed solely as a function of the molecular weight of the appended PEG.[31] By preparing a range of tartrate ligands with varying PEG chains lengths, the reversal was found to occur within a molecular weight change of only 800. As the PEG chain did not affect the inherent chirality of the ligand, the enantioreversal was proposed to occur as a result of two Ti-ligand complexes that differ in their molecularity of ligand, one monomeric in ligand and the other dimeric. These investigations into the nature of Sharpless asymmetric epoxidations catalyzed by MPEG tartrate esters have revealed several interesting details regarding the mechanism of catalysis.[31]

2.3.2. Asymmetric Oxidation of Sulfides

Unexpected inversion was observed in the course of the oxidation of sulfides over Ti-complex catalysts containing chiral (*R*,*R*)-*p*,*p*′-disubstituted 1,2-diphenylethane-1,2-diol ligands (Table 5).[32a] The use of the *p*-CF_3 substituted **L*** dramatically decreased the ee (entry 4) and, unexpecedly, gave the *p*-tolyl methyl sulfoxide with opposite stereochemistry (*R*) with respect to those obtained with other diols (entries 1 and 3). According to the authors, **L*** containing coordinating moieties (OMe and CF_3) can lead to the formation of different Ti complexes with different structures and, consequently, with new reactivities and opposite senses of ED.

The formation of (*R*)-sulfoxide may be regarded as unexpected, since the configurations of **L*** are identical.

Scheme 5. Stereochemistry of the Sharpless Asymmetric Epoxidation

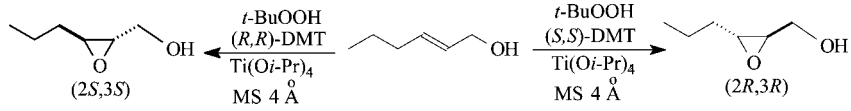
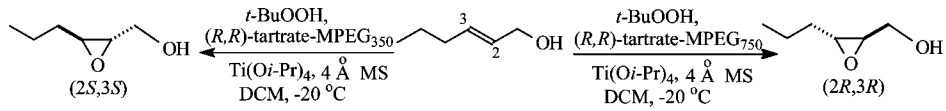


Table 4. Inversion in the Sharpless Asymmetric Epoxidation



entry	ee (%)	yield (%)	ligand	yield (%)	ee (%)	ref
1	85	94	(*R*,*R*)-DMT			30b
2	70	81	(*R*,*R*)-TA-MPEG$_{750}$			30b
3			(*R*,*R*)-TA-MPEG$_{2000}$	85	93*	30b
4			(*R*,*R*)-TA-MPEG$_{2000}$	54	75*	31
5			(*R*,*R*)-TA-MPEG$_{750}$	66	67*	31
6			(*R*,*R*)-TA-MPEG$_{550}$	85	8*	31
7	75	95	(*R*,*R*)-TA-MPEG$_{350}$			31
8	80	93	(*R*,*R*)-TA-MPEG$_{207}$			31
9	89	83	(*R*,*R*)-TA-MPEG$_{163}$			31
10	85	72	(*R*,*R*)-TA-MPEG$_{119}$			31
11	93	75	(*R*,*R*)-TA-MPEG$_{75}$			31
12	78	63	(*S*,*S*)-TA-MPEG$_{2000}$			31
13	96	96	(*R*,*R*)-DIPT			31
14	96	87	(*R*,*R*)-DIPT + MPEG$_{2000}$			31

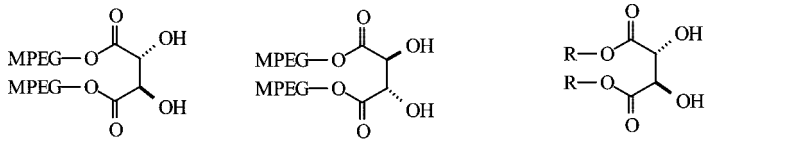
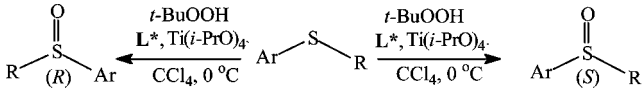
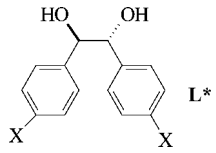


Table 5. Inversion in Oxidation of Sulfides



entry	ee (%)	yield (%)	Ar	R	X	yield (%)	ee (%)
1			*p*-tolyl	Me	H	62	80
2			Ph	Bn	H	73	99
3	26*	70	*p*-tolyl	Me	CF_3		
4			Ph	Bn	CF_3	80	18



Similar observations have been reported by other laboratories in the oxidation of sulfides in the presence of **L***[32b] of similar structures and (*R*)-BINOL.[32c]

2.4. Asymmetric Alkylations

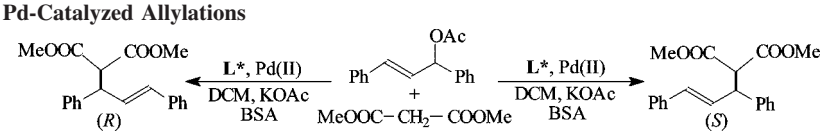
This subsection enumerates examples for allylation and Friedel−Crafts alkylation. The Pd(0)-catalyzed allylation developed by Trost and Tsuji is useful for creating organic frameworks that have a variety of polar functional groups.[33] The reaction is formally viewed as a combination of an allylic cation and a carbanion. Further results are summarized in reviews.[8–11,34] Two examples for unexpected inversion are presented below.

The effectiveness of the chiral chelate nitrogen−phosphorus ligands derived from (*S*)-valine was investigated by Anderson et al.[35a] using the standard palladium catalyzed substitution of 1,3-diphenyl-2-propenyl acetate with dimethylmalonate (Table 6, entries 1 and 2). Two common procedures were used that involved either the generation of the nucleophile in situ, using dimethyl malonate and BSA with catalytic potassium acetate in DCM, or the use of preformed nucleophile, sodium dimethyl malonate in tetrahydrofuran (THF). The palladium catalyst was formed by mixing the allyl palladium chloride dimer with 2 molar equivalents of the chiral ligand.

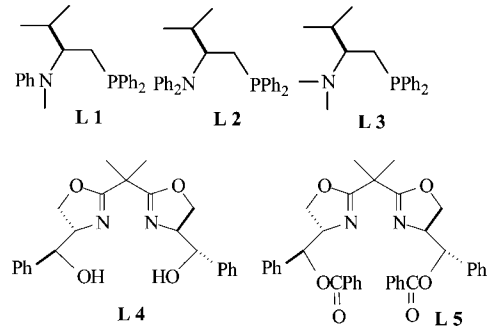
According to the authors, it is striking that, despite each ligand possessing identical backbone chirality, ligand **L1** gives (*S*)-enantiomer in excess while ligands **L2** and **L3** both give (*R*)-enantiomer in excess under each of the reaction conditions. To offer a hypothesis for the dramatic reversal of enantioselection, the authors examined the possible conformation of the allyl intermediates for this reaction, which could lead to the observed enantiomers of the product (Figure 1).

Pd-catalyzed allylic alkylations of the rac-1,3-diphenyl-2-propenyl esters with the dimethyl malonate nucleophile using carbohydrate bidentate phosphinites[35b] and various chiral mono- and bis(oxazoline) ligands also were studied.[36,37] Hoarau et al. have discovered an example of asymmetric synthesis leading to the formation of (*S*) or (*R*) isomers, both in high ee (92% and 90%, respectively) by using an enantiogenic catalyst based on ligand **L4** or **L5** characterized by the same chiral backbone and configuration (Table 6, entry 3). It was demonstrated that this shift in the control of the ED was due to the presence of a hydroxy group on the side chain. Since the configurations of the chiral C atoms in the ligands **L4** and **L5** are identical, formation of the (*R*)-product of the opposite configuration by the effect of **L5** can be regarded as unexpected inversion. The direction of the nucleophilic attack and, consequently, the absolute configuration of the product formed are determined by the structure of the ICs, which in turn depends on **L*** (Scheme 6).[36b] The stuctures of ICs were determined by XRD.

Table 6. Inversion in the Pd-Catalyzed Allylations



entry	ee (%)	yield (%)	L*	catalyst	temp. (°C)	L*	yield (%)	ee (%)	ref
1	80	96	**L2**	Pd(II)	r.t.	**L1**	94	83*	35a
2	60	93	**L3**	Pd(II)	r.t.	**L1**	94	83*	35a
3	90*	98	**L5**	Pd(II)	26	**L4**	98	92	36a



Other studies also confirmed allylations exhibiting unexpected stereochemistries: (i) *O*-allylations of phenols[38a] using chiral *P*,*N*-heterodonor ligands; (ii) *C*-allylation[38b] using chiral *P*,*S*-heterodonor ligands with a binaphthalene framework; and (iii) *N*-allylation[38c] with novel metallocene-based planar chiral diphosphine ligands.

Tang and co-workers observed dramatic solvent effects in the highly enantioselective alkylation of indoles with alkylidene malonates using novel trisoxazoline−Cu(II) complexes as catalysts (Scheme 7).[39]

The use of alcohols as the solvents not only accelerates the reaction dramatically but also improves the ee. Strongly

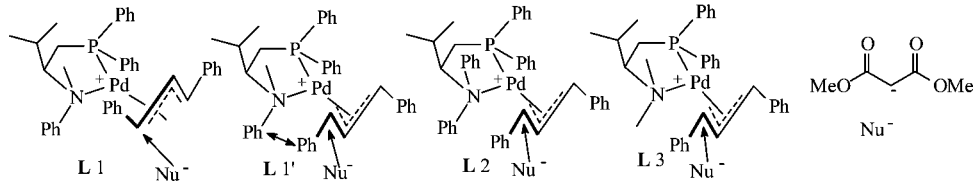
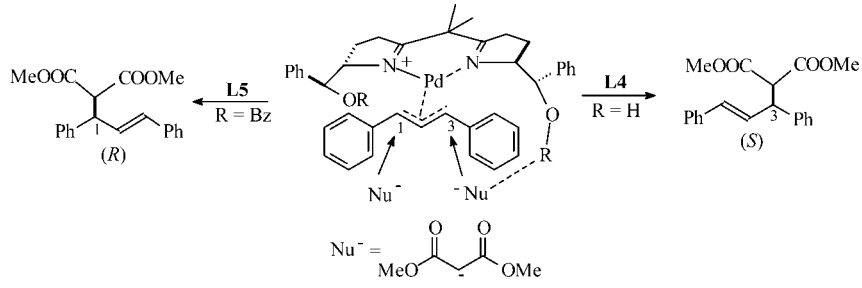
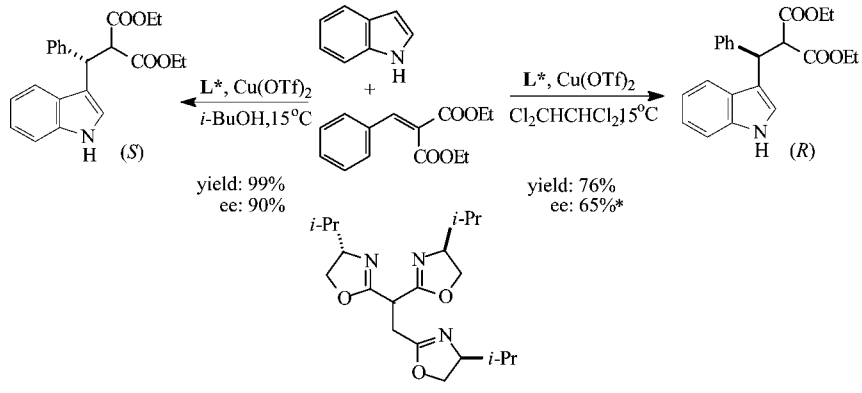


Figure 1. Possible intermediate π-allyl Pd complexes.

Scheme 6. Inversion in the Nucleophilic Attack Caused by the OH−Nu Hydrogen Bonding



Scheme 7. Inversion in the Friedel−Crafts Alkylation



coordinating solvents (e.g., alcohols) gave the product with (*S*) configuration, while weakly coordinating solvents afforded the product with the opposite configuration. It was postulated that the reversal of enantioselectivity resulted from the change of the coordination geometry of copper center in different solvents.[39] Although the attempt to develop single crystals of trisoxazoline−Cu(II) was unsuccessful, the authors could support the hypothesis by the preparation of (*R*)- and (*S*)-products and their further investigations by ^{1}H NMR and in situ spectroscopic methods (see Schemes 6−10 and Figure 1 in ref 39).

2.5. Asymmetric Aldol and Related Additions

The aldol addition is one of the most important asymmetric syntheses of carbon−carbon bonds with new chiral centers.[7,11–13] This subsection describes three examples of aldol additions that can be classified as unexpected inversions. According to Table 7, in the presence of **L1** and **L2** 1,2-diamines as ligands, the Mukaiyama-type aldol reaction yields products with opposite absolute configurations in high ee.[40]

Both diamines **L1** and **L2** were prepared from L-proline, and the absolute configuration of the C2 is *S* in both cases. The difference is the fusion point of the benzene ring connected to the piperidine moiety. It was surprising that the slight difference in the structure of the chiral sources completely reversed the enantiofacial selectivity. In addition to the unique selectivities, the reaction provides convenient methods for the preparation of both enantiomers of *syn*-2,3-dihydroxy thioesters. As shown in Table 7, adducts with the 2*S*,3*R* configuration were obtained by chiral diamine **L1**, while adducts with the 2*R*,3*S* configuration were produced by chiral diamine **L2**. In every case, the selectivities were very high; almost complete *syn* selectivities and more than 98% ee of the *syn* adducts were obtained.[40]

In order to clarify the origin of the selectivities, the structures of the tin(II) triflate−chiral diamine complexes were examined. A possible explanation for the stereoselectivity is the formation of bicyclic tin(II) intermediates of different conformations (Figure 2). In chiral diamine **L1**, the **L1**−Sn(II) conformation is favored; on the other hand, in chiral diamine **L2**, the **L2**−Sn(II) conformation is preferred, which was supported by nuclear Overhauser effect (NOE) experiments.

In another selected example, Trost et al. reported dramatic reversal of ED due to a temperature-dependence effect in the asymmetric aldol addition of methyl ynones to pyruvaldehyde ketals in the course of the optimization studies (Table 8).[41]

According to the authors' opinion, the experimental data clearly suggest that dinuclear Zn catalytic species are formed as the reaction progresses (Table 8). The recognition of enantioselective autoinduction by the authors may prove to have important implications on related systems.[41]

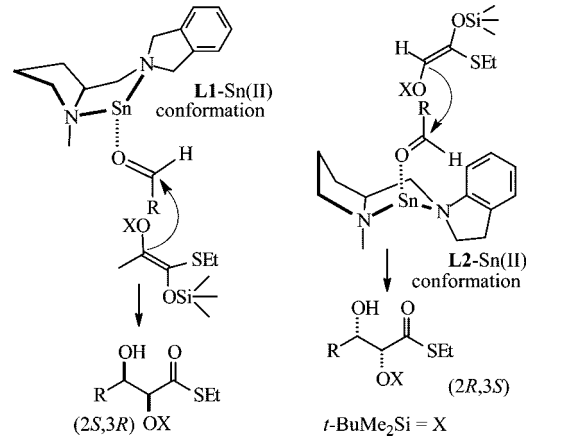
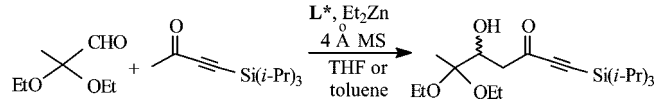


Figure 2. Assumed intermediate complexes in aldol reaction.

Table 8. Inversion in Aldol Addition of Methyl Ynones



entry	time (h)	solvent	temp. (°C)	yield (%)	ee (%)
1	4	toluene	0	63	44 (+)
2	4	toluene	−25	27	72* (−)
3	7	THF	0	61	83 (+)
4	2	THF	−25	nd	69* (−)

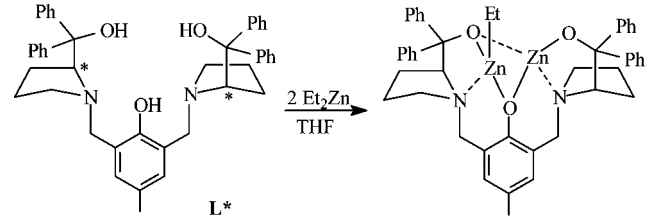
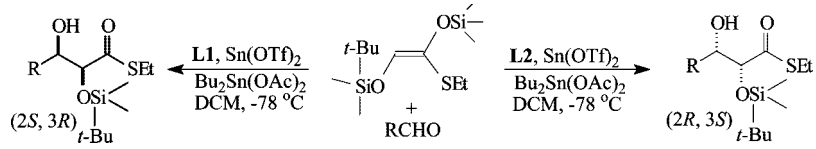
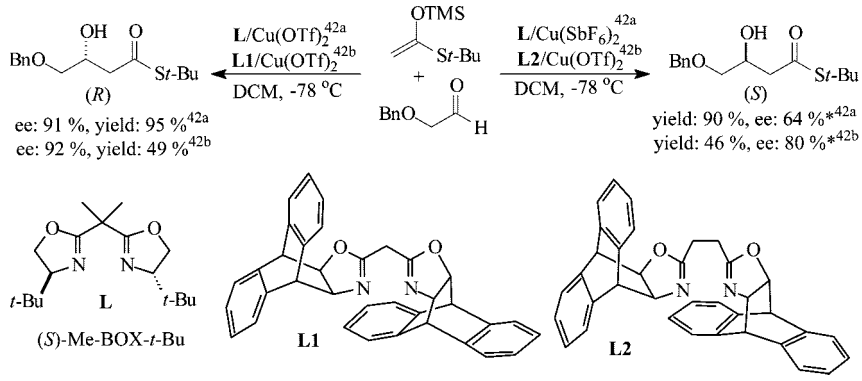


Table 7. Inversion in the Mukaiyama Aldol Addition



entry	ee (%)	yield (%)	R	yield (%)	ee (%)
1	98	86	Ph	82	98*
2	98	61	Et	63	98*
3	98	74	MeCH=CH	81	98*
4	99	71	PhCH=CH	80	98*
5	97	86	2-furyl	86	99*
6	96	86	MeCH=CHCH=CH	78	99*

Scheme 8. Inversion in Aldol Reaction with Trimethylsilyl Thioenolates



Unexpected inversions were also observed by Evans et al.[42a] and by Kunieda and co-workers[42b] in the aldol reaction with trimethylsilyl thioenolate as a competent aldol reagent catalyzed by chiral bis(oxazoline)−Cu(II) complexes (Scheme 8). The inversion was observed using PyBOX ligands, too.

In order to characterize the structure of ICs and to interpret the experimental observations, Evans et al. applied various methods to study the effect of BOX−Cu complexes,[42a,c] often tested previously in other reactions. In these studies, unexpected inversion occurred in the presence of catalysts consisting of ligands of identical configuration and structure and of identical metal ions; the only difference is in counterion composition (SbF_6^-, TfO^-) (see section 2.7 for details).

Kunieda et al.[42b] have described a new class of sterically congested and conformationally rigid chiral bis(oxazoline) ligands with methylene and ethylene spacers between the oxazoline rings, from which the derived $Cu(OTf)_2$ complexes serve as catalysts in asymmetric aldol reactions, resulting in the reversal of ee, depending on six- and seven-membered chelate sizes. The difference between the structures of the two ligands lies in the methylene and ethylene spacers; still the inversion can be regarded as unexpected, because the configurations of the chiral carbon atoms of the ligands are identical. The experimental antecedents, however, pointed to the key role of stereochemistry, namely, the length of the spacer between the oxazoline rings.

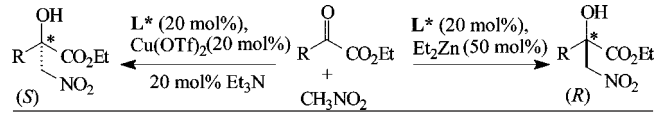
2.6. Other Asymmetric Carbon−Carbon Coupling Reactions

2.6.1. Asymmetric Henry Reaction

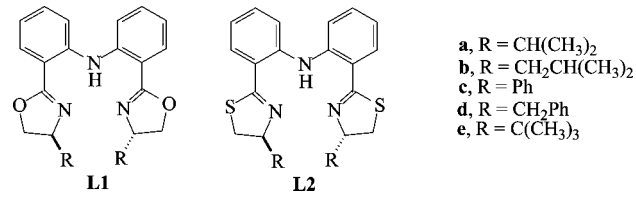
The Henry reaction is a C−C coupling reaction between a nitroalkane and a carbonyl compound.[13,43] β-Nitro alcohols can be produced by this reaction. Unexpected inversion of ED in asymmetric Henry reaction was achieved with the same chiral ligand by changing the Lewis acid center from Cu(II) to Zn(II)[44] (Table 9). In the course of their earlier experiments, the authors demonstrated that, in the presence of **L1**−Cu(II) and **L2**−Cu(II) complexes, the (*S*)-products are formed in higher ee.[44a] In the presence of the same **L1**− and **L2**−BOX ligands, under identical experimental conditions and using the same reactant, but under the effect of Et_2Zn, the (*R*)-products are found to be formed in higher ee.[44b] In both cases, ee values are up to 70−80%.

The various studies and data of literature show that the NH groups in ligands play a very significant role in controlling both the yields and ED of the Henry products. The authors assumed intermediate **B** for the **L***−Cu(II) complex catalyzed reaction and presumed intermediate **C** in Et_2Zn catalytic system (Figure 3).[44b] According to Figure 3, in the case of Cu(II)-catalyst, the α-keto ester is activated by Cu(II) and the nitronate is oriented by hydrogen bond (**B** IC); therefore, the reaction takes place from the *Si*-face. In the case of Et_2Zn, a dinuclear Zn catalyst forms. Nitronate is oriented by two Zn atoms (**C** IC): the reaction proceeds from the *Re*-face.

Table 9. Inversion in the Henry Reaction



entry	ee (%)	yield (%)	R	L*	solvent	yield (%)	ee (%)
1	50	90	Me	**L1a**	THF	80	77*
2	39	54	Me	**L1c**	THF	73	47*
3	47	76	Me	**L2a**	THF	56	38*
4	63	30	Me	**L2c**	THF	25	6*
5			Me	**L1d**	hexane	97	84*
6	70	55	Me	**L1e**			
7			Bu	**L1d**	hexane	92	82
8			$Ph(CH_2)_2$	**L1d**	hexane	95	71



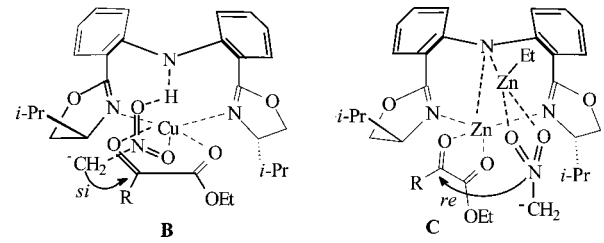
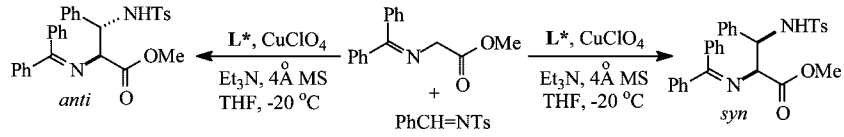


Figure 3. Assumed intermediate Cu(II)- and Zn(II)-complexes in asymmetric Henry reaction.

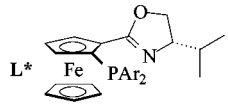
2.6.2. Asymmetric Mannich Reaction

The Mannich-type reactions are important and useful synthetic methods for the construction of nitrogen-containing molecules.[45] The Mannich reaction was also utilized in asymmetric homogeneous catalyzed reactions between glycine derivatives and imines. Unexpected inversion observed in a reaction of this type is presented in Table 10.[46]

Table 10. Inversion in the Mannich-type Reaction



entry	ee (%)	yield (%)	*anti/syn*	L*	L*	*syn/anti*	yield (%)	ee (%)
1	97	97	85/15	**L1**	**L3**	91/9	89	99*
2	99	96	88/12	**L2**	**L4**	91/9	96	96*
3	99	93	92/8	**L1**[a]	**L3**			
4	99	92	96/4	**L2**[a]	**L4**[a]	95/5	97	99*



L1, Ar = Ph
L2, Ar = 4-MeOC$_6$H$_4$
L3, Ar = 3,5-diCF$_3$C$_6$H$_3$
L4, Ar = 3,5-diF-C$_6$H$_3$

[a] −78 °C.

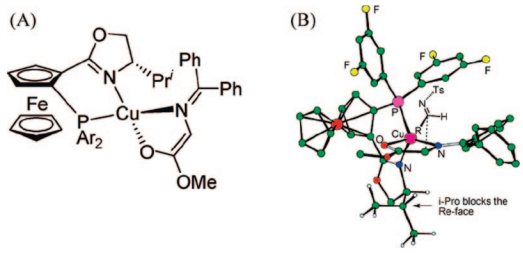


Figure 4. Calculated structures of intermediate complexes in an enantioselective Mannich reaction.

The change in the sense of diastereoselectivity elicited by the ligand of identical configuration under nearly identical conditions can be regarded as unexpected. The inversion can be attributed to a change in the electronic factor of the ligands. **L1** and, furthermore, the **L2** ligands containing an electron-donating methoxy group mainly catalyze the formation of *anti*-product, whereas ligands **L3** and **L4** having electron-withdrawing CF_3 and F groups promote the formation of *syn*-product.[46]

The stereochemistry can be understood based on the fact that the *Re*-face is blocked by the *i*-Pr group of the ligand (Figure 4B). A working model is proposed by the authors to correlate the observed stereochemistry. Imine approaches the C_a anion center in a staggered conformation with the N atom pointing to Cu. The Ts group occupies the valley formed by the two arene groups if the two rings are electron-deficient in ligand **L4**, giving a (2*S*,3*R*) product (*Si*-face for imine). The imine attacks the C_a with its *Re*-face when the arene rings are electron-rich in ligand **L2**.

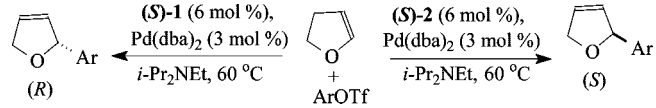
2.6.3. Asymmetric Heck Reaction

The antecedents of the asymmetric Heck reaction have been reviewed.[47] In 2008, two studies reporting on dramatic stereo- and enantiodivergency in the intramolecular asymmetric Heck reaction were published. The results reported in ref 48a are shown in Table 11.

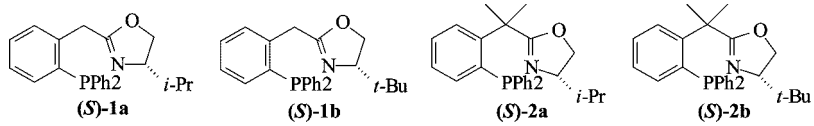
According to experimental data in Table 11, a dramatic switch in ED is realized using **(*S*)-1** or **(*S*)-2** ligands (with H or with methyl as substituents). In the case of **(*S*)-1** ligands, (*R*)-products were formed, while using **(*S*)-2** ligands, (*S*)-products were formed. X-ray analysis of **(*S*)-1a**−$PdCl_2$ and **(*S*)-2a**−$PdCl_2$ complexes as well as density functional calculations on the stereochemistry and mechanism provide a rational explanation for these interesting observations. Ligands **S1** and **S2** coordinate with Pd in *syn* and *anti* seven-membered-ring conformations, respectively; due to the stronger *trans* effect of P over N, the Pd-bound phenyl group prefers *trans* to P in the transition state so that it is more activated with a lower barrier for addition to Pd-coordinated 2,3-dihydrofuran substrate; because of the unsymmetrical environment caused by the two phenyl groups on P, the *trans-syn-Si* and the *trans-anti-Re* transition states are more favorable than others (Figure 5).[48a]

In the other article,[48b] Rubina et al. described the effect of the novel PHOX ligands with rigid chiral cyclopropyl backbones outlined in Figure 6 on the stereochemistry of the Heck reaction. They obtained unexpected inversion similar to that shown in Table 11. The new observations of

Table 11. Inversion in Intermolecular Heck Reaction



entry	ee (%)	yield (%)	L*	Ar	L*	yield (%)	ee (%)
1	78	62	**(*S*)-1a**	Ph	**(*S*)-2a**	86	81*
2	93	79	**(*S*)-1b**	Ph	**(*S*)-2b**	78	10*
3	87	66	**(*S*)-1b**	*p*-F−C_6H_4	**(*S*)-2a**	83	87*



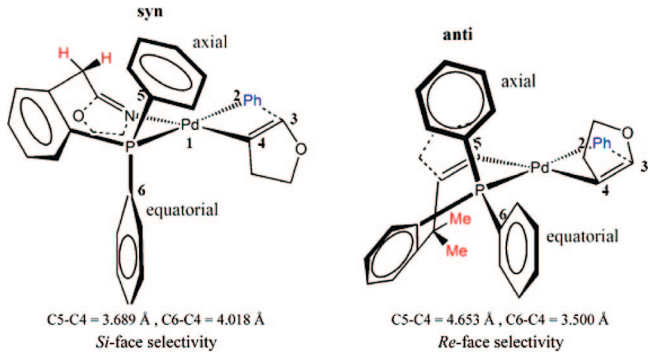


Figure 5. *syn*-Conformation **(*S*)-1a**−Pd and the *anti*-conformation **(*S*)-2a**−Pd intermediate complexes in the Heck reaction.

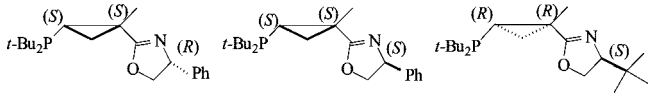


Figure 6. Novel PHOX ligands with a chiral cyclopropyl backbone in the Heck reaction.

each of these reports[48a,b] significantly enriched our knowledge of the asymmetric Heck reaction.[49]

In addition to the reactions described in section 2.6, unexpected inversions have also been observed in other carbon−carbon coupling reactions (Wittig reaction,[50] cyanosilylations[51]).

2.7. Homogeneous Catalyzed Asymmetric Cycloaddition Reactions

In this chapter, examples of unexpected inversion observed in Diels−Alder (DA) reactions, 1,3-dipolar cycloadditions, and one [3 + 2]-cycloaddition are reviewed.

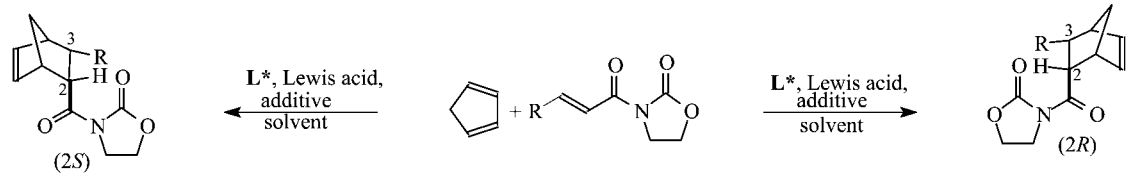
2.7.1. Diels−Alder Addition

Among homogeneous catalyzed asymmetric reactions, the DA reaction, a test reaction widely studied (especially with BOX chiral ligands), is the one suitable for an attempt of drawing conclusions based on the analysis/evaluation of the unexpected experimental results recorded.[14,52] A characteristic set of unexpected experimental observations on C_2-symmetrical bis(oxazoline)−Lewis acid complexes (BOX-complexes) are summarized in Table 12. Among various chiral Lewis acid catalysts, those containing the chiral BOX ligands have proven useful in many applications since the pioneering work of Corey and Evans.[53a,b]

The recently published review on the diverse stereochemistry of the DA reaction[52g] offers, among others, the following highlights: (i) The chiral C_2-symmetric bis(oxazoline)−Lewis acid complexes coordinate dienophiles, which react easily and enantioselectively with dienes. (ii) It appears that the stereochemistry of the reaction is affected by the substituents of BOX and their configurations, the coordination geometry of metal cations, counterions, additives, solvents, immobilizations, and experimental conditions. (iii) The 3D structure of the catalyst complex is formed by Lewis acids and BOX ligands. (iv) ICs containing readily dissociating (noncoordinating, like SbF_6^- or ClO_4^-) anions usually have tetrahedral structure, whereas the structure of those containing coordinating TfO^- anions is usually octahedral. (v) For example, in the case of (*R*)-Me-BOX-Ph-Mg(II) complexes if ICs with tetrahedral structure favor the formation of (*S*)-DA products, then ICs with octahedral structure will favor the formation of (*R*)-DA products. (vi) When several chiral centers were present in a Ph-BOX ligand, their configuration had a dramatic influence on enantioselectivity.

The first observation of unexpected inversion in the DA reaction was reported by Kobayashi et al.[54a,b] The chiral catalyst obtained from the Lewis acid $Yb(OTf)_3$, (*R*)-BINOL,

Table 12. Inversion in the Diels−Alder Reaction



1 Entry	2 ee (*S* %)	3 Conv. (%)	4 Time	5 Lewis acid	6 Additive Solvent	7 R	8 L*	9 °C	10 Lewis acid	11 Additive Solvent	12 Time	13 Conv. (%)	14 ee (*R* %)	15 Ref.
1	93	77		$Yb(OTf)_3$		Me	R-BINOL	-50	$Yb(OTf)_3$			83	81*	54
2	72	100	18 h	$Mg(ClO_4)_2$	DCM	H	(*R*)-Me-BOX-Ph	-50	$Mg(ClO_4)_2$	2MeOH, DCM	18 h	100	44*	55a
3	30	100	18 h	$Mg(ClO_4)_2$	DCM	H	(*R,S*)-Me-BOX-Ph	-50	$Mg(ClO_4)_2$	2MeOH, DCM	18 h	100	78*	55a
4	94	100	18 h	$Mg(ClO_4)_2$	DCM	H	(*R,R*)-Me-BOX-Ph	-50	$Mg(ClO_4)_2$	2MeOH, DCM	18 h	100	76*	55a
5	72	100	12 h	$Mg(ClO_4)_2$	DCM	H	(*R*)-Me-BOX-Ph	-50	$Mg(OTf)_2$	DCM	12 h	100	88*	55b
5a	30	92	1 h	$Cu(OTf)_2$	DCM	H	(*S*)-Me-BOX-Ph	-78						59a
6						H	(*R*)-Me-BOX-Ph	-50	$Mg(OTf)_2$	H_2O, DCM	12 h	100	86*	55b
7						H	(*R,S*)-Me-BOX-Ph	-50	$Mg(OTf)_2$	DCM	12 h	100	93*	55b
8	94	100	12 h	$Mg(ClO_4)_2$	DCM	H	(*R,R*)-Me-BOX-Ph	-50	$Mg(OTf)_2$	DCM	18 h	100	60*	55b
9	62	100	1 h	$Mg(ClO_4)_2$	DCM	H	(*S*)-Me-BOX-Ph	20	$Mg(ClO_4)_2$	IL [a]	2 min	100	79*	56
10	22	100	1 h	$Mg(OTf)_2$	Et_2O	H	(*S*)-Me-BOX-Ph	20	$Mg(OTf)_2$	Et_2O, SILC[b]	1 h	100	67*	56
11	51	100	1 h	$Mg(OTf)_2$	DCM	H	(*S*)-Me-BOX-Ph	20	$Mg(OTf)_2$	IL [a]	2 min	100	79*	56
12	20	100	2 min	$Cu(OTf)_2$	IL [a]	H	(*S*)-Me-BOX-Ph	20	$Cu(OTf)_2$	DCM	1 h	100	15*	56
13	90	100	2 min	$Cu(OTf)_2$	IL[a]	H	(*S*)-Me-BOX-*t*-Bu	20						56
14	20	100	40 min	$Cu(OTf)_2$	DCM, Hom.	H	(*S*)-H-BOX-Ph	-30	$Cu(OTf)_2$	DCM, Het.		100	33*	57a
15	15	100	22 h	$Cu(OTf)_2$	DCM, Hom.	Me	(*S*)-Me-BOX-Ph	20	$Cu(OTf)_2$	DCM, Het.	22 h	100	31*	58
16	98	100	20 h	$Cu(SbF_6)_2$	DCM	Me	(*S*)-Me-BOX-*t*-Bu	-15						59a
17						Me	(*S*)-Me-BOX-Ph	25	$Zn(SbF_6)_2$	DCM	8 h	100	64*	59a

[a] IL: 1-ethyl-3-methylimidazolium bis[(trifluoromethanesulfonyl)imide]. [b] SILC: silica supported ionic liquid phase catalyst. [c] Configuration refers to the stereogenic center indicated by the *. L*: see Figure 8; mainly endo additions occur.

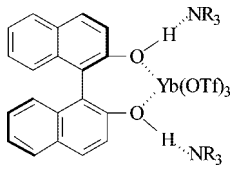


Figure 7. Kobayashi BINOL Lewis acid catalyst in the Diels−Alder reaction.

and a tertiary amine catalyzes the formation of the (*R*) and (*S*) enantiomers in high enantioselectivity by the effect of and depending on various achiral additives, under otherwise identical conditions[54a] (Table 12, entry 1). The inversion is strongly dependent on the specific coordination number of $Yb(OTf)_3$. The structure of the chiral catalyst proposed by the authors is shown in Figure 7. Two years later, Ghosh et al. confirmed the same result using chiral BOX−Lewis acid catalysts.[54c]

BOX−magnesium perchlorate and magnesium triflate chiral catalysts (Table 12) have also been successfully applied in the DA reaction.[55] Catalysts containing magnesium perchlorate used in conjunction with any of the three (*R*)-MeBOX-Ph ligands studied (Figure 8) yielded the (*S*)-product in different ee values in the absence of H_2O and ROH. When 2 equiv of OH-ligands were added, the ED is reversed and (*R*)-products were obtained (Table 12, entries 2−4). In the case of magnesium triflate, always (*R*)-products were formed (entries 5−7). The structures of the different Mg(II) complexes were verified by NMR measurements. The magnesium perchlorate intermediates proved to be tetrahedral complexes in the absence of water and alcohols; water and alcohols, however, can expand the coordination number of magnesium perchlorate, and octahedral complexes are formed (Figure 9). These experimental results are in agreement with the above conclusions. In the reactions described, DA addition products of (*R*) and (*S*) configuration were obtained in ee over 90%.[55] It has to be noted that DA addition studies have also been performed with PyBOX−Lewis acid complexes, and the formation of (*S*)- and (*R*)-DA products in higher ee was observed. Because of the significantly different structure of these catalysts, however, these experimental results cannot be classified as conversions associated with unexpected inversion.[52d,53c]

Ionic liquid (IL) effect was observed on the reversal of configuration for the (*S*)-BOX-Mg(II) and (*S*)-BOX-Cu(II) catalyzed reaction in both homogeneous and heterogeneous media (entries 9−13).[56] Compared with reaction performed in dichloromethane or diethyl ether, an enhancement in ee is observed with a large increase in reaction rate. In addition, for nonsterically hindered bis(oxazoline) ligands, that is, phenyl functionalized ligands, a reversal in configuration is found in the IL, compared with molecular solvents. Unexpected inversion was observed using heterogenized com-

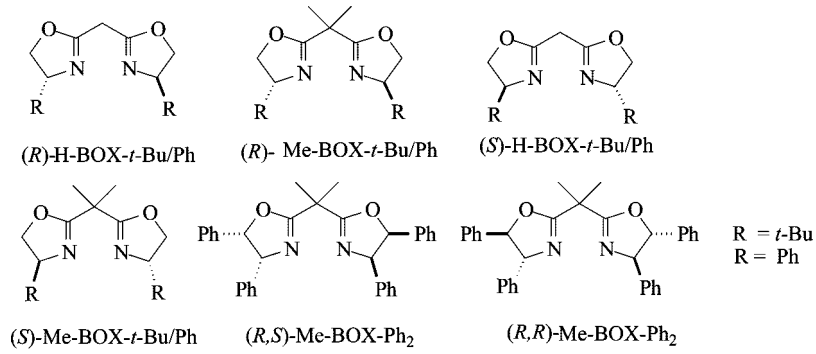


Figure 8. BOX ligands in enantioselective Diels−Alder reactions.

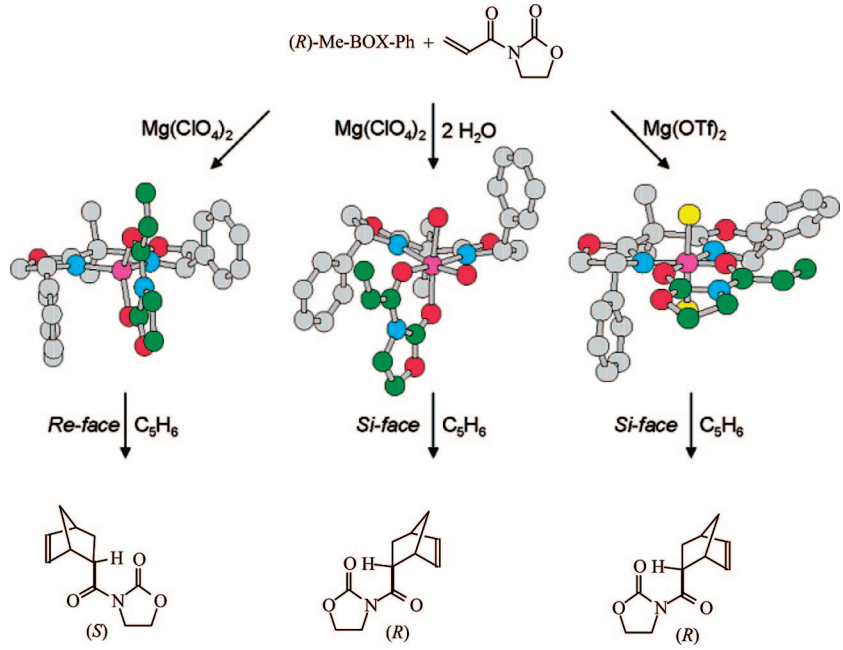


Figure 9. Stereochemistry of a Diels−Alder reaction catalyzed by tetrahedral or octahedral intermediate BOX−Mg complexes.

plexes in DA and hetero-DA reactions[56–58] (entries 10, 14, and 15; in detail, section 4).

Surprisingly, the reports on unexpected inversions in the DA reaction do not address the effect of the configuration of the BOX ligand on enantioselectivity.[55–58] The reason for this may be that no results have been obtained using BOX ligands and Lewis acids that differ only in the configuration of the chiral carbon atoms but are otherwise identical, under identical experimental conditions. Thus, it is not possible to propose a general relationship. Unfortunately, the review recently published does not adopt a definite standpoint on the effect of (*S*)- and (*R*)-BOX ligands on the sense of ED in the DA reaction.[52g] In some cases, inaccurate information can also be found (e.g., (*R*)-1 BOX data among (*S*)-1 BOX data). On the basis of experimental data adequate for this type of comparison (Table 12, entries 2, 10, and 12), both the (*R*)- and (*S*)-Me-BOX-Ph-Mg$(ClO_4)_2$ and the (*S*)-Me-BOX-Ph-Mg$(OTf)_2$ catalysts promote the formation of the (*S*)-DA product. In contrast, the (*R*)-Me-BOX-Ph-Mg$(ClO_4)_2$/Mg$(OTf)_2$ catalysts give the (*R*)-DA product at different temperatures. It cannot be determined whether the reversal ee is due to the change in BOX configuration, the presence of a different Lewis acid, or the change in experimental conditions.

Although a large number of experimental data points on the DA reaction could be collected, these do not yet allow the formulation of relationships that would explain the majority of the data. In agreement with the opinion—and hopes—expressed by Desimoni et al. in 2006, "In enantioselective catalysis with BOX complexes there are still unanswered questions, but given the spectacular development of the field, the authors are confident that these will be solved in the near future."[52g]

2.7.2. 1,3-Dipolar Cycloaddition Reactions

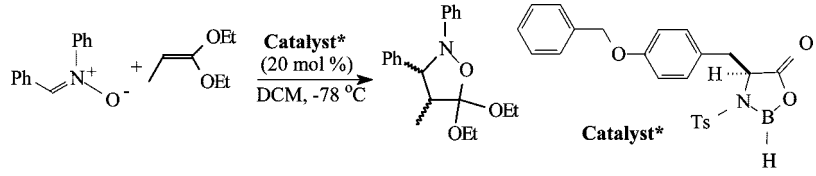
The second most important enantioselective pericyclic reaction after the Diels–Alder reaction is 1,3-dipolar cycloaddition.[52d,f,60] Numerous experiments have been performed that used Lewis acids and complexes containing BINOL, BOX, and PyBOX chiral ligands. The new results were reviewed by Desimoni et al. in 2003 and 2006.[52d,g] Unexpected inversion was first observed by Schreeren et al., who studied 1,3-dipolar cycloaddition between nitrones and ketene acetals over chiral oxazaborolidine Lewis acid catalysts in 1995[61] (Scheme 9).

As demonstrated in Scheme 9, a dramatic solvent effect—as the authors put it—on enantioselectivity was observed.[61b] When the catalyst was prepared in BH_3·THF (cosolvent is THF), the value of ee was 62% (−), whereas if it was prepared in BH_3·SMe_2 in the presence of diphenyl ether cosolvent, remarkable reversal of the ee (58 (+)) of the reaction occurred (dimethyl sulfide probably has a role in this reaction). Some characteristic data on the formation of enantiomers of different configurations, obtained using chiral BOX ligands, are listed in Table 13.

Mostly endo-addition takes place in the reaction. Enantioselectivity is found to be dependent on the presence of MS 4 Å. The stereochemistry of the process can be interpreted similarly to that of the DA reaction, i.e., it is determined by the coordination geometry of metal cations; ICs are octahedral in the presence of water, whereas in its absence (i.e., in the presence of MS), they have tetrahedral structure. The former favor the formation of the (3*R*,4*S*)-product, whereas the latter promote that of the product of the opposite absolute configuration.

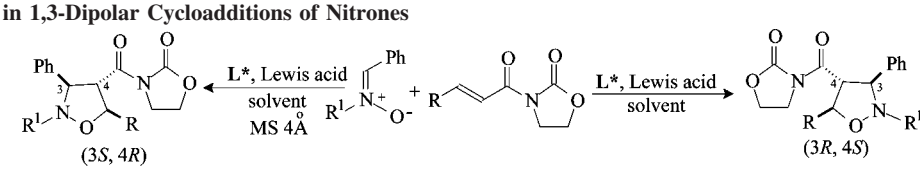
In addition to the above, Kawamura and Kobayashi found relatively high ee (85−96%) by the effect of the chiral Lewis acid catalyst Yb$(OTf)_3$ + (*S*)-BINOL + *N*-methyl-bis[(*R*)-(1-naphthyl)ethyl]amine in the presence of MS 4 Å and preferential formation of the product with the opposite configuration in its absence (76−88%).[63] They conclude their report with stating that "Further studies to clarify the role of MS 4 Å from a mechanistic point of view are now in progress." However, new information has not been published since 1999.

Scheme 9. Inversion in Asymmetric [1,3]-Cycloaddition of Nitrones with Ketene Acetals



Cosolvent	(vol.%),	ee (%)
THF	2.5	62 (-)
Ph-O-Ph	2.5	58* (+)
Ph-O-Ph	15	79* (+)
Bn-O-Bn	2.5	33* (+)
Bn-O-Bn	7.5	71* (+)

Table 13. Inversion in 1,3-Dipolar Cycloadditions of Nitrones



entry	ee (%)	yield (%)	R	L*[a]	Lewis acid	R^1	yield (%)	ee (%)	ref
1	82*	100	H	(*R*)-Me-BOX-Ph	MgI_2	Ph	100	48	62a
2	79*	72	Me	(*R*)-Me-BOX-Ph	MgI_2	Ph	73	46	62a,b
3			Me	(*S*)-Me-BOX-Ph	MgI_2	Bn	82	rac.	62b
4	70*	100	H	(*R*)-Me-BOX-Ph	Mg$(ClO_4)_2$	Ph	100	48	62c,d

[a] **L*** see Figure 8.

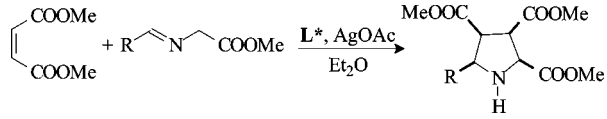
2.7.3. [3 + 2]-Cycloaddition Reaction

Inversion was recently observed in the case of [3 + 2]-cycloaddition, using ligands of identical configuration.[64] Some experimental data are presented in Table 14.

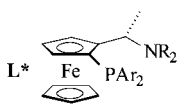
As regards the stereochemistry of the process, on first sight an unexpected inversion took place, since inversion occurred by the effect of **L*** of identical configuration (although they contain either a primary amino group or a dimethylamino group), in the presence of iminoesters of diverse compositions under identical experimental conditions.[64] As soon as the main properties of the reaction mechanism became known to the authors, however, the inversion ceased to be surprising. The reason for this is that, in the case of an **L*** containing a primary amino group, there is a hydrogen bonding interaction between **L***, Ag^+, and the substrate. Although the use of hydrogen bonding to accelerate or catalyze certain reactions has been well-documented,[65] reversal of enantioselectivity directed by hydrogen bonding has been rarely reported.[36a,66] Interpretation of the stereochemistry of the reaction was based on experiments using iminoesters and **L***s of different structures, density-functional theory studies on the structure of ICs, and, last but not least, the results of ^{1}H NMR titration measurements of hydrogen-bonding complexes. These studies confirmed the existence of the hypothetic ICs of dimethylamino (**C2−1a**) and primary amino (**C2−1b**) type (Figure 10).[64]

Figure 10 indicates that it is favorable for **C2−1b** to be attacked from the top face, while in **C2−1a**, the dimethylamino group cannot form hydrogen bonds, and the methyl group will cause steric repulsion. The dimethyl maleate, therefore, will attack from the bottom face of **C2−1a**; hence, the enantioselectivity is reversed.[64]

Table 14. Inversion in [3 + 2]-Cycloaddition of Iminoesters



entry	R	L*	temp. (°C)	yield (%)	ee (%)
1	*p*-ClC_6H_4	**1a**	0	95	−76
2	*p*-ClC_6H_4	**1b**	0	91	83*
3	*p*-ClC_6H_4	**1c**	0	95	−84
4	*p*-ClC_6H_4	**1d**	0	94	84*
5	*p*-ClC_6H_4	**1c**	−25	95	−92
6	*p*-ClC_6H_4	**1d**	−25	90	92*
7	2-naphthyl	**1c**	−25	91	−87
8	2-naphthyl	**1d**	−25	98	91*



(*S,Rp*)-**1a**: Ar = Ph, R = Me
(*S,Rp*)-**1b**: Ar = Ph, R = H
(*S,Rp*)-**1c**: Ar = $Me_2C_6H_3$, R = Me
(*S,Rp*)-**1d**: Ar = $Me_2C_6H_3$, R = H
(*S,Rp*)-**1e**: Ar = Ph, R = NHMe

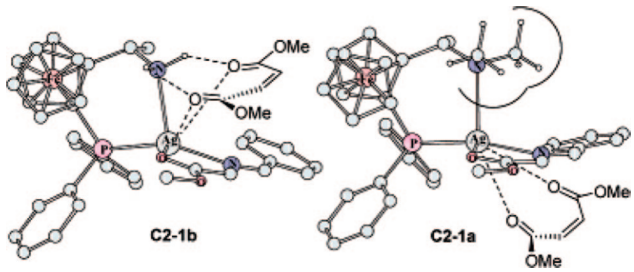


Figure 10. Optimized structures of **C2−1b** and **C2−1a** intermediate complexes of asymmetric [3 + 2]-cycloaddition (the hydrogen atoms that are not involved in the reactions are omitted for clarity).

2.7.4. Other Asymmetric Reactions

In 1998 Sibi et al. reported their experiments in which both enantiomers were obtained in the conjugate addition of α,β-unsaturated pyrazole amides in the presence of *O*-benzylhydroxylamine, BOX-complexes, and Lewis acids (depending on the latter), under otherwise identical conditions.[70a] Scheme 10, however, represents a temperature-dependent reversal of stereochemistry in asymmetric conjugate amine addition of α,β-unsaturated oxazolidinone amide in the presence of the same Lewis acid.[70b]

Specifically, at room temperature the (*R*)-product and at −60 °C the (*S*)-product is formed in higher ee. The authors varied several experimental parameters (temperature, Lewis acids, BOX ligands, substrate structure), mainly with the aim of elucidating the general character of the reaction and of maximizing ee. In the authors' opinion, expounded in detail in the manuscript, the probable cause of the phenomenon is that more than one complex may be present at a given temperature. In spite of the fact that the manuscript presents several reactions in which the only difference between the conditions of the formation of the two enantiomers is in temperature, the inversion is still unexpected, because it is not characteristic of the majority of the reactions.

2.8. Summary

Reports on unexpected inversion may be classified on the basis of several different criteria. In Table 15, the collected data are listed following the order of discussion according to reactions, indicating a few parameters. The data in the individual columns of Table 15 reflect the diversity of unexpected inversion: (i) Inversion may occur in a variety of reactions. (ii) Experimental data are available for cases with **L*** of a wide range of types. (iii) In addition to high ee values (entries 10, 12, 15, 18, 19, 27, and 28), medium and low ee values also occur, since in many cases optimization has not been undertaken. (iv) The publications call attention to the diversity of effects causing inversion. (v) In many cases, especially in more recent reports, the suggested interpretations are also supported by experimental results.

The reviewer could next set out to identify any possible relationships on the basis of expediently chosen parameters. Theoretically, such parameters could be reaction types, chiral ligands, Lewis acids (cations, counterions), other experimental conditions, or effects (supposed to bring about the unexpected inversion). In accordance with very recently published reviews, I have to note that, at present, no experimental data suitable for the formulation of generalized conclusions are available. Looking at the data in Table 15, it appears that, in the absence of suitable experimental data, it is as yet impossible to attempt even a qualitative comparison of the structural differences among chiral ligands and of other effects causing unexpected inversion. As regards the effects of the structural differences of ligands on inversion, according to the pertinent definition these can only be minor differences, since the absolute configurations of the **L*** pairs participating in the reaction must be identical (otherwise the inversion would not be unexpected). In nearly one-half of the examples listed, BOX-type ligands participated in the reactions, whereas in the rest, ligands of diverse structures were present.

Scheme 10. Inversion in Enantioselective Conjugate Amine Addition

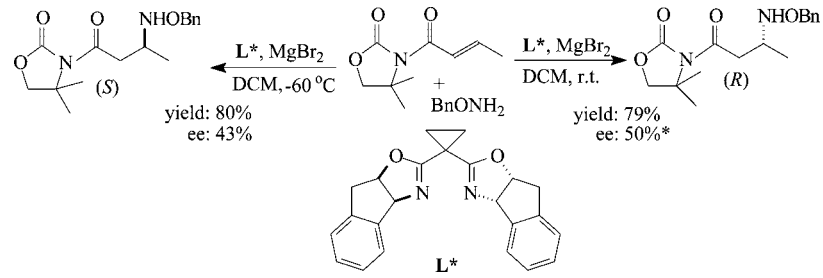


Table 15. Inversions in Metal Complex-Catalyzed Reactions

entry	reactions	chiral metal complexes	R_{max}/S_{max}	effects	interpretation[a]	Table/Scheme in manuscript	ref
1	hydrogenation	(*R*,*R*)-(*S*,*S*)-EtTRAP-Rh(III)	18/79	H_2 pressure	A	Table 1	21a
2	hydrogenation	oxazoline−imidazoline-Ir(III)	−64/+89	temperature H_2 pressure	A, C	Scheme 4	21c
3	transfer hydrogenation	Ax. biaryl-Ir(III)	60/50	[Base]	A, C	Table 2	22
4	transfer hydrogenation	amide or sulfamide-Ru(III)	20/92	**L*** structure	A, B	Table 2	23
5	hydroformylation	(*S*,*S*)-BDPP-PtCl($SnCl_3$)	17/68	temperature	A	Table 3	26
6	hydroformylation	(*S*,*S*)-BDPP-PtCl($SnCl_3$)	10/60	temperature	D	Table 3	27
7	Sharpless epoxidation	PEG-TA-Ti(IV)	75/67	additive: MPEG	A, B	Table 4	31
8	oxidation of sulfides	Ar-diols-Ti(IV)	26/80	CF_3 groups on Ph-s	A, B	Table 5	32a
9	allylation	chiral *N*,*P*-Pd(0)	80/83	subst. on N	A, B	Table 6	35a
10	allylation	BOX-diol/Bz-Pd(II)	90/92	H bonding	D	Table 6	36a,b
11	alkylation	trisoxazoline-Cu(II)	65/90	solvent	D	Scheme 7	39
12	aldolization	L-proline amines-Sn(II)	98/98	subst. on N	D	Table 7	40
13	aldolization	bisdiphenyl prolinol-Zn_2	−69/+83	temperature	A, C	Table 8	41
14	aldolization	(*S*)-BOX-Cu(II)	91/64	TfO^-, SbF_6^-	A, C	Scheme 8	42a
15	aldolization	(*S*,*R*)-BOX-Cu(II)	92/80	spacer-length	A, B	Scheme 8	42b
16	Henry reaction	BOX-Cu(II) and BOX-Zn(II)	84/76	N−H effect on Cu	A, C	Table 9	44b
17	Mannich reaction	MOX-ferrocenyl-Cu(II)	*syn*/*anti*	electronic factor of **L***	D	Table 10	46
18	Heck reaction	Pfaltz-Helmchen *P*,*N*-Pd(II)	87/87	IC conform-ation	D	Table 11	48b
19	DA reaction	(*R*)-BINOL-Ln(III)	81/93	achiral additives	A, B	Table 12 entry 1	54a
20	DA reaction	(*R*)-BOX-Mg(II)	76/94	coordination geometry	D	Table 12 entries 2−8	55
21	DA reaction	(*S*)-BOX-Mg(II) (*S*)-BOX-Cu(II)	79/62	ionic liquid	A	Table 12 entries 9−13	56
22	DA reaction	(*S*)-BOX-Cu(II)	33/59	heterogenization	C	Table 12 entry 14 Table 39 entries 8−10	57
23	DA reaction	(*S*)-BOX-Mg(II)	30/60	heterogenization	D	Table 12 entry 14 Table 39 entries 13−15	58
24	DA reaction	(*S*)-BOX-Cu(II) (*S*)-BOX-Zn(II)	64/98	Cu(II) or Zn(II)	D	Table 12 entries 16 and 17	59
25	1,3-dipol. ca.	oxazaborolidine	−62/+79	solvent	A, B	Scheme 9	61
26	1,3-dipol. ca.	(*R*)-BOX-Mg(II)	48/82	additive: 4 Å MS	D	Table 13	62
27	1,3-dipolar cycloadd.	(*R*)-BINOL-Yb(III)	−96/+88	additive: 4 Å MS	A, B		63
28	[3 + 2]-ca.	PPFA-AgOAc	−92/+92	H bonding	D	Table 14	64
29	cyclopropanation	(*S*)-BOX-Cu(II)	34/42	heterogenization, solv.	D	Table 41	68
30	aziridination	(*S*)-BOX-Cu(II)	43/82	heterogeniz.	A	Table 42	69a
31	conj. addition	(*S*,*R*)-BOX-$MgBr_2$	50/43	temperature	A, B	Scheme 10	70b

[a] A = assumed, B = planned, C = there are some experiments, and D = verified.

In the case of BOX-type **L*** pairs, the following can be established regarding the effect of minor structural changes in chiral ligands on ED: (i) In the case of allylation in the presence of BOX ligands containing OH groups, ED was controlled by the H bonding structure of the IC (entry 10). (ii) In aldol addition, the sense of ED may depend on a different counteranion (entry 14) or chelate ring size (entry 15). (iii) In the Henry reaction, in the case of Cu-BOX, ED is controlled by H bonding, whereas in the case of Zn-BOX, this is not possible (entry 16). (iv) In DA reaction, in the case of *t*-Bu-BOX and Ph-BOX complexes, inversion of the sense of ED is due to the different conformations of the IC (entry 24). (v) In DA reaction, ED is controlled by the coordination geometry of the central metal cation (tetrahedral or octahedral geometries) (entry 20).

In the case of **L*** pairs of diverse structures, the following can be stated about the effects of minor structural changes in chiral ligands: (i) In transfer hydrogenation on Ru catalyst containing amide/thioamide **L*** pairs, due to the acidity of the NH functions, inversion may arise from a different mode of coordination (entry 4). (ii) In the sulfide → sulfoxide reaction on *p*,*p*′-disubstituted-1,2-diphenylethane 1,2-diols, the inversion may arise from formation of new Ti complexes with CF_3 substituents on Ph groups (entry 8). (iii) The inversions have been interpreted on the basis of different conformations of IC complexes: in the allylation using valphos-*N*,*P*-Pd(0) catalysts (entry 9), in the aldolization using L-proline diamine−Sn(II) catalysts (entry 12), in the Heck reaction using phenyloxazolinephosphine−Pd(II) catalyst (entry 18). (iv) In Mannich reaction using oxazoline-based ferrocenyl phosphine−$CuClO_4$ catalyst, the origin of the inversion has electronic character (entry 17). (v) In [3 + 2]-cycloaddition, inversion may be interpreted by the formation of H bonding, in the case of **L*** containing a primary amino group, whereas in the case of a tertiary amine such an interaction is not possible (entry 28).

As regards the role of experimental conditions (temperature, solvents, additives, heterogenized catalysts, and, in the case of hydrogenations, hydrogen pressure), on the basis of the suggestions/conclusions of the reports compiled in this manuscript, it is impossible to derive any additional experimentally verified statements of a more specific nature.

In the course of studying the pertinent literature, I found catalysts with BOX ligands to be the most intensively studied and, therefore, the best elucidated subject. The coordination geometry of metal cations has a determinant role in developing the structure of the IC responsible for ED. It has also been shown that the geometry of the metal cation is profoundly influenced by counteranions and various additives. It is important to stress that it was systematic studies on the unexpected stereochemical changes observed in the case of BOX complexes that made possible the successful formulation of generalizable relationships for BOX-type catalysts. This and the knowledge of the properties of metal ions and counterions have permitted us to design certain chemical processes utilizing this type of chiral catalyst.

3. Unexpected Inversions in the Organocatalytic Asymmetric Reactions

Although organocatalysts have been used in organic chemistry for decades, their utilization has not skyrocketed until the years after 2000, as illustrated by the list in a figure in ref 71. The rapid development of organocatalysis is also confirmed by the monographs published in the past few years.[71–75] Our group started to study the Michael-type addition catalyzed by cinchona alkaloids at the end of the 1990s. Although studies on the stereochemistry of the reaction yielded some unexpected results,[76] our research capacity was fully engaged in enantioselective heterogeneous catalytic hydrogenations.[6a]

The present state of research in the field of the stereochemistry of enantioselective organocatalytic reactions already allows the formulation of generalized relationships in the case of certain reactions and catalysts. However, it has not been possible to define similar relationships in the large number of reaction types involved and for most of the organocatalysts applied, due to a lack of required experimental materials, because the main objective in these studies is the production of the given enantiomers in >90% ee. That may be the reason why the stereochemical relationships directing certain reactions have not yet been elucidated, and no review calling attention to the significance of the observations made to date on unexpected inversion has been published.

In accordance with the objectives listed in the Introduction, this section will describe a number of organocatalytic asymmetric reactions involving unexpected inversion, published in the literature.

3.1. Asymmetric Alkylations

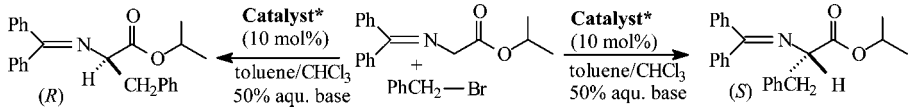
Among the procedures for creating C−C bonds, asymmetric organocatalytic alkylations are easily performable reactions.[71–74,77] The salts of chiral organic bases are especially often utilized as phase-transfer catalysts.[77]

According to the experimental data of Table 16, new cinchonidinium salts bearing a 3,5-dialkoxybenzyl group show an alkaline metal base-dependent reversal of enantioselectivity when used as phase-transfer catalysts in the asymmetric alkylation of *N*-(diphenylmethylene)glycine isopropyl ester with benzyl bromide.[78a] The use of potassium hydroxyde as base in this alkylation reaction afforded the (*S*)-enantiomer, whereas using sodium hydroxide under the same conditions afforded the corresponding (*R*)-enantiomer.

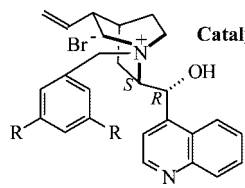
The nature of the solvent and the temperature seems to play important roles in the switching of stereoselectivity when changing the base. The concentration of the base also seems to be crucial to the change in stereoselectivity. The authors have assumed that the presence of the C9 alkoxy groups of the catalyst is a key factor in the observed inversion of enantioselectivity. A similar observation is described in ref 78b. Studies showing that the configuration of the product is determined by that of the chiral atoms of the cinchona alkaloid catalyst, irrespective of the bulkiness of the substituents of C9−OH, are also interesting,[78c–f] because different experimental observations also exist, especially in heterogeneous metal-catalyzed enantioselective hydrogenations (see below).

Denmark and Fu[79a] call attention to an unexpected chiral formamide catalyzed allylation in the "Enantioselective Catalysis" thematic issue[14] of *Chemical Reviews* (Table 17). The chiral catalyst in stoichiometric amount promotes the allylation of the aldehyde to give the (*R*)-adduct in 68% ee.[79b,c] Interestingly, when a catalytic amount of catalyst is used, the (*S*)-product is obtained in low yield and selectivity. A change in the sense of enantioselectivity is clearly indicative of the operation of dual catalytic pathways for

Table 16. Inversion in the Cinchona-Catalyzed Alkylation



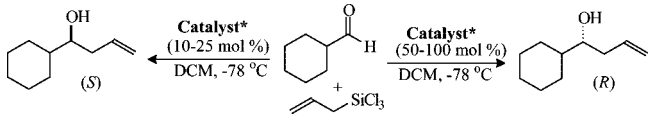
entry	ee (%)	yield (%)	base	Catalyst*	temp. (°C)	yield (%)	ee (%)
1			KOH	**1**	−20	80	24
2			NaOH	**1**	−20	70	24
3			KOH	**2**	−20	80	58
4	40*	96	NaOH	**2**	−20		
5			KOH	**2**	−40	91	66
6	40*	93	NaOH	**2**	−40		
7			KOH	**3**	−20	98	44
8	38*	80	NaOH	**3**	−20		



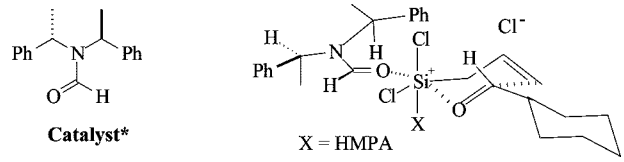
Catalyst*

1: R = H
2: R = OCH_2Ph
3: R = OMe

Table 17. Inversion in Allylation with Chiral Formamide Catalyst



ee (%)	yield (%)	Catalyst* (mol %)	HMPA	time	Catalyst* (mol %)	yield (%)	ee (%)	ref
32*	12	10	0	7 h	50	45	44	79b
30*	25	25	0	7 h	100	81	68	79b
			100	7 h	25	33	94	79c
			100	7 h	100	89	96	79c
			100	14 h[a]	20	80	98	79b



[a] Solvent: EtCN.

formamides as well. The HMPA as an additive enhances the yield and ee and accelerates the catalytic cycle. The reason why HMPA increases the yield and ee remains unclear in the author's opinion. In the interpretation of the stereochemistry of the reaction, a cyclic chairlike transition structure was assumed (Table 17).

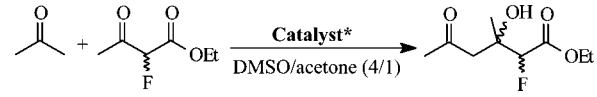
Another example for unexpected inversion depending on a slight modification of substrate structure is shown for the case of asymmetric alkylation in Scheme 11: alkylation of 2-oxygenated diphenylmethane derivatives using *s*-BuLi and (−)-spartein gave ee's up to 60% with allylbromide. When compounds with a free hydroxy in the 2-position were alkylated, the selectivity was reversed. Alkylations with methyl electrophiles were poorly selective.[80a]

According to the authors, this reversal of selectivity opens up the possibility of obtaining either enantiomer of a given derivative, as desired, by using a protected or unprotected starting material. This greatly increases the possibilities for this chemistry since only one enantiomer of sparteine is readily available. The reason for these results is not clear. The change in the sense of stereoselection from reactions of ether derivative to those of hydroxy compound is difficult to explain. The authors assume these reactions involve a thermodynamic/kinetic resolution of an equilibrating pair of complexes.[80a] Excellent results also have been obtained by several researchers using sparteine in asymmetric alkylation of benzylic methylene group.[80b,c]

3.2. Asymmetric Aldol Additions

Reviews published recently verify the importance of aldol additions.[71,72,74,81] List et al.[82a] reinvestigated the Hajos−Eder−Sauer−Wiechert reaction[82b] and found that proline is an effective organocatalyst for intermolecular direct asymmetric aldol reactions.[83a] The manuscript describes several examples for unexpected inversion observed in L-proline-catalyzed asymmetric aldol addition.[81b,83]

Table 18. Inversion in the L-Proline- and L-Prolinol-Catalyzed Direct Aldol Reaction



entry	Catalyst*	conversion (%)	selectivity (%)	ee_{anti} (%)	ee_{syn} (%)
1	L-proline	60	97	82	54
2	D-proline	68	97	−81[a]	−56[a]
3	L-prolinol	40	86	−22[a]*	−26[a]*

[a] The excess enantiomers had opposite configuration in comparison with those obtained in the reactions catalyzed by L-proline.

According to Table 18, the asymmetric organocatalytic aldol reaction has been extended to ketone + α-fluoro-β-keto ester aldol addition.[76b] It has been shown that this unprecedented reaction can be carried out with readily available chiral amine catalysts, obtaining good enantioselectivities in the reaction of the α-monofluorinated compounds. Surprisingly, when L-prolinol was used as catalyst, the sense of the ED was opposite to that obtained with L-proline. The direct aldol reaction catalyzed by L-prolinol shown in Table 18 may be considered unexpected, since the configuration of the product formed is identical with that obtained in the case of D-proline rather than L-proline.

Since many proline derivatives have become popular,[84] the authors synthesized new L-prolinamide derivatives with rigid structures and axial and central chirality for the purpose of the experiments outlined in Table 19 and tested them in the aldol reaction indicated.[85a] In the experiments, molecular sieves were used as water scavengers. Several unexpected events were observed, the interpretation of which, for the time being, was not addressed by the authors. Most conspicuously, out of the 14 experiments reported in this study, only in one case was a product with (2*R*,1′*R*) configuration formed. As the authors say, "It was noteworthy that *trans*-4-hydroxy-L-proline-derived organocatalysts **3c** and **3d** gave the opposite sense of asymmetric induction." On the basis of the experimental results available, it is impossible to formulate an unambiguous, definitive standpoint on the role of the chirality of the organocatalysts studied in determining the stereochemistry of the process. It appears as if the determinant factors of the stereochemistry were other than these absolute configurations. The authors propose the key role of MSs. They found that the presence of water had a remarkable effect on catalytic activity and stereoselectivity. Perhaps the most characteristic experimental result is that catalyst **3d** with MS 4 Å forms a (2*R*,1′*R*) adduct (entry 3), whereas with MS 3 Å it forms a (2*R*,1′*S*) adduct (entry 4)

Scheme 11. Inversion in Organocatalytic Allylation of Diphenylmethane Derivatives

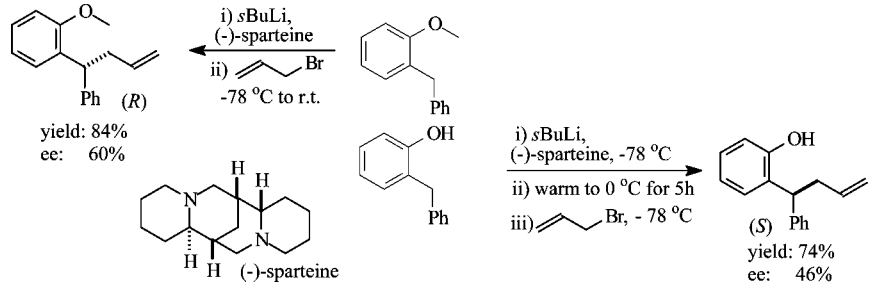
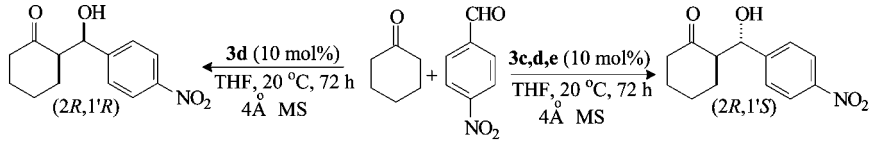
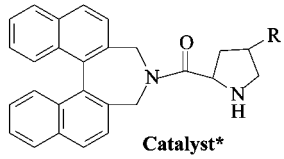


Table 19. Inversion in L-Prolinamide-Catalyzed Aldol Reaction



Entry	ee (%)	Yield (%)	Catalyst*	Configurations of Catalysts*	Catalyst*	Yield (%)	ee (%)
1	> 99*	> 99	**3d**	S_{ax}, $2S_{pro}$, $4R_{pro}$	R_{ax}, $2S_{pro}$, $4R_{pro}$	**3c**	42	91
2					S_{ax}, $2S_{pro}$, $4R_{pro}$	**3e**	67	77
3					S_{ax}, $2S_{pro}$, $4R_{pro}$ [a]	**3d**	99	> 99
4					S_{ax}, $2S_{pro}$, $4R_{pro}$ [b]	**3d**	64	82

[a] 0 °C, 24 h; [b] 3Å MS

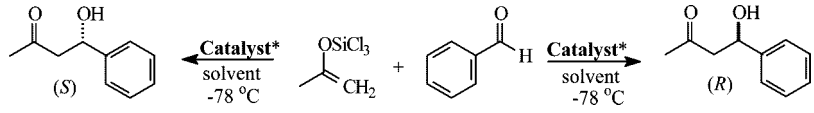


Catalyst*

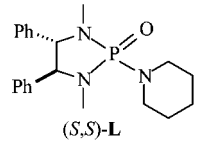
3a: R = H, (S_{ax}, $2S_{pro}$)
3b: R = H, (R_{ax}, $2S_{pro}$)
3c: R = OH, (R_{ax}, $2S_{pro}$, $4R_{pro}$)
3d: R = OH, (S_{ax}, $2S_{pro}$, $4R_{pro}$)
3e: R = OTBS, (S_{ax}, $2S_{pro}$, $4R_{pro}$)

[a] 0 °C, 24 h. [b] 3 Å MS.

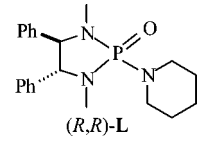
Table 20. Inversion in the Chiral Phosphoramide-Catalyzed Aldol Reaction



entry	ee (%)	yield (%)	solvent	Catalyst* (L*)	yield (%)	ee (%)
1	92	92	DCM	(*S*,*S*)-**L**		
2			DCM	(*R*,*R*)-**L**	87	92
3			EtCN	(*S*,*S*)-**L**	88	90*



(*S*,*S*)-**L**



(*R*,*R*)-**L**

with reversed ee under identical experimental conditions.[85a] Further research along these lines can be expected to yield important information.

It is mentioned that the steric and stereoelectronic effects that control the enantioselectivity in the cross-aldol addition of acetone to isatin catalyzed by L-proline have been studied by means of density functional theory (DFT) and atoms in molecule (AIM) calculations.[85b] This reaction results in a reversal of enantioselectivity compared with the corresponding cross-aldol addition to 4,6-dibromoisatin and aldehydes. Because of the relatively large difference between the two reactants compared, the result obtained cannot be regarded as unexpected; therefore, it is not described in detail in this manuscript.

Significant solvent effect and rate enhancement were also observed in the chiral phosphoramide catalyzed aldol reactions of aldehydes with trichlorosilyl enolates as competent aldol reagents (Table 20).[86]

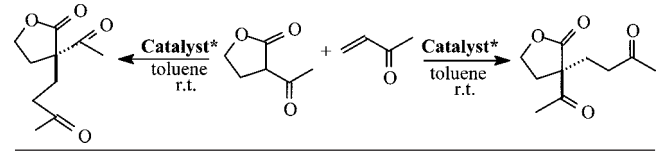
In DCM as solvent, (*S*)-aldol was produced in high optical yield in the presence of (*S*,*S*)-**L** catalyst (entry 1), whereas (*R*)-aldol was formed in the presence of (*R*,*R*)-**L** catalyst (entry 2). In propionitrile, however, in the presence of (*S*,*S*)-**L** catalyst, the product had the configuration opposite to the one expected, i.e., the (*R*)-product was produced in high optical yield. This unexpected inversion also aroused the attention of the authors of the recently published monograph.[72] The reports do not propose an explanation for the unexpected inversion.

3.3. Asymmetric Michael Reactions

Beside aldol addition, Michael additions are the most commonly applied C−C bond-forming organocatalyzed asymmetric syntheses.[72,74,77a,81b,c] Four examples of Michael-type asymmetric reactions will be presented below, with three using cinchona and one using proline as catalyst.

Table 21 summarizes the experimental data on unexpected inversion in the reaction between 2-acetylbutyrolactone and methyl vinyl ketone.[76a] Interestingly, QN gave higher ee values than CD, while QD gave slightly lower ee values than CN. The senses of the ee induced by the four basic cinchona alkaloids were surprising. The levorotatory enantiomer was

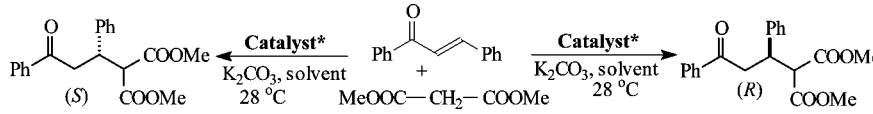
Table 21. Inversion in the Cinchona-Catalyzed Michael Reaction of 2-Acetylbutyrolactone to Methyl Vinyl Ketone



entry	Catalyst*	yield (%)	[a] $[\alpha]_D^{25}$	ee (%)
1	CD	95	−6.2	8
2	QN	95	23	33*
3	CN	82	17.4	25
4	QD	84	−15.1	22*

[a] The specific rotations of the optically pure products $[\alpha]_D^{25}$: +69.5 and −69.5 (ethyl alcohol, *c* 10).

Table 22. Inversion in the Cinchona-Catalyzed Michael Reaction of Dimethyl Malonate to Chalcon



entry	ee (%)	yield (%)	solvent	yield (%)	ee (%)
1	61	96	DMSO		
2	56	92	toluene		
3	46	94	DCM		
4			$[bmim]PF_6$	99	50*
5			$[bmim]BF_4$	97	44*
6	42	97	$[bpy]BF_4$		

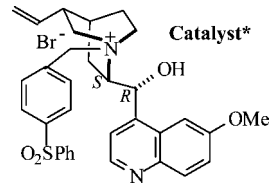
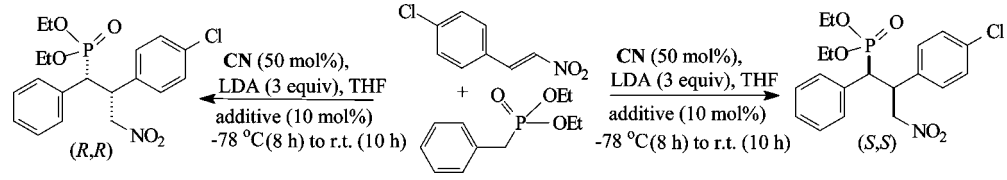


Table 23. Inversion in the Cinchonine-Catalyzed Michael Reaction of Benzyl Phosphonate to *p*-Chloronitrostyrene



entry	ee (%)	yield (%)	additive	entry	additive	yield (%)	ee (%)
1	100	81	none				
2	100	15	Me_4-ethylenediamine	7	*N*-Me-morpholine	25	80*
3	100	17	$O{=}P(NMe_2)_3$	8	4-dimethylaminopyridine	51	60*
4	100	56	ethylenediamine	9	Et_2O	60	60*
5	100	55	ethylene glycol	10	Et_2O[a]	55	100*
6	100	44	12-Crown-4				

[a] Used as solvent without any THF.

obtained in excess with CD and QD and the dextrorotatory by the use of CN and QN as catalysts. The result obtained is doubly surprising. On the one hand, the members of the catalyst pair CD−QN containing C atoms of identical configuration (8*S*, 9*R*) and those of the CN−QD pair (8*R*, 9*S*) catalyzed the formation of products with opposite configurations in higher ee. On the other hand, in the first pair, it was QN containing an OMe group, whereas in the second pair, it was CN containing no OMe group that catalyzed the formation of the dextrorotatory product in higher ee. Interpretation of the phenomenon calls for further research because, among other reasons, studies on other cyclic β-ketoesters under identical conditions revealed surprises of a different character.[76a]

Making use of the experiences of previous research[87a,d] (ILs, cinchona derivatives), Salunkhe et al. reported that the enantioselective Michael addition of dimethyl malonate to 1,3-diphenylprop-2-en-1-one (chalcon) promoted by a quaternary ammonium salt derived from QN as a PTC in different ILs, 1-butyl-3-methylimidazolium hexafluorophosphate, $[bmim]PF_6$, 1-butyl-3-methylpyridinium tetrafluoroborate, $[bpy]BF_4$, and 1-butyl-3-methylimidazolium tetrafluoroborate $[bmim]BF_4$, as in conventional organic solvents, was studied[87c] (Table 22). The reactions in ionic liquids afforded excellent yields of the product in relatively short periods of time, but interestingly and surprisingly, the ED was reversed in the reactions in $[bmim]BF_4$ and $[bmim]PF_6$, whereas it remained the same in $[bpy]BF_4$, as was the case for the conventional organic solvents under investigation.

In order to ascertain the factor responsible for the reversal of ED, the results indicated that the reversal of ED was not due to the PTC but can be attributed to the cation associated with the anion of the IL. This unexpected phenomenon was also noted by Hashimoto and Maruoka.[77a] The third Michael-type addition catalyzed by a cinchona alkaloid is shown in Table 23.

In the absence of any additives, high-yield diastereo- and enantioselectivities were obtained as reported earlier (Table 23, entry 1).[88a] Similar stereoselectivities, but low yields, were obtained when achiral additives were used (Table 23, entries 2−6).[88b] Surprisingly, the addition of other achiral additives to the precatalyst, that is, **CN**−Li complex, provided low yields and caused a reversal of enantioselectivity (entries 7−10). More importantly, data in Table 23 reveal that the two enantiomers (*R*,*R*) and (*S*,*S*) could be synthesized by performing the reaction in two different solvents, THF and ether, respectively. Although certain preliminary experiments have been performed, the authors indicate that detailed investigations to determine the exact origin of the unexpected inversion are currently underway in their laboratory. This unusual result suggested that the stereochemistry at C8 and C9 in **CN** has no influence on selectivity. In other words, the stereoinducing region of the chiral ligand is away from the reaction site in this case. This

report presents a complex system. The IC responsible for enantioselection is a CN−phosphonate−Li complex. This catalyst system appears to represent a transition between organocatalysts and metal complex catalysts. Since the publication reports several unexpected phenomena (solvent effect, inversion, achiral additives, configuration of cinchona alkaloids) in a Michael-type reaction, further results are eagerly awaited.

Knowing and fully applying the antecedents from a report published in 2008[89] disclosed a mild and efficient procedure for Michael additions of cyclohexanone to chalcones (Table 24).[90a] In the presence of L-proline−achiral IL organocatalyst, cyclohexanone reacted with various chalcones to afford Michael adducts in high yields (80−99%) and moderate to good ee (16−94%), accompanied by an unexpected solvent-dependent inversion of the ED. The authors repeated the literature data to determine the configurations of the Michael adducts.[90b]

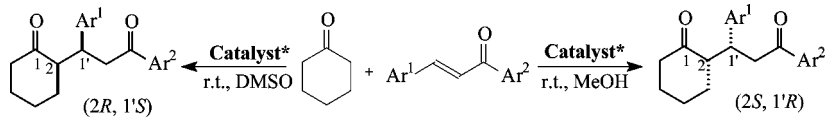
The authors assumed that the substrate is probably anchored to the catalyst through a strong hydrogen bond between catalyst and the amine group. Although attempts to detail the reaction mechanism have not yet been undertaken, the authors now propose a plausible transition state, representing the stereoselective and solvent dependence of Michael addition reactions of cyclohexanone with chalcones.[90a]

3.4. Asymmetric Baylis−Hillman Reaction

The Baylis−Hillman (BH) reaction allows the direct preparation of α-methylene-β-hydroxy carbonyl compounds from the corresponding α,β-unsaturated ketones and aldehydes.[91a,b] In the special thematic issue of *Chemical Reviews* on Organocatalysis,[71] recently published reports on asymmetric BH-type reactions are summarized in as many as two subsections.[81c,83a] Table 25 reports on an asymmetric intramolecular BH reaction, in which unexpected inversion took place.[92]

The BH reaction of hept-2-enedial with L-proline was examined in various solvents. Most reactions gave rise to the corresponding (*S*)-6-hydroxy-cyclohex-1-enecarbaldehyde, albeit with variable yields and enantioselectivities. Reactions in DMF and MeCN gave the highest yields, enantioselectivities, and reaction rates.[92] Surprisingly, the authors found that, in the presence of imidazole, the enantioselectivity of the reaction was completely reversed (entries 1−4). This selectivity is highly sensitive to the nature of the solvent and the temperature. In the case of D-proline, the phenomenon is similar, but the reaction proceeds with an ee of opposite direction (entries 5−8). This unprecedented and striking inversion of selectivity is most likely due to the formation of a new reactive intermediate, which also includes imidazole.[92] A short version of the reaction mechanism proposed by the authors is shown in Figure 11.

Table 24. Inversion in the L-Proline Ionic Liquid Catalyzed Michael Reaction



entry	ee (%)	yield (%)	Ar^1	Ar^2	yield (%)	ee (%)
1	78*	95	Ph	Ph	98	86
2	72*	98	4-MeC_6H_4	Ph	90	37
3	65*	94	4-ClC_6H_4	Ph	98	60
4	72*	88	Ph	4-ClC_6H_4	97	23
5	39*	90	4-BrC_6H_4	Ph	80	44
6	91*	85	Ph	4-$NH_2C_6H_4$	87	94
7	16*	99	2-ClC_6H_4	4-MeC_6H_4	99	29

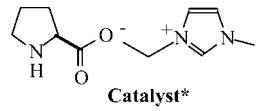
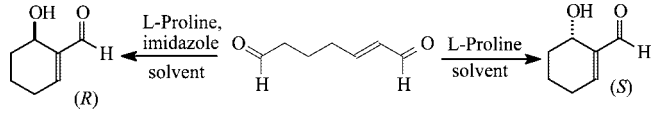


Table 25. Inversion in Intramolecular Baylis−Hillman Reaction



entry	ee (%)	conv. (%)	L-pro/imid (equiv)	solvent	temp. (°C)	L-proline (equiv)	conv. (%)	ee (%)
1	59*	71	0.1/0.1	MeCN	r.t.	0.1	67	15
2	24*	79	0.1/0.1	DMF	r.t.	0.1	73	45
3	80*	73	0.1/0.1	MeCN	0			
4	93*	72	1/1	MeCN	0			

entry	ee (%)	conv. (%)	D-proline (equiv)	solvent	temp. (°C)	D-pro/imid (equiv)	conv. (%)	ee (%)
5	41	75	0.1	DMF	r.t.			
6				MeCN	15	0.1/0.1	76	77*
7				MeCN	0	0.1/0.1	77	96*
8				MeCN	0	1/1	74	98*

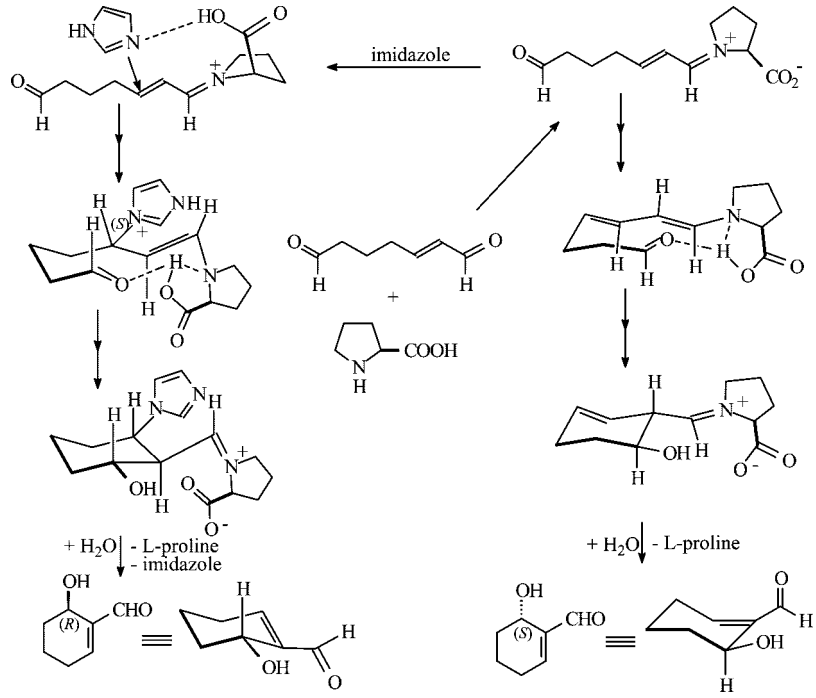


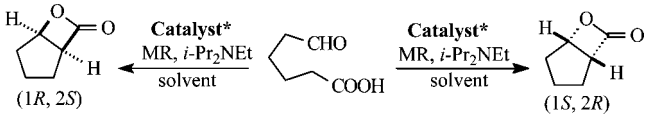
Figure 11. Proposed reaction pathways for the L-proline and the L-proline-imidazole cocatalyzed intramolecular Baylis−Hillman reactions.

3.5. Asymmetric β-Lactone Synthesis

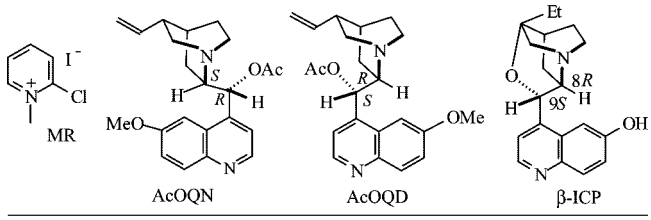
A new procedure for the synthesis of β-lactones has been developed by Wynberg et al.[93a,b] This process made use of the nucleophilic properties of *O*-acetyl quinine and *O*-acetyl quinidine to promote a [2 + 2]-cycloaddition between aldehydes and ketenes.[93c,d] Romo and co-workers disclosed the first examples of nucleophilic catalyzed aldol-lactonization reactions with nonactivated aldehydes utilizing C9-acylated cinchona alkaloids as nucleophilic catalysts.[94]

A further case of unexpected inversion was recognized in the course of studies on the stereochemistry of the reaction (Table 26).[94b] Namely, the presence of β-ICP (β-isocupreidine), a catalyst of rigid structure, was found to bring about complete reversal in the sense of ED. The result was surprising since, according to earlier concepts, the chirality of a reaction product is determined by the configurations of atoms C8 and C9 of the cinchona alkaloid present. The 3D structure of the β-lactone formed in the presence of β-ICP is (1*S*, 2*R*). This corresponded to the product obtained using AcOQN of configuration (8*S*,9*R*) rather than to that obtained in the presence of the AcOQD having identical configuration (8*R*,9*S*) with β-ICP. The authors conclude the description of this indeed surprising result by admitting that "we are not able to offer a satisfying explanation at this time".[94b] To our best knowledge, they have not published new results in this field ever since. It appears plausible that, in unexpected inversion, the OH group of β-ICP may play a role in the formation of the IC responsible for ED.

Table 26. Inversion in Intramolecular Asymmetric Aldol-Lactonization



entry	ee (%)	conv. (%)	Catalyst*	solvent	Catalyst*	conv. (%)	ee (%)
1	92	54	AcOQD	MeCN	AcOQN	51	86
2	92	54	AcOQD	MeCN	β-ICP	42	90*
3	92	21	AcOQD	DCM	β-ICP	18	90*

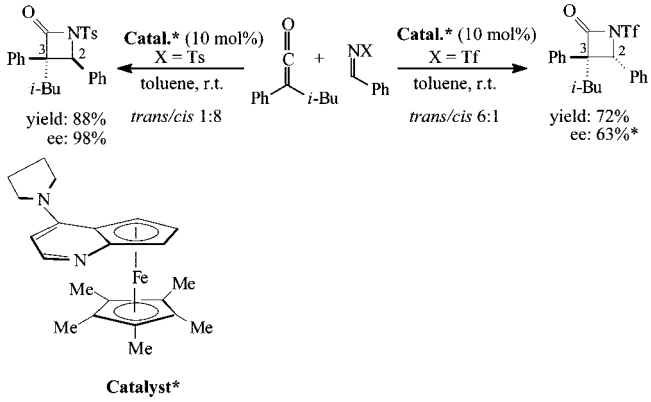


3.6. Asymmetric β-Lactams Synthesis

β-Lactams, compounds with structures similar to that of β-lactones, can be prepared by a synthesis similar to that developed by Staudinger. Owing to the significance of the type of compound involved, the method has been widely used.[93c,d,95] The planar chiral catalyst (PPY derivative **Catalyst***) applied in the interesting reversal in diastereoselectivity recognized in the Staudinger reaction is not purely an organocatalyst according to the accepted definition, because it also contains an inorganic atom.[96] Nonetheless, inversion is discussed in this section for two reasons. First, it is closely related to the previous subsection, and second, this reaction is probably discussed in ref 71 for a similar reason. The reaction exhibiting unexpected stereochemistry is shown in Scheme 12.[96b]

It is well-known that catalytic asymmetric syntheses of β-lactams are generally *cis*-selective.[96a,97] According to Scheme 12, *cis*-selectivity is reversed merely by the exchange of the protecting group for the imine from Ts to Tf. In the case of *trans* compounds, ee values as high as 89% were achieved, depending on the substituents. The probable mechanism of the process is described.[93d,96b] The key step of the reaction mechanism depends on whether the **Catalyst*** reacts with the ketone or with the imine first. Since the **Catalyst*** reacts quantitatively with an *N*-triflyl imine, in

Scheme 12. Inversion in the Staudinger Reaction to Form β-Lactam Enantiomers



this case an "imine-first" pathway is operative, whereas in the case of *N*-tosyl imine, the reaction takes the "ketone-first" pathway (Figure 12).

3.7. Asymmetric Aza-Henry Reaction

A series of chiral guanidines and bisguanidines were synthesized, and their effects on the catalyzed aza-Henry reaction were studied (Scheme 13). Lovick and Michael observed an unexpected inversion elicited by organocatalysts in the course of the aza-Henry reaction.[98]

Results with respect to the use of the two (*R*)−(*S*) enantiomer pairs achieving the highest ee values of opposite senses are outlined. In the case of monomeric catalysts (**M1**, **M2**), the (*R*)-products are formed in higher ee, whereas in the presence of dimeric catalysts (**D1**, **D2**), (*S*)-products are formed in higher ee. The mention of very recently published, unexpected preliminary data in this review is considered justifiable. A plausible model for the interpretation of unexpected inversion by authors is presented in Figure 13.

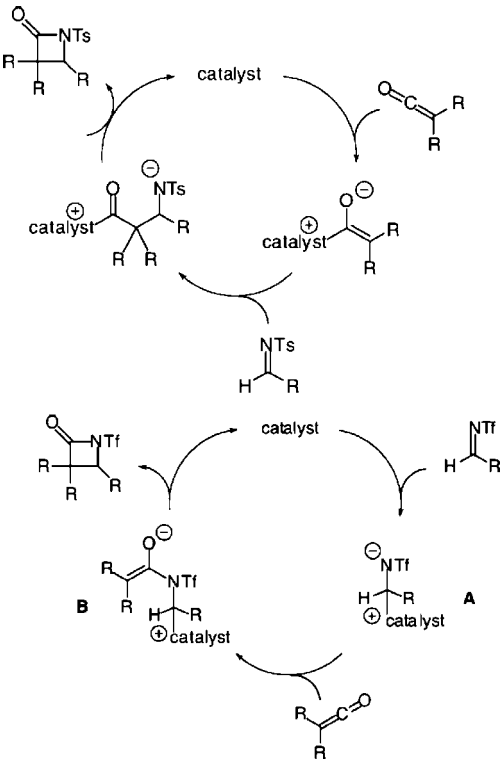


Figure 12. "Ketene-first" and an "imine-first" pathways for nucleophile-catalyzed Staudinger reactions.

Scheme 13. Inversion in Enantioselective Aza-Henry Reaction

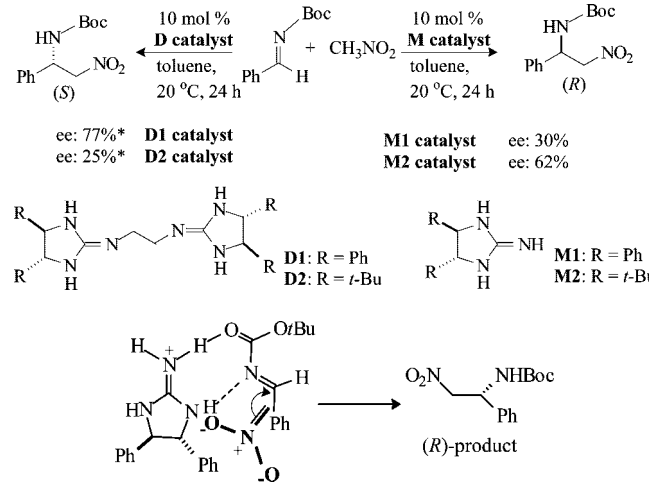


Figure 13. Assumed intermediate complex in the aza-Henry reaction catalyzed by monoguanidine-type organocatalyst.

3.8. Summary

Research on organocatalytic reactions, as compared to that of metal complex catalyzed processes, is still in the stage of data collection, in my opinion not only in the field discussed here. This is well-demonstrated by the number of examples listed in Table 27.

In Table 27, the examples collected in the literature are grouped according to reactions, with a few parameters indicated similarly to Table 15. The largest number of reactions exhibiting unexpected inversion of the sense of ED were found among aldol additions and Michael reactions. One example was identified in each of the Baylis−Hillman reaction, syntheses of β-lactone and β-lactam, and the aza-Henry reaction. The chiral organocatalysts used in these reactions can be classified into 3 groups: (i) base catalysts: alkaloids (mainly cinchona alkaloids), L-proline, and its derivatives; (ii) the salts of the former used as phase-transfer catalysts; (iii) other chiral organocatalysts (formamide- and phosphoramide-substituted, ferrocenyl-type (PPY derivative), guanidines). The largest number of examples for unexpected inversion was found among organocatalytic reactions utilizing L-proline and its derivatives, as well as cinchona alkaloids.

As regards the ee values attained, it is remarkable that it is possible to obtain both enantiomers in outstandingly high ee on the chiral catalyst of identical configuration after modifying some other parameter (Table 27, entries 6, 7, 9, and 12). The effects presumed to be responsible for the inversions are listed in column 5 of Table 27. The majority of these effects are minor differences in organocatalyst structure, achiral additives, and solvents used. The data in column 6 refer to the interpretation of unexpected inversions. This column, however, also illustrates the current state of organocatalytic research, because in this field only one experimentally verified interpretation could be found, a fact calling attention to further tasks.

The proposals of the authors regarding the interpretation of the reactions are included with the description of the experimental data. The authors usually plan to experimentally verify the observed unexpected phenomena in future experiments. On the basis of the outstanding results achieved in the field of organocatalysis in the last 10 years, it feels

Table 27. Inversions in Organocatalytic Reactions

entry	reactions	Catalysts*	R_{max}/S_{max}	effects	interpret-ation[a]	Table/Scheme in manuscript	ref
1	alkylation	$BnCD^+Br^-$	40/66	KOH, NaOH, temperature	A, B	Table 16	78a
2	allylation	formamide	68/30	[Catalyst*] HMPA	A, B	Table 17	79b,c
3	alkylation	(−) sparteine	60/46	substrate	A, B	Scheme 11	80
4	aldolization	L-proline	68/21	heterogeniz.	A	Table 38	83c
5	aldolization	L-proline, L-prolinol	−26/+54	catalyst* structure		Table 18	76b
6	aldolization	L-proline amides	99/91	additive: 4 Å MS	A, B	Table 19	85a
7	aldolization	phosphoramides	90/92	solvent		Table 20	86
8	Michael r.	$BnQN^+ Br^-$	50/61	solvent	A, B	Table 22	87c
9	Michael r.	CN	100/100	achiral addit. Solvent	A, B	Table 23	88a,b
10	Michael r.	L-$proline^- IL^+$	−78/+86	solvent	A, B	Table 24	90a
11	BH r.	L-proline	93/45	additive: imidazoline	A, B	Table 25	92
12	β-lactone synthesis	AcOQD, β-ICP	92/90	C8*, C9* configuration	B	Table 26	94b
13	β-lactam synthesis	ferrocenyl-PPY	63/98	protecting Ts or Tf	D	Scheme 12	96b
14	aza-Henry r.	guanidines	30/77	monomers, dimers	A, B	Scheme 13	98

[a] A = assumed, B = planned, and D = verified.

justified to expect the discovery of many more unexpected phenomena and significant progress in their research.

4. Unexpected Inversions in Heterogeneous Catalytic Asymmetric Reactions

The attention of researchers aware of the advantages of heterogeneous catalysis was aroused by the research of heterogeneous catalyzed asymmetric syntheses. The results achieved have been continuously summarized and evaluated by reviews and monographs.[99,6b] In the "Handbuch of Asymmetric Heterogeneous Catalysis", published very recently, the results of studies on different variations of asymmetric syntheses using heterogenized/immobilized chiral catalysts of a great variety of types are reviewed in about 200 subsections.[99j]

The new monograph reveals that the present objective of research on asymmetric heterogeneous catalysis is the development of active and reusable catalysts with stable structures. Simple test reactions are used, and studies on the reactions mechanism are not in the forefront of interest. Consequently, unexpected inversions are mostly observed in hydrogenations and only a few examples are found in the literature of other asymmetric syntheses, which naturally sets the direction of future tasks.

4.1. Asymmetric Hydrogenation

It is not surprising—following the discovery made by Sabatier and Senderens[100a]—that research addressing the preparation and investigation of the hydrogenation over heterogeneous chiral catalysts was started as early as the first one-third of the 20th century.[100b,c] It is well-known that the discovery of hydrogenations on metals with large specific surface areas significantly boosted the development of organic chemistry.

Chiral modifiers (**M***) used for the preparation of heterogeneous chiral catalysts were natural materials available such as hydroxycarboxylic acids, amino acids, chiral bases, and their easily synthesizable derivatives. Research led to the recognition of "modified catalysts".[101] Further multifaceted efforts resulted in the development of two modified chiral hydrogenation catalytic systems, namely, Ni catalysts modified by (*R*,*R*)-tartaric acid (TA-MNi)[102] and Pt catalysts modified by cinchona alkaloids (Pt-cinchona alkaloid; Orito reaction).[103] Similar catalyst systems employing other metals were also developed at the later stages of research.

It was found in the course of the experiments that, similarly to enzyme-catalyzed reactions, the two catalyst systems cannot be applied to enantioselective hydrogenations in general; in other words, they enable the attainment of high ee only in the hydrogenation of certain types of compounds. High ee values were initially achieved mainly in the hydrogenation of β-ketoesters using the TA-MNi catalyst system in the presence of NaBr (Scheme 14, Figure 14) and in that of α-ketoesters using the Pt-cinchona catalyst system (Scheme 15, Figure 15). The utilization of these two catalyst systems in various hydrogenations are the most intensively studied enantioselective heterogeneous catalytic reactions, which are also exploited on an industrial scale.[99b,104,105]

The main objective of recent studies on these two reactions was to expand their field of utilization, to elucidate the reaction mechanism, and to interpret the origin of ED. The

Scheme 14. Enantioselective Hydrogenation of β-Ketoesters over TA-MNi Catalyst

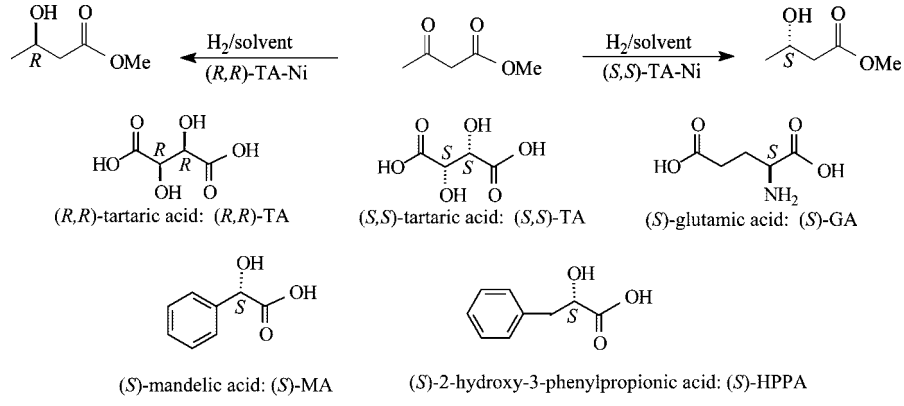
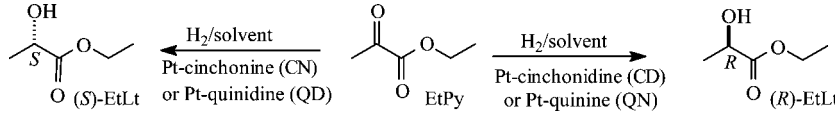


Figure 14. Chiral modifiers in preparation of modified Ni catalysts.

Scheme 15. Stereochemistry of the Orito Reaction



significance of these reactions is underlined not only by the high enantioselectivities (above 90%) observed (in the case of TA-MNi[106,107] and in the case of the Orito reaction[108–110]) but also by numerous reviews discussing and evaluating the steady flow of novel results in the heterogeneous catalytic enantioselective hydrogenations.[6,99f–i,111–115]

As regards the stereochemistry of the processes outlined in Schemes 14 and 15, it was recognized already at the time of the discovery of the reactions that the catalyst modified by (*R*,*R*)-TA promotes the formation of an excess of the (*R*)-product, whereas the one modified by (*S*,*S*)-TA promotes the formation of the (*S*)-product in excess (Scheme 14). As shown in Scheme 15, the presence of C8(*S*),C9(*R*) cinchonas (CD,QN) promotes the formation of (*R*)-α-hydroxy carboxylic acid esters in excess, whereas C8(*R*),C9(*S*) cinchonas (CN,QD) induce the formation of (*S*)-α-hydroxy carboxylic acid esters. The term "inversion of enantioselectivity" in the title of the manuscript implies the formation of products with opposite configurations from Schemes 14 and 15.

Unexpected inversion of enantioselectivity in the heterogeneous catalyzed enantioselective hydrogenations reaction had been reported,[106a,111b,116–121] but—due to the low ee values involved—these results aroused little attention. Since the publication of refs 122and 123, however, the inversion of ED has become a preferred research objective, because it yields important new information regarding the reaction mechanism.

4.1.1. Hydrogenation of Ketones over Ni Catalysts

Scheme 14 demonstrates the experimentally verified basic scheme of the stereochemical course of enantioselective hydrogenation on Ni catalyst modified by TA on the most often studied model substrate, methyl acetoacetate. According to Scheme 14, hydrogenation of methyl acetoacetate produces an excess of (*R*)-methyl hydroxybutyrate on (*R*,*R*)-TA-Ni catalyst and an excess of (*S*)-methyl hydroxybutyrate on (*S*,*S*)-TA-Ni catalyst.[111b,113d]

It was soon recognized that a careful observance of the conditions of catalyst preparation is essential for achieving high ee values. For example, according to observations made at the initial stages of these studies, the enantioselectivity of

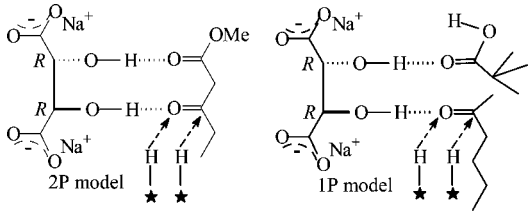
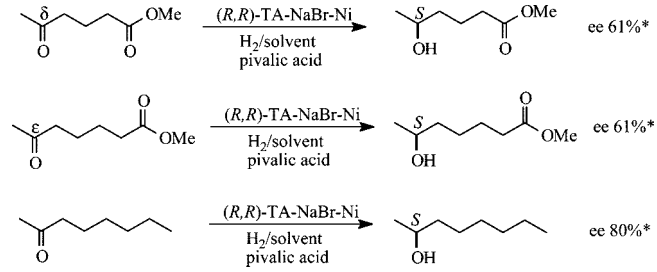


Figure 15. Proposed enantiodifferentiation models in hydrogenation of ketones over (*R*,*R*)-TA-MNi catalyst.

Scheme 17. Inversion in Enantioselective Hydrogenation of Ketones



Ni catalysts modified by various amino acids was profoundly influenced by the temperature and the pH during the preparation of the chiral catalyst[111b] (Scheme 16).

During the decades elapsed since the discovery of the reaction, research on the reaction mechanism has mostly been focused on catalyst modified by (*R*,*R*)-TA. Whether or not hydrogenation governed by a stereochemistry different from that shown in Scheme 14, i.e., one that yields an excess of the (*S*)-product on a catalyst modified by (*R*,*R*)-TA, was observed depended on the structure of the ketone to be hydrogenated (Scheme 17).

After the principles governing the direction of ee formation (namely, that on Ni catalysts modified by (*R*,*R*)-TA hydrogenation of α-, *β*-, and *γ*-ketocarboxylic acid esters yields (*R*)-hydroxycarboxylic acids in excess, whereas hydrogenation of *δ*- and *ε*-ketocarboxylic acids esters, as well as of alkanones, produces the corresponding (*S*)-compounds in excess) became widely known,[113d,f,115a] to our best knowledge unexpected inversion has not been mentioned in the literature. From the multiple variants of models interpreting the stereochemistry of these processes, two models, namely, the Two Hydrogen Bonds stereochemical model (2P model) and the One Hydrogen Bond and a Steric Repulsion model (1P model) are schematically represented in Figure 15.

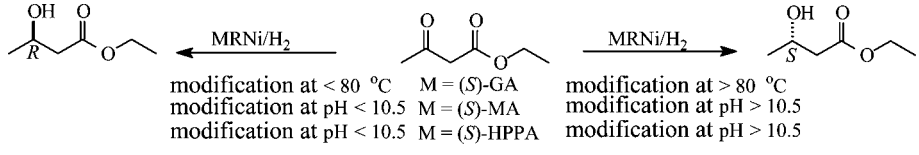
On the basis of reflection absorption infrared spectroscopy (RAIRS) and scanning tunneling microscopy (STM) studies, Baddeley et al. proposed that the altered ee can be attributed to the presence of the diketo and enol tautomers of methyl acetoacetate.[124]

4.1.2. Hydrogenation of Activated Ketones over Pt Catalysts

The chiral molecules utilized for the modification of chiral Pt catalysts are summarized in Figure 16.

Hydrogenation of Pyruvates. EtPy is the most commonly used model compound of studies on the Orito reaction; it is, therefore, not surprising that the discovery of unexpected inversion is also associated with EtPy. In 1993, Augustine et al. were the first to report unexpected inversion under the

Scheme 16. Inversion in Enantioselective Hydrogenation of Methyl Acetoacetate



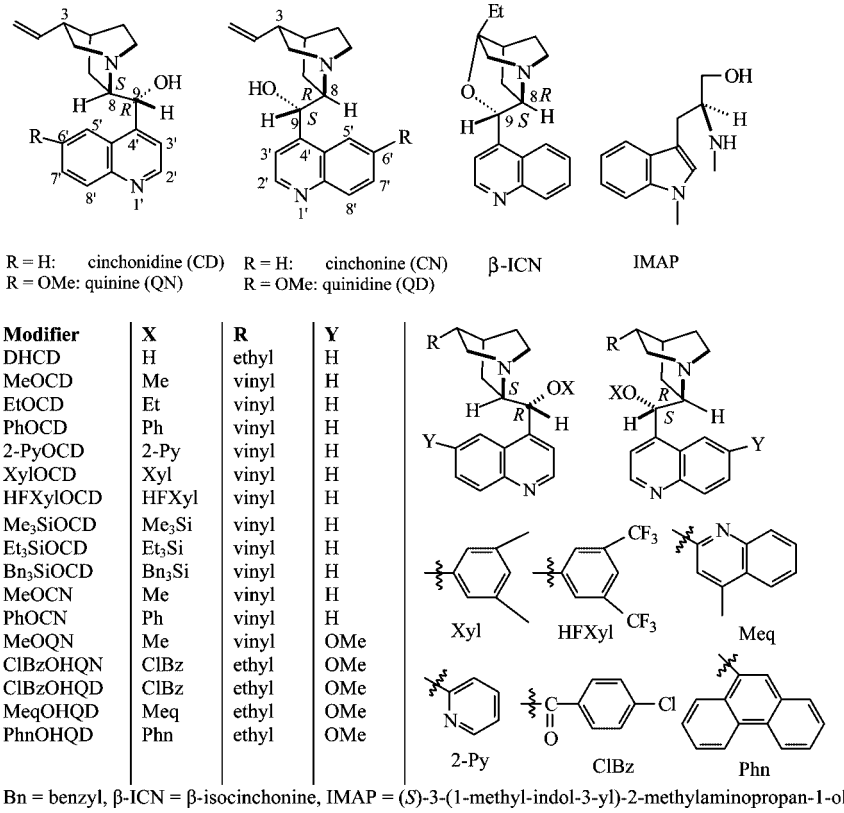


Figure 16. Cinchona alkaloids and derivatives used in this section.

conditions of the Orito reaction[118] (Table 28, entry 2), namely, the formation of (*S*)-EtLt was observed when very low concentrations of the alkaloid modifier were used, whereas at higher modifier concentrations, (*R*)-EtLt was produced. The formation of (*R*)-EtLt was accompanied by an increase in hydrogenation rate. The formation of (*S*)-EtLt is attributed mainly to the corner atoms, whereas the adatoms are considered to be responsible for (*R*)-EtLt formation. It is unfortunate that the measurements were not performed in AcOH at systematically varied CD concentrations, where high ee can be achieved. Thus, even though the surface active sites were adequately characterized, the optimal reaction conditions required for high ee were not provided. That is why the role of active sites of different types in ED could not be unequivocally verified.

In 2002, a remarkable observation made on the hydrogenation of EtPy, the most commonly studied model substrate of the Orito reaction, was reported in ref 123, methyl acetoacetate. According to ref 123, hydrogenation carried out in toluene, in the presence of β-ICN, an ether derivative with C8C9 configuration identical with CN, yielded (*R*)-EtLt in 48% ee, even though according to the relationships accepted at the time the product formed in excess should have been (*S*)-EtLt (entry 6). A significant solvent effect was observed in the course of the studies on the chiral catalyst β-ICN-Pt: in AcOH, unlike in toluene, the expected (*S*)-EtLt was formed in excess (Figure 17). This was the first significant experimental observation indicating that, in enantioselective hydrogenation initiated by cinchona alkaloids, it is not solely the C8 chiral center of the alkaloid that controls the sense of chiral induction.

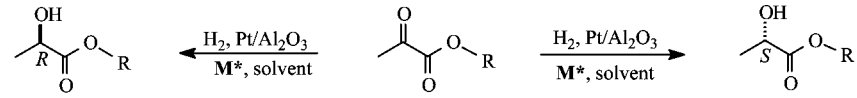
On the basis of the significant solvent effect, the inversion was explained by a change in the reaction mechanism.[123,126] It is therefore expedient, for the interpretation of inversion, to outline the existing views on the mechanism of the enantioselective hydrogenation of activated ketones, characterized by the structure of the IC responsible for ED (Figure 18).[6,114]

The quinuclidine nitrogen of β-ICN acts either as a nucleophile (**C** or **D** type in Figure 18) or as an electrophile (upon protonation) (**A**, **B**, or **F** type) to interact with the α-carbonyl group of the EtPy. Consequently, the structure of the IC responsible for chiral induction depends on the solvent applied (AcOH, toluene). The proposed structures of 1:1 β-ICN-EtPy IC-s in AcOH and in toluene are shown in Figure 19. In AcOH, β-ICN participates in the formation of the 1:1 complex as a protonated electrophile (Figure 19A), whereas in toluene it binds EtPy as a nucleophile (Figure 19B). To interpret the enantioselective hydrogenation in the Pt/β-ICN chiral catalyst, the role of other organometallic type surface complex (**E**) may not be ruled out either.[134a,b]

The ability of β-ICN to cause inversion was also demonstrated over Rh/alumina catalyst in the hydrogenation of not only EtPy but also ethyl 3-methyl-2-oxobutyrate[127] (entries 7 and 19−22). According to the authors: (i) the formation of the opposite enantiomer in small excess in protic solvents is attributed to the formation of solvent−substrate and solvent−modifier complexes that disturb the enantioselection on cinchona-modified Rh; (ii) the adsorption modes of β-ICN and CN during enantioselective hydrogenation on Rh are considerably different. The latter can be agreed with, because with adsorption being one of the steps of the mechanism, a change in adsorption mode may entail a change in reaction mechanism.

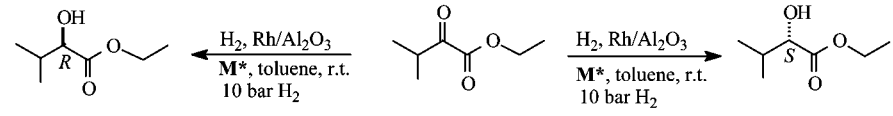
As shown in Table 28, the majority of these studies revealed unexpected inversion upon varying the concentration or structure of cinchonas (C9-OR cinchonas)[127−132] (entries 8−18). The authors of ref 128 emphasize the change in adsorption mode of the chiral modifier in their interpretation of unexpected inversion; in our opinion, such a change may

Table 28. Inversions in Hydrogenation of Pyruvates



entry	ee (%)	M*	solvent	temp. (°C)	H_2 (bar)	R	M*	solvent	ee (%)	ref.
1[a]	70	CD	EtOH	24	70	Me	CN	EtOH	65	120
2	20	High [DHCD]	MeOAc	25	1	Et	Low [DHCD]	MeOAc	8*	118
3	18*	PhnOHQD	EtOH	20	100	Et	PhnOHQD	AcOH	4	121
4	11*	MeqOHQD	EtOH	20	100	Et	MeqOHQD	AcOH	13	121
5	37	IMAP	Toluene	25	1	Et	IMAP	AcOH	9*	125
6	48*	β-ICN	Toluene	25	1	Et	β-ICN	AcOH	50	123,126
7[b]	27*	β-ICN	Toluene	r.t.	10	Et	CN	Toluene	41	127
8	74	CD	Toluene	r.t.	1	Et	XylOCD	Toluene	32*	128
9	8*	[ClBzOHQD]	DCM	r.t.	50	Et	Low [ClBzOHQD]	DCM	32	129
10	20	[ClBzOHQN]	DCM	r.t.	50	Et	High [ClBzOHQN]	DCM	14*	129
11[a]	17*	[ClBzOHQD]	Gas-phase	10	50	Et	Low [ClBzOHQD]	Gas-phase	15	130
12[a]	15	Low [ClBzOHQN]	Gas-phase	10	50	Et	High [ClBzOHQN]	Gas-phase	10*	130
13	80	CD	THF	r.t.	1	Et	Me_3SiOCD	THF	28*	131
14	80	CD	THF	r.t.	10	Et	PhOCD	THF	36*	132
15	80	CD	THF	r.t.	10	Et	Et_3SiOCD	THF	20*	131
16	80	CD	THF	r.t.	10	Et	Bn_3SiOCD	THF	19*	131
17	52	2-PyOCD	THF	r.t.	10	Et	PhOCD	THF	36*	132
18	15*	[c]	EtOH	0	60	Et	CN	EtOH	26	133

[a] Pt/silica; [b] Rh/alumina, [c] after removal the soluble fraction of the CN



entry	ee (%)	M	M	ee (%)	ref.
19	50	CD	CN	43	127
20	29	QN	QD	19	127
21	33*	β-ICN	CN	43	127
22[a]	21*	β-ICN			127

[a] solvent: AcOH

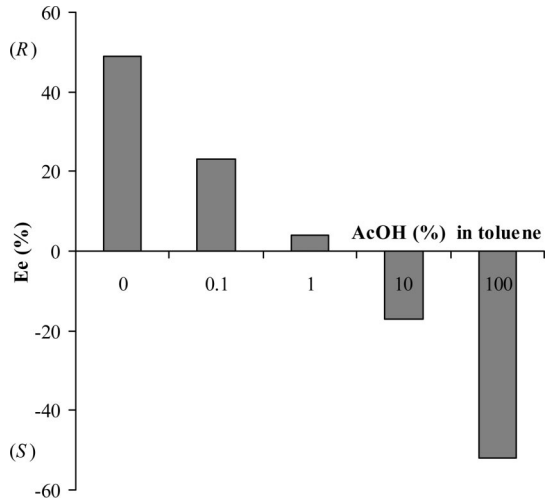


Figure 17. Hydrogenation of EtPy to (*R*)- and (*S*)-EtLt on β-ICN modified Pt/alumina in toluene and AcOH mixtures (room temperature (r.t.), 1 bar H_2).

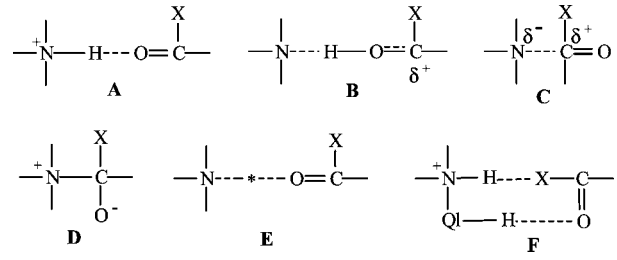


Figure 18. Assumed intermediate complexes in the enantioselective hydrogenation of activated ketones (X = activating group, Ql = quinolinyl).

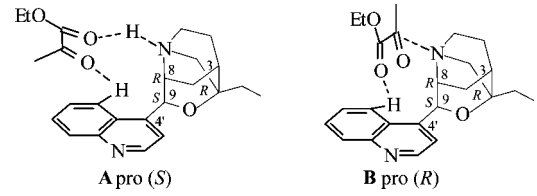


Figure 19. Proposed structures of intermediate complexes in electrophilic (A) and nucleophilic-type (B) interactions betveen EtPy and β-ICN.

be associated with changes in certain steps of the reaction mechanism. Dependence of inversion on the concentration of the chiral modifier is reported in ref 129. This was the first example where enantio-inversion was induced solely as a function of the chiral modifier concentration (entries 9 and 10).

In the study of ether derivatives of CD,[121,128,129,131,132] the crucial role of steric bulkiness of the ether groups in the inversion of the sense of enantioselection was shown as the bulky ether group occupies the chiral space available for the adsorption of the substrate in case of the CD. Demonstrative results of studies on CD, PhOCD, and 2-PyOCD under identical experimental conditions are presented in Figure 20.[132] The comparison of PhOCD and 2-PyOCD modifiers provides an even more intriguing example as their van der Waals volumes and adsorption modes on Pt/Al_2O_3 are very

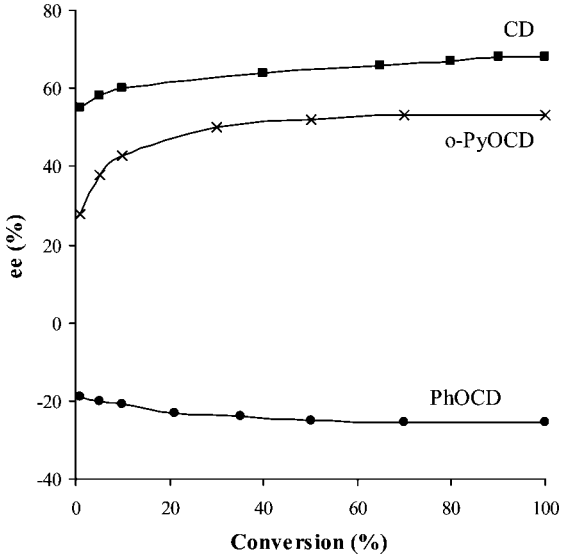


Figure 20. Hydrogenation of EtPy in THF over CD-Pt, 2-PyOCD-Pt, and PhOCD-Pt chiral catalysts.

similar, but an additional substrate-modifier interaction possible only for 2-PyOCD inverts the ee.

Inversion has also been observed under conditions other than those of the Orito reaction (entries 11 and 12).[130] It has been shown that enantioselective hydrogenation of pyruvates can be carried out using gas-phase reactants,[130] thereby avoiding the complicating factor of solvent effects. At low ClBzHQD modifier concentration, the (*S*)-lactate is the preferred product, and at higher concentrations, (*R*)-lactate is favored. The inversion effect is discussed by the authors in terms of the interaction of the substrate and modifier with the catalyst surface. The modifier interactions with different sites on the heterogeneous catalyst lead to different senses of enantioselection.

In the continuous fixed-bed reactor (CFBR), unexpected inversion was observed in the hydrogenation of EtPy over CN-Pt catalyst after removal of the soluble fraction of the modifier in 50 °C, that is, in the presence of chemisorbed CN (entry 18).[133] On the authors opinion these modifications can be summarized as (i) alteration of platinum crystallites inducing some ee retention and (ii) some sort of support effect inducing a reversal in ee.[133]

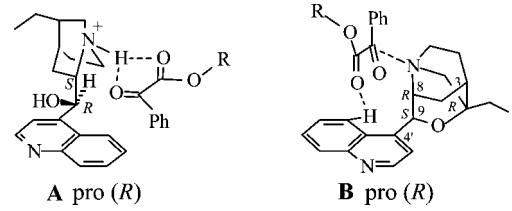


Figure 21. Assumed structures of intermediate complexes in electrophilic (A) and nucleophilic-type (B) interactions betveen phenylglyoxylic acid esters and modifiers.

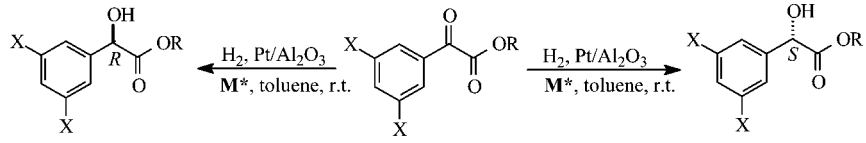
Hydrogenation of Phenylglyoxylic Acid Esters. The enantioselective hydrogenation of phenylglyoxylic acid esters was significantly slower than that of EtPy. The ee values in unexpected inversion in hydrogenations in toluene over β-ICN-Pt,[134c] but especially over PhOCD-Pt chiral catalysts, are remarkably high (Table 29). The highest ee so far reported in unexpected inversion is 78% (*S*) (entry 12).

The experimental data of conversions and ee suggest that both electronic and steric factors may play a role in determining the rate of enantioselective hydrogenation and ee. In the case of compounds containing methyl and cycloalkyl groups (entries 1−4), steric factors predominate, whereas in the case of aromatic groups, mainly electronic factors that may naturally affect hydrogenation rate and ee predominate (entries 5−7).

On the basis of investigations in the hydrogenation of the bulkier α-ketoesters, steric effects seem to play a more important role in the inversion of ED than in hydrogenation without inversion. For a CD-Pt chiral catalyst in AcOH, the IC is generated through the interaction of the protonated CD (Figure 21A). The inversion of bulky phenylglyoxylic acid esters on β-ICN-Pt chiral catalyst, like that of EtPy, was interpreted on the basis of the nucleophilic mechanism. The surface complex responsible for the enantioselection is probably formed by the interaction between the nucleophilic N atom of the quinuclidine skeleton and the electrophilic C atom of the keto group of the substrate[134c] (Figure 21B). In the case of PhOCD, the inversion is probably due to the steric bulkiness of the phenoxy group relative to that of the OH function and also to a change in the adsorption geometry on the alkaloid, resulting in a shift in the position of the interacting function, the quinuclidine N atom.[136]

Hydrogenation of Ketopantolactone. The first experimental observation was made by Baiker's group in 2003.[137]

Table 29. Inversions in Hydrogenation of Esters of Phenylglyoxylic Acids



entry	ee (%)	M*	H_2 (bar)	R	X	M*	ee (*S*%)	ref.
1	50*	β-ICN	1	Me	H	CN	78	134c,135
2	46*	β-ICN	1	Cyclohexyl	H			134c
3	50*	β-ICN	1	Adamantyl	H			134c
4	35*	β-ICN	1	Decalyl	H			134c
5	8*	β-ICN	1	Ph	H			134c
6	54*	β-ICN	1	1-Naphthyl	H			134c
7	20*	β-ICN	1	2-Naphthyl	H			134c
8	92	CD	10	Et	Me	PhOCD	52*	136
9	87	CD	10	Et	F	PhOCD	68*	136
10	66	CD	10	Et	CF_3	PhOCD	48*	136
11	94	CD	10	Et	MeO	PhOCD	73*	136
12	95	CD	10	*t*Bu	H	PhOCD	78*	136
13[a]	52	CD	1	Et	H	[b]	15*	133
14	86	CD	10	Et	H	PhOCD	31*	136

[a] EtOH, 0°C; [b] after removal the soluble fraction of the CD

The experimental data revealed that, in the presence of the chiral modifiers CD, MeOCD, and EtOCD, the product with the expected configuration, i.e., (*R*)-PL, was formed in higher ee, whereas in the presence of bulky C9-ethers (PhOCD, Me_3SiOCD) as chiral modifiers, the formation of (*S*)-PL was induced in excess (Table 30, entries 1, 2, 9, and 10).

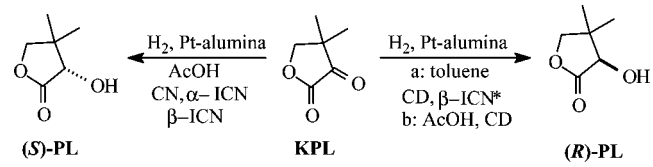
In both cases, the configurations of the C8,C9 carbon atoms of CD and its derivatives, responsible for chiral induction, were identical, which means that the inversion of enantioselectivity was brought about by the bulky C9-ethers. As no experimental evidence was available at the time for the interpretation of the phenomenon, it was concluded that introduction of the bulky trimethylsilyl or phenyl substituents changes dramatically the chiral pocket available for the adsorption of KPL over the Pt surface and leads to the favored adsorption of KPL on the opposite enantioface.

It was assumed that Me_3SiOCD and PhOCD do not adsorb via the quinoline ring, being approximately parallel to the Pt surface (π-bonding) but rather in a tilted position (*N*-lone pair bonding).[137] This change in the adsorption geometry should result in a considerably weaker adsorption of these modifiers compared to the adsorption of CD. In this tilted position, the modifier adsorbs less strongly via the quinoline N, and also the position of the interacting function, the quinuclidine N, is shifted. This shift results in a different shape and size of the "chiral pocket" available for adsorption of the activated ketone substrate.[128,141]

The performance of a new modifier, 2-PyOCD, is compared to that of PhOCD and CD.[132] In the hydrogenation of KPL, the bulky *O*-phenyl group favors the (*S*)-enantiomer, whereas in the case of the 2-pyridyl group, the (*R*)-alcohol is the major product (entry 11). Various catalytic studies, ATR-IR spectroscopy using conditions of Orito reaction, and theoretical calculations of the modifier−substrate interactions suggest that formation of two N−H−O-type H bonds—involving the quinuclidine and pyridine N atoms, and the two keto-carbonyls in the substrate—controls the adsorption of the substrate during hydrogen uptake.[132]

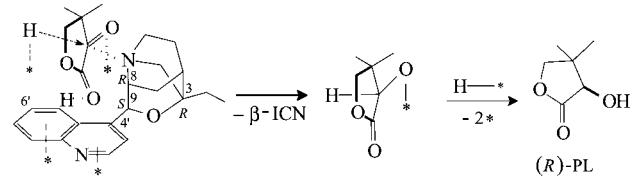
We have also studied the enantioselective hydrogenation of KPL in toluene on β-ICN-Pt chiral catalyst.[139] Enantioselective hydrogenation yielded an excess of (*R*)-PL, i.e., inversion of enantioselection took place, since the (*R*)-configuration is opposite to what is expected from the absolute configuration of the CN backbone (entries 4−6).

Scheme 18. Stereochemistry of Enantioselective Hydrogenation of Ketopantolactone



∗ inversion of enantioselectivity

Scheme 19. Nucleophilic Mechanism in Hydrogenation of Ketopantolactone over β-ICN-Pt Chiral Catalyst

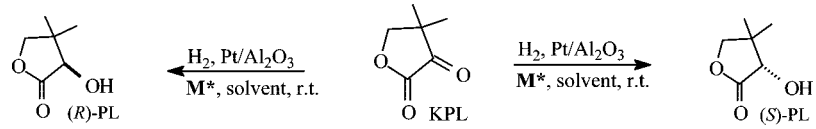


Both the reactant and the chiral modifier used in these studies were rigid molecules of well-known structures. Thus, these studies have yielded new information, contributing to a deeper understanding of the enantioselective hydrogenation of activated ketones, because structural rigidity prevents conformational movements. The stereochemistry of the enantioselective hydrogenation of KPL and its dependence on the solvent as well as the presence of chiral modifiers CD, CN, α-ICN, or β-ICN are summarized in Scheme 18.

In this case, we proposed again the nucleophilic mechanism for the interpretation of inversion (Scheme 19), in view of the fact that in toluene there was inversion, whereas in AcOH there was no inversion (entry 4).

On the basis of our experimental data and on the verified open-3 conformation of β-ICN[142,143] as well as on the widely accepted adsorption model,[6,113b,c,114,115c,144] the proposed structure of the ICs responsible for the enantioselectivity is outlined in Figure 22. The formation of such nucleophilic complexes has been verified by NMR measurements in the liquid phase.[145a] There is a correlation between the solution-state concentration of the nucleophilic 1:1 modifier−substrate complex and the ee on enantioselective hydrogenation of KPL using β-ICN-Pt chiral catalyst.[145b] These results confirm the earlier suggestion regarding the direction of ED:[145c] the sense of ED is controlled by the conformation of the adsorbed

Table 30. Inversion in Hydrogenation of Ketopantolactone



entry	ee (%)	M*	solvent	H_2 (bar)	M*	solvent	ee (%)	ref
1	40−80	CD, MeOCD	toluene	40	PhOCD	toluene	55*	137
		EtOCD	THF		Me_3SiOCD	THF	35*	
2	40−73	CD, MeOCD	$PhCF_3$	40	ArOCD	$PhCF_3$	37*−53*	128
		EtOCD			Ar = Ph, Xyl., HFXyl., β-naphthyl			
3[a]	25−40	CD	aprotic solvents	10	PhOCD	aprotic solvents	15*−25*	138
4	46*	β-ICN	toluene	1	β-ICN	AcOH	5	139
5	46*	β-ICN	toluene	1	CN	toluene, AcOH	52	139
6				1	CN		55	
7[a]	54*	β-ICN	toluene	10	CN	toluene, AcOH	25	127
8[a]	11*	β-ICN	AcOH	10	CN	AcOH	1(*R*)	127
9	16	HFXylOCD	THF	1	PhOCD	THF	21*	140
10				1	XylOCD	THF	36*	140
11	50, 31	CD, 2-PyOCD	THF	10	PhOCD	THF	21*	132

[a] Rh/alumina.

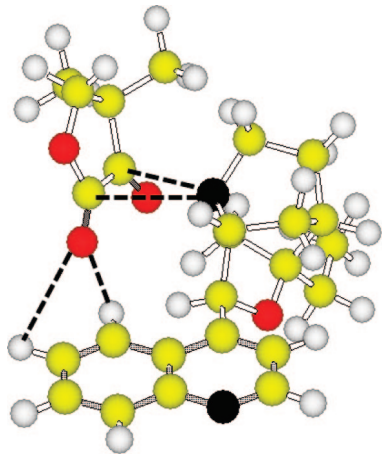


Figure 22. Proposed structure of pro (*R*)-intermediate complex between KPL and β-ICN (black spheres = N atoms, pink spheres = O atoms, yellow spheres = C atoms, white spheres = H atoms).

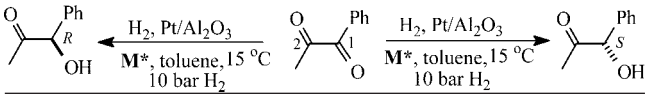
reactant−chiral modifier (1:1) complex. It was repeatedly verified that solvents may have a profound effect on reaction mechanism.

The ability of β-ICN to cause inversion was also confirmed in the hydrogenation of KPL on Rh/alumina catalyst (entries 7 and 8).[127] Comparison of the experimental data of KPL hydrogenation in toluene and AcOH, over chiral catalysts CN-Pt, β-ICN-Pt, CN-Rh, and β-ICN-Rh, reveals that, although the experimental conditions are somewhat different, studying the origin of chiral induction still demands intensive experimentation in this field.

Hydrogenation of α- and β-Diketones. The most often studied model compound of the Orito reaction of α-diketones is 1-phenylpropane-1,2-dione (PPD), whereas those of β-diketones are 1,1,1-trifluoro-2,4-diketones. Experimental results published on inversion observed in the enantioselective hydrogenation of α-diketones and β-diketones are summarized in Tables 31 and 32, respectively. Because of the presence of the two carbonyl groups, the hydrogenation process is the result of several competitive and consecutive reactions, which are illustrated for PPD hydrogenation in Scheme 20. The experimental data reported in ref 146 shed light on numerous relationships governing the individual reactions of the hydrogenation of α-diketones.

The experimental data of the unexpected inversion of the primary reactions proceeding with the highest selectivity

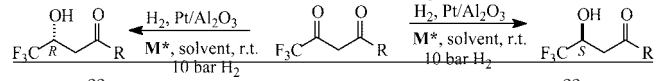
Table 31. Inversion in Hydrogenation of 1-Phenylpropane-1,2-dione



entry	ee (%)	M*	M*	ee (%)	ref
1	57	CD	MeOCD	2*	146a,b
2[a]	7	CD	MeOCD	2*	146a
3	16*	MeOCN	CN	27	146b
4	35	QN	MeOQN	3*	146b
5	60	CD	MeOCD	10*	146c
6	60	CD	PhOCD	27*	146c
7[a]	11	CD	PhOCD	5*	146c
8	32*	MeOCN	CN	18	146c
9	30*	PhOCN	CN	18	146c
10	28*	Me_3SiOCN	CN	18	146c
11	28*	*t*-$BuMe_3SiOCD$	CN	18	146c

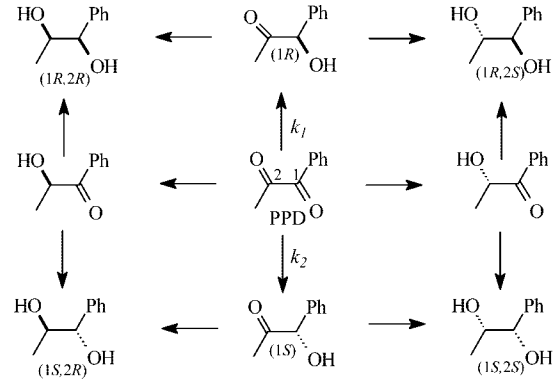
[a] Solvent = AcOH.

Table 32. Inversions in Hydrogenation of β-Diketones



entry	ee (%)	M*	solvent	R	M*	solvent	ee (%)	ref
1	31*	HFXylOCD	toluene	Me	MeOCD	toluene	68	128
2	13*	MeOCD	DMF	*t*-Bu	MeOCD	AcOH	15	147a
3	8*	CD	DMF	*t*-Bu	CD	THF	36	147a
4	22*	MeOCD	AcOH	Ph	MeOCD	toluene	2	147a

Scheme 20. 1-Phenyl-1,2-propanedione Hydrogenation



among those outlined in Scheme 20 (k_1, k_2) are shown in Table 31.[146] The data in Table 31 indicate the determinant role of modifiers in inversion. In this respect, the effect of C9-OR modifiers on the sense of ED is especially remarkable. The most extensive inversion was brought about by cinchonine ethers during hydrogenation in toluene (entries 8−11). A characteristic example is the case of MeOCN and CN: under identical experimental conditions, unexpected (*R*)-product was formed in 32% ee in the hydrogenation of the C1 ketone group of PPD, whereas the expected (*S*)-product was generated in 18% ee on CN-Pt chiral catalyst (entry 8).[146c] This is an important observation concerning the nature of the chiral site on the Pt surface. The observed inversion of ED induced by the cinchona alkaloid ether modifiers in toluene indicates that the ED steps over the Pt-cinchona alkaloid and Pt-cinchona alkaloid ether chiral systems, that is, different types of substrate−modifier complexes are involved.[146c]

To the best of our knowledge, the activated β-diketones that have been subjected to enantioselective studies are the 3 compounds shown in Table 32.[128,147] In cases where identical modifiers were used, the experimental data suggest a solvent effect (entries 2−4); in hydrogenations carried out under identical experimental conditions, the data confirm the determinant role of chiral modifiers.

In the interpretation of inversion, the authors emphasize the change in the adsorption mode of the chiral modifier, which has been discussed in detail for KPL. This assumption is in agreement with the results of studies on the hydrogenation mechanism of trifluoromethyl-β-diketones, which revealed by a combination of catalytic, NMR, and FTIR spectroscopic and theoretical methods that the two phenomena are coupled, offering the unique possibility for understanding the substrate−modifier−metal interactions. The high chemo- and enantioselectivities are attributed to the formation of an ion pair involving the protonated amine function of the chiral modifier and the enolate form of the substrate.[147b]

Hydrogenation of α-Hydroxyketones. Baiker et al. performed multifaceted investigations on the enantioselective hydrogenation of α-hydroxyketones and one of their ether

derivatives (2-methoxyacetophenone).[132,148] The experimental data on inversion that have allowed many important conclusions to be drawn are summarized in Table 33. As a result of the very first experiments, it was established[148a] that CD showed by far the best catalytic performance affording ee's, between 57 and 82% depending on the substrate. MeOCD, in turn, showed poor ED. PhOCD favored the opposite enantiomer compared to CD (entries 1 and 2). Among solvents, *t*-butyl methyl ether proved to be the most suitable. All four reactants show the same general trend with respect to dependence on solvent, hydrogen pressure, and modifier. The phenyl ring or a fixed system is essential for ED. Furthermore, the oxygen in α-position to the ketone plays a crucial role for achieving high ee.

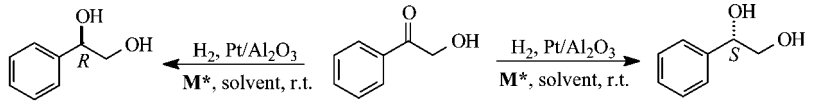
Changing the modifier from CD to PhOCD resulted in a switch of the major enantiomer of the product on Rh/alumina catalyst as well. Hydrogenation of 2-hydroxyacetophenone showed a switch from 73% ee in favor of the (*R*)-product to 68% ee for the (*S*)-product when the modifier was changed from CD to PhOCD (entry 3).[148b]

The inversion of the ee is interpreted in terms of repulsive modifier−reactant interactions, which become more pronounced as the steric demand of the C9-OR group of the modifier increases. The obvious importance of an oxygen-containing group (ketone, hydroxyl, methoxy) in α-position to the ketone that hydrogenated is rather assigned to a lowering of the transition state energy for hydrogenation due to hydrogen bonding, as previous calculations suggested.[148a] One of the latest reports on the inversion of the sense of ED presents new experimental data on the enantioselective hydrogenation of 2-methoxyacetophenone (entries 9−13) and on the effect of the new chiral catalyst 2-PyOCD-Pt.[132] The main conclusions of these studies have been discussed in the subsections on EtPy and KPL.

Hydrogenation of α-Trifluoromethylketones. This subsection summarizes inversions observed in the course of the enantioselective hydrogenation of trifluoromethylalkyl, cycloalkyl, and aryl ketones (Table 34). Ethyl trifluoroacetoacetate is hydrogenated over MeOCD-Pt catalyst, in AcOH in 90 (*S*) % ee (entry 1).[149] The authors later observed—under different experimental conditions—a so far unknown inversion at later stages of conversion (entry 2).[122] Figure 23 shows that the ee value decreased gradually after an initial constant period (87% (*S*)) and dropped to 27% (*S*) at full conversion. The sense of ED was inverted, and the (*R*)-product became dominant. According to the data obtained by NMR, inversion is not due to hydrogen addition at the carbonyl group but to hydrogenolysis of the C−O bond in the geminal diol (Scheme 21).

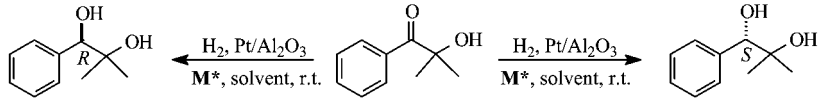
Inversion of ED sense has also been observed with the application of CD-OAr chiral modifiers (entries 3−5).[128] Inversion was interpreted on the basis of a change in the adsorption mode of the chiral modifier, similarly to the case of EtPy and KPL hydrogenation.[128] Hydrogenation of trif-

Table 33. Inversions in Hydrogenation of α-Hydroxyketones

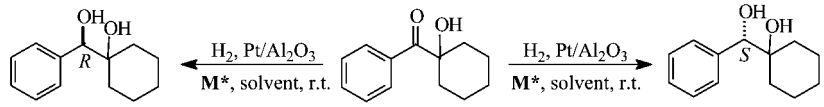


Entry	ee (%)	M*	Solvent	H_2 (bar)	M*	Solvent	ee (%)	Ref.
1	77	CD	*t*-BuMe ether	5	PhOCD	*t*-BuMe ether	31*	148a
2	10	MeOCD	*t*-BuMe ether	5	PhOCD	*t*-BuMe ether	31*	148a
3[b]	73	CD	dioxane	60	PhOCD	dioxane	68*	148b

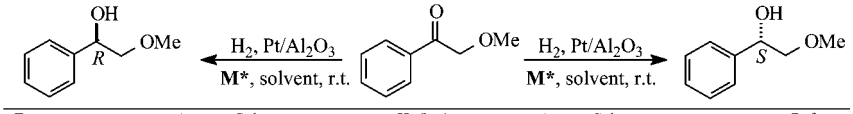
[b] Rh/alumina, 15 °C



Entry	ee (%)	M*	Solvent	H_2 (bar)	M*	Solvent	ee (%)	Ref.
4	57	CD	*t*-BuMe ether	5	MeOCD	*t*-BuMe ether	11*	148a
5	57	CD	*t*-BuMe ether	5	PhOCD	*t*-BuMe ether	33*	148a



Entry	ee (%)	M*	Solvent	H_2 (bar)	Modifier	Solvent	ee (%)	Ref.
6	76	CD	*t*-BuMe ether	5	PhOCD	*t*-BuMe ether	26*	148a



Entry	ee (%)	M*	Solvent	H_2 (bar)	M*	Solvent	ee (%)	Ref.
7	81	CD	*t*-BuMe ether	5	MeOCD	*t*-BuMe ether	5*	148a
8	81	CD	*t*-BuMe ether	5	PhOCD	*t*-BuMe ether	53*	148a
9	44	CD	THF	10	PhOCD	THF	48*	132
10	9	2-PyOCD	THF	10	PhOCD	THF	48*	132
11	1	2-PyOCD	Toluene	10	PhOCD	Toluene	36*	132
12	2	2-PyOCD	DCM	10	PhOCD	DCM	35*	132
13	6	2-PyOCD	*t*-BuMe ether	10	PhOCD	*t*-BuMe ether	54*	132

[b] Rh/alumina, 15 °C.

luoromethylalkyl and trifluoromethylcycloalkyl ketones over CD-Pt chiral catalyst proceeds in moderate ee in weakly polar solvents with and without TFA. In alcohols (EtOH, *i*-PrOH), however, inversion takes place (entries 6−8).[150,151a] The probable reason for this inversion is additional H bonding with the solvent.

In the course of the enantioselective hydrogenation of 2,2,2-trifluoroacetophenone (TFAP) and its *p*-trifluoromethyl analogue on the chiral catalyst MeOCD-Pt, a low extent of inversion was observed in 2001: instead of the expected (*R*)-product, (*S*)-alcohols were formed (entries 9 and 10)[151b] (Figure 23).

According to our new experimental data, the hydrogenation of TFAP in the presence of the chiral modifiers CN, QN, QD, and their C9-ether derivatives—unlike CD—produces low ee values, accompanied, in the majority of cases, by unexpected inversion[152] (entries 11−14). The inversion cannot be interpreted on the basis of the IC containing the protonated quinidine skeleton, because there is no inversion in the presence of TFA. In our opinion, however, the role of

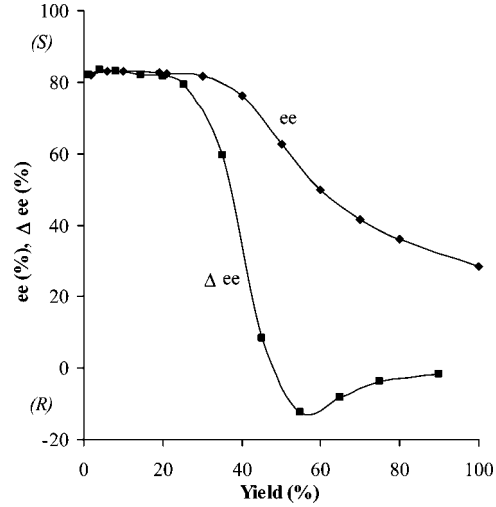
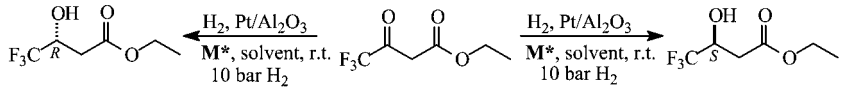


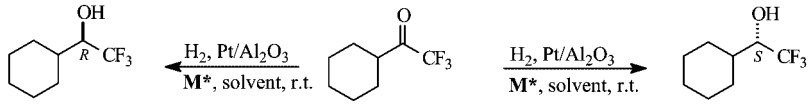
Figure 23. ee versus yield during enantioselective hydrogenation of ethyl trifluoroacetoacetate on a CD-Pt chiral catalyst.

Table 34. Inversions in Hydrogenation of α-Trifluoromethylketones

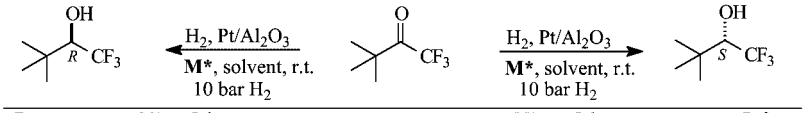


Entry	ee (%)	M*	Solvent	Solvent	M*	ee (%)	Ref.
1				AcOH	MeOCD	90	149
2	12*	MeOCD	THF/H_2O/TFA	THF/H_2O/TFA	MeOCD	87a	122
3	22*	XylOCD	THF	THF	CD	48	128
4	26*	XylOCD	Toluene	Toluene	CD	48	128
5	36*	XylOCD	$PhCF_3$	$PhCF_3$	CD	19	128

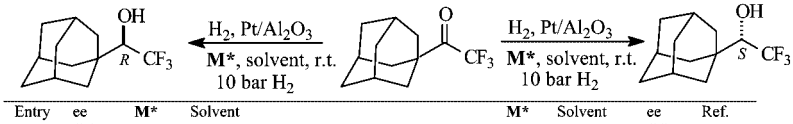
a $\Delta ee = (ee_1Y_1 - ee_2Y_2) / Y_2\text{-}Y_1$, Y = yield



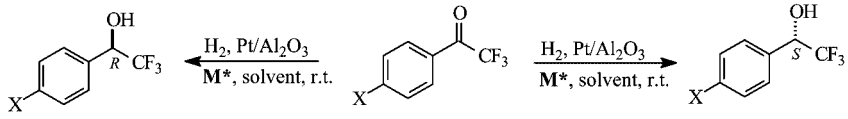
Entry	ee (%)	M*	Solvent	H_2 (bar)	M*	Solvent	ee (%)	Ref.
6	22	CD	Toluene	1	CD	EtOH	16*	150



Entry	ee (%)	M*	Solvent	M*	Solvent	ee (%)	Ref.
7	42	CD	DCM + TFA	CD	*i*-PrOH	11*	151a



Entry	ee (%)	M*	Solvent	M*	Solvent	ee (%)	Ref.
8	10	CD	*i*-PrOH + TFA	CD	*i*-PrOH	15*	151a

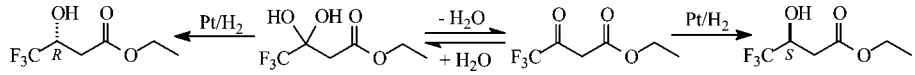


Entry	ee (%)	M*	Solvent	H_2 (bar)	X	M*	Solvent	ee (%)	Ref.
9				10	H	MeOCD	Toluene	4*	151b
10	10	CD	Toluene	10	CF_3	MeOCD	Toluene	11*	151b
11	17	CD	*i*-PrOH	1[a]	H	CN	Toluene +TFA	39	152
12	21*	CN	*i*-PrOH	1	H	CN	AcOH	11	152
13	33*	MeOCN	Toluene	1	H	CN	AcOH	11	152
14	30*	β-ICN	Toluene	1	H	CN	AcOH	11	152

[a] for CN 0 °C, 10 bar

[a] $\Delta ee = (ee_1Y_1 - ee_2Y_2)/(Y_2 - Y_1)$, Y = yield, for CN 0 °C, 10 bar.

Scheme 21. Hydrogenation of Ethyl 4,4,4-Trifluoroacetoacetate in the Presence of Water



the hydrogen-bridged IC binding to the quinuclidine skeleton—which represents an interaction weaker than the one with the protonated one—and also that of the nucleophilic complex proposed several times before (Figure 24) cannot be excluded either.[145]

Hydrogenation of Methyl Aryl Ketones. In view of the fact that, in the studies to date, the Orito reaction has been shown to be applicable only in the hydrogenation of activated ketones, it appears that only the hydrogenation of methyl aryl ketones with electron-withdrawing groups attached to the phenyl group could bring the expected result (Table 35).

The influence of the type of solvent, pressure, temperature, and modifier/substrate/Pt molar ratios was investigated in the hydrogenation of fluoro- and trifluoromethyl-substituted acetophenones (entries 2−10). Modification of a catalyst by CD afforded the corresponding (*S*)-1-phenylethanol. Working in strongly polar solvents, addition of TFA (entry 5) in a weakly polar solvent, and replacing CD by its ether derivatives (entries 7−10) resulted in the inversion of ED. According to the authors' opinion,[153a] inversion in the presence of strongly polar and acidic solvents is attributed to special interactions with the OH function of CD, and to the formation of a CD−acid ion pair, respectively. A possible explanation for the moderate ee's in the hydrogenation of ring-substituted acetophenones is that a reaction pathway without involvement of the OH function of CD is also feasible. This competing pathway is even faster and provides low ee to the opposite enantiomer. The inversion of ee is usually attributed to changes in the reaction mechanism.

Unexpected inversion of ED was also observed after replacement of CD by ether derivatives on Rh/alumina catalyst (entries 8−10).[153b] Interestingly PhOCD is a more effective chiral modifier for the reaction than CD.

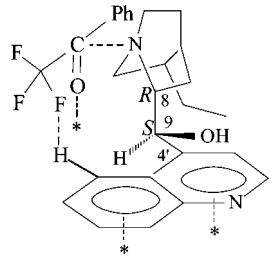
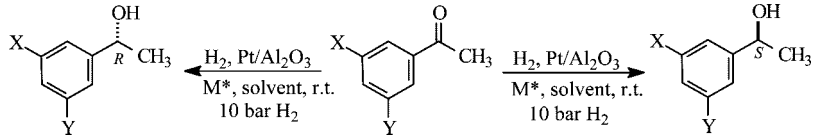


Figure 24. Proposed interaction between TFAP and CD on Pt in aprotic solvents.

4.1.3. Hydrogenation over Pd Catalyst

Hydrogenation of Pyruvates. The first observation of inversion was reported in 1988 in the enantioselective hydrogenation of activated ketones:[116] in hydrogenation of methyl pyruvate on Pd/C catalyst (i.e., on a catalyst other than Pt, the regular catalyst of the Orito reaction), in the presence of CD the formation of (*S*)-methyl lactate was observed in a very slow reaction (Table 36, entry 1). According to their most important conclusion (in 1988!), the results strongly suggest that the enhanced adsorption of the pyruvate ester is due to a stereochemically favorable interac-

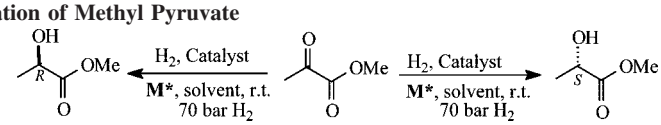
Table 35. Inversions in Hydrogenation of Methyl Aryl Ketones



entry	ee (%)	M*	solvent	X	Y	M*	solvent	ee (%)	ref
1	3*	MeOCD	toluene	H	H	CD	toluene	16	153a
2	4*	MeOCD	toluene	H	F	CD	toluene	30	153a
3	6*	MeOCD	toluene	H	CF_3	CD	toluene	43	153a
4	4*	MeOCD	toluene	CF_3	CF_3	CD	toluene	45	153a
5	10*	CD	toluene + TFA	CF_3	CF_3	CD	toluene	45	153a
6	15*	CD	DMF	CF_3	CF_3	CD	toluene	45	153a
7	5*	PhOCD	toluene	CF_3	CF_3	CD	toluene	45	153a
8[a]	3*	MeOCD	toluene	CF_3	CF_3	CD	toluene	27	153b
9[a]	7*	EtOCD	toluene	CF_3	CF_3	CD	toluene	27	153b
10[a]	33*	PhOCD	toluene	CF_3	CF_3	CD	toluene	28	153b

[a] Rh/alumina.

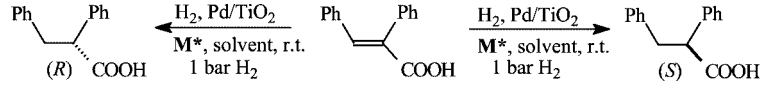
Table 36. Inversion in Hydrogenation of Methyl Pyruvate



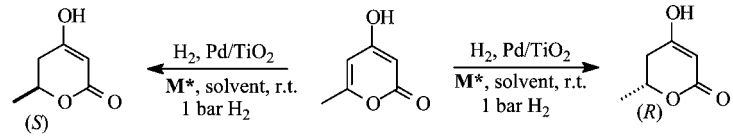
entry	ee (%)	M*	solvent	catalyst	M*	solvent	ee (%)	ref
1				Pd/C	CD	MeOH	4*	116
2	13*	CN	EtOH	Pd/Fe_2O_3	CD	EtOH	5*	117
3	12*	CN	THF	Pd/alumina	CD	THF	10*	120
4	11*	CN	EtOH	Pd/alumina	CD	EtOH	5*	120
5				Pd/alumina	CD	MEK	7*	120
6[a]	15	CD	THF	Pd/alumina or Pd/C	CD	EtOH	14*	120

[a] EtPy, 10 bar H_2.

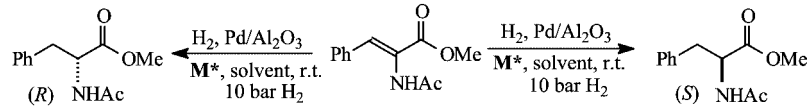
Table 37. Inversions in Hydrogenation of Prochiral Alkenes on Pd Catalyst



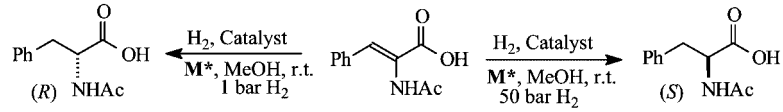
Entry	ee (%)	M*	Solvent	M*	Solvent	ee (%)	Ref.
1	12*	MeOCD	MeOH	CD	MeOH	49	119
2	18*	MeOCD	DMF	CD	DMF	61	119



Entry	ee (%)	M*	Solvent	M*	Solvent	ee (%)	Ref.
3	72	CD	MeCN	MeOCD	MeCN	2*	157
4	33	CD	*i*-PrOH	MeOCD	*i*-PrOH	10*	157
5	27	CD	AcOH	MeOCD	AcOH	12*	157
6	50	CD	*i*-PrOH	MeOCD	*i*-PrOH	14*	157



Entry	ee (%)	M*	Solvent	M*	Solvent	ee (%)	Ref.
7	3.4	Low [CD]	MeOH	High [CD]	MeOH	21.5*	158
8	2	Low [CD]	EtOH	High [CD]	EtOH	14*	158
9	1.5	Low [CD]	PrOH	High [CD]	PrOH	9.5*	158
10	0	Low [CD]	DMF	High [CD]	DMF	22*	158



Entry	ee (%)	M*	Catalyst	Additive	M*	ee (%)	Ref.
11	18	CD	Pd/alumina	BA	CD	8*	159
12	36	CD	Pd/TiO_2		CD	5*	159

tion with CD on the metal surface. In experiments carried out 8 years later[117] (1996; entry 2), they established that the hydrogenation of methyl pyruvate over Pd differed from the corresponding reaction over Pt in every important particular. The ee was low (high over Pt) and in the reverse sense (e.g., CD modification provided an *S*-excess in the product over Pd but an *R*-excess over Pt). The crucial role of the solvent in determining the stereochemistry of the Orito reaction is also verified by further experiments using cinchonas (entries 3 and 4). These experiments called attention to the solvent-dependent hydrogenation of chiral modifiers, to be taken into account in the interpretation of unexpected inversion. On the basis of studies in deuterium, it was also concluded that methyl pyruvate hydrogenation over Pd is a kinetically fast hydrogenation of adsorbed enol formed via dissociative adsorption of the α-ketoester. (On Pt, the ketone group of the substrate is directly hydrogenated.)

Hydrogenation of Prochiral Alkenes. From the catalysts most commonly used for the hydrogenation of alkenes and their various substituted derivatives, Pd-based catalysts were chosen for utilization in heterogeneous catalytic enantioselective hydrogenations.[6b,113a,114a,c,e,154] The first reproducible, although low-ee C=C hydrogenations were reported at the end of the 1980s.[155,156] The number of published results of heterogeneous catalytic enantioselective alkene hydrogenations falls behind that of ketones. Probably that is why only a handful of publications have reported on the stereochemistry of hydrogenations and, within this field, on inversion (Table 37).

The first unexpected inversion was recognized in 1988 by Nitta and Shibata in the hydrogenation of (*E*)-α-phenylcinnamic acid over MeOCD-Pd chiral catalyst.[119] In this case, the (*R*)-product was formed in higher ee as compared to the expected (*S*)-product on CD-Pt catalyst (entries 1 and 2). The authors suggested that the interaction of the hydroxyl group at C9 of CD with the carbonyl group in the substrate is crucial for the induction of high ee.[119] They proposed a two-point interaction model for the interpretation of the formation of the (*S*)-product.

Baiker et al. recognized in 2000 that 2-pyrones can be hydrogenated in high ee over Pd modified with cinchona alkaloids to produce the corresponding dihydropyrones, also known as unsaturated δ-lactones.[160] In the enantioselective hydrogenation of 4-hydroxy-6-methyl-2-pyrone, MeOCD was an inefficient modifier because the H-bonding interaction of the OH group of CD with the carbonyl group of substrate is hindered (entries 3−6). The ee was close to zero in acetonitrile, but in other solvents, such as *i*-PrOH, AcOH, and 3-pentanone, the opposite enantiomer (*R*)-product formed with 10, 12, and 14% ee, respectively.[157] The small but significant ee to the opposite enantiomer is an indication of some changes in the mechanism in the latter solvents. According to the authors, a feasible model based on 2-pyrone−CD interactions is given in Figure 25. These pro (*S*) and pro (*R*) ICs are strongly supported by the catalytic and spectroscopic studies presented in ref 157. The bidentate interaction in pro (*S*) model affords up to 85% ee to the (*S*)-enantiomer. When this interaction is disfavored by a basic or protic solvent or prevented by blocking the OH group of CD (in MeOCD), the interaction shifts to the monodentate model (Figure 25 pro (*R*)). The single attractive interaction

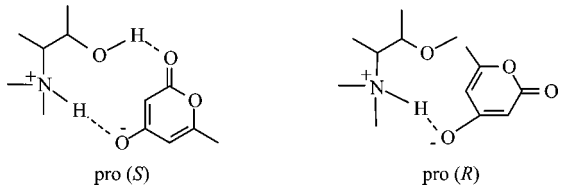


Figure 25. Proposed intermediate complexes for enantioselective hydrogenation of 2-pyrones.

is poorly effective: it afforded at best only 14% ee to the (*R*)-enantiomer.[157]

Cinchona-modified Pd/alumina catalysts can be effective for the enantioselective hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester (NADPME) to the *N*-acetyl phenylalanine methyl ester (NAPME).[158] At low alkaloid/NADPME molar ratios, CN gave (*S*)-NAPME and CD gave (*R*)-NAPME. However, at higher alkaloid concentrations, the sense of enantioselectivity inverted for CD, representing one of the first examples of this type of behavior (entries 7−10). The authors consider that the effect may be due to an interaction of the modifier with specific Pd sites at low modifier concentrations.[158]

The hydrogenation of 2-acetamidocinnamic acid resulted in (*R*)-*N*-acetyl phenylalanine of 36% optical purity over CD modified Pd/TiO_2 under low H_2 pressure. Increasing the pressure led to an interesting inversion in the sense of the ED, which was more pronounced if benzylamine was used as additive (entries 11 and 12).[159] In the hydrogenations of 2-acetamidoacrylic acid, no inversion in the ED occurred as an effect of changes in the H_2 pressure. This phenomenon seems to be a special case, characteristic of α-acetamido-β-unsaturated carboxylic acids and esters. Obviously the inversion is related with the presence of the α-acetamido group complemented with the steric effect of the β-phenyl substituent. Interestingly, the configurations of the products obtained in excess in the hydrogenation of 2-acetamidocinnamic acid and 2-acetamidoacrylic acid using the same modifier under low H_2 pressures were opposite. This observation is in accordance with our suggestion on the role of the β-substituents in determining the sense of the chiral induction in the hydrogenation of α,β-unsaturated acids over *Cinchona*-modified Pd.[161]

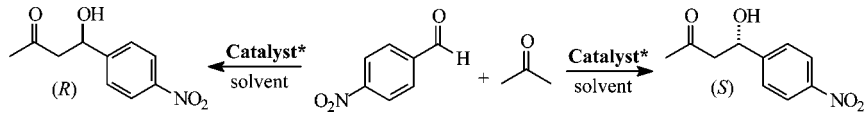
4.2. Asymmetric Aldol Addition

A few studies to immobilize L-proline on silica, MCM-41, SILC, and dendrimers for direct asymmetric aldol reactions have been reported;[162] however, an inversion phenomenon was not observed. The test reaction employed in the relevant research is shown in Table 38. Table 38 describes two examples for unexpected inversion observed in heterogenized/immobilized L-proline-catalyzed asymmetric aldol addition. In one of these, inversion was brought about by heterogenization of the L-proline organocatalyst, whereas in the other one, inversion is due to the solvent effect occurring in the course of the application of the immobilized catalyst. To our best knowledge, this was the first unexpected reversal inversion in heterogeneous asymmetric catalysis observed in a reaction other than hydrogenation.

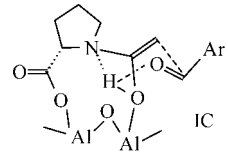
The L-proline-catalyzed homogeneous aldol reaction gave the aldol product with (*R*)-configuration (entry 1).[83c] When γ-Al_2O_3 was added to the aldol reaction mixture, the ee value was reduced (entry 2). When the concentration of γ-Al_2O_3 was decreased, aldol with an (*S*)-configuration was unexpectedly obtained and the ee values increased from 4 to 21% (entries 3 and 4). The results suggest that a unique catalyst is formed on the adsorption of L-proline on γ-Al_2O_3. This inversion phenomenon is found to be general for different types of amino acids adsorbed on γ-Al_2O_3 (entries 6−12).[83c]

To explain the inversion, the adsorption of L-proline on γ-Al_2O_3 and UV-Raman spectra of L-proline in solid form and on γ-Al_2O_3 were obtained. These experiments indicate that L-proline strongly interacts with γ-Al_2O_3 and that the carboxylate groups are involved in the interaction. The L-proline/γ-Al_2O_3 preadsorbed with pyridine resulted in a dramatically reduced ee value, clearly showing that the acidic

Table 38. Inversion in the L-Proline-Catalyzed Direct Aldol Reaction

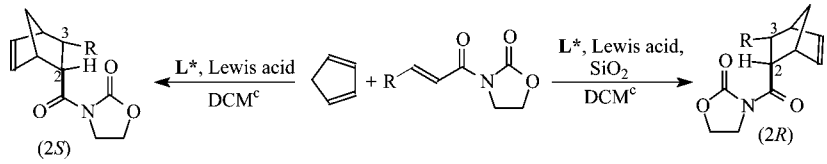


entry	ee (%)	conv. (%)	Catalyst*	Catalyst*	conv. (%)	ee (%)	ref
1	68	80	L-proline				83c
2	22	61	7.2[b]				83c
3				5[b]	80	4*	83c
4				3.3[b]	78	21*	83c
5	64	78	3.3[b] (γ-Al_2O_3 silylated)				83c
6	47		L-leucine	L-leucine + γ-Al_2O_3		15*	83c
7	48		L-alanine	L-leucine + γ-Al_2O_3		5*	83c
8	46		L-tryptophan	L-leucine + γ-Al_2O_3		8*	83c
9	23		L-phenylalanine	L-leucine + γ-Al_2O_3		4*	83c
10	20		L-threonine	L-leucine + γ-Al_2O_3		5*	83c
11	20		L-glutamine	L-leucine + γ-Al_2O_3		2*	83c
12	13		L-lysine	L-leucine + γ-Al_2O_3		6*	83c
13	77	68	PEG-Pro[a] in DMF	PEG-Pro[a] in acetone	23	21	163

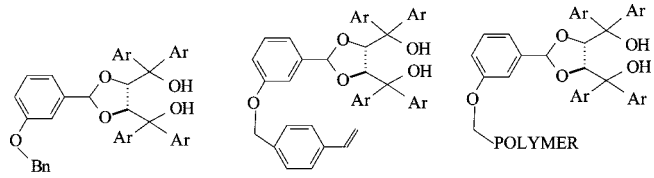


[a] PEG-Pro = poly(ethyleneglycols) supported (2*S*,4*R*)-4-hydroxyproline. [b] L-Proline/Al_2O_3 (molecules/nm^2).

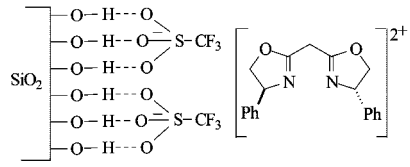
Table 39. Inversion in the Diels−Alder Reaction



entry	ee (*S* %)	conv. (%)	Lewis acid	R	**L*** [a] or **Catalyst 1−3**	Lewis acid	conv. (%)	ee (*R* %)	ref
1				Me	**Catalyst 1**		100	38	164
2				Me	**Catalyst 2**		99	3	164
3	18*	100		Me	**Catalyst 3**				164
4	3	100	$Mg(ClO_4)_2$[c,d]	H	(*S*)-Me-BOX-Ph	$Mg(ClO_4)_2$[d]	100	66*	56
5	22	100	$Mg(OTf)_2$[c,d]	H	(*S*)-Me-BOX-Ph	$Mg(OTf)_{2c}$[d]	100	67*	56
6	32	100	$Cu(OTf)_2$[c,d]	H	(*S*)-Me-BOX-*t*-Bu				56
7	4	13	$Cu(OTf)_2$[c,d]	H	(*S*)-Me-BOX-Ph				56
8	20	100	$Cu(OTf)_2$	H	(*S*)-H-BOX-Ph	$Cu(OTf)_2$	100	33*	57[b]
9	59	50	$Cu(OTf)_2$	H	(*S*)-Me-BOX-*t*-Bu				57[b]
10	57	43	$Cu(OTf)_2$[b]	H	(*S*)-Me-BOX-*t*-Bu				57[b]
11	90	97	$Cu(OTf)_2$	Me	(*S*)-Me-BOX-*t*-Bu				58
12	85	43	$Cu(OTf)_2$[b]	Me	(*S*)-Me-BOX-*t*-Bu				58
13	15	100	$Cu(OTf)_2$	Me	(*S*)-Me-BOX-Ph	$Cu(OTf)_2$	100	31*	58
14	60	95	$Mg(OTf)_2$	Me	(*S*)-Me-BOX-Ph	$Mg(OTf)_2$	46	30*	58
15	22	97	$Zn(OTf)_2$	Me	(*S*)-Me-BOX-Ph	$Zn(OTf)_2$	95	24*	58



Catalyst 1 **Catalyst 2** **Catalyst 3**



Catalyst*

[a] L*: see Figure 8; mainly endo additions occur. [b] Silica supported. [c] SILC: silica-supported ionic liquid phase catalyst. [d] Et_2O.

sites on γ-Al_2O_3 play an important role in the aldol reaction, because the preadsorbed pyridine can occupy these sites. Silylated γ-Al_2O_3 gave results similar to those obtained with the free L-proline (entry 5). These results suggest that the surface hydroxyl groups on γ-Al_2O_3 are essential to induce the inversion of enantioselectivity.

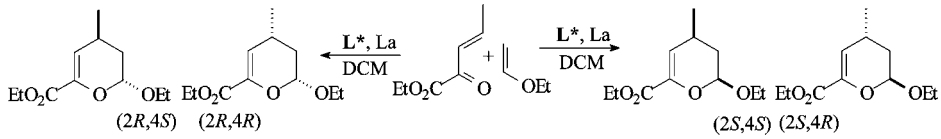
The authors have assumed that coupling of L-proline with the γ-Al_2O_3 surface gives an organo-inorganic bifunctional catalyst for direct asymmetric aldol reactions. The amine group of the adsorbed proline activates acetone, and the hydroxyl group on γ-Al_2O_3 activates the carbonyl of *p*-nitrobenzaldehyde through hydrogen bonding (see IC in Table 38). The *Si* face on the aldehyde may be more easily attacted by the enamine on γ-Al_2O_3, resulting in formation of the product with an *S* configuration. As regards the experimental observation described in entry 13, Table 38, the authors of ref 163 reported no more than stating that remarkably, and quite surprisingly, the use of acetone as the reaction solvent gave an aldol of the opposite absolute configuration. Ref 163 provides no more information regarding inversion. In addition to the test reaction, the report describes the results of the aldol condensation of other compounds and of the reuse of immobilized catalysts. The extensive studies on this chiral inversion on a solid surface help clarify the adsorption mode of modifier and its interaction with reactant and, hence, are helpful in explaining the origin of the ED.

4.3. Asymmetric Diels−Alder Addition

Important antecedents regarding the asymmetric DA reaction are summarized in subsection 2.7.1, whereas the recently published monograph reviews our present knowledge on the use of chiral heterogeneous catalysts.[99j] In the course of experiments on heterogenized catalysts of a great variety of structures, the first phenomenon of unexpected inversion was observed on a polymer with Taddol-type chiral surface sites[164] (entry 3, Table 39). In the presence of heterogenized **Catalyst 3**, the major product had an opposite configuration (2*S*) as compared to the product obtained in homogeneous phase (2*R*) that is in the presence of **Catalyst 1** and **Catalyst 2**. In the case of Taddol derivatives containing 2-naphthyl groups instead of 3,5-$Me_2C_6H_3$ groups, no inversion was observed, as the major product had (2S) configuration in all cases. Occurrences of inversion were later encountered in the course of studies on chiral BOX complexes.[56–58]

Supported IL catalysts (SILC) have been developed using surface-modified silica, which show good reactivity and reversal of enantioselectivity for the case of the magnesium-

Table 40. Inversion in the Hetero Diels−Alder Reaction



entry	ee 2*R*,4*S*(%)	ee 2*R*,4*R*(%)	conv. (%)	Lewis acid (La)	conditions	L*	Lewis acid (La)	conv. (%)	ee 2*S*,4*S* (%)	ee 2*S*,4*R* (%)	ref
1	21		94	$Cu(OTf)_2$	hom.	(*S*)-Me-BOX-Ph					165a
2					het.	(*S*)-Me-BOX-Ph	CuHY	16		41*	165a
3		56	100	$Cu(OTf)_2$	hom.	(*S*)-Me-BOX-*t*-Bu					57a
4		24	100	$Cu(OTf)_2$	het.	(*S*)-Me-BOX-*t*-Bu					57a
5					hom.	(*S*)-H-BOX-Ph	$Cu(OTf)_2$	100	27		57a
6					het.	(*S*)-H-BOX-Ph	$Cu(OTf)_2$	100	18		57a

based BOX complexes.[56] Irrespective of the anion of the Lewis acid, in the case of the application of the SILC variety of (*S*)-BOX-Ph-Mg complexes, inversion takes place in the DA reaction as compared to the reaction in IL (entries 4 and 5). In the case of the corresponding Cu complexes, no inversion happens (entries 6 and 7).

A reversal in ee when changing from a homogeneous to a heterogeneous system has been previously reported[57,58] and was thought to be due to the dissociation of the catalyst anion on the support, resulting in a change in catalyst geometry. For the SILC-mediated reactions where the catalysis takes place in a solid-supported thin ionic liquid film, it is more likely that the change in catalyst geometry is induced by the large concentration of anions in an analogous manner to that found under homogeneous reaction conditions.

Table 39 presents examples for unexpected inversion, in the majority of which the sense of ED observed in homogeneous reaction was altered by the immobilization/heterogenization of the chiral complexes.[57a,58] Two chiral BOX−Cu(II) complexes have been immobilized on silica via H-bonding interactions.[57a] The immobolized catalysts were tested in a standard DA reaction and gave surprising results. Where the immobilized (*S*)-H-BOX-Ph-$Cu(OTf)_2$ catalyst was used, the predominant enantiomer formed was the opposite of that produced using the same catalyst in a homogeneous reaction (entries 8−10). The behavior of the immobilized *t*-Bu catalyst ((*S*)-Me-BOX-*t*-Bu-Cu) is very different from that of its phenyl analogue. The phenyl-substituted catalyst maintained its activity and enantioselectivity and was highly recyclable, whereas the *t*-Bu catalyst was obviously less stable and less effective when immobilized by this technique. No further information is supplied on experimental observations relevant to the interpretation of unexpected inversion in either ref 57a or more recent publications from the same laboratory.

Chiral BOX-complexes of Cu(II)-, Mg(II)-, and Zn(II)-triflates have been immobilized on silica support via hydrogen-bonding interactions (entries 11−15).[58] Moderate or, occasionally, good ee values could be attained in the outlined DA reaction. Similar relative behavior was observed[57a] in the case of *t*-Bu- and Ph-BOX complexes.[58] A surprising observation from these studies is that the configuration of the product changed on going from the homogeneous to the heterogeneous system in the case of BOX-Ph complexes. This is of both theoretical and practical importance, as it indicates that immobilization alters the active catalytic species. The establishment of hydrogen-bonding interactions between the silanol groups of the support and the triflate anions was verified by IR studies.[58] Hydrogen bonding can provide a simple way for the immobilization of homogeneous catalysts, which requires neither modification of the catalysts nor functionalization of the surface.[165]

4.4. Asymmetric Hetero Diels−Alder Additions

Earlier results showing that Cu−BOX complexes were identified as one of the best catalyst type of DA, and hetero Diels−Alder additions (HAD) are summarized in reviews.[52g,166] Table 40 includes some experimental data from two reports describing remarkable and interesting results in HAD addition in the presence of heterogenized chiral Cu−BOX catalysts.

An unexpected effect was observed for the heterogeneous catalytic HAD reaction, which was not apparent in the homogeneously catalyzed process, namely, the reversal in enantioselectivity of the dihydropyran product.[167] Initially, the 2*R*,4*S* product is observed, and subsequently, this switches to the 2*S*,4*R* product. This reversal of enantioselectivity could be attributed to the confinement effect of the porous supports.

The peculiarity of the experimental data published in the other report is that, under identical experimental conditions, there is no difference between the senses of the EDs of the homogeneous and heterogeneous HAD reactions.[57a] However, inversion is observed in both the homogeneous and the heterogeneous reaction in the presence of BOX catalysts bearing the *t*-Bu and the Ph substituents but otherwise of identical configuration. This is another characteristic example for the reaction of heterogenized complexes: the sense of ED is significantly affected not only by the configuration of the chiral catalyst but also by the substituents attached to the chiral center.

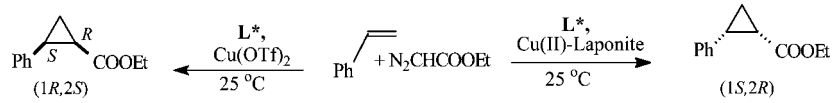
In my opinion, the experimental facts showing that, in the case of DA and HAD reactions carried out on the same chiral catalyst under identical experimental conditions, unexpected inversion takes place in one (DA) and is absent in the other (HAD) also have special significance[57a] (see data in Tables 39 and 40).

I have some doubts regarding the conclusions, because the configurations of the main products obtained under the conditions of homogeneous catalysis are not identical ((2*R*,4*S*) and (2*R*,4*R*), respectively). Consequently, neither are the configurations of the compounds with opposite configurations identical in the two reports.[57a,167a] It has earlier been suggested in studies on the mechanism of the HAD reaction that the mechanism might be stepwise rather than concerted.[167b]

4.5. Asymmetric Cyclopropanation

Reviews on asymmetric cyclopropanation have been published continuously, giving repeatedly updated information.[52d,e,g,67a] These reviews have given account of surprising experimental data classifiable as unexpected inversion. Below follows the description of cyclopropanation, in which the sense

Table 41. Inversion in Cyclopropanation



entry	(1*R*,2*S*) (%)	*trans/cis*	L*	solvent	*trans/cis*	(1*S*,2*R*) (%)
1	8	71/29	(*S*)-Me-BOX-Ph	DCM	28/72	32*
2	8	68/32	(*S*)-Me-BOX-Ph	styrene	9/91	41*
3			(*S*)-Me-BOX-*t*-Bu	DCM	53/47	10*
4			(*S*)-Me-BOX-*t*-Bu	styrene	15/85	48*

of ED observed in homogeneous catalysis was reversed by immobilization of the chiral complex. In the cyclopropanation of styrene with ethyl diazoacetate, inversion was observed in the presence of (*S*)-Me-BOX-Ph-Cu catalyst immobilized on clay (laponite) by electrostatic interaction.[68]

Mayoral et al. studied cyclopropanation and observed an interesting change in stereoselectivity: both *cis/trans* selectivity and enantioselectivity were changed when laponite-immobilized catalyst was used. In DCM, in both the homogeneous-phase and the heterogeneous-phase reaction, the *trans*/*cis* selectivity was changed (Table 41, entry 1).[68a,d]

An unexpected observation was made in styrene: in homogeneous phase, the trend is the same as in DCM, whereas on the immobilized catalyst both the *trans*/*cis* ratio and the sense of enantioselection was reversed in each of the apolar solvents studied. Unexpected inversion brought about by heterogenization has also been confirmed in DCM by recent studies.[68d] As shown in Table 41, heterogenization shifted the product ratio toward the formation of the *cis* enantiomers. The phenomenon has also been observed on supported ionic liquid films.[68e] Although there is some difference between the effects of *t*-Bu- and Ph-BOX complexes, it is less characteristic than those observed in, e.g., the DA reactions.

The authors explain that this solvent effect is due to the difference in the distance between the BOX complex and laponite. In the case of apolar solvents, this distance is shorter, which leads to considerable changes in both conformational relations and steric interactions. To explain the formation of the (1*S*,2*R*)-product in higher ee as a result of unexpected inversion, the authors refer to the IC[68b] outlined in Figure 26, which is also supported by DFT calculations.[68c]

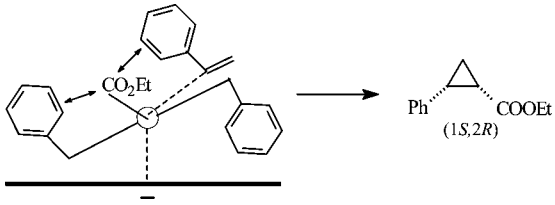


Figure 26. Assumed intermediate complex on the clay surface in cyclopropanation.

In their latest publications, they emphasize the role of surface-confinement effects. According to the authors, experimentally verifying the mechanistic proposal is not possible. Only indirect evidence and molecular modeling studies are able to shed light on these interesting but extremely complicated catalytic systems.

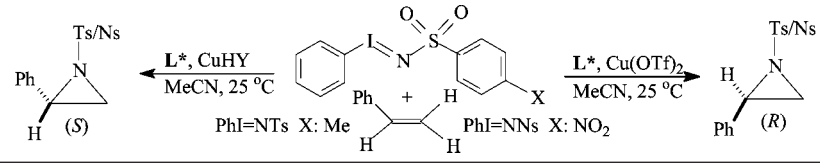
4.6. Asymmetric Aziridination

The first enantioselective aziridination catalyst was found only in 1998.[168] The achieved results have been reviewed.[52d,e,g,67b] Rechavi and Lemaire[52e] summarized the experimental results of Hutchings et al.[69a] according to Table 42. Namely, the (*S*)-BOX−Cu(II) complexes gave the (*R*)-aziridines, whereas in the heterogeneous phase the (*S*)-aziridines were obtained.[69a] This reversal of induction indicates that, in this case, the zeolite HY pores significantly influence the substrate−catalyst interaction. Similarly to cyclopropanation, the surface significantly affects conformational interactions.

4.7. Summary

In the previous chapters, examples for unexpected inversion in a variety of reactions, using a large selection of catalysts, were enumerated. In consideration of the shortage of published experimental observations of unexpected inversion in the field of heterogeneous catalytic asymmetric reactions (with the exception of hydrogenation) (see the introduction of section 4), this summary reviews the large number of experimental data points obtained in hydrogenations. Observations made in other heterogeneous catalytic asymmetric reactions were mentioned in subsections 2.8 and 3.8. Namely, these unexpected inversions take place in the heterogenized variants of homogeneous catalytic reactions. The conclusion that can be drawn from the few inversion reactions observed to date is that, in the heterogeneous asymmetric reactions,

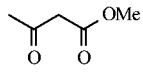
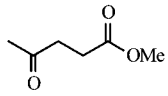
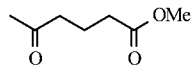
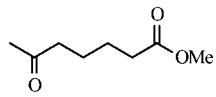
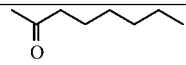
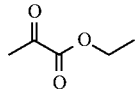
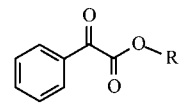
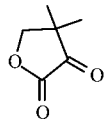
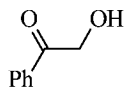
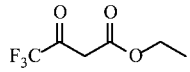
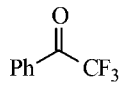
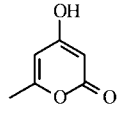
Table 42. Inversion in Aziridination



entry	ee (*S*%)	yield (%)	L*[a]	X	yield (%)	ee (*R*%)
1	28*	80	(*S*)-H-BOX-*t*-Bu	Me	85	8
2	24*	58	(*S*)-Me-BOX-*t*-Bu	Me	78	35
3	77*	72	(*S*)-H-BOX-*t*-Bu	NO_2	42	31
4	82*	68	(*S*)-Me-BOX-*t*-Bu	NO_2	79	43

[a] **L***: see Figure 8; HY zeolite.

Table 43. Inversions in Heterogeneous Catalytic Enantioselective Hydrogenations

Entry	Substrate	Catalyst [a]	C8,C9 config.	Solvent, Additive	Product ee (%)	Product config.	Ref.
1		(*R,R*)-TA-Ni		THF, AcOH	91	(*R*)	115b
2		(*R,R*)-TA-Ni		THF, pivalic acid	51	(*R*)	115b
3		(*R,R*)-TA-Ni		THF, pivalic acid	61*	(*S*)	115b
4		(*R,R*)-TA-Ni		THF, pivalic acid	61*	(*S*)	115b
5		(*R,R*)-TA-Ni		THF, pivalic acid	80*	(*S*)	115b
6		**CD-Pt**	**(*S*),(*R*)**	**THF**	**80**	**(*R*)**	**131**
7		**β-ICN-Pt**	**(*R*),(*S*)**	**Toluene**	**48***	**(*R*)**	**123,126**
8		**β-ICN-Pt**	**(*R*),(*S*)**	**AcOH**	**50**	**(*S*)**	**123,126**
9		2-PyOCD-Pt	(*S*),(*R*)	THF	52	(*R*)	132
10		**PhOCD-Pt**	**(*S*),(*R*)**	**THF**	**36***	**(*S*)**	**132**
11		β-ICN-Rh	(*R*),(*S*)	Toluene	33*	(*R*)	127
12		CN-Rh	(*R*),(*S*)	Toluene	43	(*S*)	127
13	 R=Me	CN-Pt	(*R*),(*S*)	Toluene	78	(*S*)	134,135
14	R=Me	β-ICN-Pt	(*R*),(*S*)	Toluene	50*	(*R*)	134,135
15	R=*t*-Bu	**CD-Pt**	**(*S*),(*R*)**	**Toluene**	**95**	**(*R*)**	**136**
16	R=*t*-Bu	**PhOCD-Pt**	**(*S*),(*R*)**	**Toluene**	**78***	**(*S*)**	**136**
17		**CD-Pt**	**(*S*),(*R*)**	**Toluene**	**50**	**(*R*)**	**137**
18		**PhOCD-Pt**	**(*S*),(*R*)**	**Toluene**	**55***	**(*S*)**	**137**
19		CN-Pt	(*R*),(*S*)	Toluene	25	(*S*)	127
20		β-ICN-Pt	(*R*),(*S*)	Toluene	46*	(*R*)	139
21		β-ICN-Rh	(*R*),(*S*)	Toluene	54*	(*R*)	127
22		CN-Pt	(*R*),(*S*)	Toluene	18	(*S*)	146c
23		MeOCN-Pt	(*R*),(*S*)	Toluene	32*	(*R*)	146c
24		CD-Pt	(*S*),(*R*)	*t*-BuMe-ether	77	(*R*)	148a
25		PhOCD-Pt	(*S*),(*R*)	*t*-BuMe-ether	31*	(*S*)	148a
26		**CD-Rh**	**(*S*),(*R*)**	**Dioxane**	**73**	**(*R*)**	**148b**
27		**PhOCD-Rh**	**(*S*),(*R*)**	**Dioxane**	**68***	**(*S*)**	**148b**
28		CD	(*S*),(*R*)	Toluene	48	(*S*)	128
29		XylOCD	(*S*),(*R*)	Toluene	26*	(*R*)	128
30		**CN-Pt**	**(*R*),(*S*)**	**Toluene, TFA**	**39**	**(*S*)**	**152**
31		**β-ICN-Pt**	**(*R*),(*S*)**	**Toluene**	**30***	**(*R*)**	**152**
32		MeOCN-Pt	(*R*),(*S*)	Toluene	33*	(*R*)	152
33		CD-Pd	(*S*),(*R*)	*i*-PrOH	50	(*R*)	157
34		**CD-Pd**	**(*S*),(*R*)**	**MeCN**	**72**	**(*R*)**	**157**
35		**MeOCD-Pd**	**(*S*),(*R*)**	***i*-PrOH**	**14***	**(*S*)**	**157**

[a] For abbreviations, see Figures 14 and 16.

the reversal of enantioselectivity could be attributed to the confinement effect of the porous supports.

Section 4 discusses only two widely studied examples that have stereochemistries not fitting in with empirical rules and that have been observed in the presence of a great variety of substrates and chiral modifiers, in hydrogenations also utilized in industrial applications. Table 43 shows a selection of these experimental data, namely, the results showing the largest values of unexpected ee. On the one hand, these can be compared to the

methyl acetoacetate (MAA) reference compound on TA-MNi; on the other hand, the data obtained on Pt modified with cinchona alkaloid derivatives can be compared to those obtained on Pt modified with the parent cinchonas.

At the time of its discovery, the TA-MNi catalyst was eminently suitable for the hydrogenation of β-oxoesters. Hydrogenation of methyl acetoacetate on TA-MNi yielded (*R*)-product (Scheme 14, Table 43, entry 1). In the case of a γ-oxoester (entry 2), ee was found to decrease, and in the case of the other oxoesters and simple ketones, it was already the (*S*)-products that were formed in higher ee (entries 3−5). This finding was at that time unexpected.

Studies using Pt catalysts modified with cinchona alkaloids gave unexpected results when derivatives of the parent alkaloids were used (Table 43). The objective of these studies was the elucidation of the reaction mechanism because, after adequate optimization, the four inexpensive parent cinchonas (CD, CN, QN, QD) allowed the attainment of high ee values (over 90%). According to the generally accepted empirical rule, ED is determined by the configuration of the C8 and C9 atoms of cinchonas. CD and QN (both 8(*S*),9(*R*) configurations) yield (*R*)-products, whereas CN and QD (both 8(*R*),9(*S*) configurations) give (*S*)-products. Deviations from this rule were unexpected. The unexpected inversion was the first significant experimental observation indicating that, in enantioselective hydrogenation over cinchona alkaloids modified catalysts, it is not the C8 chiral center of the alkaloid that controls the sense of the chiral induction.[123] Maximal unexpected inversion in ee was caused by the modifiers β-ICN and PhOCD in the hydrogenation of each substrate studied (Table 43, accented in bold).

It was revealed in the course of research that those of the real effects, which do not alter the configuration of stereogenic centers C8 and C9, can be attributed to a modified conformation of the substrate−modifier surface complex responsible for ED. According to some research groups, this means a change in adsorption mode, whereas others assume that a change in the reaction mechanism or one of its steps is responsible. These details have been discussed above.

As regards the experimental verification of the interpretation of these inversions, in contrast to those discussed in the previous sections, there exists only indirect evidence with respect to the existence of the short-lived surface ICs of fast surface reactions. The following indirect confirmations of substrate−modifier interactions have been published: (i) ATR-IR spectroscopy;[141,169] (ii) NMR spectroscopy[145a,b] under conditions similar to hydrogenation in solution; (iii) RAIRS and STM studies on Pt(III) in ultrahigh vacuum conditions;[170] and (iv) theoretical (DFT calculations).[171]

5. Conclusion

Asymmetric reactions proceeding on three different types of catalyst systems (chiral metal complexes, chiral organocatalysts, and chiral heterogeneous catalysts), in which the formation of enantiomers was accompanied by unexpected inversion, were collected. The experimental data compiled are summarized in Tables 15, 27, and 43. The results of the reviewed research can be summarized in the following (without going into the details of subsections 2.8, 3.8, and 4.7): (i) Unexpected inversion is not a unique phenomenon among enantioselective catalytic reactions of various types. (ii) Since the necessary experimental data are not available, it is not yet possible to formulate general relationships between the chiralities of the individual catalyst types and the sense of ED. (iii) Whereas chiral catalysts are naturally responsible for the origin of chiral induction, determination of the sense of ED can be attributed not only to the absolute configuration of chiral catalysts but also to a large number of other factors (Tables 15, 27, 43). (iv) A sensitive equilibrium of attractive and repulsive interactions depending on the structures of the chiral catalyst, **L***, **M***, and the substrates controls the conformation of the IC responsible for ED, which favors either *Re*-face or *Si*-face selectivity. (v) The theoretical as well as the practical importance of detailed investigations on the unexpected phenomena accompanying enantioselective reactions will increase in the future. (vi) It is of theoretical importance to explore the origin of chiral induction as thoroughly as possible, and it is of practical importance to create the means for the synthesis of enantiomer pairs in high ee using the same chiral raw material.

On the basis of the summary tables cited above, a large number of questions can be posed to which it is as yet impossible to give answers supported by concrete experimental evidence. In order to find the answers to these questions and, most importantly, to attain the goals listed above, many tasks await realization, including the following: (i) Due to the great significance of asymmetric syntheses, detailed analysis of unexpected phenomena revealed in the course of research is not only justified but also necessary. (ii) In spite of the availability of a large number of experimental data points, studies varying only one parameter, e.g., the absolute configuration of the chiral atoms of catalysts and keeping the experimental conditions, the techniques applied, and the origin of the starting materials constant are regrettably rare. (iii) The development of the heterogenized versions of enantioselective reactions requires more extensive research. (iv) Reactions with unusual ED are expected to be discovered in increasing numbers in futures studies, and their interpretation requires novel research techniques. (v) The solution to these problems may become part of designable synthetic procedures.

Because of volume restrictions, many important topics in enantioselective reactions are not even mentioned in this review that focuses on a relatively narrow field. The author asks for the reader's forgiveness for any possible deficiencies.

6. List of Abbreviations

AcOQD	*O*-acetylquinidine
AcOQN	*O*-acetylquinine
ATR-IR	attenuated total reflection spectroscopy
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BDPP	2,4-bis(diphenylphosphino)pentane
BH	Baylis−Hillman
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	2,2′-binaphthol
[bmim]BF_4	1-butyl-3-methylimidazolium tetrafluoroborate
[bmim]PF_6	1-butyl-3-methylimidazolium hexafluorophosphate
[bpy]BF_4	1-butyl-3-methylpyridinium tetrafluoroborate
Boc	*t*-butoxycarbonyl
BOX	bis(oxazoline)
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
CD	cinchonidine

CFBR	continuous fixed-bed reactor
CN	cinchonine
DA	Diels−Alder
dba	dibenzylideneacetone
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DuPhos	substituted 1,2-bis(phosphonalo)benzene
ED	enantiodifferentiation
ee	enantiomeric excess
ee*	unexpected ee (in tables)
EtLt	ethyl lactate
EtPy	ethyl pyruvate
HMPA	hexamethylphosphoramide
IC	intermediate complex
ICN	isocinchonine
ICP	isocupreidine
IL	ionic liquid
KPL	ketopantolactone
L*	chiral ligand
laponite	laponite RD (clay from Laponite Inc.)
LDA	i-Pr_2NH + BuLi
M*	chiral modifier
MPEG	poly(ethylene glycol) monomethyl ether
MR	Mukaiyama's reagent
MRNi	modified Raney-Ni
MS	molecular sieves
Ns	*p*-nitrophenylsulphonyl
Nu^-	nucleophile
PEG	poly(ethylene glycol)
PhOCD	*O*-phenylcinchonidine
PHOX	phosphanyloxazoline
PPD	1-phenylpropane-1,2-dione
PTC	phase-transfer catalyst
p-TSA	*p*-toluenesulfonic acid
PyBOX	pyridine-2,6-bis(oxazoline)
QD	quinidine
QN	quinine
RAIRS	reflection absorption infrared spectroscopy
SILC	supported ionic liquid catalysts
STM	scanning tunneling microscopy
TA	tartaric acid
TA-MNi	(*R*,*R*)-tartaric acid modified Ni catalyst
TBS	*t*-butyldimethylsilyl
Tf	triflyl
TFA	trifluoroacetic acid
TFAP	2,2,2-trifluoroacetophenone
TMS	trimethylsilyl
TRAP	bis[(dialkylphosphino)ethyl]biferrocenes
Ts	*p*-toluenesulfonyl

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