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Enantioselective protonations: fundamental insights and new concepts

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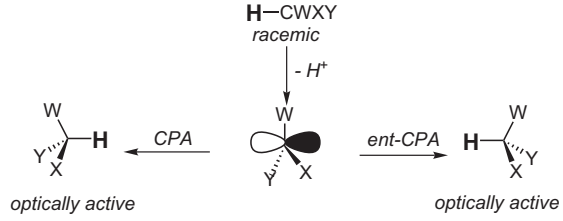
Abstract—This review deals with the main results obtained in the field of enantioselective protonations. This method allows easy access to various enantiomerically enriched compounds starting from either the corresponding racemic mixture (deracemization process) or various prochiral precursors. Discussions about different factors governing the stereoselectivity as well as a compilation of literature data are given.

Contents

1. Introduction

Introduced for the first time in 1976 by one of us along with the concept of deracemization,[1a] the kinetically controlled conversion of an electron-rich prostereogenic center into a stereogenic one, by enantioselective protonation, using a chiral protonating agent (CPA), (Scheme 1)



Scheme 1.

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is nowadays a well-known broad avenue for the access to optically active compounds.[1–17]

The most important advances in this field are due to the groups of Fehr,[2] Fuji,[3] Hunig,[4] Jacquier,[5] Koga,[6] Pète-Hénin-Muzart,[7] Takeuchi,[8] Vedejs,[9] Yamamoto[10] and more recently of Eames,[11] Asensio,[12] Brunner,[13] Koizumi,[14] Kosugi,[15] Mikami,[8f,g] Nakai,[16] and Tomioka.[17] For reviews, see Refs. 1i, 2b, 2g, 4f, 10e, 11c, and 18.

The term 'deracemization' was first proposed by one of us[1a,i] for describing the transformation of a racemic mixture into one of its enantiomers using an enantioselective protonation, in order to differentiate this new type of reaction from the well-documented asymmetric transformation occurring with thermodynamically controlled protonation. In the recent literature, the term asymmetric transformation is more and more replaced by thermodynamically controlled deracemization.[19] Thus, to be unambiguous, it seems necessary at the present time to specify if the deracemization involving protonation is either thermodynamically or kinetically controlled.[20] The deracemization can also be extended to compounds bearing one atom or a group differing from hydrogen provided that it could be mobilized and reintroduced asymmetrically.[1i,21]

The first enantiomerically pure compound obtained using an enantioselective protonation was reported as early as 1983.[1h,i]

Surprisingly, the creation of a stereogenic center by the formation of a C–H bond using enantioselective protonation was unexploited until our first reports,[1a,i,22a] whereas methods using either a hydride anion (as part of a chiral reagent) or molecular hydrogen (in the presence of a chiral catalyst) have previously been reported.[22] Biocatalytic deracemizations are beyond the topic of this review.

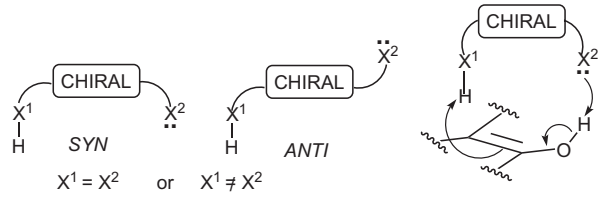
In order to be successful in such work, one needs not only to think about classical parameters concerning the chiral protonating agent, prochiral substrate, reaction medium and so on, but also to take into account the *E*/*Z* configuration of the substrate (Latent Trigonal Center concept, vide infra, part 4.1).[1m–o] Moreover, availability, cost, and easy recovery of the chiral protonating agent after use, must obviously be taken into consideration as well.

2. Chiral protonating agents (CPA)

First of all, regarding the chiral protonating agent, the usual requirements relating to structure and acidity must be fulfilled.

2.1. Structural requirements

Good enantiomeric excesses for the protonation of enolic systems are generally obtained when chiral agents (i) bear in a vicinity two sites with one acting, as a proton donor and the other as a proton acceptor, (ii) when these two sites are in a *syn* arrangement. Obviously, this *syn* conformation maximizes chiral–prochiral interactions when protonation occurs. We suggested previously that these two sites were involved in the tautomerization of an enol.[1j] (Scheme 2 and T10, entry 2).

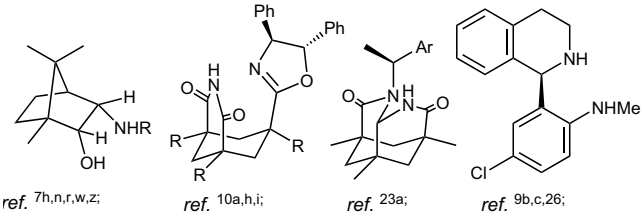


Scheme 2.

In support to this proposal, we noticed that with other things being equal, an increase in the crowding of the R substituents of *O*,*O*-diacyltartaric acids, encouraging the *syn* form, led to an important increase in the ee (Scheme 3 and T6, entry 1).[1g] Conversely, locking the two operating groups of tartaric acid in an *anti* position by an acetalic linkage resulted in a dramatic decrease in enantioselectivity (Scheme 3).[1g]

Scheme 3.

The following CPA with locked type *syn* or *gauche* forms gave, as expected, very high enantiomeric excesses (Scheme 4).



ref. [7h,n,r,w,z]; *Scheme 22; T2, entry 5; T7, entries 29-30; T9, entries 7-8*

ref. [10a,h,i]; *T7, entries 9-10*

ref. [23a]; *T8, entry 5*

ref. [9b,c,26]; *Scheme 7; T5, entries 2-5*

Scheme 4.

Although necessary, this condition is obviously not sufficient enough and in order to be successful in the findings of new CPA, the thought process should be firstly, to choose a structure where the two functional groups are in a *syn* (or *gauche*) relationship and secondly, to test variations of the backbone substituents in order to favor the optimal match between the CPA and the prochiral

substrate (T2, entry 5; T6, entry 1; T7, entries 11, 29; T9, entries 5 and 7).

In brief, the most efficient CPA reported until now are polyfunctional compounds,[4c] whose structures allow an increase of the rigidity of the protonation model by means of a better coordination between the CPA and the substrate.

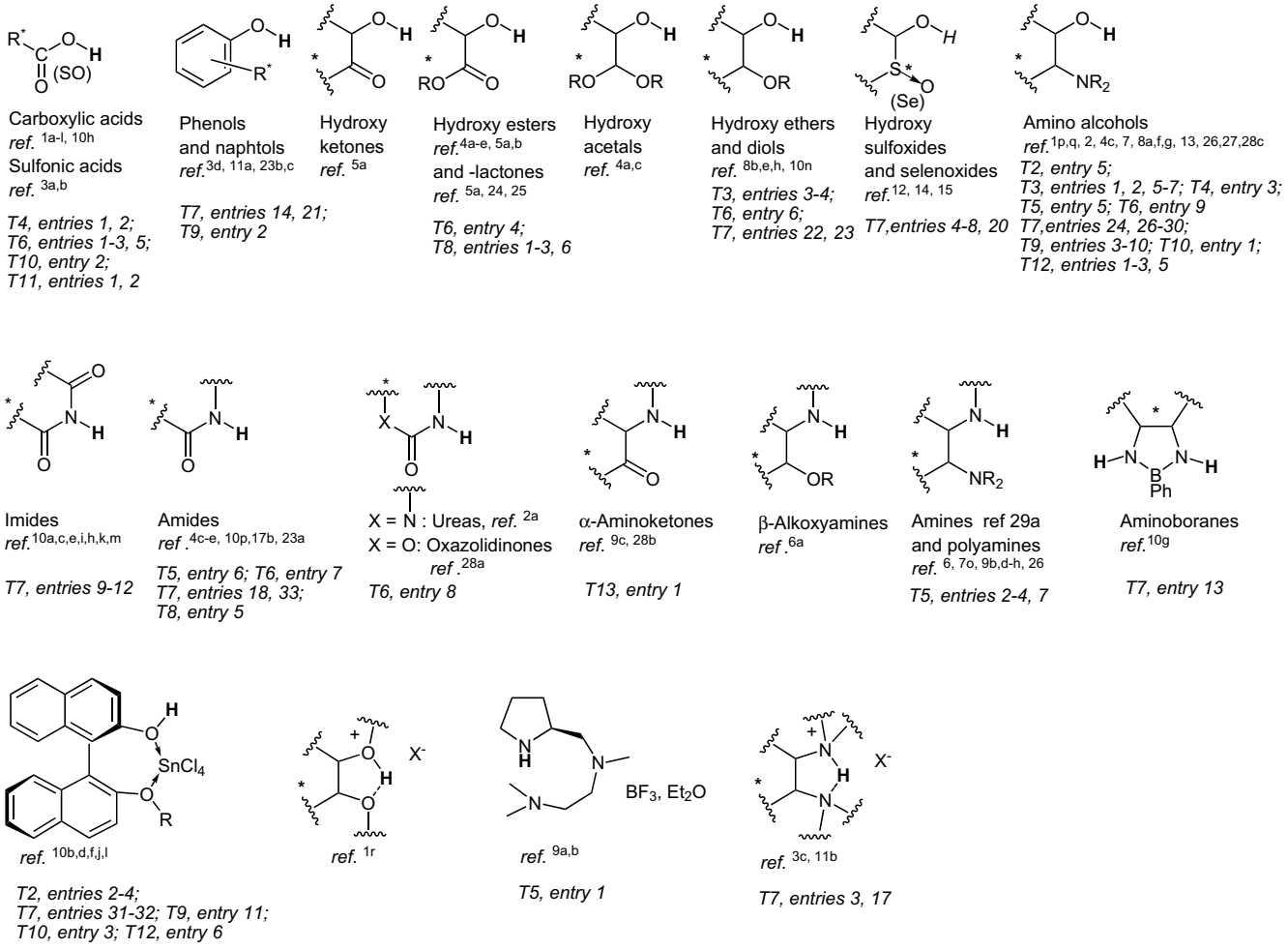
2.2. Acidity requirements

In most chiral agents, a proton is linked either to an oxygen atom (carboxylic acids, phenols, alcohols) or to a nitrogen atom (ureas, imides, amides, amines, aminoboranes). In some cases, the acidity is enhanced either by coordination with a Lewis acid or by adding a proton to afford an onium salt (Scheme 5).

If their acidity is sufficient, they act as a CPA. On the other hand, if the acidity is insufficient (chiral aliphatic amines for example), they act as chiral ligands of the prochiral substrates with the protonation step occurring possibly during the work-up by means of an achiral protonating agent (for instance,[6,29b] Schemes 35, 36 and T5, entry 1; T7, entries 1, 2, 19).

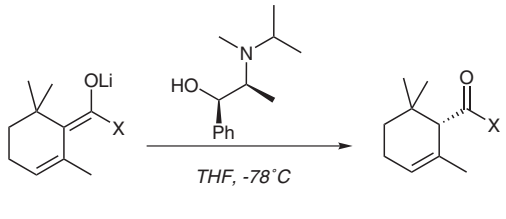
The most commonly used CPAs exhibit a large range of pK_as, with a mobile proton belonging to functional groups, such as carboxylic acids ($pK_a \approx 5$), phenols ($pK_a \approx 10$), imides ($pK_a \approx 11$), amides ($pK_a \approx 15$), alcohols ($pK_a \approx 17$), and aromatic amines ($pK_a \approx 25$).

In a typical enantioselective protonation, the protonation must be as complete as possible. Otherwise, the remaining substrate will be protonated during the work-up, mostly without or with a low enantioselectivity. According to standard pK_a calculations, pK_a differences ($\Delta pK_a = pK_a$ substrate $- pK_a$ HA*) of 2, 3 or 4 units lead, respectively, to a 91%, 97%, or 99% protonation. However, not only the thermodynamic, but also the kinetic acidity has to be taken into account.[9g] There is often a correlation between the kinetic and the thermodynamic acidity.[30] So it is assumed that as the ΔpK_a decreases, the rate of proton transfer is lowered, which in turn increases enantioselectivity. A priori, the compromise for the best enantioselectivity (requiring the lowest ΔpK_a) and for a complete protonation (requiring the highest ΔpK_a) is $2 \leqslant \Delta pK_a \leqslant 4$. Unfortunately, the pK_as of the substrates and of HA* have usually not been established.



Scheme 5.

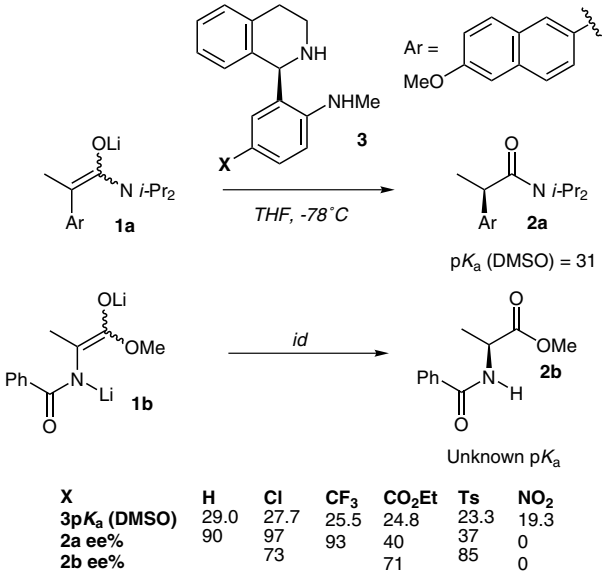
Fehr was the first to emphasize, the importance of the acidity parameter by using the same chiral acid; he established that the lower the pK_a of the substrate, the higher the ee[2d] (Scheme 6).



X	OMe	OPh	SPh
ee%	36	77	99
Ref	2f	2g	2f

Scheme 6.

The importance of this parameter was thoroughly investigated by Vedejs.[9g] Lithium enolates **1a** and **1b** were protonated by a series of anilines **3** whose pK_as have been estimated (Scheme 7). A good correlation was observed between the ee of **2a** and the pK_a of CPA **3**. The best results (ee >93%) were obtained for $\Delta pK_a = 3–5$ with an optimal value (ee = 97%) for $\Delta pK_a = 3$.[31] For the deracemization of **2b**, the optimal ee (85%) observed with **3** (X = Ts) suggests that the pK_a of the monoprotonated enolate **1b** is lower than that of **1a**.

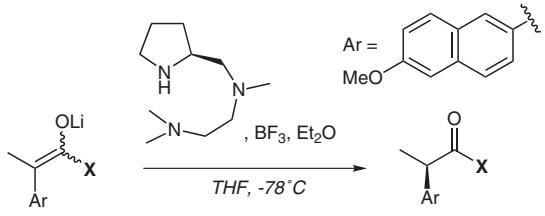


X	H	Cl	CF_3	CO_2Et	Ts	NO_2
3pK_a (DMSO)	29.0	27.7	25.5	24.8	23.3	19.3
2a ee%	90	97	93	40	37	0
2b ee%		73		71	85	0

Scheme 7.

To take advantage of Vedejs results, it is essential to know the pK_as of the studied enolates in order to choose the adequate protonating aniline **3** involving a ΔpK_a of approximately 3. (*R*)-Aniline **3** (X = Cl) is commercially available while the synthesis of the (*S*)-**3** analogue (X = H) has already been reported.[9f]

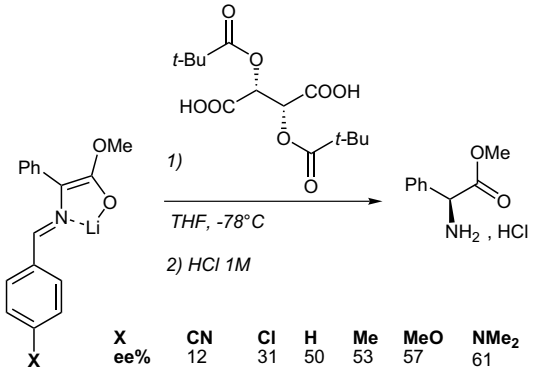
It is very probable that not only the ΔpK_a but also other variables play a role in the enantioselectivities. For instance, if the pK_a is modified by substituting the aniline nitrogen atom of **3** instead of the aromatic nucleus, comparisons become difficult because the steric and electronic changes near the aniline nitrogen may be large enough to obscure the role of ΔpK_a.[9g] Also difficult to explain are the ee of the deracemization of a carboxylic acid by protonation of its esters enolates and amides enolates. The highest ee expected from the less basic esters enolates have not been observed (Scheme 8).[9d,32]



X	pK_a (THF)	ee%
OEt	23-24	33
NMe_2	# 31	33
NEt_2	# 31	47
N *i*-Pr_2	# 31	77

Scheme 8.

Lastly, previous results of our group concerning the protonation of a series of enolates of increasing basicities by the same CPA have shown that the higher the ΔpK_a the higher the ee (Scheme 9).[1g,33]

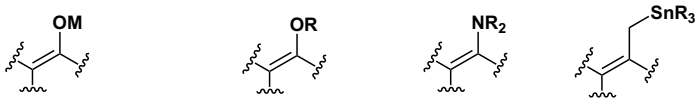


X	CN	Cl	H	Me	MeO	NMe_2
ee%	12	31	50	53	57	61

Scheme 9.

3. Prochiral substrates

The substrates generally used, had an sp^2 prostereogenic center being part of either enolates of ketones, esters, lactones, amides, or enols, silylenolethers, ketene acetals, enamines, or allyltins (synthetic equivalents of allylic anions). The metallic cations of enolates are mainly the lithium cation and less usually the sodium, potassium, magnesium, samarium, copper, and zinc cations. Enolates of cobalt, rhodium, palladium,[34] and tetraalkylammoniums have also been used (Scheme 10). A large increase in the ee was reported



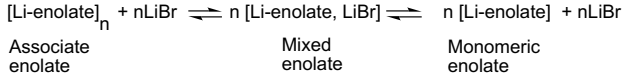
M	R		
Li*	H *ref 1h,p,q, 7; T2, entry 5; T3, entries 5-7; T4, entry 3; T7, entries 26-29; T9, entries 5-10; T10, entry 2; T12, entry 5*	*ref 1f, 35; T4, entries 1-2*	*ref 10f; Scheme 15*
Na *ref 10h*			
K *ref 1h, 10h*			
Mg *ref 3d; T7, entry 21*			
Sm *ref 8, Scheme 16; T3, entries 3, 4; T7, entries 22-24; T10, entry 1; T12, entry 4*	$OSiR_3$*		
Co *ref 55; T5, entry 8*			
Rh *ref 54; Scheme 40*			
Pd *ref 16, 53; Schemes 38-39; T3, entry 7; T7, entries 25, 30*			
Cu *ref 27; T9, entry 3*			
Zn *ref 14; T7, entry 20*			
N^+R_4 *ref 13a; T2, entry 1; T9, entry 4*			

* See numerous examples, Tables 2-13.

Scheme 10.

by replacing the lithium cation by either magnesium[3d] or zinc.[14a]

There are some questions about the degree of aggregation of lithium enolates. In many cases, the addition of metallic salts (LiBr, LiCl),[4d,6a,10i] or lithium alkoxides[2b] have a favorable effect concerning the enantioselectivity (T7, entries 1, 10, 15, 19; T8, entry 3). In fact, lithium enolates are generally obtained as associate contact ion pairs of different orders.[36] Addition of lithium salts results in the disaggregation and formation of mixed aggregates (Scheme 11).[36b,37]



Scheme 11.

In the presence of a large excess of LiBr, the mixed aggregate is largely predominant. The results depend both on the concentration of each species and on its reactivity. Obviously, according to the Curtin–Hammett principle, the minor species may be predominantly involved if its reactivity is large enough, as reported for the alkylation reaction where kinetic studies have shown that the monomeric lithium enolate is the dominant reactant, although the mixed aggregate is largely predominant.[38]

Symmetrical 1,2-enediols[1h] and 1,2-enediols bistrimethylsilyl ethers[39a] have also been transformed into optically active acyloins by enantioselective protonation (T10). Particular benzylic lithium anions have been successfully protonated (T5, entry 7, T13).[9c,29a,39b] The first deracemization of a phosphine oxide[9c,28b] was reported by Vedejs (T13, entry 1).[9c] The sole enantioselective protonation of an sp^3 prostereogenic center was described by Fuji (T11, entry 1).[3a,b] Data taken from the literature are given in Tables 2–13.

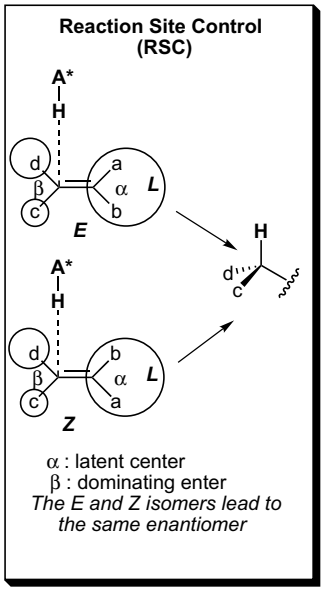
4. Enantioselective protonation reaction

In the following section is discussed the different factors governing enantioselective protonations, such as the geometry of the prochiral substrate, temperature, and presence of an amine in the reaction medium. Another important question is the possibility of *O*- versus *C*-protonation of enolates. However, oxygen protonation is generally reversible while carbon protonation, which is the asymmetric step, is not. It has been shown that low pH stabilizes the enolic tautomer, while *C*-protonation via the enolate occurs rapidly under relatively neutral conditions.[40]

4.1. Influence of the *E*/*Z*-configuration: RSC and NSC reactions

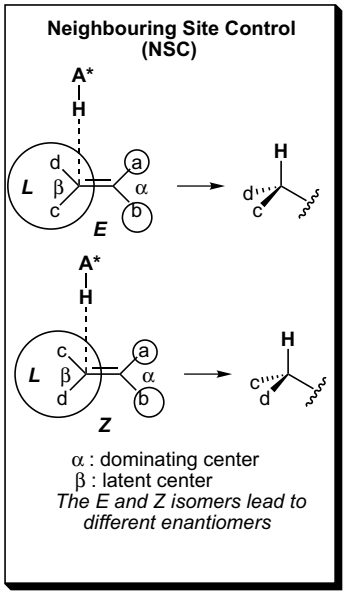
Concerning the regioselectivity, in all cases the fixation of the proton occurs, as expected, on the most electron rich prostereogenic center designated by β (Schemes 12 and 13).

Concerning the chiral recognition when the chiral protonating agent H-A* approaches the substrate, it is faced not only with one, but with two stereogenic centers α and β (Schemes 12 and 13). According to the LTC concept (Latent Trigonal Center concept),[1m–o] we have proposed that one of these two centers (the dominating center) prevails over the other (the latent center). Inside of the circle *L* including the latent trigonal center (Schemes 12 and 13), the protonating agent H-A* cannot distinguish the *Re*-face from the *Si*-face. Therefore, it cannot appreciate the difference when the two substituents are permuted inside of the circle *L*, although this variation results in a change of the configuration of the double bond. Thus the LTC behaves as one of the three substituents of the trigonal dominating center. Two extreme cases are resulting depending on the coincidence (Scheme 12) or not (Scheme 13)



H-A*: Chiral Protonating Agent
a and / or b : electron donating substituents
c and / or d : H or alkyl substituents
L : latent center

Scheme 12.



See footnotes, Scheme 12

Scheme 13.

of the dominating center (α or β) and the reaction center β:

Reaction site control (RSC) (Latent Trigonal Center: α-carbon atom, Scheme 12): Accordingly, the dominating center and the β-reaction site coincide. Therefore, the linkage of H-A* occurring on the same face of the β-trigonal center, starting, respectively, from the *E*- and *Z*-isomers affords the same enantiomer as the reaction product (Scheme 12 and Table 1, entry 1).[41a]

Neighboring Site Control (NSC) (Latent Trigonal Center: β-carbon atom, Scheme 13): In this case, the dominating α center does not coincide with the reaction site (β-carbon). The approach of the β-trigonal center by the chiral reagent occurs always in front of the same face of the α dominating trigonal center, which is in the neighborhood of the β reaction site. This is the reason why we say that such a reaction occurs with a NSC. In the case of the *E*-isomer, H-A* binds to one face of the β-reaction site center whereas in the case of the *Z*-isomer, it binds to the other face of the β-center. Thus two products of opposite configurations are obtained from the *Z*- and *E*-isomers (Scheme 13 and Table 1, entry 2).

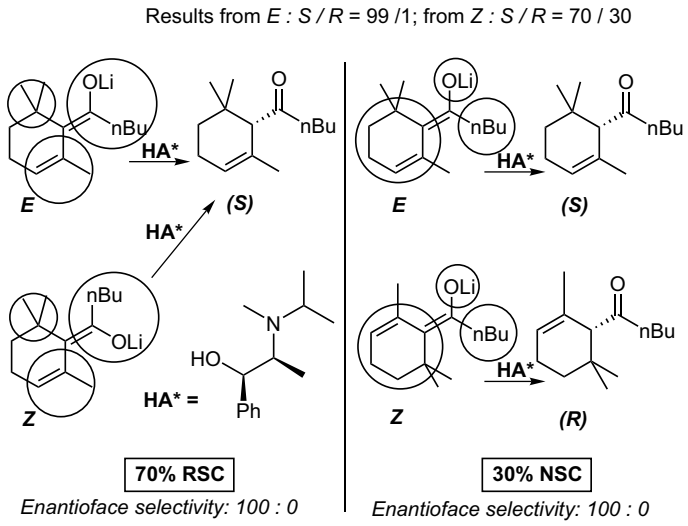
For these two RSC and NSC ways, we have to consider the enantioface selectivity (% attack on each face). In cases of partial enantioselectivity, products with ee <100% are obtained from the *E*- and *Z*-isomers, with the same ee and the same configuration for the RSC way and with the same ee and an opposite configuration for the NSC way. Beside these two extreme ways, mixed cases are involved.

Mixed RSC/NSC reactions: In this case, electrophilic attacks occur partly by the RSC way and partly by the NSC way.[41b] It is noteworthy that a racemic product can be obtained by ways involving a total enantioselectivity (100/0): in the particular case of mixed ways RSC/NSC = 50/50, a racemic product is obtained from a single geometrical isomer, while the other geometrical isomer affords one enantiomerically pure enantiomer (Table 1, entry 5).[42]

Literature examples: Only a few examples concerning the influence of the *E*- and *Z*-configuration of the prochiral substrates have been reported. Protonation of lithium enolates of damascone analogues by *N*-*i*-propyl ephedrine published by Fehr is RSC predominant.[2g] Protonation of silyl enol ethers obtained from thiol esters of α-aryl propionic acids by binaphthol/$SnCl_4$

Table 1. Theoretical results with enantioface selectivity: 100:0

	RSC (%)	NSC (%)	From pure E isomer product	Ee (%)	From pure Z isomer product	Ee (%)
1	100	0	One enantiomer	100	The same enantiomer	100
2	0	100	One enantiomer	100	The other enantiomer	100
3	75	25	One enantiomer	100	The same enantiomer	50
			or one enantiomer	50	The same enantiomer	100
4	25	75	One enantiomer	100	The other enantiomer	50
			or one enantiomer	50	The other enantiomer	100
5	50	50	One enantiomer	100	Racemic	0
			or racemic	0	One enantiomer	100

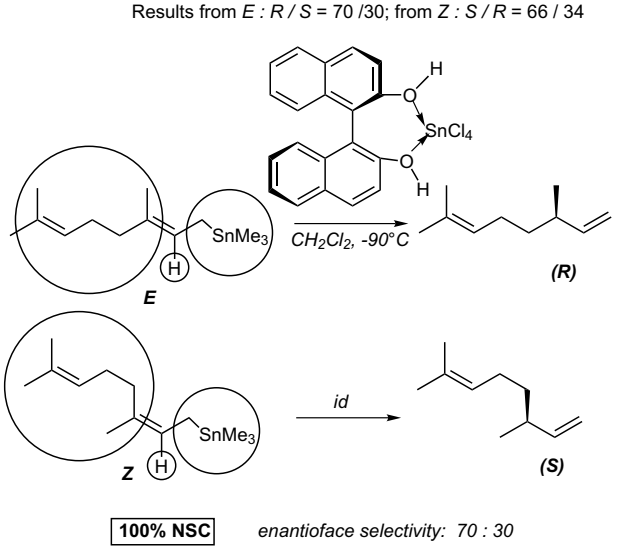


Scheme 14.

led to enantioselectivities, which were independent of the *E*/*Z* ratio (RSC reaction) (T12, entry 6).[43,44] Protonation of *Z*- and *E*-enamines of phenylhydratropic aldehyde by DPTA[1b] as well as protonation of *E*- and *Z*-allyltins reported by Yamamoto[10f] are NSC preponderant.

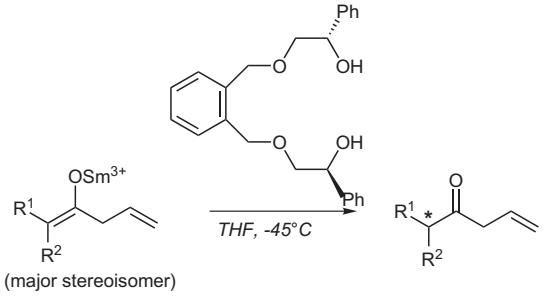
In the Fehr example[2g] (Scheme 14), the results could be explained by mixed reactions with RSC/NSC = 70/30 and an enantioface selectivity near of 100:0 for each type of reaction; from the *E*-isomer, the RSC and NSC routes could lead independently to the same (*S*)-enantiomer, whereas from the *Z*-isomer, they could lead to products with opposite configurations.

In the Yamamoto example (Scheme 15), the *E*- and *Z*-isomers lead to products with opposite configurations (NSC reactions).[10f] Moreover, as the ees are nearly identical, the participation of the RSC-type reaction is negligible. The results can be explained by a nearly pure NSC reaction with a moderate enantioface selectivity of about 70:30.[45]



Scheme 15.

Takeuchi has reported the enantioselective protonation of a series of samarium enolates with known configurations (Scheme 16).[8b] Although in each case the results from the *E*- and *Z*-enolates are not given, the excellent correlation observed between the enantiomeric excesses and the *E*/*Z* ratio suggests a pure NSC reaction.



R^1	R^2	*Z*/*E*	*R*/*S*
i-Pr	p-C_6H_4	12/88	8/92
Ph-CH_2	*i*-Pr	14/86	16/84
Et	Ph-CH_2	35/65	35/65
Ph	Et	93/7	92/8
Ph	Me	96/4	96/4
Ph-CMe_2	Me	>99/<1	97/3

Scheme 16.

Discussion: From a more general point of view in the studies of asymmetric reactions, when a product is obtained either racemic or with a modest ee from one geometrical isomer using a chiral electrophilic reagent, before searching a more efficient chiral reagent, it is

worthwhile to know the result from the other geometrical isomer.

In cases of a pure RSC route, it is not necessary to work with pure geometrical isomers since the two pure forms *E* and *Z*, as well as their mixtures, afford the same enantiomer with the same ee. Consequently, obtaining the other enantiomer requires the use of a chiral reagent of opposite configuration.

In cases of a pure NSC route, it is necessary to work with pure *Z*- and *E*-isomers, since products of opposite configurations are obtained from each of them, with the same ee. The advantage is that by using the same chiral reagent, it is possible to access to the enantiomers of opposite configurations starting, respectively, from the *E*- or *Z*-material. Nevertheless, when only one pure stereoisomer (*E* or *Z*) is available, the two desired enantiomers can be obtained using the two chiral reagents of opposite configuration. Obviously, most of asymmetric reactions behave as more complex mixed processes.

The preceding considerations suggest that at the beginning of the study of a new asymmetric reaction it is essential to determine if the process is of NSC or RSC type. If the two isomers *E* and *Z* are not available in their pure forms, it is sufficient enough to know the results from two different mixtures of *E*- and *Z*-isomers.

In the cases of asymmetric reactions involving a substrate bonded to a chiral auxiliary (covalently or not), and an achiral reagent, the same NSC and RSC schemes have to be considered. Numerous examples of asymmetric reactions exhibiting very high ee, both from *E*- and *Z*-isomers, are described (pure NSC- or RSC-type reactions).[46] In the field of enantioselective protonations, high ee have been reported from one geometrical isomer, whereas in most cases, the results from the other are not known. Obviously, in the case where the a and b substituents are identical (Schemes 12 and 13), the only possibility is the RSC way.

4.2. Protonation in the presence of amines

When the protonation of a lithium enolate is performed in the presence of an amine, we may consider not only the direct protonation of the Li-enolate complexed by the amine via the protonating agent H-A* but also the protonation of the Li-enolate by the intermediary of the ammonium salt $^{+}NHR_3$, $^{-}A^*$. An oversimplified representation of these two cases is presented in Scheme 17.

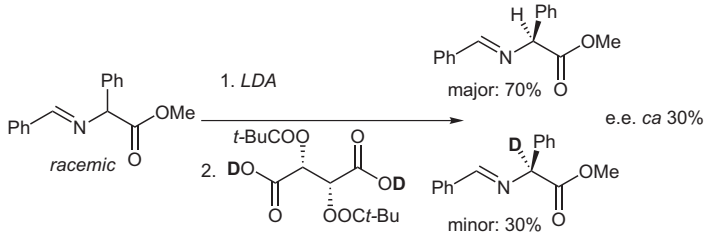
Scheme 17.

The formation of molecular complexes between Li-enolates and amines in the solid state as in solution is very well documented.[47] The enantioselectivity of the protonation of an enolate is generally influenced by the presence of an amine, its nature, and its structure (T6, entries 2 and 3).[1g,i,k,6] In some cases, products with opposite configurations are obtained using LDA instead of LiHMDS in order to prepare the enolate (T6, entry 4).[24] Protonation of a Li-enolate prepared in the presence of a chiral amine by an achiral acid led us to a significant ee (T6, entry 2)[1g,i] opening up the chemistry of chiral bases in asymmetric synthesis. Examples of this type of protonation have been reported (Schemes 20, 35, 36; T7, entries 1, 2, 16, 19; T8, entry 2),[4d,6,11b,29b] some of which with very high ee.[6a,b,d]

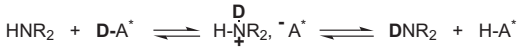
Additionally, we observed that the addition of a deuterated chiral acid D-A* to a Li-enolate generated from a carboxylic ester and LDA does not furnish the desired α-deutero carboxylic compound, but mainly the α-protonated product (Scheme 18) whereas the quenching of an aliquot with D_2O gave a total incorporation of deuterium.[1e]

Many observations of this type have been reported.[4d,6a,b,36f,48] It should be noted that the deuterating (or protonating) agent is confronted to many basic sites such as the solvent, the liberated secondary amine, the *C*- and *O*-centers of the enolate and can encounter them before bonding thermodynamically to the carbon center of the enolate.

According to Scheme 19, in order to enhance the deuteration versus the protonation the factors lowering the stability of the intermediate ammonium salt must be considered. These are, for a given amine, the decreased acidity of D-A*, and for a given D-A*, the decreased basicity of the amine.



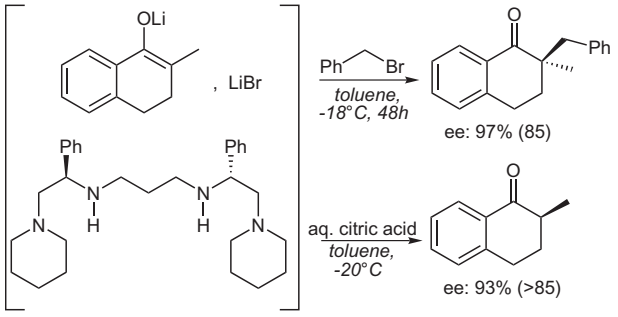
Scheme 18.



Scheme 19.

Accordingly, it was observed for a given enolate, that the deuterium incorporation decreases in accordance with the following orders: D_2O, DOR > DOAc (opposite of the acidity order) and HMDS > *i*-Pr_2NH > TMP (opposite of the basicity order).[4d] It also depends on the aggregation degree of the Li-enolate: deuteration is increased by adding LiCl[4d] and in toluene upon increasing amounts of THF, well-known conditions to decrease the aggregation degree.[48d]

Arguments favorable to the first or second proposal of Scheme 17 are known. The use of AcOH to protonate the Li-enolate of 2-methyltetralone coordinated with a chiral diamine led to a significant ee of 48% while using the corresponding chiral ammonium acetate gave only 5% ee (T7, entries 16 and 17).[11b] This result has been reported as an argument in favor of a direct *C*-protonation following an initial coordination of the lithium atom by the amine. On the other hand, in a particular example, the attack in alkylation[49] and in protonation[6d] of a Li-enolate complexed by a chiral amine follows opposite directions (Scheme 20). This observation as well as an incomplete deuteration by AcOD suggests different mechanisms for the two reactions and is not in contradiction with a protonation reaction via an ammonium cation.[6b]

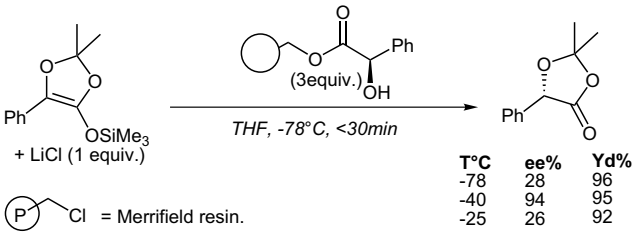


Scheme 20.

An ammonium cation can also be considered in the protonation of an enol by H-A*, performed in the presence of an amine.

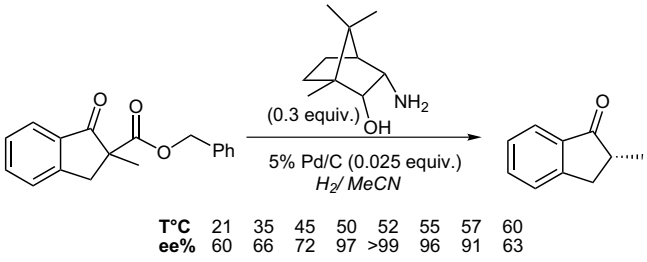
4.3. Influence of temperature

Many protonation reactions are carried out at low temperatures (<−50 °C) since it has been observed that by lowering the reaction temperature of the protonation step, an increase in the ee is observed. Contrary to this some examples where the ee goes through a maximum when the temperature increases have been reported. One example is the enantioselective protonation of a silyl enol ether achieved by a proton donor supported on a polymeric resin. The optimal ee was obtained at −40 °C (Scheme 21).[5b]



Scheme 21.

Another example is the palladium-induced cleavage of a β-keto ester in the presence of a chiral aminoalcohol leading to α-methylindanone, by cascade reactions involving deprotection, decarboxylation, and enantioselective protonation of the enolic species. Impressive ees (96–99%) were obtained within a narrow range of temperature (50–55 °C) (Scheme 22).[7t]



Scheme 22.

Such results can be analyzed by the isoinversion principle.[50]

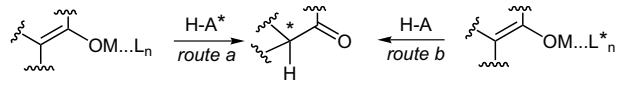
4.4. Catalytic enantioselective protonations

Catalytic methods are especially useful when the chiral tool is expensive and difficult to prepare and recover.

4.4.1. Enols. The enantioselective protonation of an enol can be carried out in the presence of a catalytic amount of CPA because the protonating agent is regenerated in the protonation process. This type of reaction has been extensively studied by the group of Reims.[7] High ees have been reported although the enol can compete with the CPA. Protonation of dienols generated by irradiation of α,β-unsaturated-esters[7b–h,l,p,q,w] (T9, entries 5–8), -lactones,[7a,c,f,h] -acyclic ketones (T3, entries 5 and 6), and cyclic ketones[7i] having been studied since 1985. The same group also reported the protonation of simple arylenols (T7, entries 26–30).[7n,o,r–v,x] High ees were obtained using aminoalcohols of ephedrine[7g] type and hydroxy aminobornane[7h,m] type as chiral catalysts (ephedrine series: T3, entries 5 and 6; T7, entries 26 and 27; T9, entries 5 and 6. Aminobornane series:

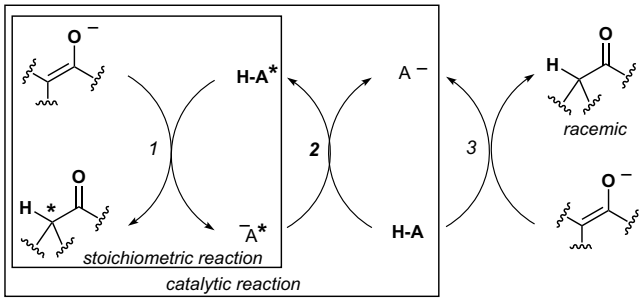
Scheme 22 and T2, entry 5; T7, entries 29 and 30; T9, entries 7–10).

4.4.2. Enolates. In order to present the literature results, two types of reactions have been considered, according to the starting materials: (route a) the prochiral enolate is brought into the presence of a chiral acid H-A*; (route b) the prochiral enolate, part of a chiral aggregate is brought into the presence of an achiral acid (Scheme 23).



Scheme 23.

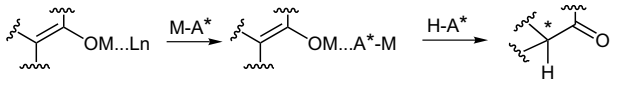
4.4.2.1. Protonation by a chiral protonating agent (Scheme 23, route a). The chiral protonating agent H-A* can be used in a catalytic amount if it is regenerated by introducing a stoichiometric amount of an achiral acid H-A (Scheme 24, routes 1 and 2). However, the achiral acid H-A is solicited by two bases: the anion A^{*-} (route 2) and the enolate (route 3). Obviously, for an optimum catalytic cycle, route 3 must be avoided, requiring k_1 and $k_2 \gg k_3$.



Scheme 24.

To minimize route 3, the ratio H-A*/H-A must be as high as possible. This result is obtained when H-A is introduced slowly,[2d,8c,9e,10c] or when a liquid–liquid biphase system[8e] or solid–liquid biphase system[8e] is used.

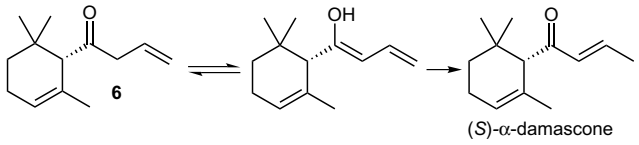
In fact, at the beginning of the protonation step, the liberated M-A* can behave as a ligand of the enolate (L = M-A*) and acts upon its protonation. Thus a chiral aggregate is protonated by a chiral acid H-A*, involving a double stereodifferentiation (Scheme 25).



Scheme 25.

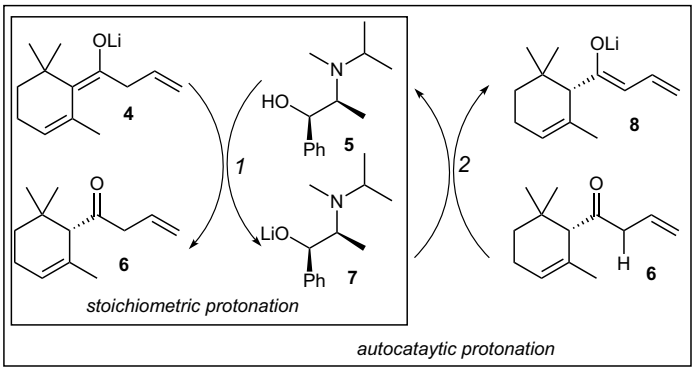
Moreover, the chiral acid H-A* often contains a basic site able to complex the cation (see Section 2.1). Thus, route a is a simplified representation. The first examples of catalytic enantioselective protonation of enolates were reported in 1993 and 1994, by Fehr.[2d,e] Protonation of Li-enolate **4** by a stoichiometric amount of aminoalcohol **5** led to ketone **6** with an excellent enantioselectivity (95%) (Scheme 26, route 1).[2e] In fact, preliminary mechanistic studies have shown that this reaction did not need an equivalent of H-A* **5** since protonation of the Li-aminoalkoxide **7** by ketone **6** regenerates aminoalcohol **5** with concomitant formation of isomeric Li-enolate **8** (Scheme 26, route 2). Using only 0.3 equiv of chiral protonating agent, **5** afforded ketone **6** with 93% ee and 86% yield.[2e]

Li-enolate **8** was transformed during the work-up into ketone **6**, which can be easily isomerized into (*S*)-α-damascone, a fragrance material (Scheme 27).[2e,g] It was established that enolate **4** was not enantioselectively protonated by ketone **6**.



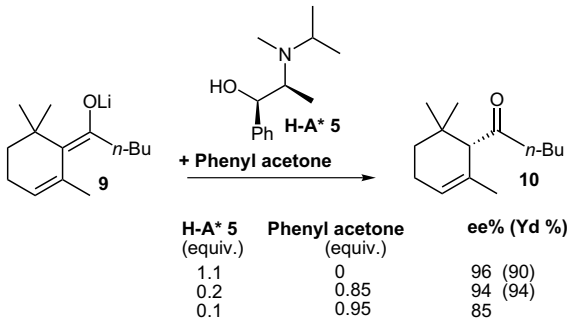
Scheme 27.

Generally, the resulting carbonyl compound did not have sufficient acidity to regenerate the chiral protonat-



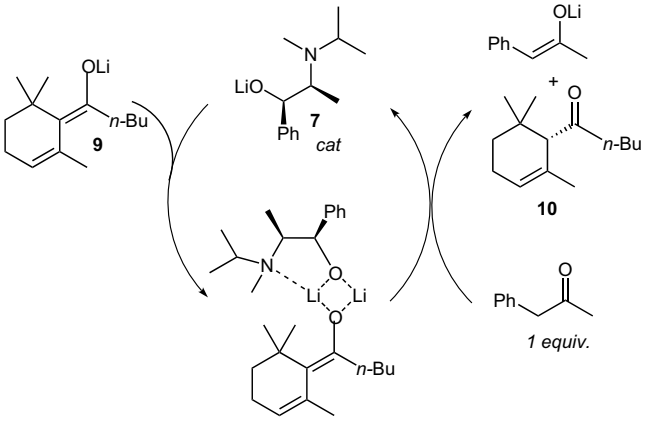
Scheme 26.

ing agent, as in this particular case of autocatalytic enantioselective protonation. To circumvent this problem, the authors added an achiral acid with adequate pK_a, in stoichiometric amount.[2e] Li-enolate **9**, an analogue of **4**, was transformed into ketone **10** by protonation with a catalytic amount of chiral aminoalcohol **5**, in the presence of phenyl acetone (Scheme 28).



Scheme 28.

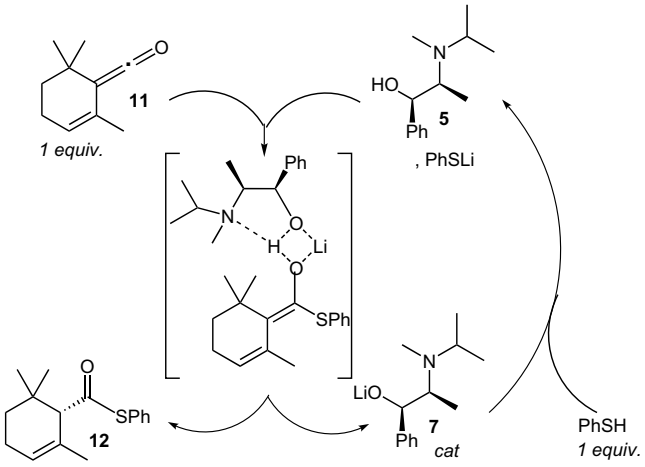
Although these results apparently agree with route a (Scheme 23), mechanistic studies suggest a pathway related to route b, as it was observed that phenyl acetone protonates Li-enolate **9** much faster than Li-aminoalkoxide **7**. The authors suggested that phenyl acetone furnishes its proton to a chiral complex formed from Li-enolate **9** and Li-aminoalkoxide **7**, leading to chiral ketone **10** and regenerating chiral Li-aminoalkoxide **7** (Scheme 29).[2e,g,51] Unlike the general Scheme 23 (route a), the enolate is not directly protonated by a chiral acid, but is transformed into a chiral aggregate, which is protonated by an achiral acid.



Scheme 29.

In this catalytic cycle, the achiral acid (phenyl acetone) may be replaced by β-keto esters, thiophenol, 2,6-dimethyl-4-methylphenol, H_2O, and carboxylic acids.[2e]

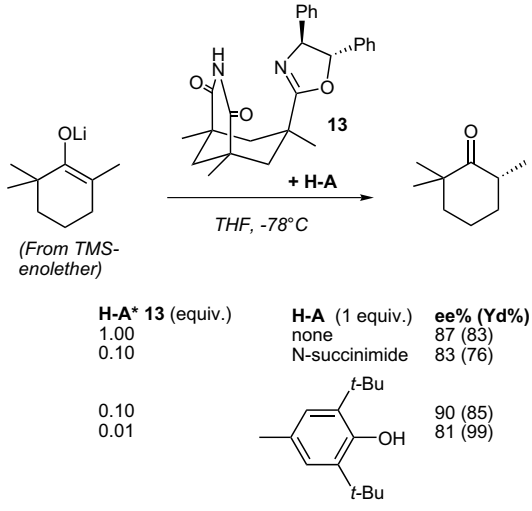
Similarly, excellent results were obtained for the deracemization of thioaryl esters, using catalytic conditions (T12, entries 1 and 2).[2c,f,g] As chiral thioarylesters can also be prepared by the addition of Li-thioarylalkoxides to ketene **11** at −55 °C, in the presence of 1 equiv of chiral protonating agent **5** (ee: 95–97%),[2c] a clever catalytic process was reported. Addition of PhSH to a mixture of ketene **11** in the presence of 5% of chiral Li-aminoalkoxide **7** afforded thiophenyl ester **12** with 89% ee and 86% yield (Scheme 30).[2c] The added thiol acts as a proton source and the Li-thioarylalkoxide as a nucleophile.



Scheme 30.

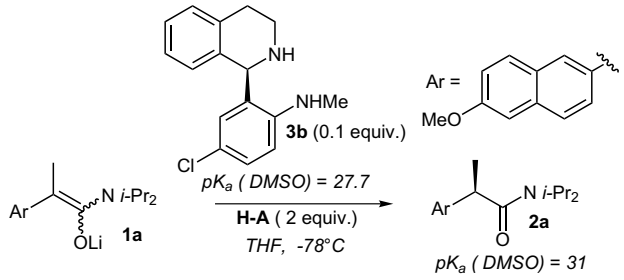
Moreover, this catalytic process has the advantage of taking place at −27 °C given that the thioester enolate is consumed as soon as it appears, thus avoiding its reverse transformation into ketene **11** and PhSLi, which occurs at $T > -80$ °C and requiring in the case of the stoichiometric protonation of the enolate prepared from racemic **12**, to work at −100 °C.[2c]

Enantioselective protonation of a single enolate, using as the chiral protonating agent a catalytic quantity of chiral imide **13** in the presence of 1 equiv of an achiral acid such as *N*-succinimide or a phenol (BHT) was reported by Yamamoto.[10c,m] Using only 0.01 equiv of chiral imide **13** afforded the reaction product with 81% ee, versus 87% for the stoichiometric conditions (Scheme 31).[10a]



Scheme 31.

Good results were also obtained with phthalimide, pentafluorophenol, or dipivaloylmethane in the presence of less than 0.10 equiv of chiral imide **13**.[10c] Chiral imide **13** and its enantiomer can be readily prepared from Kemp's tricarboxylic acid and enantiomeric β-aminoalcohols.[10a] Vedejs reported the catalytic enantioselective protonation of enolate **1a** using 0.1 equiv of chiral aniline **3b** in the presence of achiral carbon acids H-A of increasing pK_a (Scheme 32).[9e]

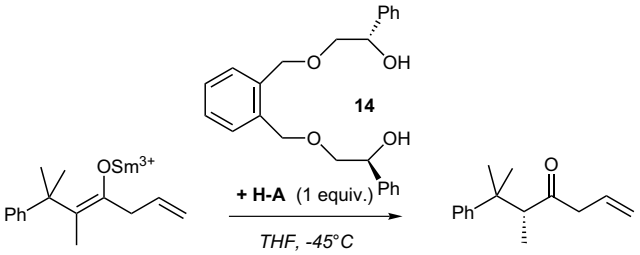


H-A	pK_a (DMSO)	ee%
Ph-CH_2-CO-CH_3	20	6
Ph-CH_2-CN	22	40
Ph-CH_2-CO_2Et	22.7	92
Ph-CH_2-CO_2 *t*-Bu	23.6	94
CH_3-CO_2Et	27.5 - 30	85
CH_3-CN	31	0

Scheme 32.

The protonation occurs with a very low ee using the more and the less acidic carbon acids H-A of a series. In the first case (lowest pK_a) route 3 of Scheme 24 is favored, in the second case (highest pK_a), route 2 of Scheme 24 is locked, preventing the regeneration of H-A* **3b**. Optimum conditions (ee 94% vs 97% for the stoichiometric conditions) were encountered when using *tert*-butyl phenylacetate as H-A. Good levels of enantioselectivities were obtained for carbon acids H-A with 22 < pK_a (DMSO) < 30. According to Vedejs, this large range of pK_a is due to a proton transfer between a heteroatom base (aniline **3b**) and a carbon acid H-A (Scheme 24, route 2), which is inherently much faster than the proton transfer involving a carbon acid and a carbon base (Scheme 24, route 3).[9e] Similarly, deracemization of a β, γ-unsaturated amide using 0.05 equiv of aniline **3b** was reported with an ee of up to 92% (T5, entry 3).[9e]

Takeuchi has extensively studied the enantioselective protonation of samarium enolates. Excellent results were obtained with C_2 symmetrical chiral diols, such as **14**, which act as chiral proton sources (and/or as tetradentate ligands of the samarium cation) (T3, entry 3; T7, entries 22–24).[8f] The author succeeded in extending this reaction to its catalytic version (ee 93% vs 95% for the stoichiometric conditions), using trityl alcohol as achiral acid H-A (Scheme 33).[8c] Various other achiral proton sources such as *tert*-butanol, BHT, acetylacetone, dipivaloylmethane,[8c] a fluorous tertiary alcohol[8e] were also effective (Scheme 33).



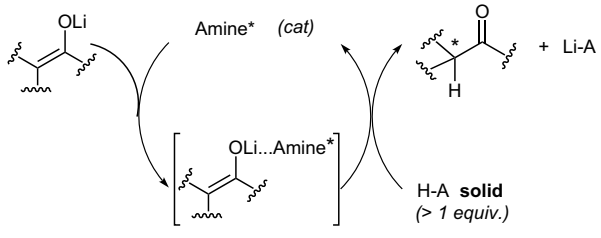
H-A*14	H-A (1 equiv)	ee% (Yd%)
1 equiv.	none	95 (59) TAs 94
0.15 equiv.	Ph_3C-OH	93 (55) THL 96
0.15 equiv.	(*n*-C_6F_{13}-CH_2-CH_2)$_3$C-OH	89 (55) THL 98
	(THF / FC-72)	

Scheme 33.

Takeuchi introduced fluorous chiral and achiral acids H-A and H-A* associated with the use of fluorous solvents such as FC-72 (*n*-C_6F_{13}).[8e,h] Catalytic conditions have been realized (ee 89%, Scheme 33) in a biphasic system THF/FC-72, using **14** as a chiral acid and a fluorous alcohol as an achiral proton source.[8e] The fluorous achiral alcohol remains in the fluorous solvent, while the chiral protonating agent **14** and/or its conjugate base shuttles between the THF and the FC-72 phases. The advantage of this procedure is that the achiral proton source H-A does not need to be added slowly to the reaction mixture as in the usual way, since in such a system, the ratio of H-A*/H-A is very high in the THF phase where the protonation occurs. Moreover fluorous products are easily separated from non-fluorous compounds by simple extraction with a fluorous solvent such as FC-72.

4.4.2.2. Protonation of chiral aggregates by achiral acids (Scheme 23, route b)[52]. Koga[6c] and Nakai[16] reported in 1997 this type of catalytic enantioselective protonation.

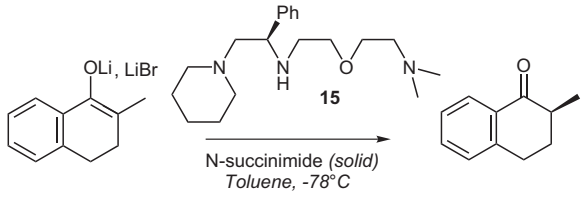
Koga studied alkylation[49] together with the protonation[6c] of Li-enolates in the presence of stoichiometric and catalytic amounts of chiral tetradentate amines. The first example of catalytic enantioselective protonation involved a solid–liquid biphase system using achiral acids, such as *N*-succinimide, which are solid and not soluble in toluene, allowing a slow reaction of the achiral proton source, even when added in one portion. A simplified catalytic cycle is depicted in Scheme 34. Catalytic chiral amine with the starting enolate gives a chiral aggregate, which is protonated by the achiral acid H-A. The reaction of the starting



Scheme 34.

enolate with H-A must be slower than the formation of the chiral aggregate and its reaction with H-A.

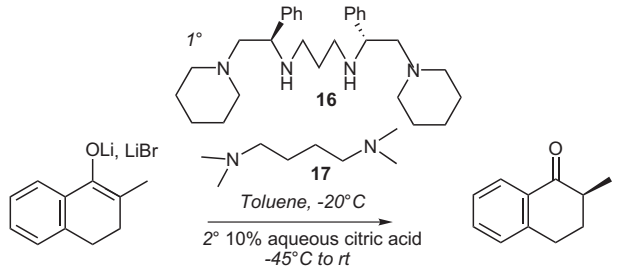
Thus, the Li-enolate of 2-methyltetralone in the presence of 0.2 equiv of chiral amine **15** with an excess of *N*-succinimide affords the corresponding ketone with an ee up to 83%,[6c] versus 91% for the stoichiometric reaction (Scheme 35).[6a]



15 (equiv.)	*N*-succinimide (equiv.)	ee% (Yd%> 88)
1.03	none	91
0.1	1.2	72
0.1	10	73
0.2	10	83

Scheme 35.

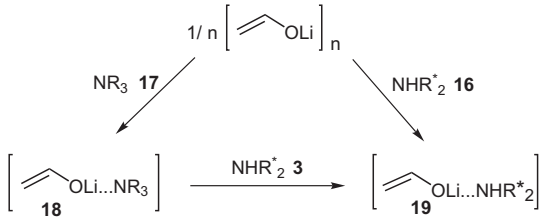
A second example involves a liquid–liquid biphase system with a large excess of water as the proton source in the presence of a catalytic amount of chiral tetramine **16** used together with 2 equiv of achiral bidentate diamine **17** in toluene (Scheme 36).[6d]



16 (equiv.)	17 (equiv.)	ee% (Yd>85%)
1	none	93
0.1	2	93
0.05	2	91
0.025	2	88

Scheme 36.

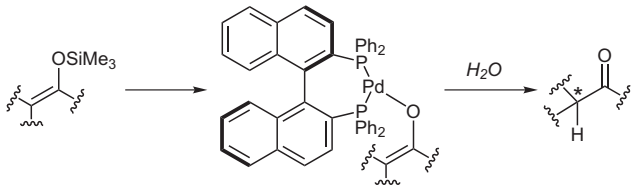
Using 0.1 equiv of chiral amine **16**, enantioselective protonation was achieved with the same ee of 93% as in the stoichiometric conditions. With only 0.025 equiv of **16**, the enantioselectivity did not decrease substantially (ee 88%). A possible role of the achiral diamine **17** is the disaggregation of the starting Li-enolate by complexation affording achiral aggregate **18**, which is a relay to accede to chiral aggregate **19**, thus obtained more easily than by the direct way. Chiral aggregate **19**, which is more reactive and more hydrophilic than achiral aggregate **18**, is protonated more rapidly in the biphasic system toluene/H_2O (Scheme 37). Lithium bromide, which is necessary for an enantioselective protonation, has been omitted in Schemes 34 and 37.[6a]



Scheme 37.

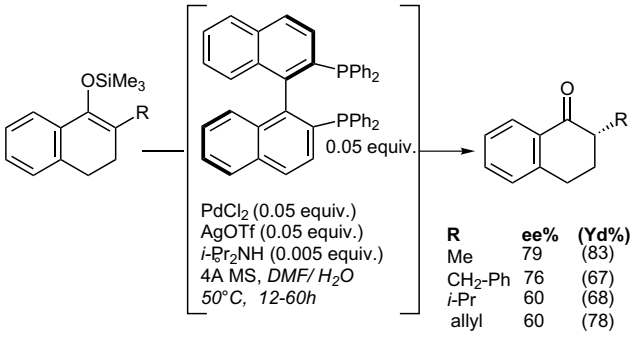
Using the catalytic conditions with 0.1 equiv of chiral amine **16** afforded 2-*n*-butyltetralone with an ee of 90% versus 92% for the stoichiometric procedure.[6d]

Nakai reported the protonation of a transient chiral palladium enolate generated by reaction of a chiral cationic Pd complex with a trimethylsilyl enol ether, using water as the proton source (Scheme 38).[16]



Scheme 38.

The protonation of this chiral palladium enolate afforded the enantiomerically enriched carbonyl compound with regeneration of the chiral Pd complex, thus working as catalyst. Addition of diisopropylamine or trimethylamine modifies the catalyst, thus making the reaction slower and providing an enhanced enantioselectivity. Cyclic ketones were obtained with ees up to 79% (Scheme 39 and T7, entry 25).

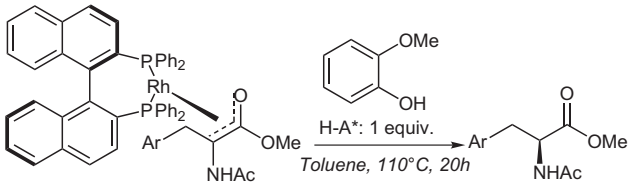


R	ee%	(Yd%)
Me	79	(83)
CH_2-Ph	76	(67)
i-Pr	60	(68)
allyl	60	(78)

Scheme 39.

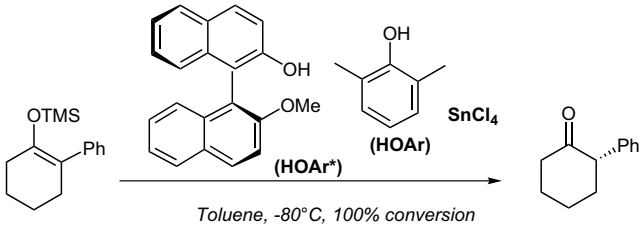
Genêt developed an access to α-amino esters with ee up to 90% using the protonation of (*R*)-BINAP complexed rhodium enolates, by guaiacol (Scheme 40).[53]

These enolates were obtained by the addition of Ar-BF_3K to 2-methyl acetamido acrylate in the presence of $[Rh(cod)_2][PF_6]$ and (*R*)-BINAP.



Ar	ee%
Ph	90 (89)
m-MeO-C_6H_4	90 (89)
p-F-C_6H_4	83 (82)
p-Br-C_6H_4	81 (75)
3-Thienyl	81 (68)

Scheme 40.



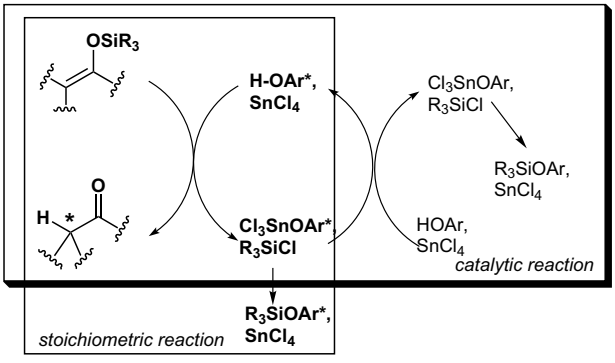
HOAr* (equiv.)	HOAr (equiv)	$SnCl_4$ (equiv)	ee%*
1.00	0	1.0	89 (98)
0.02	1.1	1.1	87 (90)
0.05	1.1	1.1	83 (91)
0.02	1.1	0.5	90

* Values in parentheses were corrected for the regioisomeric purity.

Scheme 42.

Transient samarium[54] and cobalt[55] enolates complexed by chiral ligands have been protonated by achiral acids (T5, entry 8; T12, entry 4), with success.

4.4.3. Enol ethers and ketene acetals. Yamamoto et al. went extensively into the enantioselective protonation of silyl enol ethers and disilyl ketene acetals.[10a,d,f,j,l,o] Using stoichiometric conditions, excellent results were obtained with chiral binaphthol derivatives (represented as HOAr* in Scheme 41) as Brønsted acids associated with Lewis acids such as $SnCl_4$, which restricts the orientation of the proton and raises its acidity (T2, entries 2–4; T7, entries 31 and 32; T9, entry 11; T10, entry 3; T12, entry 6). Mechanistic studies have shown that the silyl group of the starting material was transferred to the binaphthol derivative via a tin oxide intermediate (Scheme 41). A catalytic version can be realized if the chiral proton source HOAr* is regenerated from an achiral proton donor HOAr, if $SnCl_4$ is preferentially coordinated to HOAr* and if the reactivity of HOAr*, $SnCl_4$ is greater than that of HOAr, $SnCl_4$ (Scheme 41).[10d,f,j,l]



Scheme 41.

Thus, enantioselective protonation of TMS enol ether of 2-phenylcyclohexanone was achieved with ees up to 90% using stoichiometric amounts of 2,6-dimethylphenol and catalytic amounts of monomethyl ether of optically active binaphthol, in the presence of $SnCl_4$ (Scheme 42).[10d,m]

Similarly, the following ketones were obtained from the corresponding tetrasubstituted TMS enol ethers with corrected ees of 97% and 95% (Scheme 43).[10m]

ee%: 84 (97) ee%; 91 (95)

Scheme 43.

Examples of catalytic enantioselective protonation of disilyl ketene acetals are reported in T2, entry 2.

5. Conclusion and outlook

In this review we have discussed the main concepts for realizing enantioselective protonations. We expect that this will be a useful tool for chemists interested in this area.

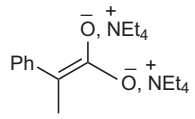
Access to various classes of organic compounds is reported in Tables 2–13. Numerous examples concern *perfumery*: α- and γ-damascones (T12, entries 1 and 2), vulcanolide (T3, entries 1 and 2; T12, entry 3), lavandulol (T9, entry 9), *medicinal chemistry*: ibuprofen (T2, entries 2 and 4; T5, entry 2; T12, entry 6), naproxen (T2, entries 3 and 4; T5, entries 1 and 2; T9, entries 2, 4, 11), epibatidine (T7, entry 7) muscarinic receptor antagonist (T5, entries 4 and 5), neutral endopeptidase inhibitors (T9, entry 10, T12, entries 4 and 5) and *biochemistry*: α-amino acids (T6), β-amino acids (T5, entry 6), chromanones (T7, entry 30), pheromones (T11, entry 1).

Various chiral structures have been obtained in high ee, proving that enantioselective protonation reactions are now powerful tools in asymmetric synthesis, for academic and industrial laboratories.

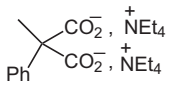
Table 2. Acids

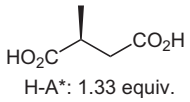
Substrate | **Chiral Agent** | **Product**

1



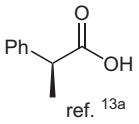
From





H-A*: 1.33 equiv.
+
cinchonine: 1.53 equiv.

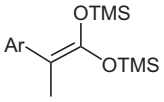
CH_3CN, 60°C, 3h
+ CuCl (0.03 equiv.)



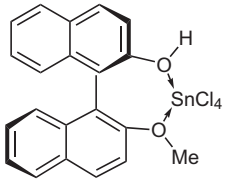
ref. [13a]

ee: 28% (quant.)

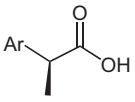
2



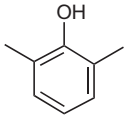
Toluene, -80°C, 1h.



H-A*, $SnCl_4$

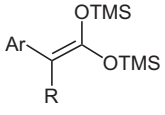


ref. [10l]

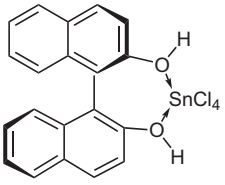


Ar	H-A equiv.	$SnCl_4$ equiv.	H-A* equiv.	ee% (Yd%)
C_6H_5	0	1	1	92 (quant)
	1.1	0.08	0.1	94 (quant)
	1.1	0.04	0.05	80 (quant)
p-i-Bu-C_6H_4	0	0	1	94 (quant)
	1.1	0.08	0.10	93 (80)

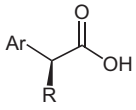
3



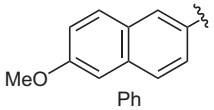
Toluene or CH_2Cl_2
-78°C, 1h.



H-A* : 1.0 equiv.



ref. [10l]

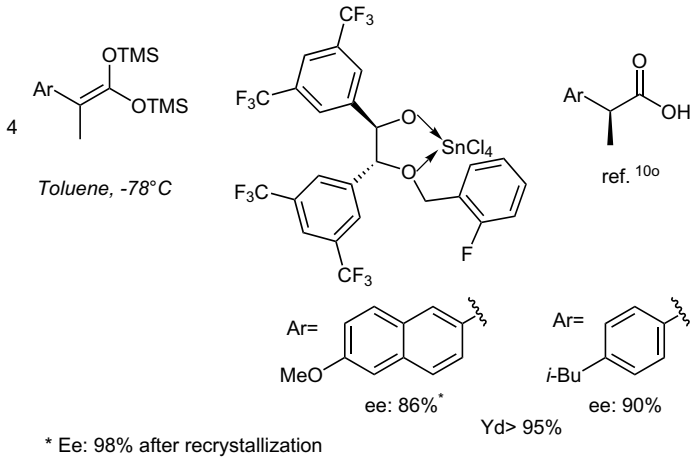


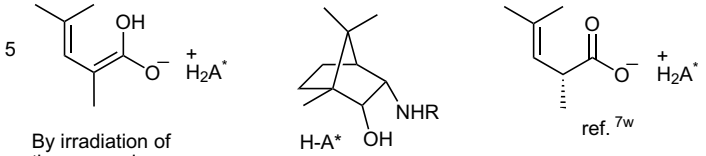
Ar	R	ee%
Ph	OMe	87
	Me	92*
Ph	F	70
Ph	Cl	91
Ph	Br	83

* ee: 98% after recrystallization

(*continued on next page*)

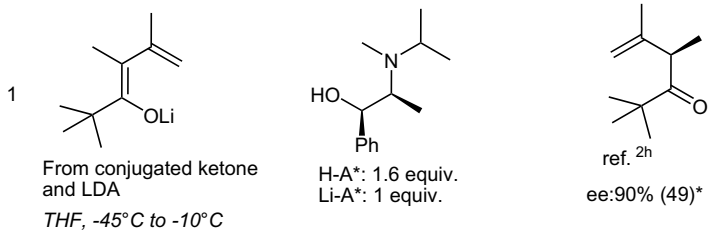
Table 2 (*continued*)





R	T°C	10	0	-10	-20	-30	-40	-46
H	ee%	17	16	17	27	32	40	45
H	Yd%	60	59	62	55	62	60	60
i-Pr	ee%	56	49	40	50	66	79	85
i-Pr	Yd%	58	62	61	60	57	61	65

Table 3. Acyclic ketones



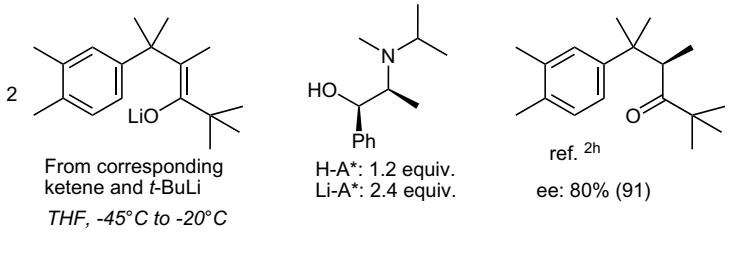
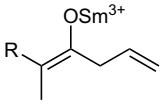


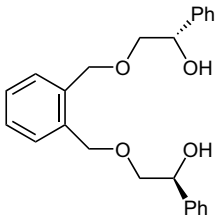
Table 3 (*continued*)

3

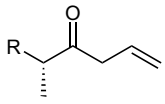


From ketene/
alkyl iodide/ SmI_2

THF, HMPA, -78°C to RT



H-A*: 1.5 equiv.

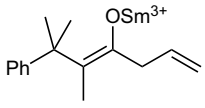


ref. [8b]

R	**ee% (Yd%)**
t-Bu	93 (21)*
Ph	91 (51)*
Ph-Me_2C	97 (65)*

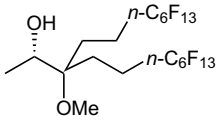
*With trace of conjugated ketone.

4



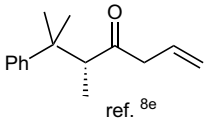
From ketene/
alkyl iodide/ SmI_2

THF, HMPA, -45°C



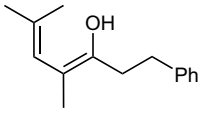
H-A*: 2 equiv. ee: 66% (55)

H-A*: 0.16 equiv.: ee: 60% (59)
H-A: $(n\text{-}C_6H_{13}\text{-}CH_2\text{-}CH_2)_3C\text{-}OH$,
THF/ FC-72)



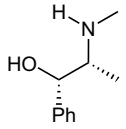
ref. [8e]

5

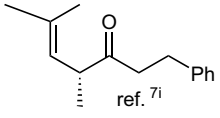


By irradiation of
the α ,β-unsaturated
ketone

CH_2Cl_2, - 40°C



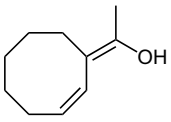
H-A*: 0.1 equiv.



ref. [7i]

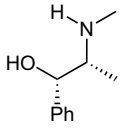
ee: 52% (75)

6

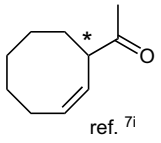


By irradiation of
the α ,β-unsaturated
ketone

CH_3CN, - 40°C



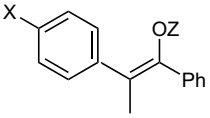
H-A*: 0.1 equiv.



ref. [7i]

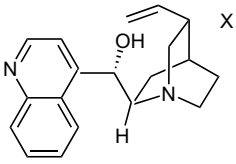
ee: 36% (40)

7

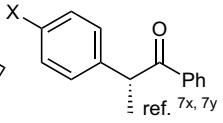


(unknown conf.)
Z= H or PdL_n
By Pd-cat hydroge-
nolysis of benzyl 2-
benzoyl-2-aryl-
propanoate

AcOEt, RT, 1-2h



H-A*: cinchonine

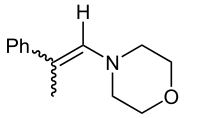


ref. [7x, 7y]

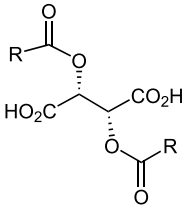
X	**H-A* equiv.**	**ee%**
H	0.3	71 (100)
H	0.05	68 (100)
p-OMe	0.025	75 (92)
p-Me	0.025	71 (99)
p-Ph	0.025	72 (95)
p-F	0.025	66 (99)

Table 4. Aldehydes

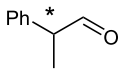
1



E-isomer: crystallisation with isomerization of *E/Z* mixtures
Z-isomer: cracking of racemic aminal of hydratropic aldehyde



H-A*: 4 equiv.

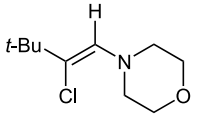


ref. [1b]

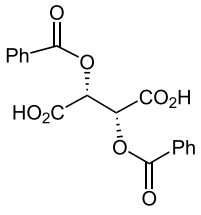
R	*E*	*Z*
t-Bu	13 (*S*)	14 (*R*)
t-Bu-CH_2	6 (*S*)	25 (*R*)
Ph	20 (*S*)	4 (*R*)
2-Me-C_6H_4	25 (*S*)	3 (*R*)

Et_2O, -30°C

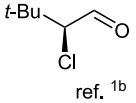
2



From racemic chloro aldehyde



H-A*: 1.5 equiv.

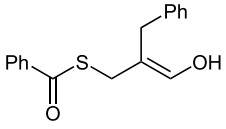


ref. [1b]

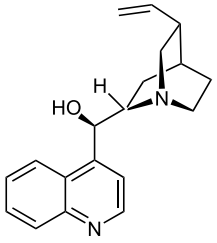
ee: 32%

Et_2O, -50°C

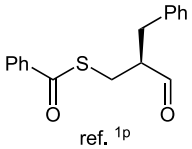
3



Isolated from benzylacroleine with thiobenzoic acid



H-A*: cinchonidine: 1 equiv.



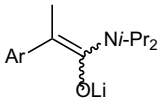
ref. [1p]

ee: 71% (95)

CH_2Cl_2, -70°C, 48h

Table 5. Amides

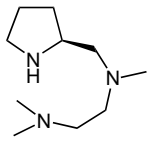
1



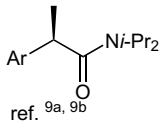
From racemic amide and *s*-BuLi

THF, -78°C

+ *s*-BuLi: 1.0 equiv.

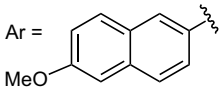


2 equiv.
BF_3, Et_2O: 2 equiv.



ref. [9a, 9b]

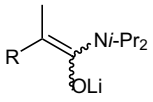
Ar =



ee: 77% (99)*

* ee: 97% (70), after elimination of the less soluble racemate

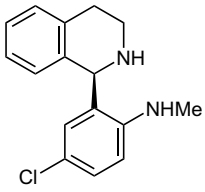
2



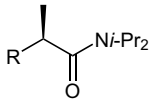
From racemic amide and *s*-BuLi

THF -78°C

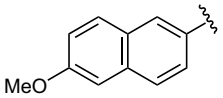
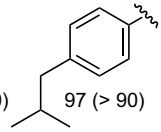
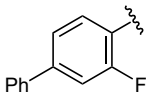
+ *s*-BuLi: 0.75 equiv.



H-A*: 2 equiv.



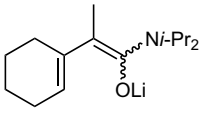
ref. [9b, 9h]

R		Ph		
ee% (Yd%)	97 (> 90)	97 (> 90)	97 (> 90)	97 (> 90)

R						
ee% (Yd%)	97 (quant.)	95 (18)*	97	93 (60)*	**	50

* With conjugated amide ** Mainly conjugated amide

3

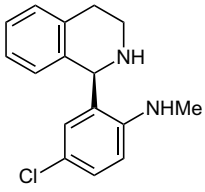


From racemic amide and *s*-BuLi

THF, -78°C

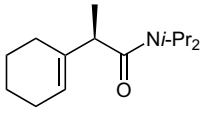
+ *s*-BuLi: 0.75 equiv.

+ *s*-BuLi: 0.50 equiv.



H-A*: 2 equiv.

H-A*: 0.05 equiv.
H-A: 2 equiv.:
p-Me_2N-C_6H_4-CH_2-CO_2Et

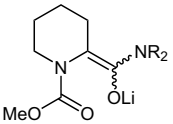


ref. [9b, 9f]

ee: 97% (> 90)

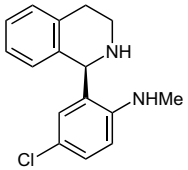
ee: 92% (94)

4

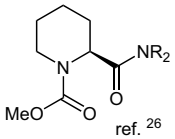


From racemic amide and *s*-BuLi, LiBr

THF -78°C



H-A*: 2 equiv.



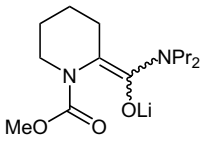
ref. [26]

NR_2	**ee%**
NPr_2	95 (74)
$N(CH_2)_5$	>99

(*continued on next page*)

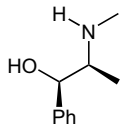
Table 5 (*continued*)

5

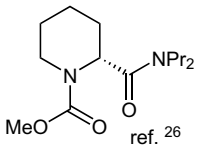


From racemic amide and *s*-BuLi, LiBr

THF -78°C



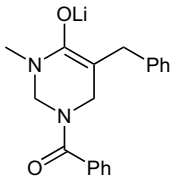
H-A*: 2 equiv.



ref. [26]

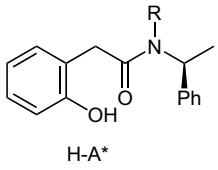
ee: 93%

6

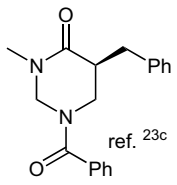


From racemic pyrimidone and LDA

Toluene, -78°C, 1h



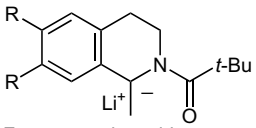
H-A*



ref. [23c]

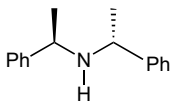
R	ee%
H	62 (90)
	68 (89)

7

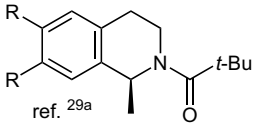


From racemic amide, *t*-BuLi, TMEDA

THF, -78°C



H-A*: 1 equiv.
LiCl: 1 equiv.

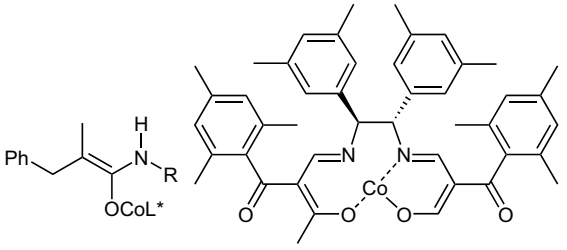


ref. [29a]

R	ee%	Yd%
H	86	>90
OMe	86*	94

* ee: 96% after elimination of the less soluble racemate

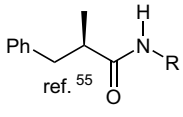
8



By $NaBH_4$ reduction of α-methyl cinnamic amide

Tetrahydrofurfuryl alcohol, MeOH, CH_2CCl_2, rt

L*: 0.02 equiv.



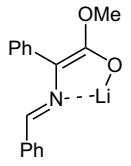
ref. [55]

R	ee%
H	50
Me	59
CH_2Ph	60

Yd >95%

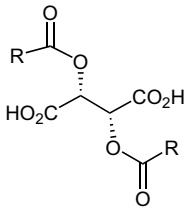
Table 6. Amino esters

1

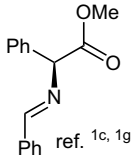


From racemic amino ester Schiff base and LDA

THF, -70°C



H-A*: 3 equiv.



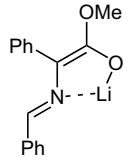
ref. [1c, 1g]

R	ee%
Me	3
i-Pr	12
Ph	12
t-Bu	50
adamantyl	53

80< yd%* <85

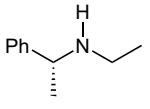
* Isolated as amino ester hydrochloride

2

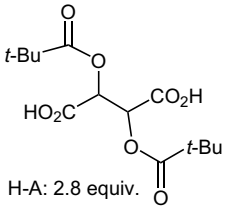


From racemic amino ester Schiff base and chiral Li-amide (1.42 equiv.)

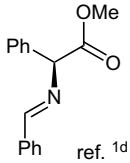
THF, -70°C



L*: 1.42 equiv



H-A: 2.8 equiv.

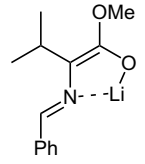


ref. [1d]

H-A	ee%*
meso	24 (85)
racemic	40 (75)
2R, 3R	70 (84)
2S, 3S	6** (85)

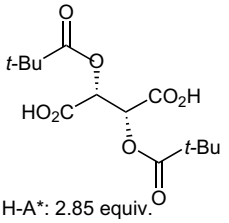
* Isolated as amino ester hydrochloride
** *R*-configuration

3

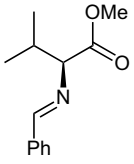


From racemic amino ester Schiff base and LiHMDS (1.42 equiv.)

THF, -70°C



H-A*: 2.85 equiv.

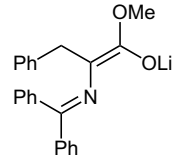


ref. [1k]

Added amine	ee%
none	34
$EtNH_2$ (1.42 equiv.)	**55**
$EtNH_2$ (0.25 equiv.)	53
Et_2NH (1.42 equiv.)	44
Et_3N (1.42 equiv.)	18
i-Pr_2NH (1.42 equiv.)	50

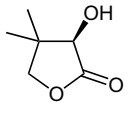
* Isolated as amino ester hydrochloride

4

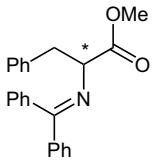


From racemic amino ester Schiff base.
-85°C, + LiCl (3 equiv.)

Using LDA
Using LiHMDS



H-A*



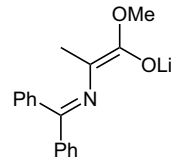
ref. [24]

ee%	*conf.*
40	*(R)*
76	*(S)*

(*continued on next page*)

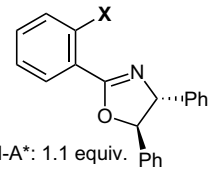
Table 6 (*continued*)

5

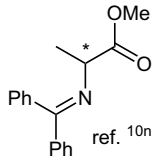


From racemic Schiff base and LDA

THF, -78°C

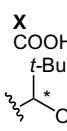


H-A*: 1.1 equiv.



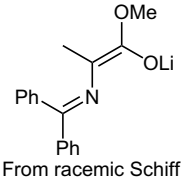
ref. [10n]

X	ee%*
COOH	29 (91)
t-Bu	49



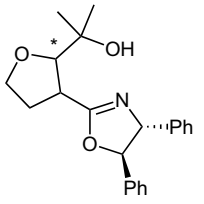
* Corrected ee based on the percentage of the protonated product

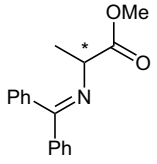
6



From racemic Schiff base and mesityl Li

Et_2O, -78°C



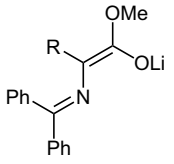


ref. [10n]

H-A*: 1 equiv.	ee%*	(Yd%)	*conf*
One diastereomer	53	(84)	*S*
The other diastereomer	48	(99)	*R*

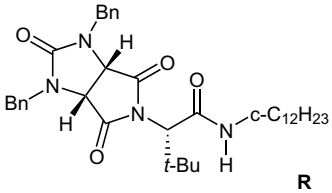
* Corrected ee based on the percentage of the protonated product

7

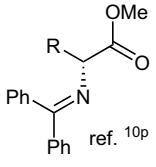


From racemic Schiff base and mesitylLi

Et_2O, -20°C, 2.5 h



H-A*: 1.1 equiv.

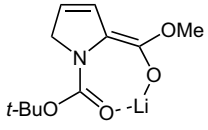


ref. [10p]

R	ee%*	(Yd%)
Me	87	73
i-Bu	85	66
CH_2-Ph	65	27

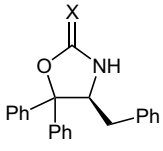
* Corrected ee based on the percentage of the protonated product

8

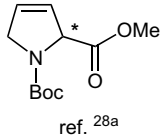


By Birch reduction of methyl *N*-Boc pyrrole-2-carboxylate

THF, -78°C



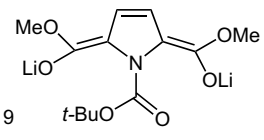
H-A*: 2.1 equiv.



ref. [28a]

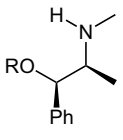
X	ee%	Conf
O	68 (50)	*R*
S	31 (55)	*S*

9

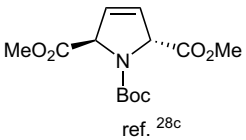


By Birch reduction of dimethyl *N*-Boc pyrrole-2,5-dicarboxylate

THF, -78°C



H-A*: 2.5 equiv.



ref. [28c]

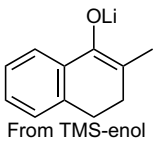
R	ee%
H	74* (84)**
Me	0 (35)**

* Ee:94% after recrystallization

** A 1/1 mixture of cis/trans diesters is obtained

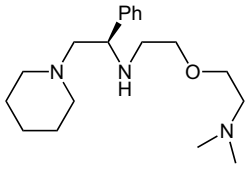
Table 7. Cyclic ketones

1

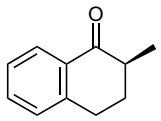


From TMS-enol ether and MeLi

Toluene, -78°C



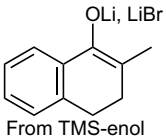
L*: 1 equiv.
H-A: 1.2 equiv. : AcOH



ref. [6a]

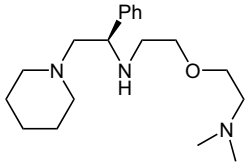
Without LiBr	ee: 0% (87)
With LiBr (1 equiv.)	ee: 91% (88)

2

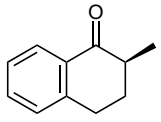


From TMS-enol ether and MeLi

Toluene, -78°C



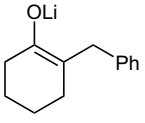
L*: 1 equiv.
H-A: 1.2 equiv. : AcOH



ref. [6a]

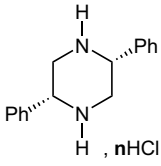
R	ee%	(Yd%)
Me	91	(88)
n-Bu	90	(88)
i-Pr	67	(89)
CH_2Ph	83	(86)

3



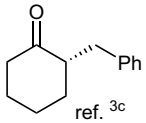
From enolacetate and MeLi (2 equiv.) in Et_2O

Et_2O/ CH_2Cl_2 (1:1), -78°C, 1h



, **n**HCl

H-A* : 3 equiv.

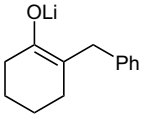


ref. [3c]

n	ee%	(yd%)
1	63	(89)
	70*	(85)*
2	50**	(89)**

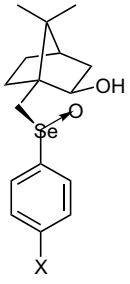
* Protonation at -90°C.
**Protonation in Et_2O.

4

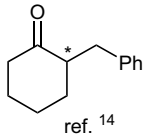


From enolacetate and MeLi (2 equiv.) in Et_2O

CH_2Cl_2, -100°C



H-A*: 4.3 equiv.

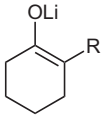


ref. [14]

X	ee%	(Yd%)	*conf*
H	29	51	*R*
F	0	68	
OMe	64	47*	*S*

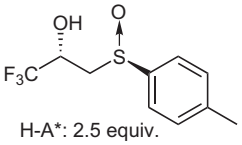
* Obtained with a mixture of unidentified compounds.

5

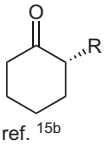


From enolacetate and MeLi (2 equiv.) in Et_2O

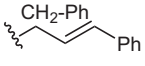
CH_2Cl_2, -100°C



H-A*: 2.5 equiv.



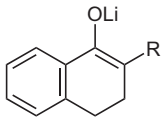
ref. [15b]

R	ee%	(Yd%)
	97	93
	92	93

(*continued on next page*)

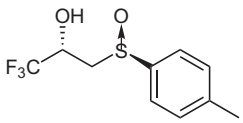
Table 7 (*continued*)

6

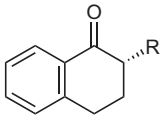


From enolacetate and MeLi (2 equiv.) in Et_2O

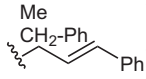
CH_2Cl_2, -100°C



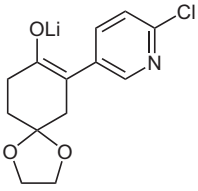
H-A*: 2.5 equiv.



ref. [15b]

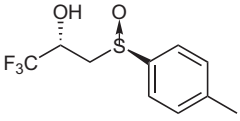
R	ee%	(Yd%)
Me	94	94
CH_2-Ph	78	94
	87	97

7

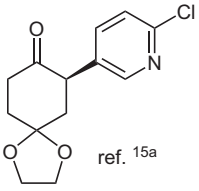


From enolacetate and MeLi (2 equiv.) in Et_2O

CH_2Cl_2, -90°C



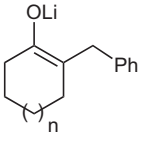
H-A*: 2.5 equiv.



ref. [15a]

ee: 82% (63)

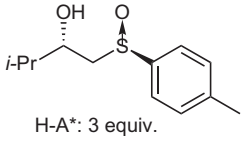
8



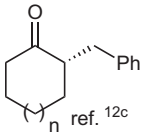
From enolacetate and MeLi, LiBr (2 equiv.) in Et_2O

CH_2Cl_2, -100°C

* Corrected ee for the regioisomeric purity of the starting material



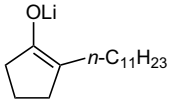
H-A*: 3 equiv.



ref. [12c]

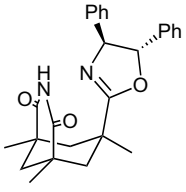
n	ee%*	(Yd%)
0	85	89
1	88	95

9

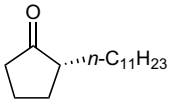


From TMS enol ether and MeLi

Et_2O / THF, -78°C



H-A*: 1 equiv.

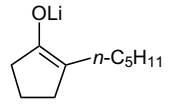


ref. [10a, 10h]

ee: 96% (95)

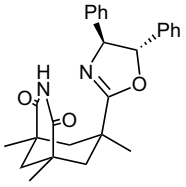
Table 7 (*continued*)

10

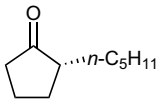


From TMS enol ether and MeLi

Et_2O, -78°C



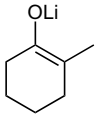
H-A*: 1 equiv.



ref. [10h, 10i]

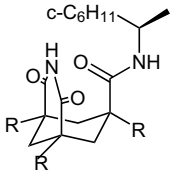
LiBr (equiv.)	**ee%(Yd%)**
0	74 (79)
1	83 (90)
2	85 (99)
5	90 (> 99)
10	88 (82)

11

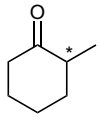


From TMS enol ether and *n*-BuLi

THF, -78°C, 2h



H-A* : 1.1 equiv.

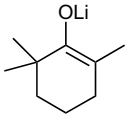


ref. [10k, 10m]

R	Me	*n*-Pr	CH_2-Ph	*i*-Bu	*i*-Pr	*c*-Pent	*c*-Hexyl
ee%	85	25	44	73	79	80	91
Conf.	*S*	*R*	*R*	*R*	*R*	*R*	*R*

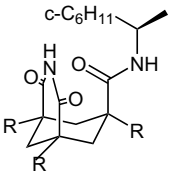
Yd%>86

12

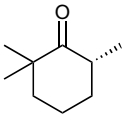


From TMS enol ether and *n*-BuLi

THF, -78°C



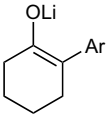
H-A* : 1.1 equiv.



ref. [10h]

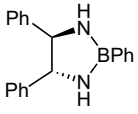
R	**ee%**	**(Yd%)**
Me	58	(88)
c-C_6H_{11}	97	(80)

13

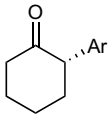


From TMS enol ether and *n*-BuLi

THF, -78°C



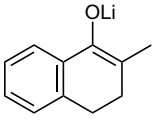
H-A*: 1.5 equiv.



ref. [10g]

Ar	**ee% (Yd%)**
Ph	84 (94)
2-Naphtyl	89 (93)

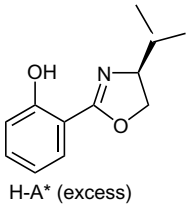
14



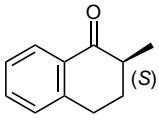
Toluene, -78°C

From racemic ketone and LDA, LiCl

From TMS-enol ether and MeLi, LiBr



H-A* (excess)



ref. [11a]

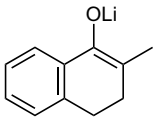
ee: 14% (89)

ee: 14% (92)

(*continued on next page*)

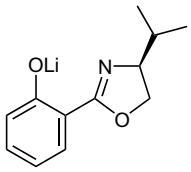
Table 7 (*continued*)

15

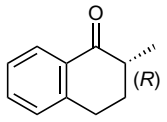


From TMS-enol ether and MeLi

Toluene, -78°C



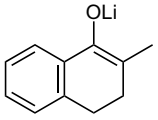
L*: 1 equiv.
H-A: HOAc (excess)



ref. [11a]

Without LiBr ee: 8% (84)
With LiBr (2 equiv.) ee: 29% (87)

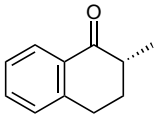
16



From TMS-enol ether and MeLi

Toluene, -78°C

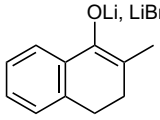
L*: 1 equiv.
H-A: HOAc (excess)



ref. [11b]

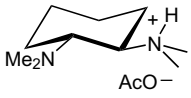
Without LiBr ee: 16% (45)
With LiBr (2 equiv.) ee: 47% (48)

17

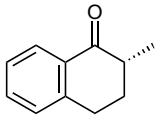


From TMS-enol ether and MeLi, LiBr

THF, -78°C



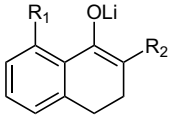
H-A*: 1 equiv.



ref. [11b]

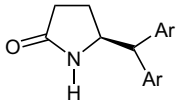
ee:5% (55)

18

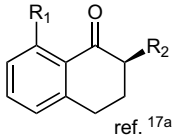


From TMS-enol ether and MeLi

Toluene, -78°C



Ar= 4-*t*-Bu-C_6H_4
H-A*: 1.5 equiv.

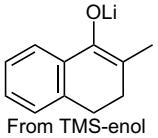


ref. [17a]

R^1	R^2	ee%
H	Me	63
Me	Me	72
H	Ph-CH_2	64

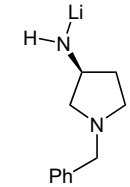
78 <Yd%<82

19

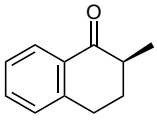


From TMS-enol ether and MeLi

Toluene, -78°C



L*: 1.1 equiv.
H-A: 2 equiv. : AcOH

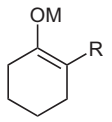


ref. [29b]

Without LiBr ee: < 3% (90%)
With LiBr (2 equiv.) ee: 40% (90%)

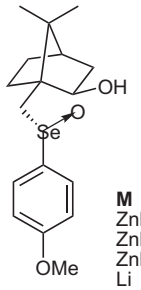
Table 7 (*continued*)

20

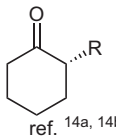


From enolacetate, MeLi (4 equiv.) and $ZnBr_2$ (M=ZnBr) or MeLi (2 equiv.) (M=Li), in Et_2O

CH_2Cl_2, -100°C



H-A*:4.3 equiv.

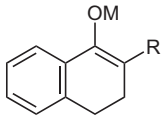


ref. [14a, 14b]

M	R	ee%	(Yd%)
ZnBr	*n*-Pr	88	76
ZnBr	*i*-Pr	65	39
ZnBr	CH_2-Ph	89	81
Li	CH_2-Ph	62	35*

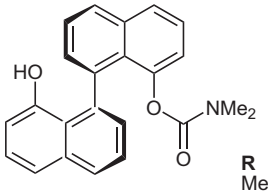
* Obtained with a mixture of unidentified compounds.

21

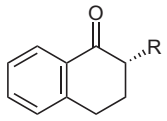


From enolacetate and MeLi or MeMgI in Et_2O

Et_2O, -78°C, 0.5h



H-A*

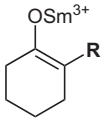


ref. [3d]

R	M	ee%	(yd%)
Me	Li	10*	(66)
	MgI	58	(73)**
i-Pr	Li	9	(72)
	MgI	92	(90)**

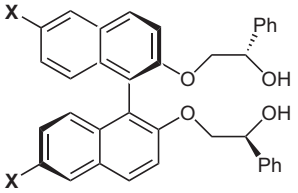
*(*S*)-configuration.
** Yield based on the recovered starting material.

22

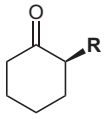


From 2-OMe 2-R cyclohexanone / SmI_2

THF, -45°C



H-A*: 2 equiv.

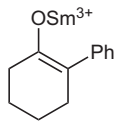


ref. [8g, 8h]

X	R	ee% (Yd%)	
H	Ph	87 (70)*	ref. [8h]
	p-MeO-C_6H_4	87 (79)	id
	p-Me-C_6H_4	94 (75)	id
	1-Naphtyl	16 (81)	id
	2-Naphtyl	90 (86)	id
	i-Bu	65 (81)	id
	CH_2Ph	80 (70)	id
$(C_6F_{13}$-CH_2-$CH_2)_3Si$	Ph	95 (crude product) 81-89 (73-82) after purification*. ref. [8h]	

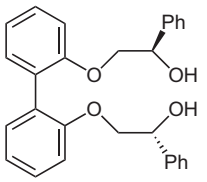
* A partial racemization might occur during the work-up.

23

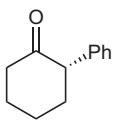


From 2-OMe 2-Ph cyclohexanone / SmI_2

THF, -45°C, 120 min.



H-A*: 2 equiv.



ref. [8f, 8g]

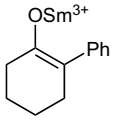
ee: 85% (88)*

* A partial racemization might occur during the work-up. (ref. [8h])

(*continued on next page*)

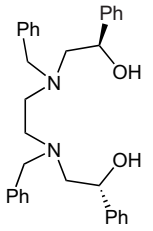
Table 7 (*continued*)

24

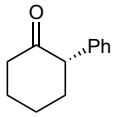


From 2-OMe 2-Ph cyclohexanone / SmI_2

THF, -45°C, 30 min.



H-A*: 2 equiv.

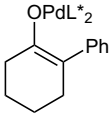


ref. [8g]

ee: 76% (91)*

* A partial racemization might occur during the work-up. (ref. [8h])

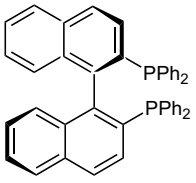
25



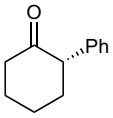
From TMS-enol ether

DMF, 50°C

Conditions: see scheme 39



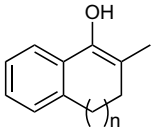
L*: 0.05 equiv.
H-A: 2 equiv. : H_2O



ref. [16]

ee: 74% (86)

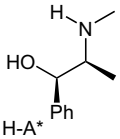
26



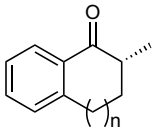
(a) By irradiation of 2-Me-2*i*-Bu -indan-1-one or 1-tetralone
(b) By Pd-deprotection of the corresponding allyl carbonate
(c) By decarboxylation of 2-carboxy-2-methyl-1-tetralone

CH_3CN

* solvent: Ph-Me

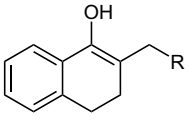


H-A*



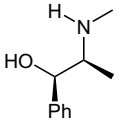
	H-A* equiv.	n	T°C	ee%	ref
(a)	0.1	0	-40	53 (82)	7n
(a)	0.1	1	-40	54 (52)	7n
(b)	2.0*	1	rt	50 (86)	7r
(c)	0.2	1	rt	30 (74)	7u

27

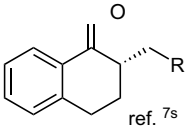


By Pd-cat.hydrogenation of the corresponding *E*-enone

CH_3CN, rt



H-A*: 0.5 equiv.

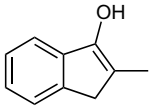


ref. [7s]

R	ee%
Ph	32*(100)
i-Pr	30 (67)
H	28 (68)

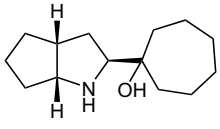
* ee:36% at 0°C

28

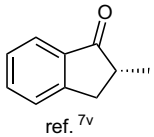


(a) By Pd-deprotection of the corresponding benzyl carbonate
(b) By Pd-decarboxylation of 2-Me-2-CO_2-CH_2Ph-indane-1-one

CH_3CN, 55°C



H-A*: 0.3 equiv.

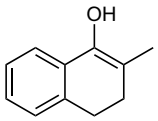


ref. [7v]

(a) ee: 48% (79)
(b) ee: 72% (64)

Table 7 (*continued*)

29

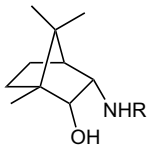


(a) By irradiation of 2-Me-2*i*-Bu-1-tetralone

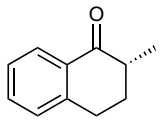
(b) By Pd-deprotection of the corresponding benzyl carbonate

CH_3CN, -40°C, 1h

* H-A*: 0.3 equiv., rt



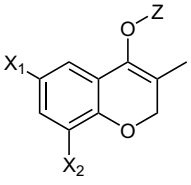
H-A*: 0.1 equiv.



(a) ref. [7n], (b) ref. [7r]

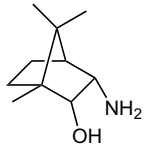
	R	ee%
(a)	H	71 (57)
(a)	Me	76 (56)
(a)	Benzyl	83 (47)
(a)	*i*-Pr	89 (40)
(b)	H*	64 (90)

30

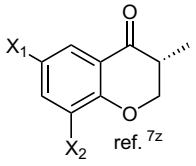


Z = PdL_n or AH_2
By Pd deprotection and decarboxylation of corresponding benzyl β-keto ester

AcOEt, rt, 4-9h



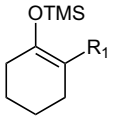
H-A*: 0.3 equiv.



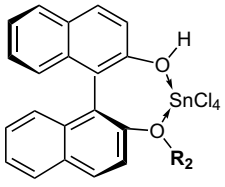
ref. [7z]

X^1	X^2	ee%
H	H	73 (99)
OMe	H	69 (94)
Cl	H	60 (97)
t-Bu	H	75 (89)
H	OMe	69 (78)

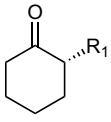
31



Toluene, -78°C, 1h. 100% conversion



H-A* : 1.0 equiv.

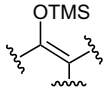


ref. [10l]

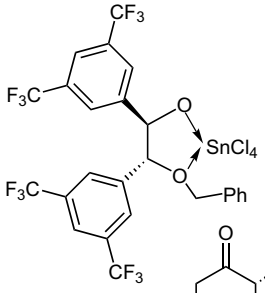
R^1	R^2	ee%*
Ph	H	91 (97)
	Me	94 (98)
p-MeO-C_6H_4	H	96
2-naphtyl	H	91 (99)**
Me	H	40 (42)
	Me	51 (53)
Cl	H	83 (84)
	Me	87 (88)

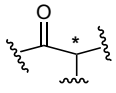
* In parenthese: corrected ee for the regioisomeric purity of starting material
** ee: 99% after recrystallisation

32

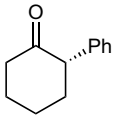


CH_2CCl_2, -78°C

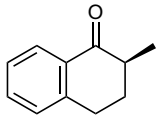




ref. [10o]



ee: 96%



ee: 83%

Yd> 95%

(*continued on next page*)

Table 7 (*continued*)

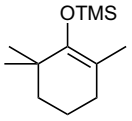
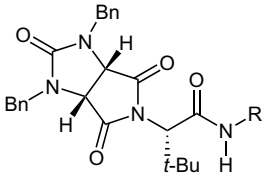
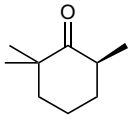
33			 ref. [10p]	
	THF, -20°C, 1h	H-A*: 1.1 equiv.	**R**	**ee%** **(Yd%)**
			i-Pr	69 98
			c-C_6H_{11}	71 >99
			c-C_7H_{13}	53 88
			c-$C_{12}H_{23}$	78 62

Table 8. Dioxolanones

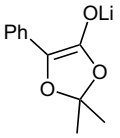
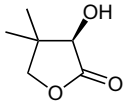
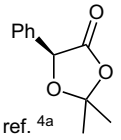
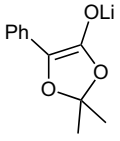
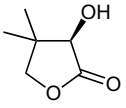
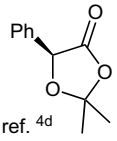
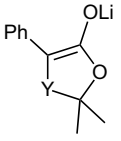
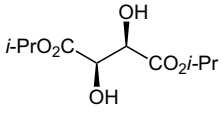
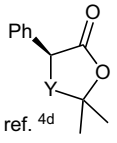
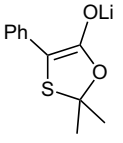
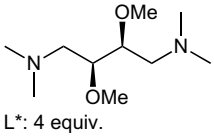
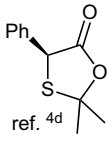
1			 ref. [4a]
	From racemic dioxolanone and LiHMDS or from TMS derivative and MeLi *THF -78°C*	H-A*: 2 equiv.	ee: 53%
2			 ref. [4d]
	From racemic dioxolanone and LiHMDS *Solvent, -78°C*	H-A*: 6 equiv.	**Solvent** **ee%** Et_2O 27 Et_2O: THF = 90: 10 72 THF 44
3			 ref. [4d]
	From racemic lactone and LiHMDS *THF, -78°C*	H-A*: 6 equiv.	**Y** **LiCl** (equiv.) **ee%** S 0 39 S 5 77 O 0 46 O 3 69
4			 ref. [4d]
	From racemic lactone and LiHMDS *THF, -78°C*	L*: 4 equiv. H-A : AcOH: 10 equiv	ee: 25%

Table 8 (*continued*)

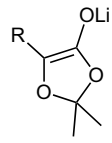
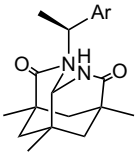
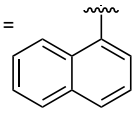
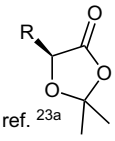
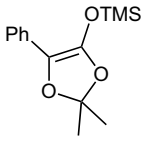
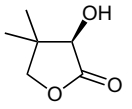
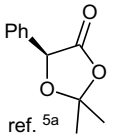
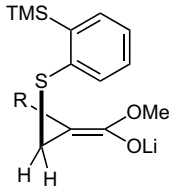
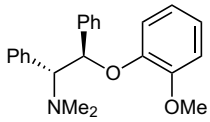
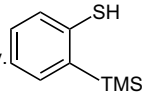
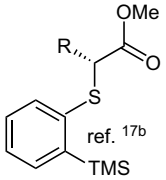
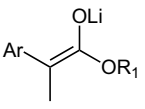
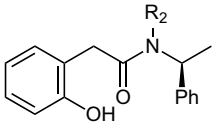
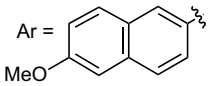
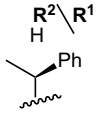
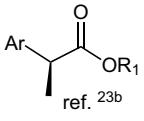
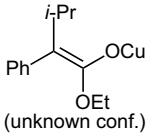
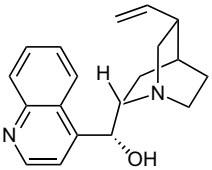
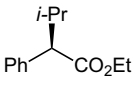
5	 From racemic dioxolanone and LDA *THF, -78°C* * *R* configuration	 H-A* : 1-7 equiv. Ar = 	 ref. [23a]	**R** **ee%** Me 9* Et 28 *n*-Bu 33 *i*-Pr 76 *t*-Bu 91 benzyl 50
6	 From dioxolanone LDA , TMS *THF, -78°C, <30min*	 H-A*: 3 equiv. + LiCl : 1 equiv.	 ref. [5a] ee: 50% (88)	

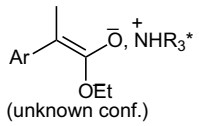
Table 9. Esters

1	 From conjugated ester (1equiv.) and 2-TMS-C_6H_4-SLi (0.01 equiv.) *Toluene/ hexane, -78°C* *The protonation conditions were slightly modified	 L*: 0.012 equiv; H-A: 1.2 equiv. 	 ref. [17b]	**R** **ee%** **(Yd%)** Ph 92 (99) 1-Naphthyl 88 (99) 2-Naphthyl 91 (93) 6-MeO-2-naphthyl 90 (99)*
2	 From racemic ester and LDA *Toluene, -78°C*	 H-A*: 1.2 equiv. Ar =  	 ref. [23b]	R^2 \ R^1 Me *i*-Pr *t*-Bu H 69 72 76 Ph 78 70 93 Yd > 87%
3	 (unknown conf.) From phenylmalonic hemiester and CuCl (0.2 equiv.) CH_3CN, *60°C, 2h*	 L*: cinchonidine 0.4 equiv.	 ee:31% (>85) ref. [27]	

(*continued on next page*)

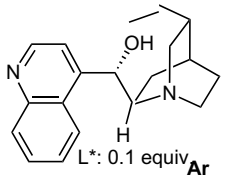
Table 9 (*continued*)

4

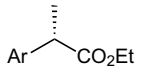


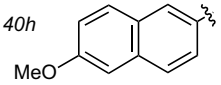
(unknown conf.)

From arylmalonic hemiester and cinchonine (cat)

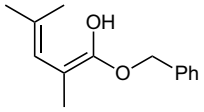


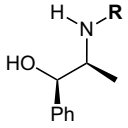
L*: 0.1 equiv



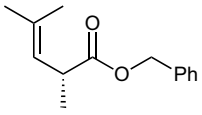
Ar	ee% (Yd%)
THF, 20°C, 20h Ph	35 (> 85) ref. [13b]
THF, 25°C, 40h 	40 (quant.) ref. [13d]

5





H-A*: 0.1 equiv.



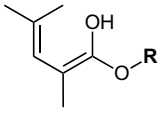
ref. [7e, 7g]

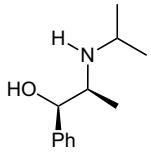
By irradiation of the conjugated benzyl ester

CH_2Cl_2, -40°C

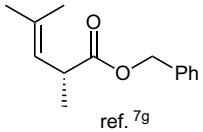
R	H	Ph					
ee%	14	9	32	70	57	28	44	8

6





H-A*: 0.1 equiv.



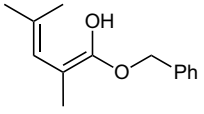
ref. [7g]

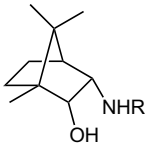
By irradiation of the conjugated ester

CH_2Cl_2, -40°C

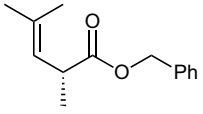
R		Ph					
ee%	40	70	43	68	68	45	24

7





H-A*: 0.1 equiv.

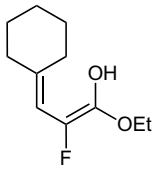


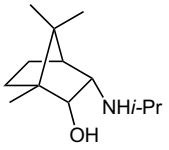
R	ee%	
H	54	42
i-Pr	89	97
ref	7h	7w

By irradiation of the conjugated benzyl ester

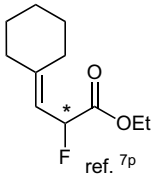
CH_2Cl_2, -45 or -55°C

8





H-A*: 0.15 equiv.



ref. [7p]

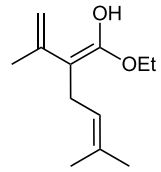
ee: 40% (86)

By irradiation of the conjugated ethyl ester

CH_2Cl_2, -35°C

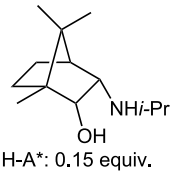
Table 9 (*continued*)

9

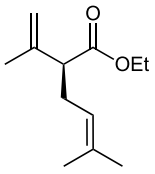


By irradiation of the conjugated ethyl ester

CH_2Cl_2, -40°C



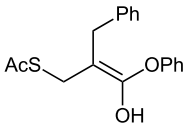
H-A*: 0.15 equiv.



ref. [7q]

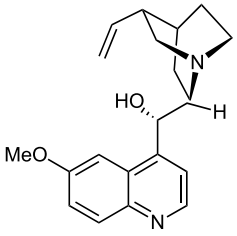
ee: 41% (>67%)

10

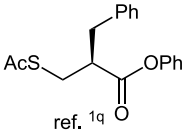


From conjugated ester and AcSH (unknown configuration)

Toluene, rt



H-A*: quinidine: 0.01 equiv.

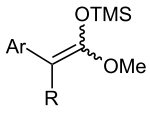


ref. [1q]

ee: 37% (85)

See also Thio esters, ex 5

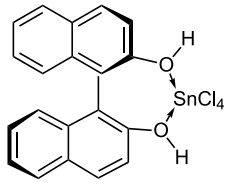
11



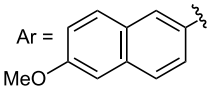
From racemic methyl ester of naproxen

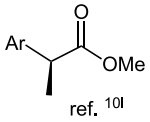
E/ Z = 63:37

Toluene or CH_2Cl_2 -78°C, 1h.



H-A* : 1.0 equiv.





ref. [10l]

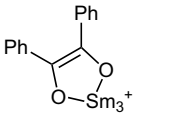
ee: 79%

(compare with T2, entry 3)

See also T12, entry 5.

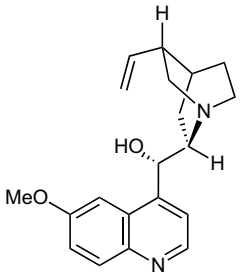
Table 10. Hydroxy ketones

1

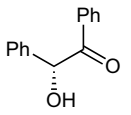


From benzil/ SmI_2

THF, HMPA, rt



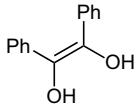
H-A*: Quinidine 3 equiv.
(O_2 bulbing before work-up)



ref. [8a]

ee: 91% (61)

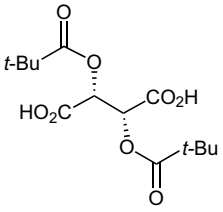
2



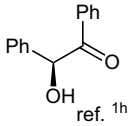
From K-enediolate obtained from racemic benzoine and KH

THF, -70°C, 15h

* Ee: 100% after one crystallization



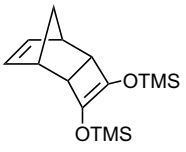
H-A*: 1.06 equiv.



ref. [1h]

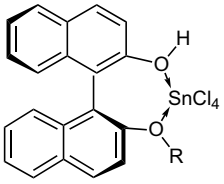
ee; 80%* (83)

3

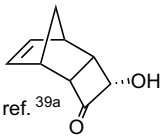


From racemic acyloin

Toluene, -78°C, 3h.



H-A*: 1.2 equiv.

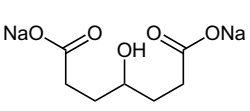


ref. [39a]

R	ee%	(Yd%)
H	9	(88)
Me	72	(86)
i-Pr	90	(87)

Table 11. Lactones

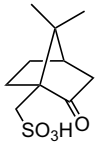
1



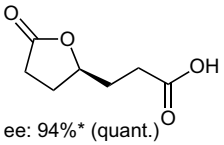
From racemic lactonic acid

EtOH, -78°C

* Ee:100% after one recrystallisation



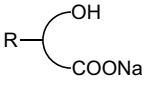
H-A*: 1 equiv.



ee: 94%* (quant.)

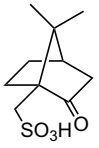
ref. [3a]

2

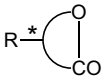


From racemic lactone

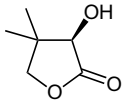
EtOH, -78°C



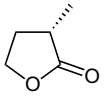
H-A*: 0.1 equiv.



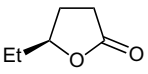
ref. [3b]



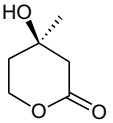
ee: 99.4% (79)



ee: 93% (57)



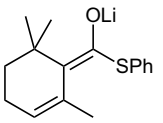
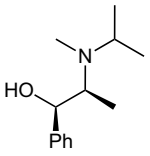
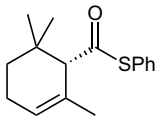
ee: 79% (71)



ee: 86% (62)

Table 12. Thio esters

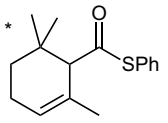
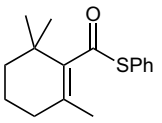
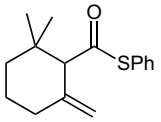
1

From α-thiocyclogeraniate* and *n*-BuLi

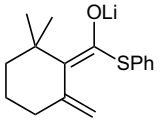
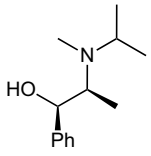
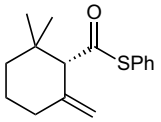
THF-hexane, -100°C

+ *n*-BuLi: 0.50 equiv.	H-A*: 2 equiv.	ee: 99% (87) ref. [2c]
+ *n*-BuLi: 0.50 equiv.	H-A*: 0.5 equiv. H-A: 1.55 equiv.: phenylacetone.	ee: 98% ref. [2g]
+ *n*-BuLi: 0.50 equiv.	H-A*: 0.20 equiv. H-A: 1.85 equiv.: phenylacetone	ee: 81% ref. [2g]

α-Thiocyclogeraniate β-Thiocyclogeraniate γ-Thiocyclogeraniate

2

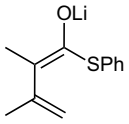
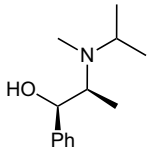
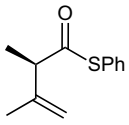
From β-thiocyclogeraniate and LDA

THF-hexane, -100°C

+ LDA: 0.50 equiv.	H-A*: 2 equiv.	ee: 99% (84)* , ref. [2f]
+ LDA: 0.50 equiv.	H-A*: 0.50 equiv. H-A: 1.50 equiv.: phenylacetone.	ee: 88% (80)*, ref. [2f]

* With 44-55% β-thiocyclogeraniate

3

From conjugated thioester and LDA*

THF, -100°C to -10°C

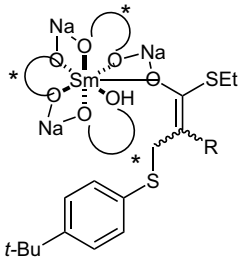
H-A*: 1.6 equiv.
Li-A*: 1.0 equiv.

ref. [2h]

ee: 59% (22)**

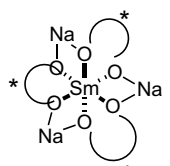
* The configuration of the Li-enolate is not given
** Crude product: unconjugated ester/ congugated ester: 35/ 65.

4

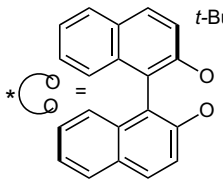


From conjugated thioester (1 equiv), 4-*t*-Bu-C_6H_4-SH, and chiral agent

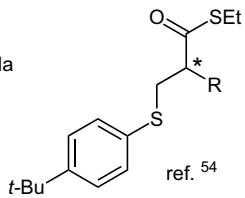
CH_2Cl_2, -78°C



L*: 0.1 equiv.*



H-A: 4-*t*-Bu-C_6H_4-SH: 1 equiv.



ref. [54]

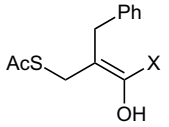
R	ee%	*conf*
Me	93	*S*
i-Pr	90	*
Ph	84	*
Ph-CH_2	87	*

76< Yd %< 98

(*continued on next page*)

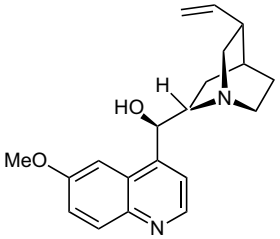
Table 12 (*continued*)

5

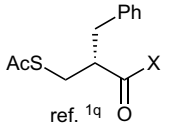


From conjugated ester and AcSH (unknown configuration)

Toluene, rt



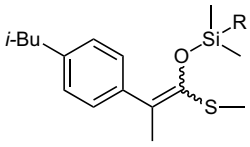
H-A*: quinine: 0.01 equiv.



ref. [1q]

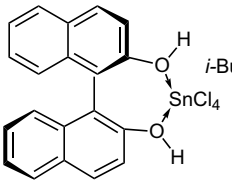
X	ee%	(Yd%)
OPh	46	70
SEt	55	87

6

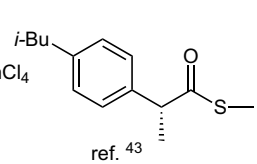


From racemic thiol ester

CH_2CCl_2 (R = Me) or toluene (R= t-Bu), -90°C



H-A* : 1 equiv.



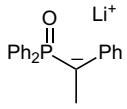
ref. [43]

R	*E*/*Z*	ee%*	(Yd%)
Me	15/85	64	78
Me	32/68	66	45
Me	92/8	68	78
t-Bu	15/85	76	99
t-Bu	48/52	80	98

* Determined after conversion to ibuprofen by oxidative hydrolysis

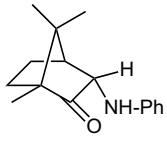
Table 13. Miscellaneous

1

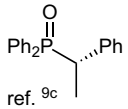


From racemic phosphine and *n*-BuLi

Toluene, -78°C



H-A*: 1.15 equiv.

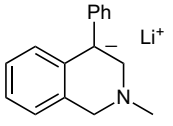


ref. [9c]

ee: 83%*

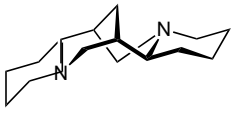
* ee> 99% (78) after one crystallization

2

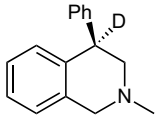


From racemic tetrahydroisoquinoline and *s*-BuLi (4 equiv.)

Et_2O, -45°C



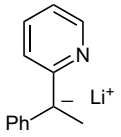
L*: (-)-sparteine: 4 equiv.
H-A: MeOD



ref. [39b]

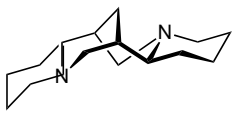
ee: 88% (60)

3

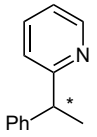


From racemic diaryl-ethane and *s*-BuLi (2 equiv.)

Et_2O, -78°C



L*: (-)-sparteine: 2 equiv.



ref. [39b]

H-A	ee%	Yd%	Conf
Et-OH	50	85	*S*
t-Bu-OH	50	85	*R*

References

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