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Synthetic pathways to salsolidine

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Dedicated to Professor Edmundo A. Rúveda on occasion of his 70th birthday

Abstract—Salsolidine is a simple 1-substituted tetrahydroisoquinoline isolated from many natural sources as the racemate and in its enantiomeric modifications. The wide variety of synthetic strategies leading to this natural product, mainly in its optically active forms, is discussed.

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1. Introduction

Isoquinolines comprise of the largest family of naturally occurring alkaloids, being found abundantly but not exclusively in the plant kingdom. The 1-substituted tetrahydroisoquinolines constitute an important group among the isoquinolines; while many of them have been isolated as both of their enantiomers from independent sources or just as the racemate, most of these natural products have been characterized as only one enantiomer with either the (1*S*)-absolute configuration or the opposite (1*R*)-geometry. The construction of the 1,2,3,4-tetrahydroisoquinoline ring system has been a popular area of research in natural products chemistry since the early 1900s, with activity in this field almost as old as the discovery of the isoquinoline system itself.

Despite its simplicity, the elaboration of the isoquinoline ring has been approached in various ways. In a systematic classification of the methods for the synthesis of the isoquinoline ring system, Kametani[1] described five different types, according to the mode of formation of the pyridine ring (Fig. 1). The first type involves the ring closure between the carbon atom, which constitutes the C-1 position of the isoquinoline and the aromatic ring, while in the second type the heterocycle is formed between C-1 and the nitrogen. Type 3 necessitates C–N bonding between the nitrogen and the atom, which forms the C-3 position in the resulting isoquinoline.

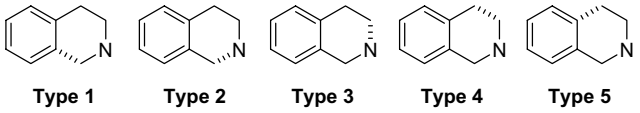


Figure 1. Classification of the synthetic strategies toward the isoquinoline ring system, according to Kametani.

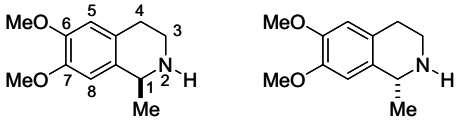
Likewise, the fourth type involves cyclization at the C-3 and C-4 level while the fifth type is meant to describe the process in which the isoquinoline ring is concluded by the generation of a C–C bond between the aromatic moiety and the C-4 position. Although the literature records examples of all of the five types, synthetic protocols of types 1, 2, and 5 have been demonstrated to be the most widely used for the elaboration of tetrahydroisoquinolines.

Among the protocols of the currently available methodological arsenal, some are only suitable for the synthesis of 1-substituted tetrahydroisoquinolines as racemic compounds, while others, in spite of having been tested for only one enantiomer, can provide each one of the constituents of the enantiomeric pair of 1-substituted tetrahydroisoquinolines, in some cases with their absolute stereochemistry known in advance.

The enantioselective synthesis of simple isoquinoline alkaloids was pioneered by Brossi et al.,[2] Kametani et al.,[3] Yamada et al.,[4] and others in the 1970s and gained strong interest as a consequence of their initial breakthroughs, while some simple alternatives for accessing tetrahydroisoquinolines in enantiomerically pure forms, such as the resolution of racemates, can be traced back to an earlier time. Many novel strategies have been explored with a range of approaches becoming useful over the past few years. Most importantly, a considerable group of the newly developed synthetic protocols are general and have already found use in the elaboration of other related alkaloids and even more complex structures. A recent review by Rozwadowska[5] shows the many different strategies devised for the enantioselective synthesis of simple 1-substituted tetrahydroisoquinoline alkaloids.

Strikingly, as early as in 1987, Huber and Seebach[6] pointed out that all possible methods of synthesizing enantiomerically pure compounds have been applied to the elaboration of homochiral 1-substituted tetrahydroisoquinolines, including resolution, catalytic, and stoichiometric enantioselective reactions as well as the incorporation of components from the pool of chiral building blocks.

Salsolidine **1** (1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline, CAS 493-48-1) is a simple tetrahydroisoquinoline alkaloid (Fig. 2), which can be isolated from different natural sources, mainly *Cactaceae* and *Chenopodiaceae* and has been the subject of numerous total syntheses, both as racemate and in its homochiral forms up to the point that nowadays, the observation made by Huber and Seebach also holds true for the enantioselective synthesis of salsolidine itself, as this review will make evident.



1*S*-(-)-Salsolidine, (-)-1 **1*R*-(+)-Salsolidine, (+)-1**

Figure 2.

On the other hand, there are no examples recording the elaboration of salsolidine by Kametani's type 4 synthesis; only one publication discloses the elaboration of the natural product following a type 3 strategy while many reports describe the syntheses of salsolidine in which the starting material is already an isoquinoline derivative, built according to one of the five above mentioned types.

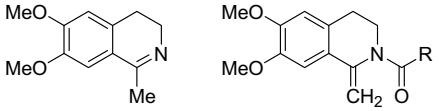
The variety of syntheses of salsolidine reported to date, especially those leading to the natural product in its optically active form, can be accounted for in many ways. First, the cardinal significance of chiral amines in the pharmaceutical and agrochemical industries, as well as their increasing importance among flavors and fragances, which have placed great demand and strong pressure for the search of new strategies for their efficient and cost-effective syntheses. Thus, in light of the resulting developments over the past 25 years and since the salsolidine enantiomers have often been used as targets for testing newly developed synthetic methods, it

is not surprising that the enantioselective preparation of the salsolidines has been thoroughly studied and, therefore, experienced an enormous growth in this time. Methods for the asymmetric preparation of amines have recently been reviewed by Johansson.[7]

Secondly, the continuous expansion of the arsenal of reagents and reactions at the disposal of the modern synthetic organic chemist, coupled to the structural features and simplicity of salsolidine, constitute an additional reason for chemists being inclined to prepare the natural product, especially in its homochiral forms.

On the other hand, 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline **2**, which is readily accessible by the Bischler–Napieralski reaction,[8a–e,9a] as well as by oxidation of salsolidine itself (81% yield) with 3 equiv of diphenylselenium bis(trifluoroacetate),[8f] is a representative cyclic imine, which has been repeatedly employed for testing the efficiency, scope, and limitations of many new hydride reducing agents and hydrogenation catalysts, with salsolidine being the expected reaction product of these transformations.

Moreover, the related and easily available *N*-acetyl enamine **3a**[9a] (Fig. 3) has been employed as a representative enamide, having been often used as a starting material for the elaboration of the natural product, while enamides **3b** and **3c**[9b,c] have also found some use as starting materials for the synthesis of **1**.



2 **3a** R= Me
3b R= H
3c R= OMe

Figure 3.

Additionally, there is general interest in enantiopure tetrahydroisoquinoline systems, since many isoquinoline alkaloids exhibit valuable physiological activities or unique structures.[10] Such a situation has continuously attracted the attention of the synthetic organic chemists.

Finally, multiple syntheses of salsolidine can also be considered in part by the use of salsolidine itself and other related simple tetrahydroisoquinolines as starting materials for the elaboration of bioactive substances[11a–c] and in biological studies,[11d] mostly associated to the pathogenesis of Parkinson's disease and other pathogenic processes of the central nervous system.

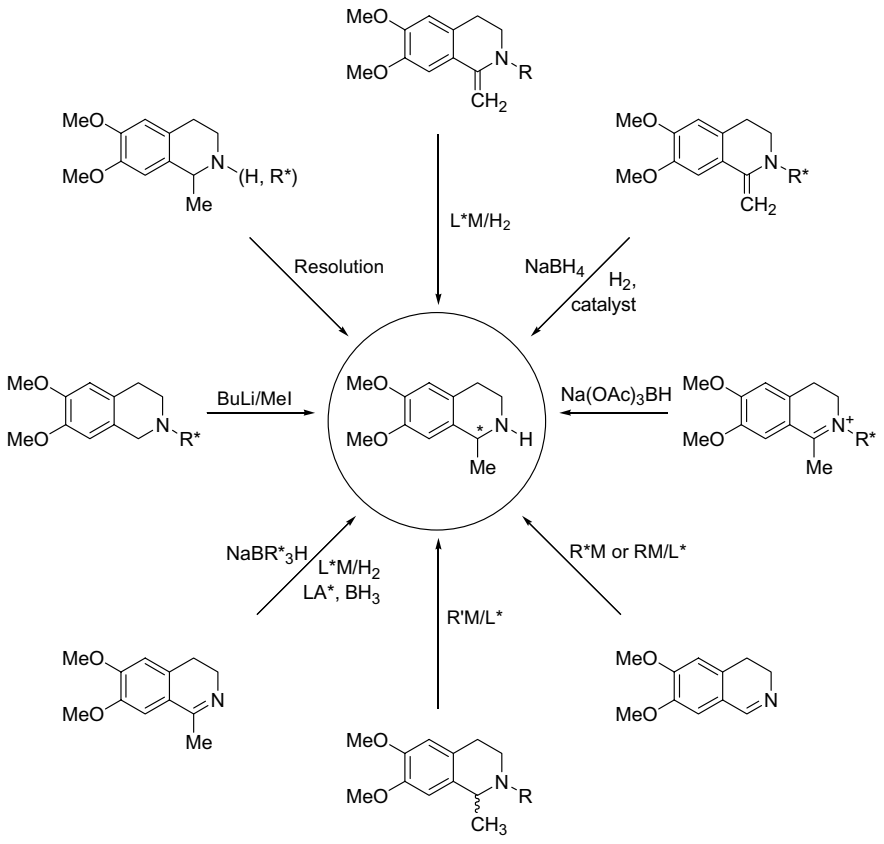
Most of the enantioselective syntheses of salsolidine reported to date are based on more or less subtle but generally highly interesting modifications of a handful of different basic strategic schemes, including the resolution of diastereomeric mixtures, stoichiometric chirality transfer through hydride reduction of optically active α-alkylbenzylamine derivatives and structurally related compounds (chiral iminium ions), diastereoselective hydrogenation of chiral enamides, enantioselective hydrogenation of imines and enamides with chiral catalysts, catalytic asymmetric reduction of imines, diastereoselective addition of organometallic reagents to chiral iminium compounds, addition of organometallics to iminium compounds in the presence of chiral ligands, and the addition of chiral organometallic reagents to iminium derivatives, as shown in Scheme 1. Other strategies include the intramolecular addition of amines to chiral vinyl sulfoxides, the asymmetric Pictet–Spengler reaction, and the reduction of 1-alkyl-3,4-dihydroisoquinolines by chiral sodium(triacyloxy)borohydrides.

The aim of this review is to consider the literature and most relevant advances achieved over the past 25 years concerned with the synthesis of salsolidine, emphasizing the enantioselective preparation of the natural product. Accordingly, synthetic strategies are divided into protocols leading to racemic salsolidine and those furnishing this product in its homochiral form. Among the latter, the methods covered are divided into five main categories: (1) resolution of racemates and separation of diastereomeric mixtures, (2) reduction of C=N and C=C double bonds, (3) metallation of isoquinoline derivatives with or without formation of new C–C bonds, (4) alkylation of azomethines, and (5) the use of organochalcogen derivatives. A brief comment on the occurrence of salsolidine in nature, as well as a summary of the reported effects of salsolidine, mainly on enzymatic systems are also reported herein.

2. Isolation, natural occurrence, and interaction of salsolidine with biomolecules and biological systems

Salsolidine was first isolated by Proskurnina and Orékhov from *Salsola richteri* (Chenopodiaceae) as the levorotatory enantiomer (−)-**1** [(*S*)-salsolidine];[12] a couple of years later, the same group reported the occurrence of this natural product in *Salsola arbuscula*.[13] The originally proposed structure for the natural product was confirmed by chemical tests and a series of specific rotation measurements and mixed melting point determinations with semi-synthetic (*S*)-salsolidine, prepared via (+)-tartaric acid-assisted resolution of racemic salsoline **4**, followed by methylation of the free levorotatory base with ethereal diazomethane. Additional evidence of identity was gained from mixed melting point measurements of the hydrochloride, picrate and picrolonate of both, natural and semi-synthetic (−)-**1**, which showed no melting point depression.

Both enantiomers of the natural product, as well as the racemate, have been isolated from natural sources.[14] Thus, (*R*)-(+)-salsolidine was found in the leaf, fruit, and stem of *Genista pungens* (Leguminosae),[15] while the racemate (or the natural product without disclosure of the characteristics of its stereogenic center) was found, among others, in *Carnegiea gigantea* (the first report of its occurrence in cacti)[16] and *Pachicereus*



Scheme 1.

pectenaboriginum (Cactaceae) from Mexico and USA,[16] *Bienertia cycloptera*,[17] *Corispermum leptopyrum*,[18] *Salsola kali*,[19] *S. soda*,[20] and *S. ruthenica*[20] from Poland, *Hamada articulata* ssp. Scoparia,[21] *Haloxylon articulatum*,[22] and *H. scoparium* (Chenopodiaceae), as well as in the stem of *Alhagi pseudalhagi* from India,[23] and *Calycotome spinosa*,[24] *Desmodium cephalotes*,[25] and *D. tiliaefolium*[15] among the Leguminosae. The recent detection of trace amounts of salsolidine and other simple tetrahydroisoquinolines in *Neobuxbaumia multiareolata, N. scoparia*, and *N. tetetzo* (Cactaceae) employing GC–MS techniques is a finding with high chemotaxonomic significance; it suggests that genus *Carnegiea* is different from *Neobuxbaumia* and is probably derived from it.[26]

Relevant physical properties and spectral data of the natural product in racemic and homochiral forms have been recently compiled by Shamma et al.[27a] Its NMR spectra were interpreted[27a–c] as well as its mass spectrum[27d] and other relevant data being disclosed.[27e] Additionally, its chiroptical properties were examined as part of the development of a new semiempirical quadrant rule based on one-electron theory, useful for predicting the configuration of 1-methyl tetrahydroisoquinolines.[28] Finally, X-ray diffraction data of the hydrochloride hydrate as well as the hydrochloride dihydrate have also been published.[29]

Experiments using tissue-cultured cells from *Callus pallida* var. *tenuis* and *Callus incisa* fed with (±)-[1-D and 1-methyl-CD_3]-salsolinol (salsolinol-D_4), allowed the HPLC, mass spectra, and ^{1}H NMR detection of minor amounts of salsolidine among the resulting metabolites; it was also shown that (±)-salsolinol **5** metabolized to produce salsolidine, among other related tetrahydroisoquinolines, in the tissue-cultured cells of *Corydalis ochotensis* var. *raddeana*, *Corydalis ophiocarpa*, and *Macleaya cordata* R. Br. Moreover, it was found that (±)-**5** metabolized in live whole plants with results similar to those observed in tissue-cultured cells.[30a]

Furthermore, by using an LC/API-MS system, it was shown that 3,4-dihydroxy-phenethylamine (dopamine) condenses with acetaldehyde to give salsolinol **5**, which is further metabolized to produce 6-*O*-methylsalsolinol **6a** (isosalsoline), which in turn, is O- and N-methylated to provide salsolidine **1** and *N*-methylisosalsoline **6b**, respectively, in several plant tissue cultures of *Papaveraceae* (Fig. 4).[30b]

The earliest preparations of **1** in homochiral form were made by the chemical manipulation of products accessed by classical Bischler–Napieralski[8a–e] as well as Pictet–Spengler[31] condensations, which furnished the racemate, followed by resolution with (+)-tartaric acid.[12] It was Battersby and Edwards in the early 1960s who unequivocally determined that natural (−)-salsolidine had an (*S*)-configuration, by its degradation to 2-carboxyethyl-L-alanine and comparison with this aminoacid derivative.[32]

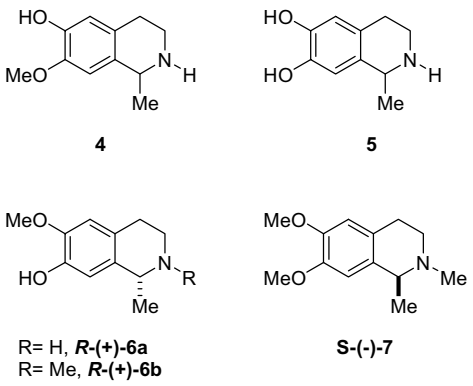


Figure 4.

Some efforts toward the measurement of salsolidine as an analyte have already been published. Interestingly, a spectrophotometric assay of **1** based on its reaction with ammoniacal copper sulfate in carbon disulfide, leading to the production of a copper–dithiocarbamate complex soluble in benzene, has been reported. The complex can be extracted from the reaction medium and measured at its absorbance maximum of 448 nm.[33a] An alternative spectrophotometric procedure for the quantification of **1** and **4** was disclosed earlier by Russian authors[33b] with the fluorometric determination of salsolidine as an impurity in the preparations of **4** also being reported.[33c] Interestingly, the HPLC separations of the enantiomers of salsolidine as *N*-α-naphthoyl ($\alpha = 1.21$)[34a] and *N*-β-naphthoyl ($\alpha = 1.83$)[34b] derivatives, employing 3,5-dinitrobenzoyl phenylglycine and (*S*,*S*)-[*N*-(3,5-dinitrobenzoyl)]-amino-3-methyl-1,2,3,4-tetrahydrophenanthrene-based chiral stationary phases, respectively, were recently reported. However, the chiral HPLC with β-cyclodextrin as chiral selector was unable to separate salsolidine enantiomers as previously reported by Stammel et al.[34c] Additionally, the production of highly specific antibodies, with a high affinity against (±)-salsolidine ($K = 1.5 \times 10^9\ M^{-1}$) by immunization of rabbits with bovine serum albumin–salsolidine conjugates, was demonstrated.[34d] These antibodies were employed to develop a radioimmunoassay for the alkaloid and thus may find use in the determination of trace amounts of tetrahydroisoquinolines in organic tissues and biological fluids.

Several biological activities have been ascribed to (or involved) the natural product. A study by Oxenkrug demonstrated that **1** and other alkaloids such as **4** (Fig. 4) and papaverine, inhibit the uptake of 5-hydroxy tryptamine by human blood platelets,[35] showing a 30–60% inhibition at a concentration of 10^{-4} M. The stereospecific N-methylation of (*S*)-**1** [to (*S*)-(−)-carnegine, **7**] and of the endogenous alkaloid (*R*)-isosalsoline (*R*)-**6a** by the enzyme amine *N*-methyl transferase from bovine liver has been shown by Bahnmaier et al. This group found the enantiomers (*S*)-**1** and (*R*)-**6a** to be those preferentially methylated.[36] These authors also revealed that certain tetrahydroisoquinolines are capable of mimicking direct but not receptor-mediated inhibitory effects of estrogens and phytoestrogens on testicular endocrine function; salsolidine, however, was ineffective in this assay.[37] Moreover, Brossi et al. studied the effect of simple isoquinoline alkaloids on monoamine oxidase (MAO) inhibition, finding that 3,4-dihydroisoquinolines were more potent than isoquinolines and their 1,2,3,4-tetrahydro- congeners in MAO A inhibition, while only a few heterocycles inhibited MAO B. Among the dihydro- and tetrahydroisoquinolines, a stereoselective competitive inhibition of MAO A caused by the (*R*)-enantiomers was observed. These results were supportive of the view that the topographies of MAO A and MAO B inhibitor binding sites are different.[38]

Salsolidine was also reported to inhibit competitively the methylation of the catecholamine metabolite 3,4-dihydroxybenzoic acid by an enriched rat liver preparation of the enzyme catechol-*O*-methyltransferase, with $K_i = 0.19$ mM.[39] Dostert et al.[40] reviewed the role of dopamine-derived alkaloids in alcoholism and Huntington's disease and the group of Airaksinen, after studying the binding of β-carbolines and tetrahydroisoquinolines to opiate receptors of the δ-type, concluded that tetrahydroisoquinolines, like salsolidine, with K_i values higher than 100 μM, were less potent than β-carbolines and that opiate receptors do not appear to be the major sites of action of simple tetrahydroisoquinolines.[41a] The neurotoxicity of several tetrahydroisoquinoline derivatives against SH-SY5Y cells has also recently been studied; salsolidine proved to be less neurotoxic than the dihydroxylated compound **5**, contrasting with the tendency observed among the monosubstituted 1-methyl tetrahydroisoquinolines.[41b] On the other hand, a trimethoprim analogue made by the incorporation of a 2,4-diaminopyrimidine unit to the salsolidine nucleus provided an active dihydrofolate reductase inhibitor[41c] and phenylpropionylamido-diphenylalkyl-tetrahydroisoquinolines, including the salsolidine moiety, have been reported as luteinizing hormone releasing hormone (LHRH) antagonists.[41d] Dibenzo-18-crown-6 derivatives of salsolidine, prepared by condensation of the crown acid dichloride with the natural product, have also been described.[41e]

3. Synthetic strategies leading to salsolidine in racemic form

Racemic salsolidine has been elaborated in several ways, including the reduction of isoquinolines and their benzopyrylium precursors, metallation–alkylation of tetrahydroisoquinoline derivatives and modifications of the classical Bischler–Napieralski, Pictet–Spengler, and Pomeranz–Fritsch isoquinoline syntheses.

Despite that racemic salsolidine (±)-**1** being the result of many published syntheses, some of these can be modified in order to become synthetic protocols suitable for the elaboration of salsolidine in optically active form, transforming this into a highly attractive test field for novel synthetic methodology.

Contemporary with the Minter synthesis of *N*-carboxymethyl salsolidine **8** from 1-methyl-6,7-dimethoxy

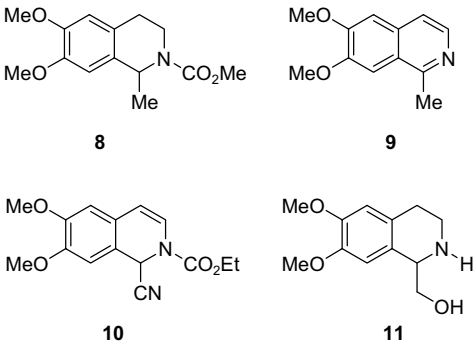
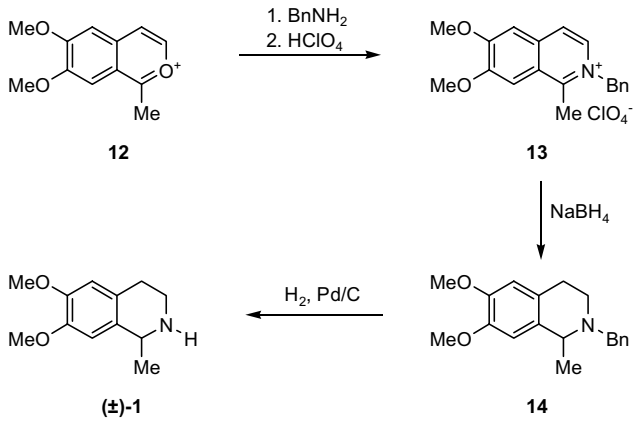


Figure 5.



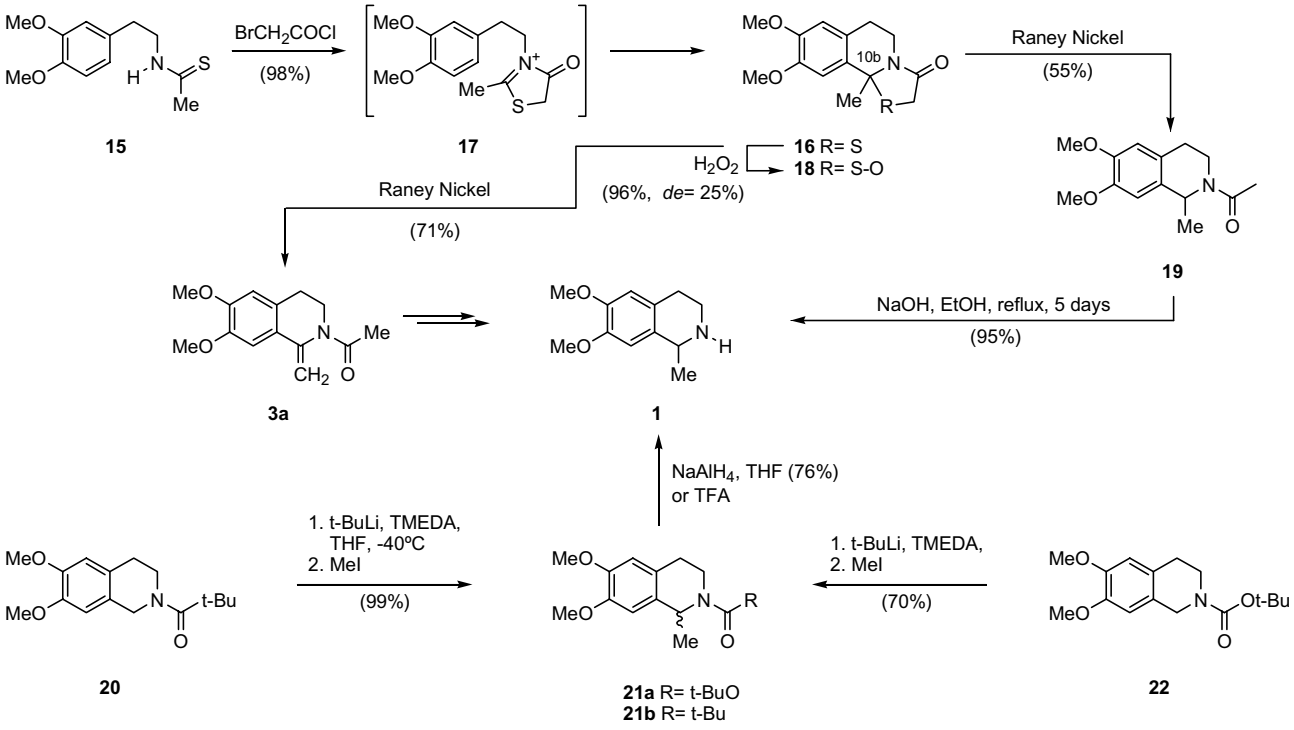
Scheme 2.

isoquinoline **9** by DIBAL-H mediated reduction of its isoquinoline–borane complex and subsequent reaction with methyl chloroformate (Fig. 5),[42] Rozwadowska and Brózda described the synthesis of (±)-**1** by intermediacy of 6,7-dimethoxy-2-ethoxycarbonyl-1,2-dihydroisoquinaldonitrile **10**, a Reissert compound,[43] which proved to be a convenient starting material for the elaboration of related 1-substituted tetrahydroisoquinoline natural products, such as the ubiquitous calycotomine **11** and carnegine **7**.

The reaction of 2-benzopyrylium salts with amines has been reported by Russian scientists as an alternative approach to (±)-**1**. In their sequence, submission of 6,7-dimethoxy-1-methyl-2-benzopyrylium salt **12** to a reaction with benzylamine formed a mixture of the corresponding *N*-benzyl isoquinolinium salt **13**, isolated as the perchlorate, and the related naphthylamine (Scheme 2); reduction of the former with sodium borohydride to *N*-benzylsalsolidine **14**,[44a] followed by hydrogenolytic cleavage of the *N*-benzyl group afforded the natural product, albeit in a moderate overall yield.[44b]

As an example of the usefulness of thio *N*-acyliminium ions as electrophilic partners in cationic π-cyclizations, Padwa et al.[45] have recently shown that the reactive *N*-acyliminium ions, formed from thioamides like **15** and bromoacetyl chloride, can react with activated π-nucleophiles in the form of an appropriately substituted aromatic ring tethered on the nitrogen of a thioamide. Upon cyclization, the resulting N,S-acetals can be further manipulated leading to different products; among them 1-substituted tetrahydroisoquinolines.

A Kametani type 1 formal synthesis of salsolidine, shown in Scheme 3, was employed to demonstrate this



Scheme 3.

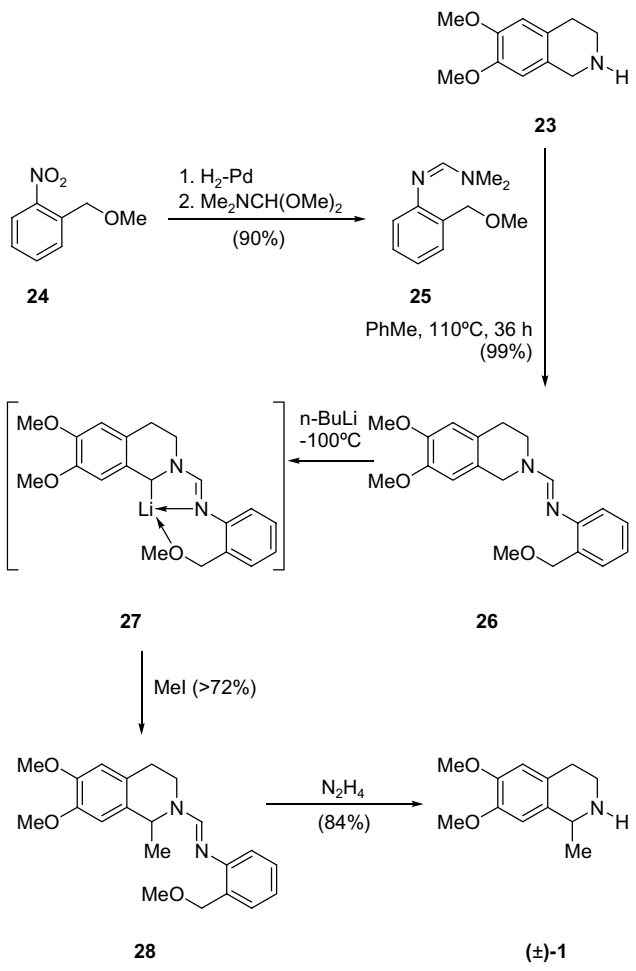
principle. To this end, thioamide **15** was converted into the related N,S-acetal **16** by way of an iminium ion derivative **17**. In turn, **16** was transformed into the known *N*-acetyl enamine **3a** with Raney nickel, in 71% yield. As mentioned above, this enamide has been repeatedly employed as a key precursor of salsolidine, including the enantioselective synthesis of the natural product.[46]

Recently, a Polish team led by Rozwadowska et al.[47] disclosed a variant of Padwa's group strategy in one of their syntheses of (±)-salsolidine, using the thiazolino[2,3-*a*]isoquinoline (S)-oxide **18**, easily prepared in high yield and 25% de (in favor of the *anti*-diastereomer with an α-oriented sulfoxide oxygen and a β-position for the 10b methyl substituent) by a 30% hydrogen peroxide-mediated oxidation of **16**, as intermediate. Raney nickel treatment of sulfoxide **18**, furnished 55% of *N*-acetyl salsolidine **19** instead of the related enamide **3a**, which afforded the natural product in an almost quantitative yield upon basic hydrolysis.

As alternative strategies, the elaboration of salsolidine derivatives by alkylation of α-sulfoxide carbanions has also been reported[47] and Indian researchers have described an AcOH-promoted Pictet–Spengler type synthesis of (±)-**1** in 60% yield from 3,4-dimethoxyphenethylamine, employing a perhydro-oxazine as the carbonyl equivalent.[48] A different approach, consisting of a heteroatom-facilitated metallation process followed by alkylation, was taken by Coppola[49a] and more recently by Simpkins et al.[49b] In the former case, *N*-Boc-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **22** was lithiated with the *t*-BuLi–TMEDA complex, leading to *N*-Boc salsolidine **21a** (yield ≈70%), which afforded the natural product upon a facile TFA-mediated deprotection.

Analogously, in the latter synthesis racemic *N*-pivaloyl salsolidine **21b** was obtained as part of a sequence leading to (−)-**1**, by MeI alkylation of the 1-lithio derivative of *N*-pivaloyl-6,7-dimethoxy-tetrahydroisoquinoline **20**. The pivaloyl protecting group was reductively removed in high yield, by treatment with sodium aluminum hydride.

In a series of elegant studies, Meyers et al. experimented during the 1980s and the beginning of the 1990s with the alkylation of α-amino carbanions derived from formamidines, the repeated formation of salsolidine, among other relevant targets.[50] Thus, transformamidination of tetrahydroisoquinoline **23** with formamidine **25**, readily accessible from 2-methoxymethyl nitrobenzene **24**, furnished almost quantitative yield of formamidine **26**. After metallation with *n*-BuLi at −100 °C and alkylation with MeI, **26** afforded the methylated derivative **28**, probably through intermediacy of lithiated species **27**, in over 72% yield; final hydrazinolysis of **28** provided 84% of racemic salsolidine, as shown in Scheme 4.[50a] The chiral version of their developments in the area of diastereoselective carbon–carbon bond forming strategies employing chiral formamidines, is discussed below.

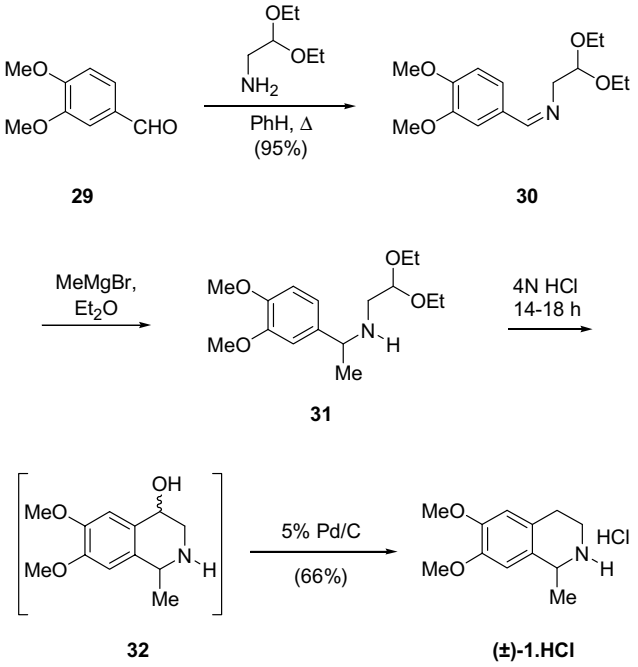


Scheme 4.

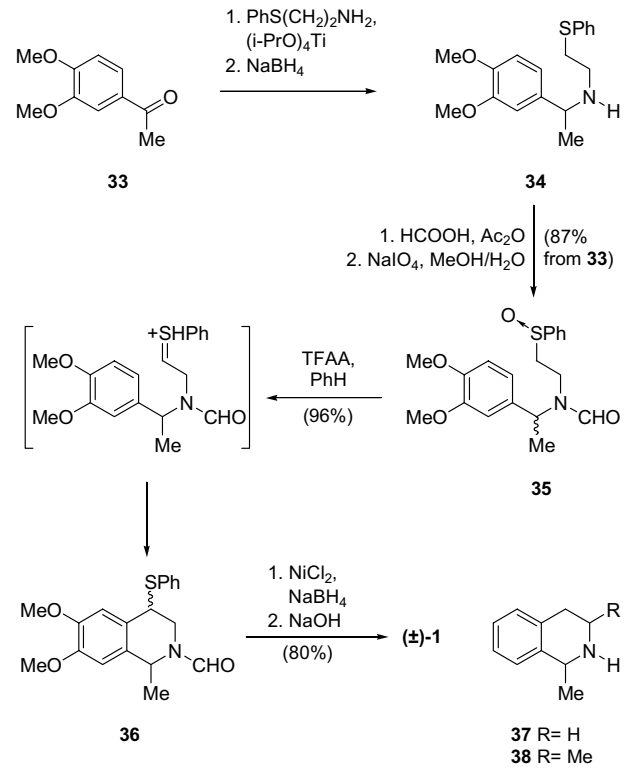
As an example of their proposed modification of the original Pomerantz–Fritsch isoquinoline synthesis leading to tetrahydroisoquinolines, Bobbitt et al.[51] described a preparation of (±)-**1** starting from veratraldehyde **29**, involving methyllithium addition to the intermediate Schiff base **30** formed by condensation of **29** with aminoacetal, to furnish **31** (Scheme 5). Salsolidine was isolated in good yield as its hydrochloride salt after Pd/C-mediated hydrogenolysis of the epimeric tetrahydroisoquinolin-4-ols **32**, the overall sequence involving a Kametani type 5 synthesis.

The Pummerer sulfoxide rearrangement, coupled to an electrophilic aromatic cyclization reaction, devised by Japanese scientists, constitute the key steps of another example of a Kametani type 5 tetrahydroisoquinoline synthetic strategy. The general protocol has been developed only recently, as a special case of the Bobbitt strategy and thus has been explored not as extensively as other classical cyclizations leading to tetrahydroisoquinoline derivatives. Initial work was done by Takano et al. and Sano et al.,[52] inspired in other sulfoxide-mediated electrophilic reactions.[53]

For the synthesis of (±)-**1**, the required *N*-acylsulfoxide **35** was prepared (Scheme 6) in 87% overall yield from 3,4-dimethoxy acetophenone **33**. Thus, reductive



Scheme 5.



Scheme 6.

amination of the latter with 2-phenylthioethylamine under titanium isopropoxide promotion[54] in an EtOH–AcOH medium furnished **34**, which in turn was acylated with mixed formyl–acetyl anhydride and then oxidized to the diastereomeric mixture of sulfoxides **35** with $NaIO_4$ in aqueous MeOH. Treatment of **35** with TFAA in benzene at room temperature for 18 h, gave 96% of the cyclized product **36**, which was reductively desulfurized in 88% yield with the sodium borohydride–nickel chloride reagent and then subsequently deformylated to the natural product in 91% yield by alkaline hydrolysis.[55]

In a systematic study,[56] it was demonstrated that this type of cyclization is sensitive to the solvent and the nature of the *N*-acyl substituent. In CH_2Cl_2, a complex mixture of products was obtained with the formyl moiety as an N-protecting group apparently playing an important role in facilitating the intramolecular cyclization to take place. Despite that only the elaboration of racemic salsolidine has been reported following this route to date, the strategy has been adapted to large scale preparation of both enantiomers of 1-methyl tetrahydroisoquinoline **37**[57a] as well as the four stereoisomers of 1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **38**,[57b] which suggests its potential applicability to an enantioselective synthesis of salsolidine. This route seems to be very attractive for preparing substrates for use in biological studies, since isotope labeling at the C-4 position is possible by reductive elimination of the phenylthio group.

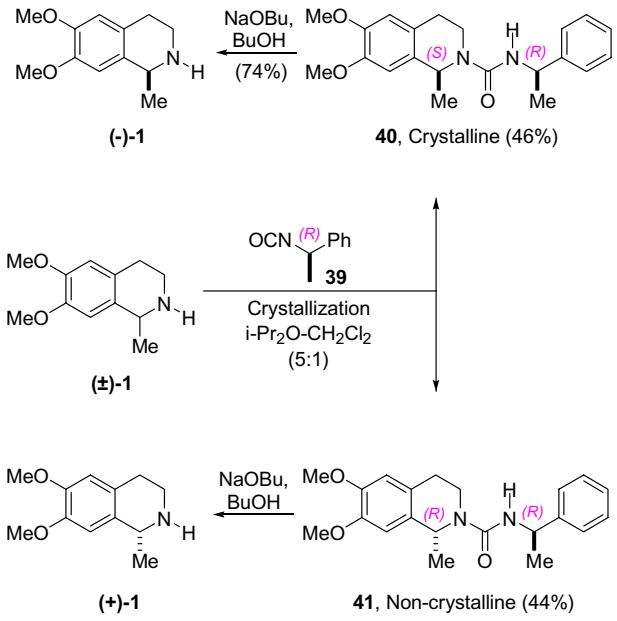
Finally, the clean indium metal-mediated reduction of 3,4-dihydroisoquinoline **2** to salsolidine in a quantitative yield has recently been reported by Moody et al.[58a] Contrary to the outcome of related heterocyclic ring systems when zinc metal was employed as reducing agent, no evidence of any dimeric products formed by coupling of the heterocyclic rings was found by these authors.[58b]

4. Syntheses of the salsolidines in their optically active forms

Stereoselective synthesis is one of the most relevant advances in synthetic organic chemistry over the last few decades. In addition to the resolution of racemates through the formation of diastereomeric salts with chiral acids and the separation of diastereomeric mixtures prepared with the aid of chiral derivatizing agents, access to salsolidines in their homochiral forms has been repeatedly achieved by diastereo- and enantioselective syntheses, exploiting strategies such as C=N and C=C double bond reduction (hydrogenation, hydrosilylation, and hydride addition), C=N double bond alkylation, diastereoselective alkylation of chiral tetrahydroisoquinoline derivatives, and enantioselective protonation. Other alternatives involving enantioselective C=O reduction and chiral aminoselenenylation have also successfully yielded chiral modifications of the natural product.

4.1. Resolution of racemates and separation of diastereomeric mixtures

The resolution of racemic salsolidine or related simple tetrahydroisoquinolines by the formation of tartrate salts, was the first strategy aimed at the acquisition of the natural product in optically active form.[12]



Scheme 7.

A modern example of the resolution of (±)-**1** by the formation of diastereomeric mixtures was provided by Brossi et al.[59] Their strategy was based on the preparation, separation, and decomposition of diastereomeric ureas by a reaction of (±)-**1** with an optically active isocyanate.

Reaction of (±)-**1**, prepared by the Bischler–Napieralski route involving the related 3,4-dihydroisoquinoline **2**,[8,9] with (*R*-(+)-α-phenethylisocyanate **39**, furnished a mixture of diastereomeric products (Scheme 7), which once submitted to crystallization in an isopropyl ether–methylene chloride (5:1) solvent mixture, afforded the crystalline urea **40**, while its diastereomer **41** remained in the mother liquors; basic hydrolysis of the purified diastereomers with 2 M BuONa in BuOH, provided both enantiomers of salsolidine in around 35% overall yields each, and enantiomeric excesses comparable to those obtained by the tartaric acid resolution procedure.

The same group prepared diastereomeric *p*-nitrophenyl urea derivatives of (±)-**1** employing the known (*R*)-[1-(*p*-nitro-phenyl)ethyl]amine as the derivatizing agent;[60a] these diastereomeric compounds were easily separated by HPLC. Interestingly, the same principle was also employed in the opposite sense; Russian scientists reported the use of (*S*)-salsolidine as a reagent for the configurational determination of isocyanates such as α-phenethylisocyanate, by kinetic resolution. This strategy can also be applied to alcohols with stereogenic centers.[60b]

4.2. Hydride reduction and catalytic hydrogenation of C=N and C=C double bonds

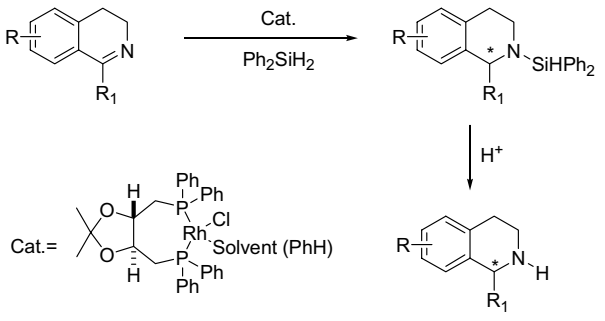
4.2.1. General. Being complementary to the C=O reduction, the asymmetric reduction of heterotopic C=N double bonds to diastereo- or enantio-enriched amine functionalities is an important approach for accessing chiral amines, as is the enantioselective reduction of the C=C double bond of enamine derivatives.

Hydride reduction of the C=N bond of 3,4-dihydroisoquinolines and 3,4-dihydroisoquinolinium derivatives constitutes one of the first strategies, which have been evaluated for the enantioselective elaboration of chiral 1-substituted tetrahydroisoquinolines. As it has made striking progress over the last two decades, driven by the ubiquity of amine groups in natural products, pharmaceuticals, herbicides, and other bioactive materials, it still remains an actively explored strategy and an active area of research. This topic has recently been reviewed.[61a–c]

Nowadays being a core technology, catalytic enantioselective processes have also been explored.[61d] In the field of isoquinoline alkaloids, several examples of catalytic enantioselective syntheses have appeared in the literature by which a large quantity of nonracemic compounds can be secured using small amounts of a chiral catalyst. The performances of the catalysts based on Ti, Ru, Rh, and Ir were tested through enantioselective syntheses of salsolidine. Most of them were used to carry out C=N hydrogenations, while others such as those based on Rh and Ru have been employed for the somewhat less explored enantioselective reduction of the C=C bond of enamides.

Although less successful, other processes have also been investigated for the enantioselective reduction of C=N double bonds. Cho and Chun were the first to report the asymmetric reduction of N-substituted ketimine derivatives with stoichiometric amounts of chiral oxazaborolidines and borane; however, their procedure proved to be effective only for aromatic ketimines, since N-substituted alkyl ketimines gave poor results (9% ee with 2-butanone-phenylimine).[62]

Furthermore (although it has not been applied to the elaboration of salsolidine itself) Kagan provided the first example toward catalytic enantioselective synthesis of 1-substituted tetrahydroisoquinolines by assembling an enantioselective hydrosilylation of 1-alkyl-3,4-dihydroisoquinolines catalyzed by a DIOP–Rh(I) complex (Scheme 8). The transformation, however, proceeded at best with a modest enantioselectivity of 39%.[63]



Scheme 8.

Interestingly however, Kutney et al. disclosed that 1-alkyl-3,4-dihydroisoquinolines were nonreducible with (*R*)-(+)-Cycphos-Rh, a reagent which proved useful as a catalyst for the asymmetric hydrogenation of prochiral noncyclic Schiff bases, furnishing amines with up to 91% ee (enantiomeric excess).[64]

4.2.2. Enantioselective reduction of 3,4-dihydroisoquinolines. Chiral borohydrides. While in the seventies the asymmetric reduction of prochiral ketones with chirally modified metal hydrides was capable of delivering optically active alcohols with reasonable enantiomeric excess, the asymmetric reduction of cyclic imines still remained unsuccessful.[65]

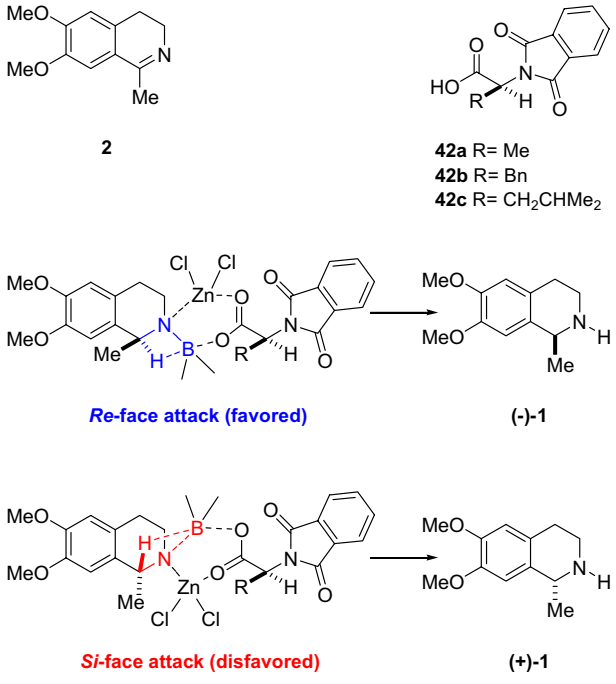
In 1971, Grundon et al. reported that the reduction of 3,4-dihydropapaverine with lithium hydro(methyl)-dipinan-3-α-ylborate followed by a reaction with methyl iodide provided (−)-laudanosine methiodide in 8.9% ee.[66] Sometime later and based on the reports of Gribble and Ferguson, Brown and Rao, Liberatore and Morracci,[67a–c] on the synthesis and isolation of triacyloxyborohydrides, Iwakuma et al. disclosed the asymmetric reduction of cyclic imines with isolated chiral sodium triacyloxy borohydrides, easily obtained from the reaction of $NaBH_4$ and 3 equiv of *N*-acyl derivatives of optically active α-aminoacids.[68] These authors improved the enantiomeric excess of chiral laudanosine, reporting the synthesis of the (+)-enantiomer in 71% ee with the help of an *N*-benzyloxycarbonyl-proline derived catalyst in methylene chloride at room temperature. Resorting to the same strategy, (*S*)-salsolidine was acquired in 85% yield and 70% ee, with the chiral auxiliary being recovered nearly quantitatively.

By analogy with earlier observations of Reetz[69] along with results of the analysis of the reaction products between picoline and trifluoroacetoxyborohydrides, the formation of an intermediate borane–amine complex upon reaction of the reductant with the starting 3,4-dihydroisoquinoline **2** was postulated as a first step for this transformation. In this proposal, products are generated in a second stage by inter- or intra-molecular hydride reduction of the imine.

Evidence favoring this proposed mechanism was gained from the reaction of trifluoroacetoxyborohydride with 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline **2** in THF at 0 °C, which afforded 80% yield of the imine–borane complex. Upon reflux in THF for 48 h, this produced racemic salsolidine in only 30% yield.[70]

A recent and highly improved variation of this strategy was contributed by Hajipour and Hantehzadeh.[71] These Iranian authors prepared bulky triacyloxyborohydrides derived from *N*,*N*-phthaloyl aminoacids **42a**–**c**,[72] which initially provided up to 78% of salsolidine in only 71% ee starting from dihydroisoquinoline **2**, when the reaction was run in THF at room temperature (Table 1).

Important solvent and additive effects were observed (entries 1–7), with the transformations run in THF being the quickest and more selective ones; moreover, in the presence of $ZnCl_2$, the selectivity of the catalyst showed a slight improvement, leading to salsolidine in 70% yield and 79% ee. Interestingly, however, when this asymmetric reduction was carried out with the reagents impregnated on alumina, under solid state conditions (entry 8), 90% salsolidine was produced, exhibiting a remarkable 100% ee. In all reductions, the (*S*)-enantiomer was predominant; Scheme 9 provides a mechanistic



Scheme 9.

Table 1. Reduction of **2** with chiral triacyloxyborohydride **42c**, derived from *N*,*N*-phthaloyl valine

Entry no	Solvent	Time (h)	Additive	Yield (%)	Ee (%)
1	THF	5	—	78	71
2	THF	8	—	79	75
3	Et_2O	12	—	45	52
4	CH_2Cl_2	144	—	50	56
5	DME	123	—	55	58
6	$ClCH_2CH_2Cl$	40	—	65	62
7	THF	8	$ZnCl_2$ (1.2 equiv)	72	80
8	—	1	Al_2O_3 (solid state)	90	100

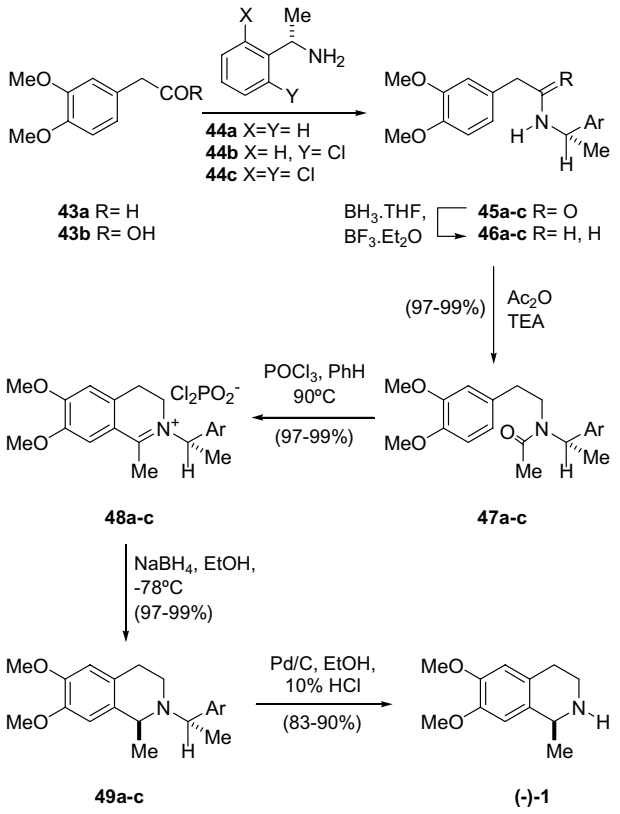
explanation accounting for the enhanced selectivity observed when the transformation was carried out in the presence of $ZnCl_2$.

4.2.3. Diastereoselective reduction of chiral activated azomethines (chiral iminium ions). The stereoselective nucleophilic addition of hydride ion to the endocyclic C=N bond of chiral iminium ions derived from optically active amines constitutes a powerful tool for the elaboration of saturated nitrogen heterocycles with high diastereomeric excess. The mechanism accounting for that success was most probably the stereocontrolled formation of an iminium ion–borohydride ion pair prior to reduction, followed by a diastereoselective attack of a hydride ion to the activated iminium moiety, with concomitant generation of a new stereogenic center. Facile removal of chiral auxiliaries was critical for the success of this strategy, leading to products with excellent levels of enantiomeric excess.

The numerous stereoselective syntheses of enantioenriched salsolidine and related alkaloids accomplished over the past 25 years with the aid of hydride reduction of optically active iminium ions, attest to how this strategy has also evolved into a chirally efficient process, making use of various chiral auxiliaries and reagents. The use of such a strategy can be traced back to a series of studies on the syntheses of heterocyclic compounds performed by Kametani et al.

This Japanese group discovered that when *N*-alkyl-3,4-dihydroisoquinolinium compounds, prepared from 3,4-dimethoxyphenyl acetaldehyde **43a** by the $POCl_3$-assisted Bischler–Napieralski closure of their *N*-acyl-β-phenethylamine derivatives, were reduced with $NaBH_4$ at 0 °C or hydrogenolyzed over 10% palladium hydroxide on charcoal, the corresponding tetrahydroisoquinolines were obtained in moderate yields;[73] most interestingly, however, was the discovery that when the *N*-alkyl groups were chiral, diastereomeric mixtures of optically active compounds were produced. In this way, after removal of the chiral auxiliary, (*R*)- and (*S*)-salsolidine were accessed in 15–44% ee employing chiral dihydroisoquinolinium precursors **48** derived from (*R*)-(+)-α-phenethylamine, (*S*)-(−)-α-phenethylamine **44a**, (*S*)-(−)-α-ethylbenzylamine, and (*S*)-(−)-1-(1-naphthyl)-ethylamine, being the products arising from the chiral α-methylbenzylamines those obtained in better enantiomeric excess (36–44% ee). In spite of the excellent chemical yields attained, the performance of the overall sequence in terms of diastereoselection, however, was rather poor.

Sometime later, while studying the conformational preference of these iminium ions whose asymmetry originates from a stereogenic center appended to the nitrogen atom of the iminium ion moiety, Polniaszek and McKee[74a] described an interesting improvement to Kametani's original procedure (Scheme 10). Carrying out the reduction of the 3,4-dihydroisoquinolinium salt derived from **44a** with sodium borohydride at −78 °C, (1*S*)-**49a** was obtained in 77% yield and 86% de. To



Scheme 10.

complete the synthesis, the *N*-benzyl moiety was efficiently removed by palladium on carbon-mediated hydrogenolysis.

In a further improvement, Polniaszek prepared 'second generation' chiral amines such as (*S*)-(−)-1-(2-chlorophenyl)ethylamine **44b** and (*S*)-(−)-1-(2,6-dichlorophenyl) ethylamine **44c** via directed metallation of silyl derivatives of commercially available (*S*)-(−)-α-phenethylamine.[75] For comparative purposes, the chiral inductors **44a**–**c**, which possess enhanced steric differences between the aryl and methyl groups, were incorporated into dihydroisoquinolinium type iminium ions **48a**–**c**.

To that end, a carbonyldiimidazole-mediated reaction of **44a**–**c** with 3,4-dimethoxy phenylacetic acid **43b** was followed by a reduction of the resulting amides **45a**–**c** to the corresponding amines **46a**–**c** with a BH_3·THF/BF_3·Et_2O reagent. These were conveniently acylated with acetic anhydride furnishing **47a**–**c** and then subjected to a $POCl_3$-mediated cyclization to the corresponding iminium salts **48a**–**c**, which upon $NaBH_4$ reduction at −78 °C afforded chiral 1-substituted tetrahydroisoquinolines **49a**–**c**. Conventional catalytic hydrogenolysis of their *N*-benzyl group provided (*S*)-(−)-salsolidine, showing that the reduction proceeded with great diastereoselection. Diastereomeric ratios (1*S*/1*R*) of salsolidine derivatives were 91:9 for **44a**, 100:0 for **44b** and 98.4:1.6 for **44c**, representing efficient examples of 1,3-asymmetric induction. Interestingly enough, when

bulkier substituents were placed at the C-1 position of the resulting tetrahydroisoquinoline, the 2,6-dichlorophenyl derivative was at least as efficient as its monochloro congener.

In this monotonic series of 2,6-diH, 2-Cl, and 2,6-diCl derivatives, it was seen that the degree of diastereoselection observed in the reduction of iminium ions **48a–c** seemed to be governed by steric factors; apparently, the single stereogenic center appended to the nitrogen atom of the iminium ion moiety creates different steric environments at the two iminium ion diastereofaces in the transition state of this nucleophilic addition reaction.

This transformation is ionic in nature, in which a reasonable first step may be an ion metathesis, with the formation of an iminium ion–borohydride ion pair prior to the second step, consisting in a hydride addition to the iminium. Since these compounds possess a C=N double bond embedded in a rather rigid six-membered ring, it appears that only two conformational degrees of freedom are accessible to these structures: (1) rotation about the C–N bond linking the *N* to the stereogenic center and (2) rotation about the C–C bond linking the stereocenter to the aromatic moiety.

The data provided by these researchers supports the view that iminium ions prefer transition state conformations in which the *si* face is more hindered to nucleophilic approach (Scheme 25). Substitution with chlorine increases the net steric shielding of the *si* diastereoface, thus increasing the diastereoselection.

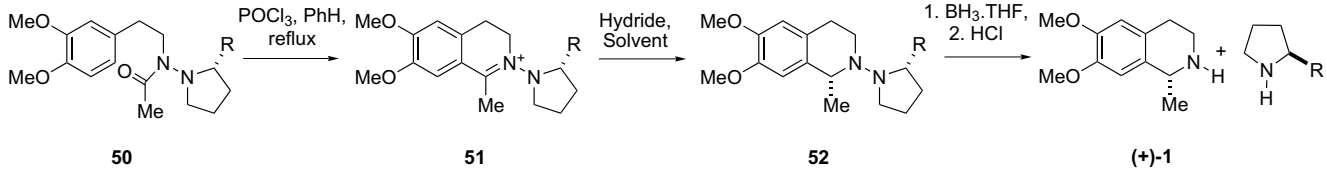
A chirally complementary, modification of the strategy depicted in the above sequence was reported by Kibayashi et al.[76] This consisted of the synthesis and reduction of isoquinolinium salts, such as **51**, bearing an hydrazonium moiety derived from natural proline.

With different precursors, easily elaborated by the Bischler–Napieralski cyclization of conveniently substituted β-phenethylamides **50**, salsolidine derivatives **52** carrying a (1*R*)-configuration were isolated in 42–88% yield and 84–96% de. As shown in Table 2, solvent, reducing agent, and reduction temperature were more influential in the recovery yields than in the enantiomeric excesses recorded for the isolated products. Removal and recovery of the proline derived chiral auxili-aries were carried out by refluxing first with BH_3·THF, followed by the destruction of the resulting tetrahydroisoquinoline–borane complexes with refluxing HCl.

The preferential formation of one of the enantiomers of the natural product was rationalized on the basis of the pyramidal stability of the trivalent nitrogen of the chiral pyrrolidine ring, constituting an efficient asymmetry inducing a stereogenic center, and the existence of an energetically favored conformer, which can be attacked from its less hindered face.[77] An alternative strategy involving hydrazonium ions, which is discussed below, was reported to lead to the opposite enantiomer of the natural product; this entails the nucleophilic addition of carbon nucleophiles to hydrazonium salts.

4.2.4. Enantioselective borane reduction of azomethines activated with chiral Lewis acids. A fundamentally different approach to that consisting of reduction of chiral activated azomethines was reported by Kang et al.[78] Their protocol employed a borane-mediated reduction of 1-alkyl-3,4-dihydroisoquinoline derivatives using enantioface-selective coordination on the amine nitrogen assisted by chiral Lewis acids, which produces activated iminium species. These authors tested various Lewis acids, such as thiazazincolidine complexes **53a** and **53b**,[79] TADDOL–Ti complex **54**,[80] Ohno's catalyst **55**[81] and L-DPMPM–Zn complex **56** (Fig. 6),[82] and found that the zinc complex **53a** gave the optimal enantioselectivity.

Table 2. Synthesis of salsolidine derivatives **52** by reduction of **51**



50 **51** **52** **(+)-1**

Entry	R	Hydride	Solvent	Temperature (°C)	De **52** (%)	Yield **52** (%)
1	Me	$NaBH_4$	MeOH	−50	84	73
2	$CH(CH_3)_2$	$NaBH_4$	MeOH	−50	86	71
3	CH_2OBn	$NaBH_4$	MeOH	−10	90	88
4	CH_2OBn	$NaBH_4$	MeOH	−50	92	84
5	CH_2OBn	$NaBH_4$	MeOH	−90	94	81
6	CH_2OBn	$LiBEt_3$ H	THF	−50	92	68
7	CH_2OBn	Vitride	THF	−50	92	63
8	CH_2OBn	DIBAL-H	THF	−50	92	42
9	CH_2OBn	K-Selectride	THF	−50	96	44

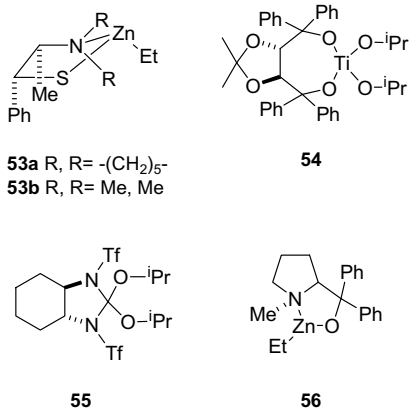


Figure 6.

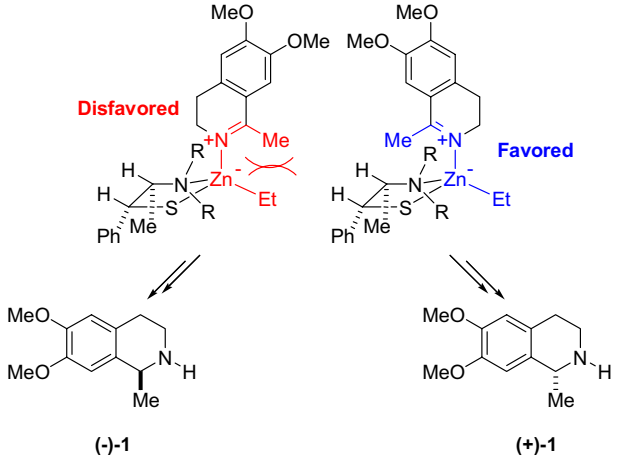
The borane source proved to be influential in the reaction's outcome. Good chemical yields (60–81%) and enantiomeric excesses ranging from 62% to 86% were achieved when BH_3.THF was employed; other boranes examined, such as borane–dimethylsulfide complex, bis(2,6-dimethylphenoxy)borane (BDMPB), and pinacol borane furnished enantiomeric excesses in the range 4–45%. Interestingly, the reaction provided a mixture of salsolidine and a second compound, presumably a borane complex of dihydroisoquinoline **2**, which could not be forced to undergo reduction but reverted to the starting material upon aqueous work-up.

Selectivity [(*R*)-salsolidine was obtained in all cases] was explained (Scheme 11) on the basis of the coordination of the chiral Lewis acid to the nitrogen lone pair of the dihydroisoquinoline, which can occur in two ways; the preferred one is that in which the unfavorable $A^{1,3}$ strain between the bulky methyl group and the ethyl group on zinc is minimized. In addition to this steric reason, the anti-relationship between the C=N bond in the dihydroisoquinoline and the C–Zn bond in the catalyst, seems to make the complex leading to (+)-**1** the lower energy species, presumably due to electronic reasons.[78]

This model also explains the lower enantioselectivity found when coordinating solvents such as dimethyl sulfide or THF are used, on the basis of interference of the coordination of the chiral catalyst to the substrate in the transition state.

The enantiomeric excess (Table 3) was found to improve as the reaction temperature was lowered from 10 to −5 °C (entries 1–3); conversely, chemical yields dropped from 81% to 65% as a result of this change in reaction conditions. BH_3·THF seemed to be the most efficient reducing reagent within this system.

Cho et al. found that 3,4-dihydroisoquinoline **2** was inert to Itsuno's reagent **57a**;[83a] interestingly, however, oxazaborolidine-type catalysts have been employed for the elaboration of 1-substituted tetrahydroisoquinoline alkaloids.[83b,c] More recently, Bolm and Felder reported that **2** was refractory to the β-hydroxy sulfoximine-catalyzed enantioselective reduction with borane, when **57b** was employed as catalyst (Fig. 7);[84] it is believed that under the reaction conditions, cyclic imines like **2** form borane adducts, which prevent hydride reduction.



Scheme 11.

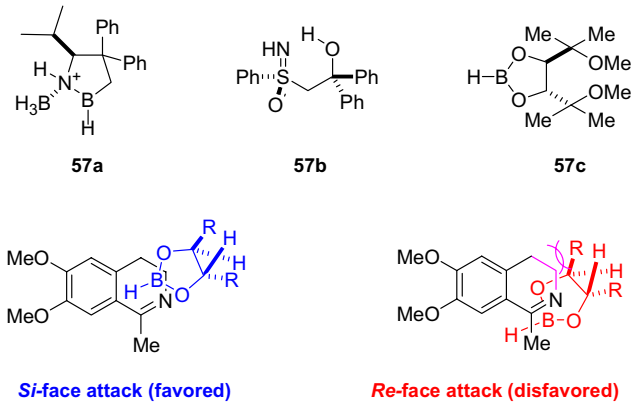


Figure 7.

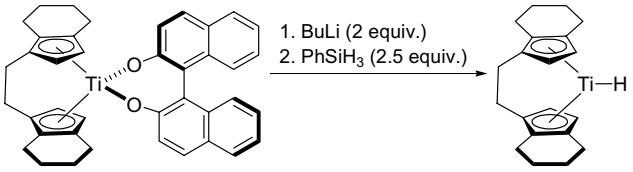
Table 3. Reduction of **2** with boranes in toluene, in the presence of thiazazincolidine catalyst **53a**

Entry no	Borane (equiv)	Temperature (°C)	Time (h)	Yield (%)	Ee, % (config.)
1	BH_3·THF (2)	10	12	81	62 (*R*)
2	BH_3·THF (2)	0	12	75	79 (*R*)
3	BH_3·THF (2)	−5	12	65	86 (*R*)
4	BDMPB (3)	−10	15	32	87 (*R*)
5	BH_3·SMe_2 (3)	−20	12	4	60 (*R*)
6	Pinacolborane (2)	−5	12	45	82 (*R*)

Interestingly, chiral oxaborolidines of the dialkoxyborane type, like **57c** available from the commercial dimethyl L-tartrate, were observed to reduce cyclic and acyclic azomethines.[85] However, **57c** is a stoichiometric reductant, which has to be used in approximately five-fold excess in the presence of 1.2 equiv of a mild Lewis acid, such as $MgBr_2{\cdot}OEt_2$ for the reaction to be more stereoselective. In this way, (+)-**1** (isolated as the *N*-carboxymethyl derivative, **8**) was accessed in very modest 50% yield and 28% ee.

The *si*-face directing effect leading to the preferential formation of the (1*R*)-enantiomer can be explained (Fig. 7) by considering a transition state, which avoids non-bonding interactions between the methylene protons (H-3) of **2** and the bulky substituent of the dialkoxyborane ring.

4.2.5. Catalytic enantioselective reduction of 1-alkyl-3,4-dihydroisoquinolines. The catalytic enantioselective reduction of 1-alkyl-3,4-dihydroisoquinolines has been achieved with different degrees of success employing titanium, ruthenium, and iridium-based catalysts. While studying the viability of titanium catalysts for the catalytic reduction of unsaturated organic compounds, Willoughby and Buchwald discovered a titanocene-derived catalytic system (Scheme 12) valuable for the asymmetric hydrogenation of imines.[86] Their catalyst **58b** was generated in situ by metallation with *n*-BuLi of the 1,1′-binaphth-2,2′-diolate derivative **58a**, a previously described *ansa*-titanocene precatalyst,[87] and a subsequent reaction of the metallated species with phenyl silane under a hydrogen atmosphere.



58a **58b**

Scheme 12.

This catalytic system does not require a coordinating group on the substrate and impressive levels of selectivity are achieved, taking into account that the catalyst operates by discrimination on the basis of the shape of the substrate. In the reaction cycle, the titanium(III) hydride form of the catalyst **58b** reacts with the imine producing a 1,2-insertion and forming a titanium amine complex, which is then hydrogenolyzed via a sigma bond metathesis reaction to regenerate the catalyst, releasing the amine product.

Reactions were typically run at 65 °C and, interestingly, enantiomeric excesses achieved by the use of this catalyst were higher with cyclic imines than with their acyclic counterparts; they also required less pressure and the hydrogenation outcome was less sensitive to changes in hydrogen pressure. In the case of the *Z*-imine 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline **2**, however, a small pressure effect was observed; at 2000 psig the observed ee of the product was 98%, while at 80 psig the ee obtained was 95%. This substrate, which has a *syn* geometry, upon hydrogenation with the (*R*,*R*,*R*)-catalyst gave (−)-**1**, which is consistent with the general reaction mechanism proposed for the catalyst.

In recent publications, Noyori et al.[88a,b] studied the asymmetric transfer hydrogenation of 1-substituted-3,4-dihydroisoquinolines with different preformed chiral Ru(II) catalysts of general structure **59** (Fig. 8), employing formic acid–triethylamine media.

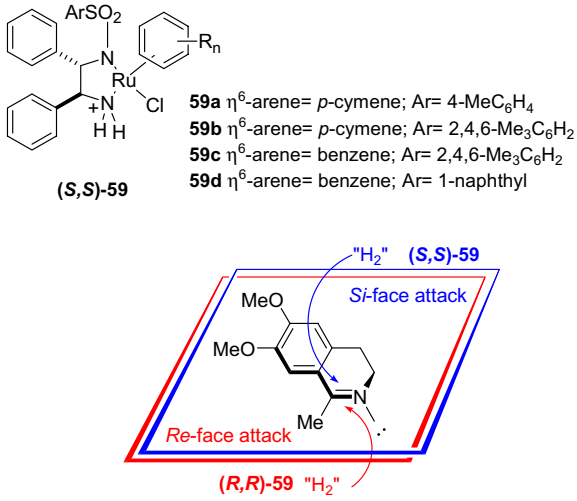
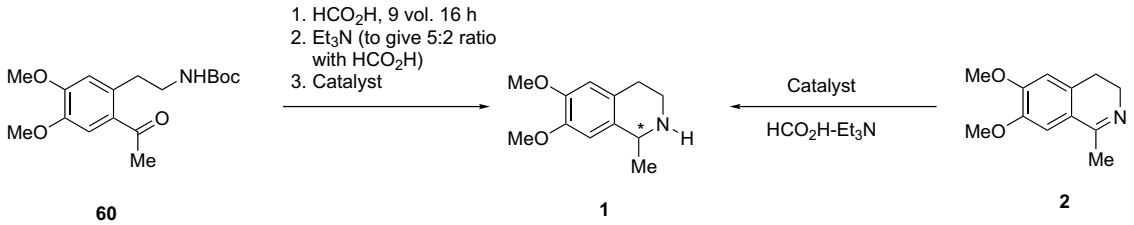


Figure 8.

Transfer hydrogenation with stable organic hydrogen donors is highly attractive because of its operational simplicity, high cost performance and the less hazardous properties of the reducing agents. Screening experiments revealed that the transformation was best effected with a 5:2 formic acid–triethylamine azeotropic mixture in acetonitrile at 28 °C, a substrate concentration of 0.5 M, a substrate/catalyst ratio of 200 and 6 equiv of HCO_2H; these conditions provided a stereodirected synthesis of (+)-**1** in remarkable 99% yield and 95% ee (Table 4, entries 1 and 2).

Interestingly, the reaction did not take place without the addition of triethylamine or in alcoholic and ethereal media with the rate and enantioselectivity of the reaction being influenced by the η^6-arene and 1,2-diamine ligands. It is also known that the alkyl substituents on the *p*-cymene ligand as well as the free amine and tosyl group play crucial roles with regards to the reactivity. The general sense of asymmetric induction with this catalytic system is illustrated in Figure 8; it has been proposed that in the stereodetermining hydrogen-transfer step, the chiral Ru species (probably a hydride) formally discriminates the enantiofaces at the sp^2 nitrogen atom of the imine, generating a stereogenic sp^3 carbon (α-control according to the latent trigonal center rule).[88c]

Table 4. Reaction of **2** and **60** with catalyst **59a** in MeCN to enantioselectively afford salsolidine **1**



Entry no	Substrate	Catalyst	S/C ratio	Time (h)	Yield (%)	Ee, % (config.)
1	**2**	(*S*,*S*)-**59a**	200	3	>99	95 (*R*)
2	**2**	(*S*,*S*)-**59a**	1000	12	97	94 (*R*)
3	**2**	(*R*,*R*)-**59a**	400	120	95	88 (*S*)
4	**60**	(*R*,*R*)-**59a**	400	20	85	88 (*S*)

Very recently, Wills et al. reported a one-pot process for the enantioselective synthesis of salsolidine from the Boc–phenethylamine derivative **60**,[9c] employing a reductive amination strategy, under transfer hydrogenation conditions.[88d]

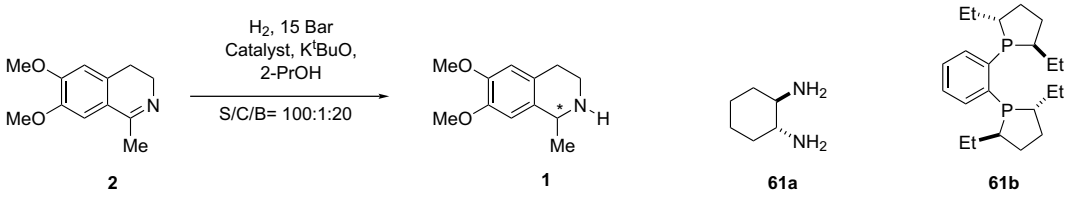
These authors were able to demonstrate that formic acid-mediated removal of the Boc protecting group of **60**, followed by the addition of enough triethylamine to give a 5:2 ratio with the formic acid, and submission of the mixture to an enantioselective transfer hydrogenation reaction in acetonitrile, in the presence of the ruthenium(II)-based catalyst (*R*,*R*)-**59a** (prepared in situ) provided the natural product with the same enantiomeric excess obtained when **2** was hydrogenated under similar conditions (Table 4, entries 3 and 4). For the synthesis of certain amines, this is a potentially valuable procedure, since imine formation and imine reduction are carried out in one synthetic step, avoiding the isolation of the imine intermediate.

Cobley et al.[89] disclosed another series of ruthenium-based complexes involving chiral diphosphines and diamines as ligands, as robust and highly useful tools for the catalytic asymmetric hydrogenation of imines. One of these optically active complexes was considered the preferred one for the enantioselective hydrogenation of **2**; this transformation employed (*R*,*R*)-1,2-diaminocyclohexane [(*R*,*R*)-DACH, **61a**] as a diamine, while (*R*,*R*)-Et–DuPHOS **61b**, a phosphethane type auxiliary, was used as chiral diphosphine; unlike others, this catalytic system requires a strong base, such as potassium *tert*-butoxide. In this work, conversions were determined by ^{1}H NMR, while the percentages of ee were obtained by chiral GC analysis of volatile derivatives, with the results shown in Table 5.

Using for asymmetric catalytic hydrogenation catalysts similar to those employed in the pioneering hydrosilylation work of Kagan et al. (Scheme 8),[63] James et al. disclosed[64] that when imine **2** was treated with a rhodium catalyst, including DIOP **62a** as ligand in MeOH, the reaction did not proceed to salsolidine, evidencing the formation of **63**. Under different reduction conditions (H_2, 1 atm, CH_2Cl_2), a related complex, which existed as a couple of isomers **64a** and **64b** in solution state, was also observed (Fig. 9). These authors also found that no reduction product was obtained when (+)-cycphos **62b** (1 mol%, PhH–MeOH, 1:1, H_2, 1000–1500 psig) was employed as chiral ligand.

For acyclic imines, these researchers[64b] suggested that the coordination of the nitrogen atom of the imine to the rhodium center is the first step of the reaction. Due to the importance of the solvent system in the reactions studied (PhH–MeOH, 1:1), the existence of a five-coordinated Rh(I) intermediate and its transformation

Table 5. Catalytic hydrogenation of **2** leading to salsolidine with the (*R*,*R*)-Et–DuPHOS–$RuCl_2$-(*R*,*R*)-DACH catalytic system



Catalyst	Temperature (°C)	Time (h)	Conversion (%)	Ee (%)
(*R*,*R*)-Et–DuPHOS–$RuCl_2$ (*R*,*R*)-DACH	65	68.5	79.5	79
(*R*,*R*)-Et–DuPHOS–$RuCl_2$ (*R*,*R*)-DACH	80	68.5	96	76

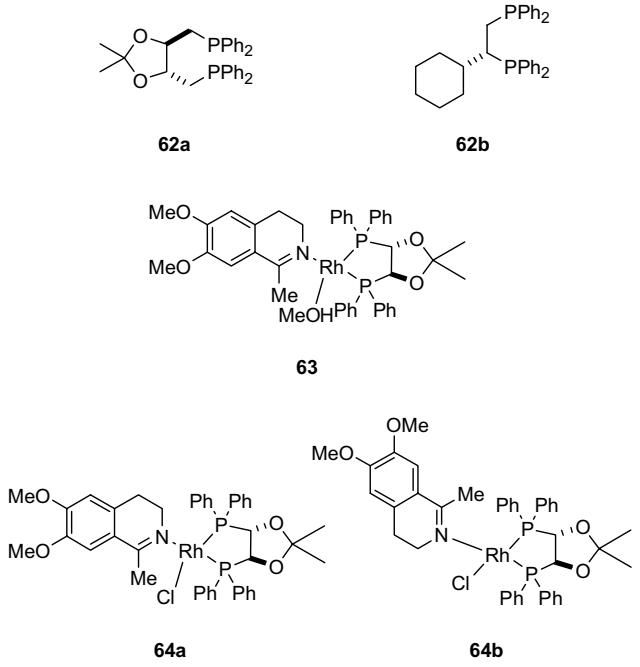
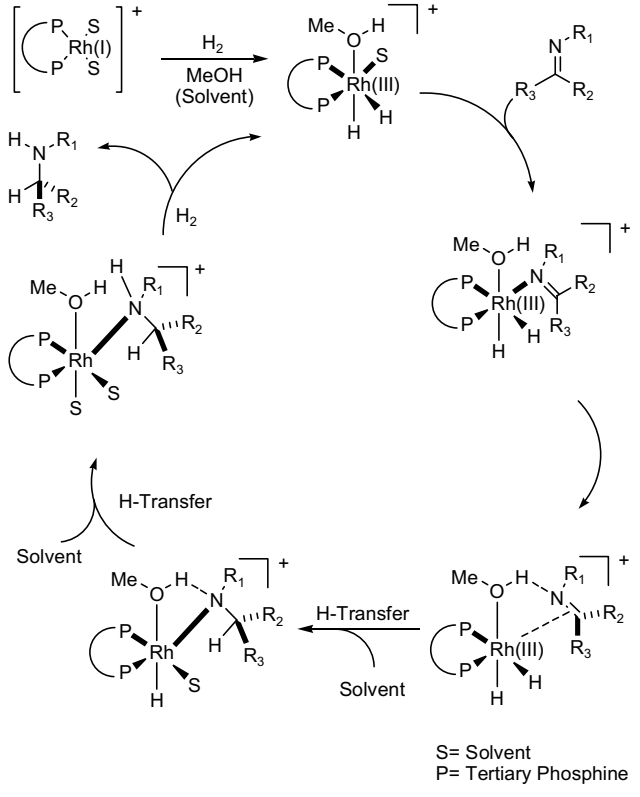


Figure 9.

into a monohydride species was assumed, as shown in Scheme 13. In the case of cyclic imines such as **2**, the reaction would not proceed beyond the first step.



Scheme 13.

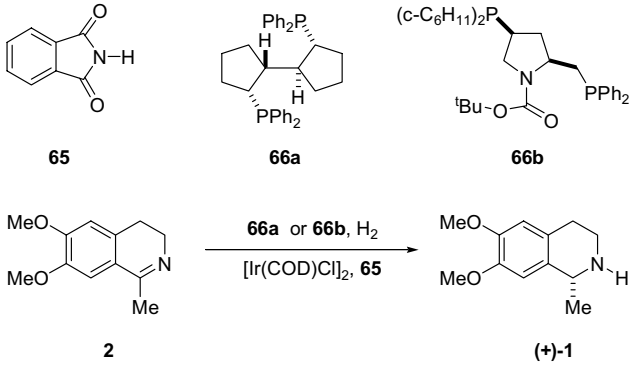
The late transition metal complexes in which a coordinating group is often necessary for the catalytic asymmetric hydrogenation of cyclic imines, thought time ago to be somehow less successful, have also been employed for the enantioselective synthesis of salsolidine, as a demonstration of the remarkable progress made in this area.

Iridium–iodine based catalytic systems like Ir(I)–MOD–DIOP–TBAI and Ir(I)–BCPM–bismuth(III) iodide, which are efficient for the asymmetric hydrogenation of certain cyclic ketimines leading to enantiomeric excesses up to 91%, were found unable to hydrogenate 1-alkyl-3,4-dihydroisoquinolines with enantiomeric excesses higher than 20%.[90a,b]

These systems seem to require fine tuning; it has been recorded that addition of phthalimide **65** (4 mol%) to an iridium(I)–(*R*,*R*)-BICP **66a** system gave high conversion to salsolidine but with very poor enantiomeric excess (94.6% and ee = 4.0%), while addition of benzylamine (5%) to the same catalytic system provided the natural product in no more than 41.3% ee,[91a] while the use of an iridium(I)–BINAP-phthalimide complex for the successful elaboration of the related (*S*)-calycotomine (*S*)-**11** in 86% ee has been recorded[91b] and a modified DIOP ligand (*R*,*R*)-MOD-DIOP, **62d** was used as part of a neutral iridium complex, which in the presence of TBAI gave 91% of (*R*)-**1**, in 27.5 ee (S/C = 100, H_2 at 100 atm).[91d]

On the other hand, Morimoto et al. recently demonstrated that the addition of imides as co-catalysts allowed a remarkable improvement in the asymmetric hydrogenation of 1-alkyl-3,4-dihydroisoquinolines when the BCPM **66b** type of chiral diphosphine–iridium(I) complex catalysts was employed (Table 6).[90c–e] These improvements have found uses in other, related systems.[91c]

Enantiomeric excesses of (−)-**1** of up to 93% (entry 6) were obtained with 4 equiv of phthalimide as additive; the reaction was run in toluene at 2–5 °C, under an initial hydrogen pressure of 100 atm and 1 mol% of catalyst, conveniently prepared in situ from $[Ir(COD)Cl]_2$ and (2*S*,4*S*)-BCPM (Scheme 14).



Scheme 14.

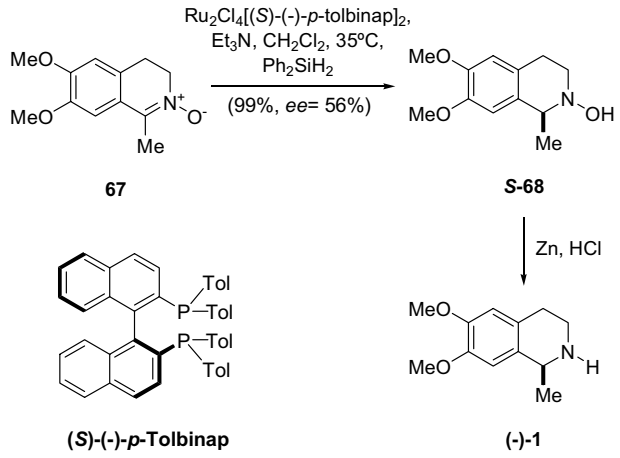
Table 6. Asymmetric hydrogenation of **2** with the diphosphine–iridium(I) catalyst system, employing (2*S*,4*S*)-BCPM **66b** as the chiral ligand

Entry no	Additive	Solvent	Temperature (°C)	Time (h)	Conversion (%)	Ee, % (config.)
1	None	PhH–MeOH	20	24	90	18 (*R*)
2	None	PhMe	20	24	22	14 (*S*)
3	Succinimide	PhH–MeOH	−10	72	94	67 (*S*)
4	Phthalimide	PhH–MeOH	−10	48	98	76 (*S*)
5	Phthalimide	PhH	20	24	96	70 (*S*)
6	Phthalimide	PhMe	2–5	24	95	85–93 (*S*)
7	Phthalimide	THF	20	20	95	41 (*S*)
8	Phthalimide	CH_2Cl_2	20	20	94	70 (*S*)
9	Succinimide	PhH–MeOH	−10	72	94	67 (*S*)
10	Saccharin	PhH–MeOH	20	45	82	4 (*R*)
11	Hydantoin	PhH–MeOH	20	30	96	49 (*S*)
12	4-Cl-Phthalimide	PhMe	20	20	97	81 (*S*)
13	4-Cl-Phthalimide	PhH–MeOH	20	30	95	56 (*S*)
14	4,4-Cl_2-Phthalimide	PhMe	20	20	95	76 (*S*)

Clear solvent effects were observed, with less polar solvents showing higher enantioselectivities; the ee observed in toluene (>85%) dropped to 41% when THF was employed, under similar conditions. Five membered cyclic imides proved to be the best co-catalysts, while the use of benzamide as co-catalyst provided (+)-**1**, in only 25% ee.

As mentioned above, the hydrosilylation reactions for the enantioselective elaboration of 1-substituted tetrahydroisoquinolines were pioneered by Kagan et al. with limited success and so this strategy was not applied to the elaboration of salsolidine.[63]

More recently, however, a two-step synthesis of (*S*)-salsolidine by means of the asymmetric hydrosilylation of the precursor nitrone **67** using the Ru_2Cl_4[*S*-(−)-*p*-tolbinap]$_2$–Et_3N–Ph_2SiH_2 catalyst system, has been reported.[92] The intermediate hydroxylamine (2-hydroxy salsolidine, **68**), obtained in 99% chemical yield and 56% ee after a 2 h reaction period at 35 °C, was finally reduced with zinc–HCl to the natural product (Scheme 15).



Scheme 15.

Production of *N*-hydroxylamine (*S*)-**68** was rationalized by assuming a mechanism, which involved insertion of the Ru–phosphine complex into the Si–H bond of the silane to give a silylhydridoruthenium species. In turn, this underwent enantioselective insertion into the nitrone, depending on the configuration of the latter. Both, the silane and the catalyst had an influence on the enantiomeric excess of the product, with Ph_2SiH_2 being the most appropriate silane.

The biomimetic reduction of **2** with the NADH analogue **69** (Fig. 10) was achieved, yielding salsolidine in 36% yield.[93] Surprisingly, in spite of the availability of chiral NADH models, its enantioselective reduction was not reported in this work. Finally, it is worth mentioning that the reduction of **2** with baker's yeast has also been attempted, but proved to be unsuccessful.[94]

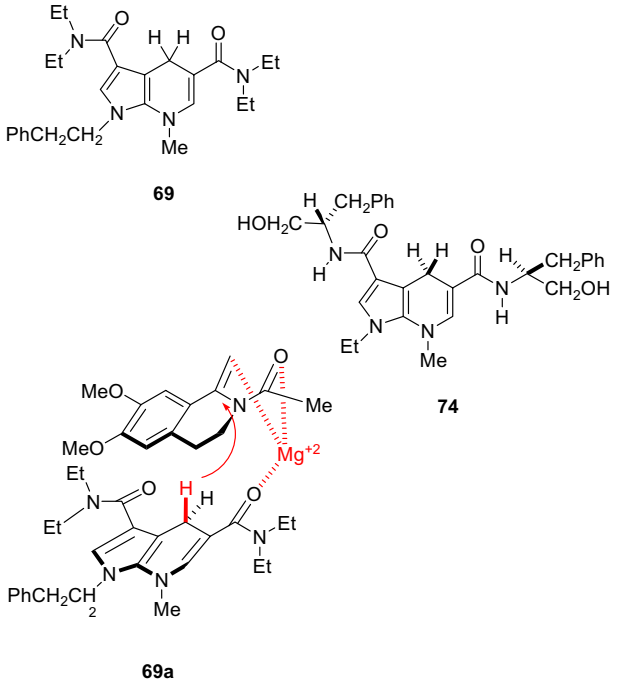


Figure 10.

4.2.6. Diastereoselective catalytic hydrogenation or hydride reduction of chiral enamides. A series of reports by

Czarnocki et al.[95] indicated the achievement of the enantiodivergent syntheses of (*R*)- and (*S*)-*N*-acetyl salsolidine **19** and its related compounds by catalytic hydrogenation or borohydride reduction of enamides **70** and **71**. The starting enamides were prepared in 50–80% overall yield by acylation of **2**, which is readily accessible by the Bischler–Napieralski reaction,[8,9] with acetonide derivatives of the natural (*R*,*R*)-tartaric acid as chiral auxiliaries (Scheme 16).

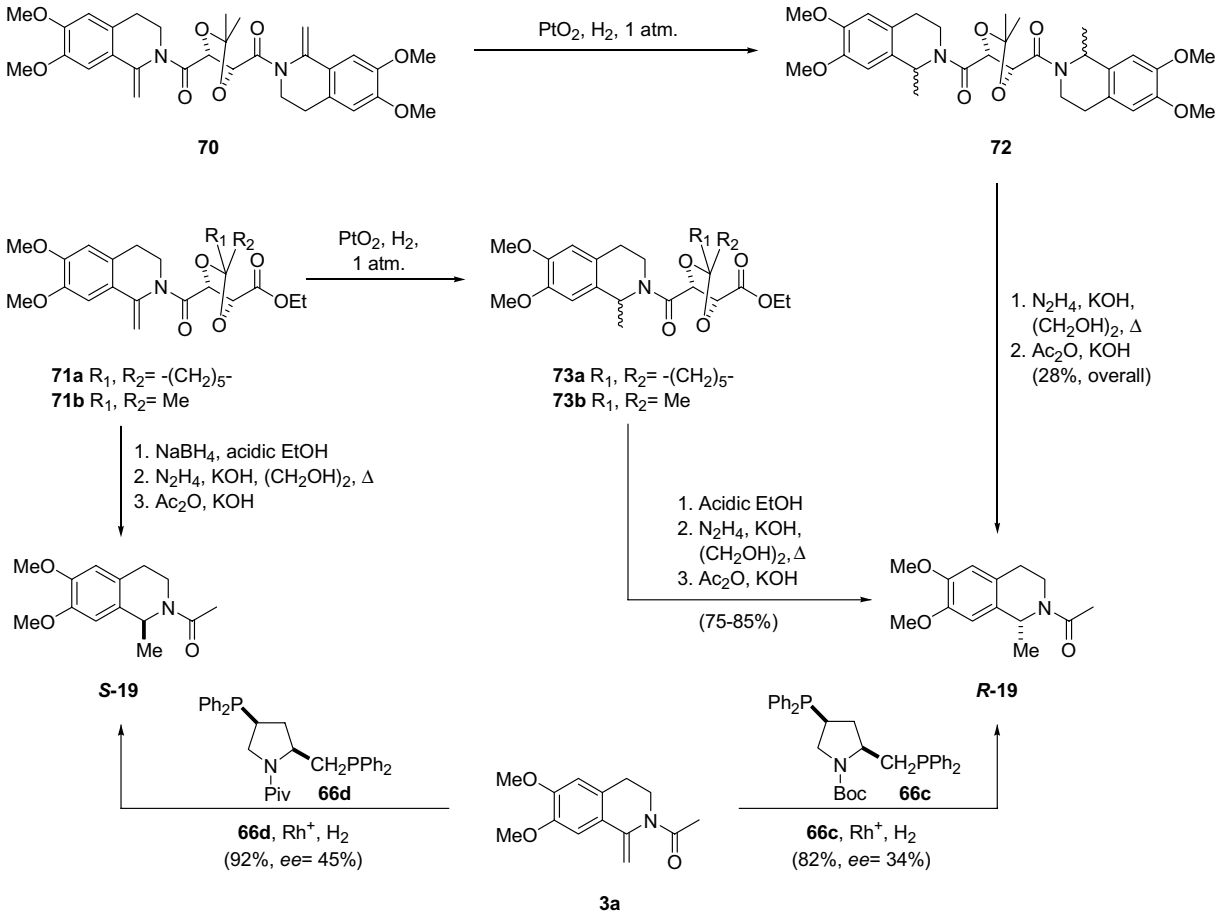
Hydrogenation of the enamides over Adams catalyst provided a mixture of diastereomers **72** and **73** enriched in the C-1 (*R*)-isomers (ee = 9.7–42.4% after hydrazinolysis and N-acylation), while a mixture enriched in the C-1 (*S*)-isomer (81% chemical yield, ee = 15%) was recovered from enamides bearing unprotected hydroxyl groups on the 2-tartaroyl moiety, upon reduction with $NaBH_4$ in acidic EtOH at −5 °C.

4.2.7. Enantioselective reduction of enamides with chiral catalysts. The enantioselective reduction of enamides with chiral catalysts was accomplished (in several cases with a high degree of enantioselectivity) with NADH mimics as well as by catalytic hydrogenation employing chiral rhodium(I) and ruthenium(II) complexes as catalysts.

The hydrogenation of enamide **3a** was repeatedly employed as the model reaction, furnishing *N*-acetyl salsolidine **19**, the transformation of which into salsolidine in high chemical yield and without loss of stereochemical integrity, is known (Scheme 3).

Bourguignon et al. studied the reduction of enamides with NADH models as hydride donors. The chiral NADH mimic **74** (Fig. 10), derived from (*S*)-phenylalaninol, reduces C=O and C=N bonds in the presence of a large excess (8 equiv) of $Mg(ClO_4)_2$; in this way, enamide **3a** was reduced to give 95% of (1*R*)-*N*-acetylsalsolidine (*R*)-**19** in up to 87% ee. Addition of excess $Mg(ClO_4)_2$ to the reaction medium was critical, since the use of 1 equiv of the salt provided the product in only 32% ee;[93] however, the related methyl carbamate **3c** was reduced to furnish 95% of (*R*)-**8**, but in only 26% ee. Curiously, inversion of selectivity, which was dependent upon the amount of $Mg(ClO_4)_2$ employed, occurred during the reduction of methyl benzoyl formate to methyl mandelate; however, no such inversion was observed when the reduction of 3,4-dihydroisoquinoline enamides was carried out.

The use of nonchiral NADH models, such as **69** to provide racemic **19** and its conversion to racemic salsolidine, have also been described by this group in ear-



Scheme 16.

lier publications.[96] A ternary complex **69a** between the substrate, the NADH mimic **69**, and Mg^{2+} was assumed to be responsible for the hydride transfer; in the case of the chiral NADH mimic **74**, this model correctly explains the preferential *si*-face hydrogen transfer to **3a**, leading to enantioenriched (*R*)-**19**.

Rhodium and ruthenium-based chiral catalysts have been employed for the catalytic enantioselective hydrogenation of *N*-acyl enamines. In a pioneering communication by Achiwa[97] on the hydrogenation of enamide **3a** catalyzed by chiral bisphosphine–Rh complexes, the enantioenriched elaboration of both enantiomers of salsolidine by simple modifications in reaction conditions was reported (Scheme 16).

Employing the rhodium complex of (2*S*,4*S*)-*N*-Boc-4-diphenyl phosphino-2-diphenyl phosphinomethyl-pyrrolidine **66c** (BPPM), (*S*)-salsolidine was prepared in 34% ee. However, when the same catalytic cycle was performed with PPPM **66d**, the enantiomeric (*R*)-salsolidine was obtained in 45% ee after deacetylation; in related work, the catalytic enantioselective hydrogenation of **3a** with the Rh–BICP **66a** complex acting as a catalyst to (*R*)-**19** in quantitative yield and ee = 77.8%, was also reported,[91c] as well as the elaboration of (*R*)-**1** and (*S*)-**1** by asymmetric hydrogenation of **3a** with different Rh(I) complexes based on DIOP **62a**,**c**,**d** and (2*R*, 3*S*)-MOCBP, **75**, and diarylphosphino-pyrrolidine **66e** and **66f** motifs, as shown in Table 7.[91d]

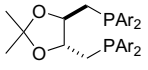
A cationic rhodium(I) complex was found to exhibit better enantioselectivity than the related neutral one (entries 3 and 4) and pressure (entries 2 and 3) as well as ligand (entries 2, 5, and 6) effects on enantiomeric excesses were also observed.

In several contributions, Noyori et al. reported the highly enantioselective synthesis of 1-substituted tetrahydroisoquinolines by the BINAP–Ru(II)-catalyzed hydrogenation (Fig. 11) of *N*-acyl-1-alkylidene-tetrahydroisoquinolines. In this way, (−)-**1** was quantitatively accessed from the precursor *N*-acetyl enamide **3a**, in 97% ee employing Δ-(*S*)-**76**, while use of the related *N*-formyl enamide **3b** as starting material furnished the product in quantitative yield and 96% ee.[98] A mnemonic picture for the prediction of the sense of the enantioselective hydrogenation of *N*-acyl-1-benzylidene-1,2,3,4-tetrahydroisoquinolines with BINAP–Ru(II) catalysts was derived from experimental data; catalytic hydrogenation of acyl-enamines such as **3a** seem to obey the same principles.[46]

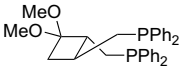
Hydrogenation conditions are rather mild and very practical, employing 0.5–1% of catalyst and hydrogen (4 atm) at room temperature in EtOH–CH_2Cl_2 (5:1) mixtures. Since both enantiomers of the catalyst are readily available, the synthesis is stereochemically flexible with either of the enantiomers of the natural product can be potentially synthesized with equal ease, by choosing the appropriate handedness of the catalyst.

The synthetic scheme is also general, with other tetrahydroisoquinolines being obtained in high chemical yield and enantiomeric excess following analogous sequences. Interestingly however, with a given

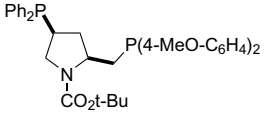
Table 7. Asymmetric hydrogenation of enamide **3a** to *N*-acetyl salsolidine **19** catalyzed by bis-phosphine–Rh(I) complexes



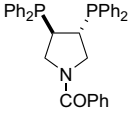
62a (*R*,*R*)-DIOP, Ar= C_6H_5
62c (*R*,*R*)-p-MeO-DIOP, Ar= 4-MeO-C_6H_4
62d (*R*,*R*)-MOD-DIOP, Ar= 3,3'-Me_2-4MeO-C_6H_2



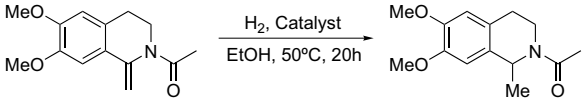
75



66e



66f



3a **19**

Entry no	Ligand	Rh source	S/C ratio	H_2 (atm)	Conversion (%)	Ee, % (config.)
1	**62b**	$Rh^+(COD)BF_4^-$	1000	5	72	40.5 (*S*)
2	**62c**	$Rh^+(COD)BF_4^-$	1000	5	100	51.6 (*S*)
3	**62c**	$Rh^+(COD)BF_4^-$	200	1	100	62.4 (*S*)
4	**62c**	$[Rh^+(COD)Cl]_2$	200	1	100	48.4 (*S*)
5	**62d**	$Rh^+(COD)BF_4^-$	200	1	100	29.1 (*S*)
6	**66e**	$Rh^+(NBD)ClO_4^-$	200	1	100	25.6 (*S*)
7	**66f**	$Rh^+(NBD)ClO_4^-$	200	1	98	46.2 (*R*)
8	**75**	$Rh^+(COD)BF_4^-$	200	1	100	80.6 (*R*)
9	**75**	$Rh^+(COD)BF_4^-$	500	1	100	80.6 (*R*)
10	**75**	$Rh^+(COD)BF_4^-$	200	5	100	76.6 (*R*)

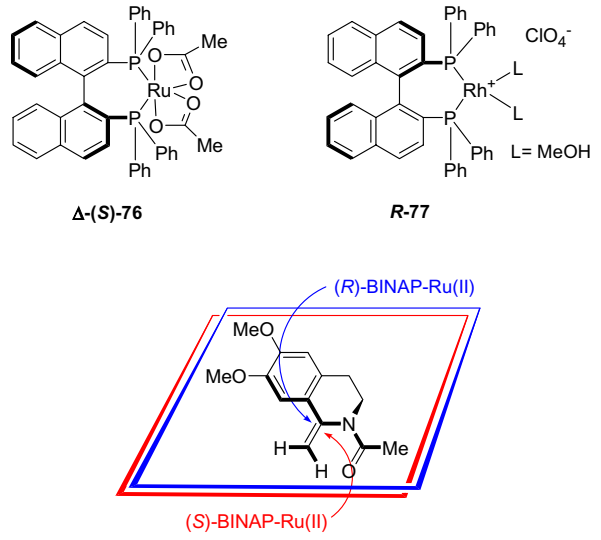


Figure 11.

handedness, the related rhodium-based BINAP catalysts such as **77** deliver the opposite configuration at the C-1 position through hydrogenation; therefore, not surprisingly, hydrogenation of the same *N*-acetyl derivative **3a** with the rhodium catalyst (*R*)-**77** gave (*S*)-*N*-acetylsalsolidine (*S*)-**19** in 82% chemical yield and 60% ee.[46]

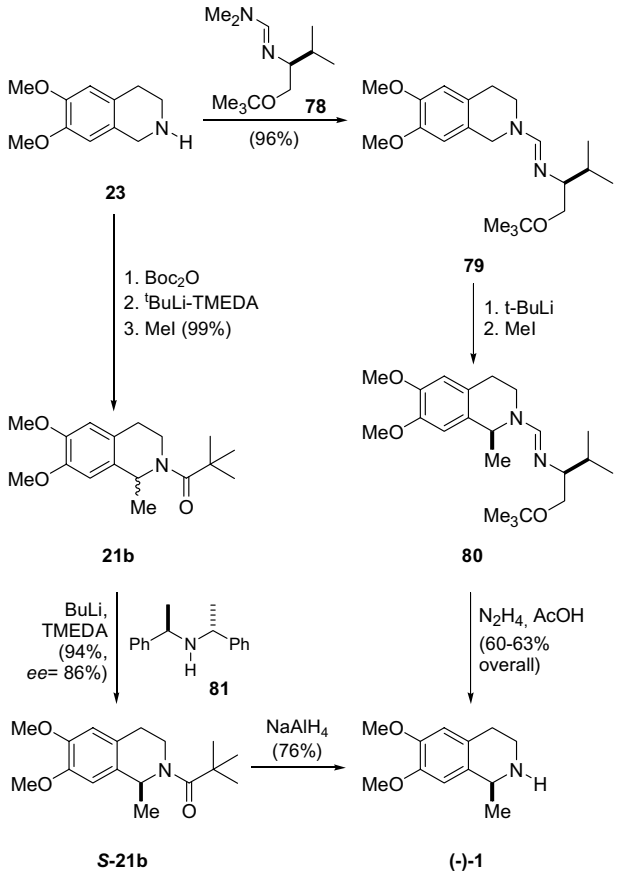
It was also found that the *N*-acyl function is crucial for the appropriate reaction with Rh(I) catalysts because it acts like a tether, binding the heterocycle to the catalytic metal center. Another interesting difference between Ru(II) and Rh(I) catalysts is that when **77** is employed, the *N*-formyl substrates, such as **3b**, are not hydrogenated under conditions where **3a** is easily reduced.

4.3. Metallation of tetrahydroisoquinoline derivatives

4.3.1. Diastereoselective alkylation of metallated chiral tetrahydroisoquinoline derivatives. Substituents can be introduced at the α-position of secondary amines via metallation, followed by treatment of the metallated species with the appropriate electrophile, by alkylation of azomethines as well as their synthetic equivalents or activated forms, or by catalytic oxidation and subsequent treatment of the oxidized intermediates with appropriate nucleophiles.[99,100]

Throughout their studies on the alkylation of α-amino carbanions derived from chiral formamidines, carried out during the 1980s and the beginning of the 1990s, Meyers et al. were among the first to study the enantioselective formation of new C–C bonds adjacent to nitrogen atoms.[101] As a result, several model tetrahydroisoquinolines were enantioselectively alkylated with various alkyl halides in 50–70% yields and excellent enantiomeric excesses, employing different chiral formamidines, and many natural products were synthesized in this way.[102]

The most consistent results were observed with the chiral auxiliary derived from (*S*)-valinol *tert*-butyl ether, while others gave products in 80–99% ee. For instance, (*S*)-**1** was obtained by this procedure in 60–63% yield and >97% ee, by way of the formamidine derivative **79**, easily available from the known 6,7-dimethoxytetrahydroisoquinoline **23** and formamidine **78** (Scheme 17).[103a]

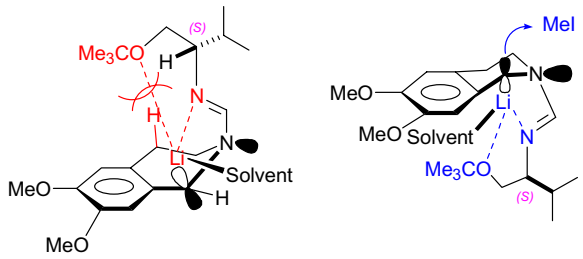


Scheme 17.

Removal of the chiral auxiliary from the resulting alkylated derivative **80** was conveniently carried out by hydrazinolysis. Formamidines derived from (*S*)-salsolidine itself were also employed for the elaboration of asymmetric 1,1-disubstituted tetrahydroisoquinolines.[103b]

By analogy with models proposed for other optically active formamidines,[101c] the high stereoselectivity observed for the (*S*)-valinol *tert*-butyl ether chiral auxiliary in **80** may be attributed to the different conformational preferences of the diastereomeric lithium salts **82a** and **82b**; in the former, the chiral auxiliary appeared to lie over the plane of the isoquinoline ring, while in the latter, the auxiliary was placed out and away from the

isoquinoline, as a consequence of the (*S*)-configuration of the stereogenic center (Fig. 12).



82a 82b

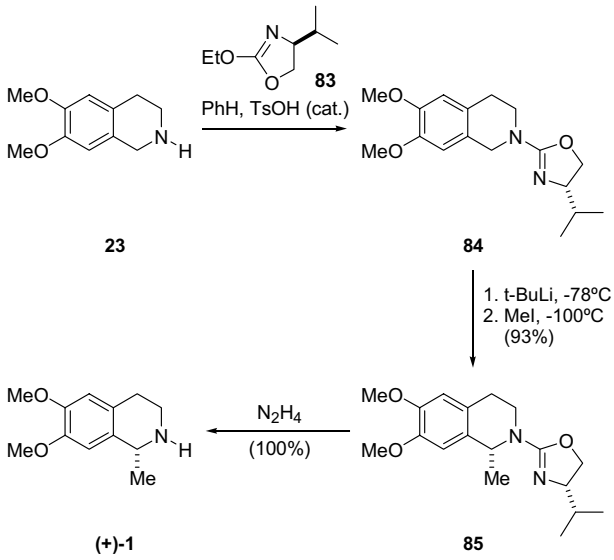
Figure 12.

Steric factors disfavored the production of **82a**, while the steric blockade of the bottom side of the preferred diastereomer **82b**, resulted in alkylation occurring from the top side, furnishing the observed (*S*)-configuration of the product. The role of the chiral auxiliary versus the configurational stability of the C–Li bond was studied. Interestingly, metallation and alkylation of optically active salsolidine carrying an achiral formamidine moiety afforded completely racemic material.[103c]

Resorting to an analogous sequence of transformations, Gawley et al. reported the synthesis of (*R*)-salsolidine by the use of oxazolines as chiral auxiliaries for the asymmetric alkylation of amines,[104] thus providing a chirally complementary sequence to that disclosed by Meyers et al. for the synthesis of the natural product.

To that end, tetrahydroisoquinoline **23** was transformed into **84** via reaction with (*S*)-ethoxyoxazoline **83**, derived from (*S*)-valine. In turn, this was metallated with *t*-BuLi at −78 °C and the resulting species quenched with MeI at −100 °C, to furnish 93% of a chromatographically separable mixture (9:1) of diastereomeric oxazolines **85**. Hydrazinolysis of **85** caused removal of the oxazoline moiety, providing (+)-**1** quantitatively, as shown in Scheme 18, in excellent enantiomeric purity.[34a] Similarly, Quirion et al.[104c] were able to prepare (+)-**1** in 53% yield and up to 93% ee from the tetrahydroisoquinoline **23** through the diastereoselective alkylation of amides derived from gulonic acid.

4.3.2. Enantioselective protonation of metallated tetrahydroisoquinoline derivatives. Recently, Simpkins et al. disclosed another interesting and complementary strategy toward chiral salsolidine (Scheme 17), involving the enantioselective protonation of metallated tetrahydroisoquinoline derivatives.[50] Thus, metallation of *N*-pivaloyl salsolidine **21b** with the *t*-BuLi–TMEDA complex at −40 °C in the presence of **81**, a chiral amine derived from α-phenethylamine provided 94% of *N*-pivaloyl-(*S*)-salsolidine (*S*)-**21b** in 86% ee, an enantiomeric excess,



Scheme 18.

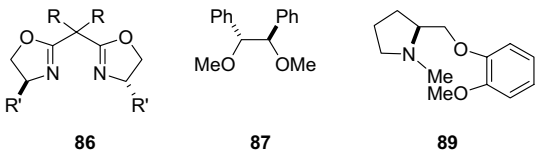
which was raised to 96% upon crystallization from petroleum ether. Reductive deprotection of the *N*-pivaloyl moiety with sodium aluminum hydride afforded (−)-**1** in 76% yield. The asymmetric reactions of organolithium reagents under control of chiral ligands have recently been reviewed.[105]

4.4. Alkylation of azomethines

4.4.1. Enantioselective alkylation of azomethines in the presence of chiral auxiliaries. The asymmetric addition of carbon nucleophiles to prochiral carbonyls in the presence of an optically active catalyst is nowadays an established synthetic process; the analogous catalytic, asymmetric, 1,2-addition of carbon nucleophiles to prochiral imines in order to produce enantiomerically enriched secondary amines has only recently been investigated. Results of these extensive studies and progress in this area have been described in several review articles.[106a–d] Compared to the 1,2-addition to the carbonyl group, this transformation is somewhat limited by the poor nucleophilicity of the azomethine carbon atom; however, the reaction can be considerably accelerated by activation of the azomethine moiety employing chiral catalysts or chiral ligands added to the reaction medium, to form chiral organometallic intermediates. With regard to the enantioenriched synthesis of salsolidine, variations of this theme have been extensively explored by a group of Polish researchers.

Four main types of catalysts have been reported for the asymmetric addition of organolithium reagents to imines: oxazolines such as **86**, chiral dimethyl dihydroxybenzoin **87**, (−)-sparteine **88**, and aminoacid **89** (phenylalanine, proline) derivatives. Some of them are shown in Figure 13.[106e–g]

In one study, Rozwadowska et al. tested the effectiveness of chiral ligands **91** bearing oxazoline rings, for the

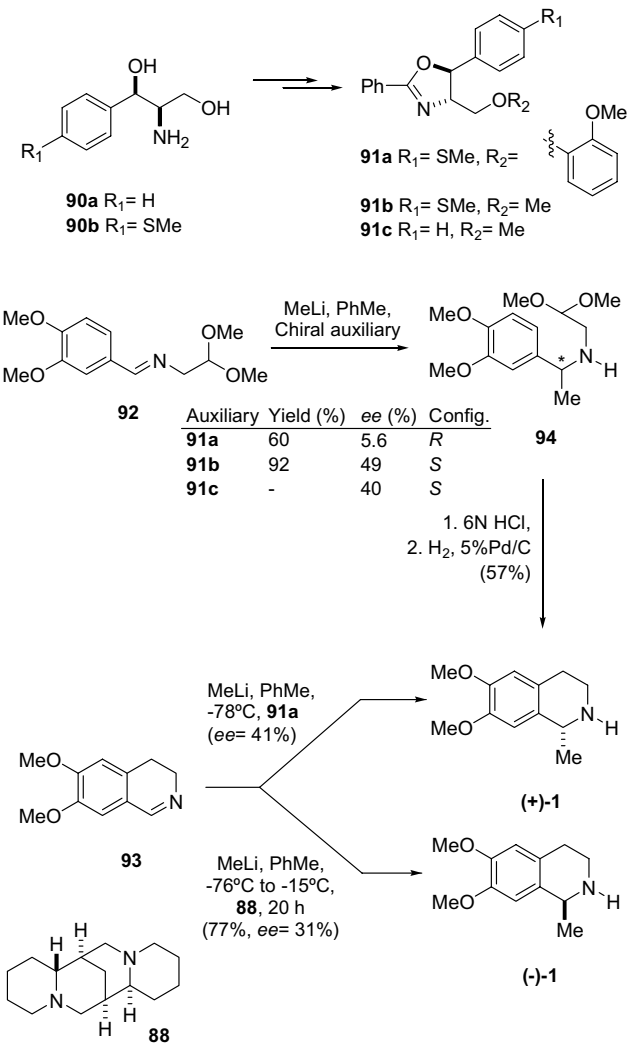


86 **87** **89**

Figure 13.

asymmetric addition of organometallic reagents to prochiral imines such as the Schiff base **92** and 3,4-dihydroisoquinoline **93**, which is readily accessible through the Bischler–Napieralski protocol.[8,108] These chiral oxazolines are readily available from (+)-thiomicamine **90b**, a synthetic industrial waste product.

In the former case (Scheme 19), their development provided a new example of a Kametani's type 5 approach to isoquinoline synthesis and is one of the few available examples of a stereochemical modification (compare with that of Scheme 5) of the Pomerantz–Fritsch–Bobbitt cyclization[51] resulting in a chiral nonracemic isoquinoline alkaloid.



Scheme 19.

Unfortunately, the stereochemical result of the additions which are controlled by the oxazolines **91** added as external ligands,[109] was not as satisfactory as might have been expected with a ligand incorporating two structural fragments capable of a high degree of asymmetric induction. Enantiomeric excesses were rather low; 41% for (*R*)-salsolidine from **93** and 5.6% for its acetalic precursor **94** from **92** were achieved when using the guaiacoyl derivative **91a**, being the additions best carried out in toluene, a noncoordinating solvent.

Interestingly, further studies with related catalysts, such as **91b** ($R_1 = SMe$, $R_2 = Me$) and commercially available **91c** ($R_1 = H$, $R_2 = Me$) derived from **90a**, improved the ee of the products from additions to iminoacetal **92** to 49% and 40%, respectively; however, the opposite enantiomer (*S*)-**94** was formed, from which (−)-**1** and the related *N*-methyl derivative (*S*)-**7** were synthesized with no loss of stereochemical integrity.[110]

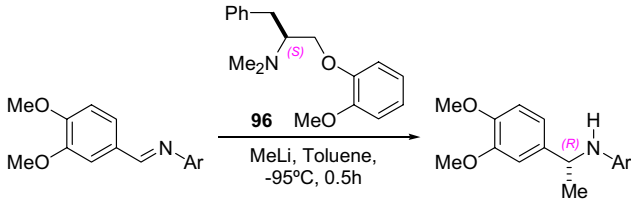
In this, like in the following cases employing the same methodology, no covalently bound chiral auxiliary was involved in the creation of the C-1 center. The stereochemistry of the different products was established by NMR experiments recorded in the presence of TADDOL, and by HPLC with a chiral column. The divergence in the steric course of the additions to **92** in the presence of **91a** and **91b** is probably associated with the number of complexing sites in the two types of structurally related oxazolines.[85] While **91a** is a tridentate ligand, in the other analogue only two donor atoms are available.[109,111]

An interesting differential characteristic of the syntheses of salsolidine starting from precursors such as **92** and **93** is that the stereogenic center is established at an early stage of the synthesis in the former case, while in the latter, it constitutes the last transformation of the synthetic sequence.

More recently, the analogous methyllithium addition reaction to 3,4-dihydroisoquinoline **93** in the presence of the lupine alkaloid (−)-sparteine **88**, an inexpensive and commercially available chiral diamine, was also reported.[112a] This furnished 77% of (*S*)-salsolidine in only 31% ee, when the reaction was run in toluene for 30 h with 1 equiv of the chiral auxiliary (Scheme 19). The authors showed that the use of sub-stoichiometric amounts of the chiral auxiliary or running the reaction at −20 °C for 2 h had adverse effects on the enantiomeric excess of the resulting product.

The enantioselective addition of organolithium reagents to isoquinoline in the presence of (−)-sparteine has also been recorded. Use of MeLi led to 1-methyl-1,2-dihydroisoquinoline in an enantiomeric excess of 57%.[113] Employing an analogous strategy,[107] Tomioka et al. studied the enantioselective addition of organolithium reagents to different *N*-aryl azomethines **95** in the presence of stoichiometric amounts of chiral ligand **96** derived from phenylalanine. The results, collected in Table 8, show high chemical yields and enantiomeric excesses of the resulting secondary amines **97**, revealing that

Table 8. Enantioselective addition of MeLi to *N*-aryl-azomethines **95** in the presence of chiral ligand **96**



95 **97**

Entry no	Ar	Yield (%)	Ee (%)[a]
1	4-MeOPh	99	78
2	4-Me_2NPh	99	88
3	4-ClNaph	95	73
4	1-Naph	99 (71)[b]	94 (>99)[b]
5	4-Me_2Nnaph	99 (74)[b]	97 (>99)[b]
6	4-MeONaph	97	97

[a] Product configuration was always *R*.
[b] After recrystallization.

lowering the electrophilicity from the imine gives rise to higher enantioselectivities, probably due to the formation of a tight, three component complex between the imine, MeLi, and ligand **96**.

Interestingly, essentially racemic salsolidine was obtained when the addition was carried out in THF with very low enantiomeric excesses being recorded when it was run in other ether solvents; furthermore, it was observed that better results were obtained when the transformation was carried out with acyclic imines.[112b]

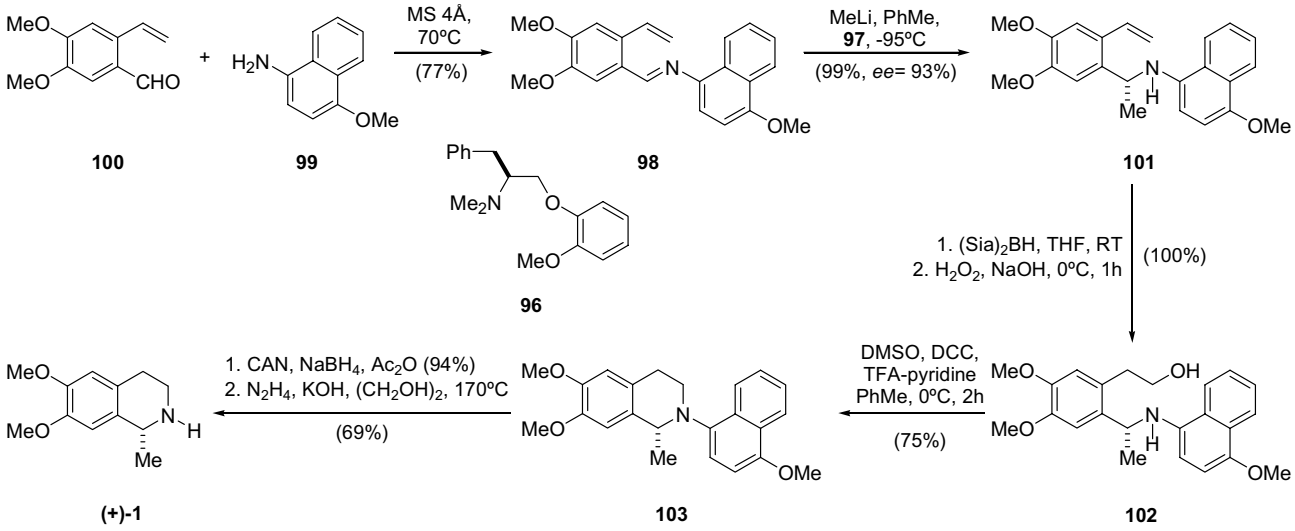
By employing this strategy, a facile asymmetric synthesis of (+)-**1** involving this highly efficient asymmetric addition of methyl lithium to the *N*-naphthaleneimine **98**, derived from naphthylamine **99** and styryl aldehyde **100**, in toluene at −95 °C was developed; interestingly, this constitutes one of the infrequent examples of Kametani's type 3 isoquinoline synthesis (Scheme 20).[114]

Chemical yields and enantiomeric excesses of the key step were 99% and 93%, respectively, when a stoichiometric amount of chiral ligand **96** was employed. Hydroboration–oxidation of the resulting **101** was followed by oxidative ring closure of the aminoalcohol **102**, yielding *N*-naphthyl tetrahydroisoquinoline **103** in good yield. Removal of the naphthyl group in **103** was carried out by oxidative treatment with ceric ammonium nitrate (CAN) in the presence of acetic anhydride and sodium borohydride, to reduce the resulting quinone to the corresponding diphenol and trapping of the latter, thus avoiding its back oxidation to the quinone.

A catalytic cycle for this type of catalyst has been proposed by Tomioka et al.[114c] The outcome of the addition is a weighted sum of simultaneously occurring catalytic and noncatalytic reactions; in nonpolar, noncoordinating hydrocarbon solvents, the formation of a reactive chiral ligand–organolithium complex would favorably compete with the noncatalyzed reaction. Interestingly, imine **92** is essentially unreactive toward MeLi in the absence of the chiral ligand, underscoring the importance, and catalytic activity of the latter.[110]

The use of the sulfoxide functionality to induce diastereoselectivity has been the focus of many research endeavors, including some in the field of simple isoquinoline synthesis.[115a,b] Addition of optically active (*R*)-(+)- and (*S*)-(−)-methyl *p*-tolyl sulfoxides to 3,4-dihydro-isoquinoline *N*-oxides, as activated azomethines, has been studied to some extent, by employing the resulting tetrahydroisoquinolines to more complex isoquinoline alkaloid syntheses.

Addition of optically active sulfinyl carbanion **104** to nitrone **105**, easily accessible from **23**,[100] provided β-sulfinyl hydroxylamine **106** as key intermediate for the elaboration of (*R*)-salsolidine.[115c] For optimal performance, it was noted that the transformation required the addition of a chiral auxiliary; in fact, while under conditions employed for asymmetric addition to



Scheme 20.

aliphatic nitrones a 64:36 (*R*/*S*) ratio of hydroxylamines was obtained, the incorporation of the lithium salt of quinidine **107** improved the diastereomeric ratio to 92:8.

Further improvements in enantiomeric excess were realized by recrystallization. Finally, reduction of the β-sulfinyl hydroxylamine with W-2 Raney nickel efficiently produced (+)-**1**. The higher diastereoselectivity obtained with the addition of the chiral auxiliary was ascribed to the formation of a facial discriminating organometallic reagent derived from quinidine and the α-sulfinyl carbanion **104**, as illustrated in Scheme 21.

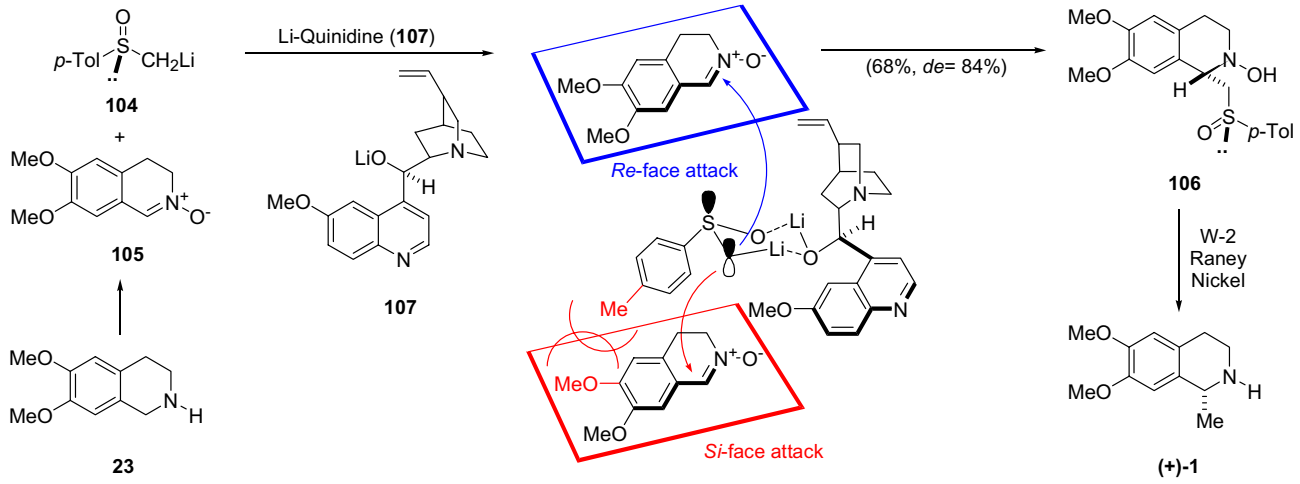
An analogous approach was taken by Ukaji et al.[116] who reported the enantioselective elaboration of (+)-**1** in 84–96% yield and 50–63% ee by asymmetric addition of dimethyl zinc to nitrone **105** in the presence of **109**, the bromomagnesium derivative of (2*S*,3*R*)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butoxide **108** (Chirald®) and 0.3 equiv of bromo magnesium triphenylmethoxide **110**, which proved to be crucial in order to achieve a higher stereoselection (Scheme 22). In the absence of **110**, chemical yields of *N*-hydroxy-salsolidine (*R*)-**68** were 96% and 91% after 17 and 19 h of reaction, while ee's were 50% and 57%, respectively. The cycle involving **105**, **109** and **110**, which promoted the final conversion of the former into (*R*)-**69** through the intermediacy of **111**–**113**, is depicted in Scheme 22.

The exact mechanism of this transformation is unknown; however, it was proposed that the dialkylzinc reacts with the nitrone coordinated to the magnesium alkoxide of **108**, from the less hindered *re* face to afford the intermediate **112**, which in the presence of **110** smoothly regenerates the chiral ligand **109** and furnishes **113**. In turn, **113** releases alkoxide **110**, accompanied with the production of **114**, a precursor of *R*-**68**, which is reduced to (+)-**1** with zinc in refluxing aqueous HCl, furnishing the natural product in 92% yield. In a more recent communication,[116c] the same group disclosed a complementary, quite simplified, and substantially improved strategy, showing an alternative access to the (*S*)-salsolidine enantiomer (−)-**1** through the catalytic asymmetric addition of dimethylzinc to nitrone **105**, employing alkoxides derived from tartaric acid esters, such as **115**, as chiral auxiliaries (Scheme 23).

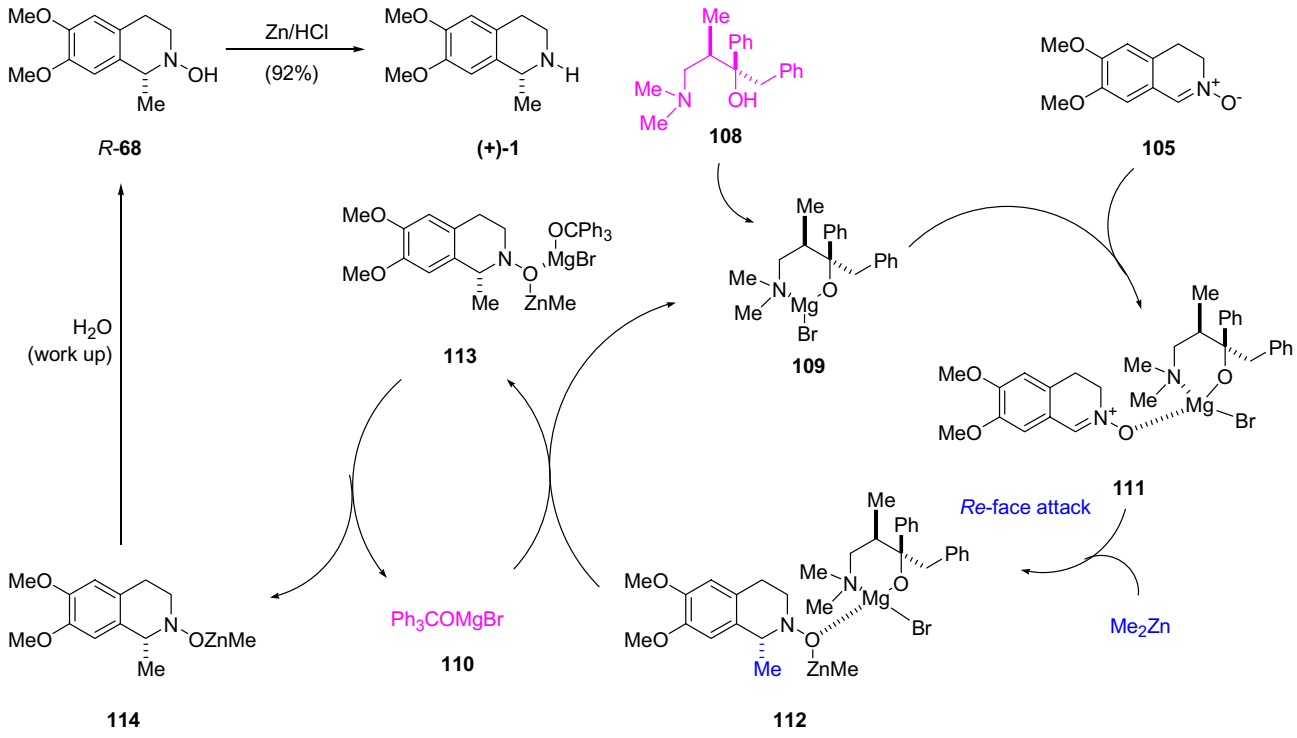
In the presence of 0.2 M amount of chiral alkoxide **115** and 2.8 equiv of Me_2Zn, this gave the intermediate (*S*)-**68**, in 89% yield and 64% ee, which was conveniently reduced to the natural product as before. With both enantiomers of tartaric acid being easily available, this method is stereochemically flexible, providing a useful way for preparing both enantiomers of salsolidine, as well as those of other 1-substituted tetrahydroisoquinolines in their enantioenriched forms.

Moreover, employing (*R*,*R*)-dicyclopentyl tartrate, model reactions evidenced a dialkylzinc concentration-dependent reversal of the enantiofacial selection. In systems with up to 1.0 M amounts of added dialkylzinc, the (*R*)-enantiomer of the product was predominant. However, when more than 2.0 M amounts of the dialkylzinc reagent were added, the prevailing species was the (*S*)-enantiomer, suggesting the participation of different species in the delivery of the alkyl group to the activated azomethine.

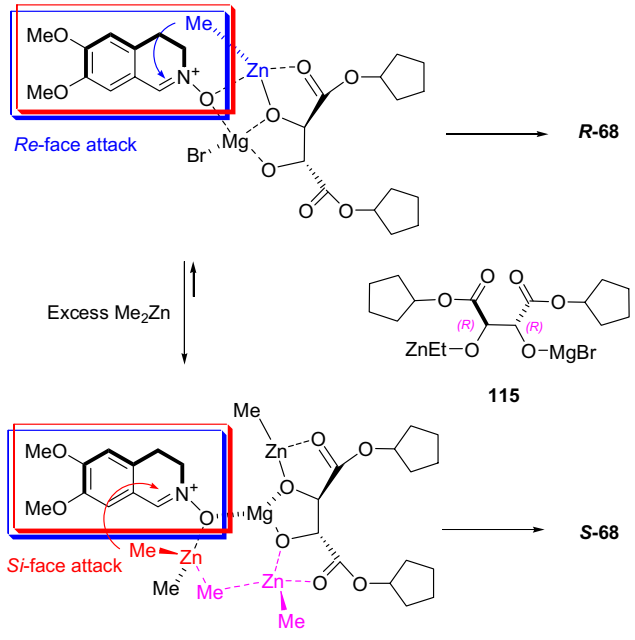
4.4.2. Diastereoselective alkylation of chiral activated azomethines (chiral iminium ions). Polniaszek et al.[74] studied the diastereoselective addition of organometallic reagents to chiral iminium ions derived from substituted α-phenethylamines, as a complement to their previous work on the elaboration of 1-substituted optically active tetrahydroisoquinolines by hydride-mediated reduction of chiral iminium ions.[75] As shown in Scheme 24, elaboration of the required starting materials **117a**–**c** was straightforward, employing a Bischler–Napieralski type closure of chiral secondary amides **116a**–**c** with $POCl_3$; in turn, **116a**–**c** were accessed by amidation of optically active secondary amines **46a**–**c** with formyl pivaloyl anhydride.



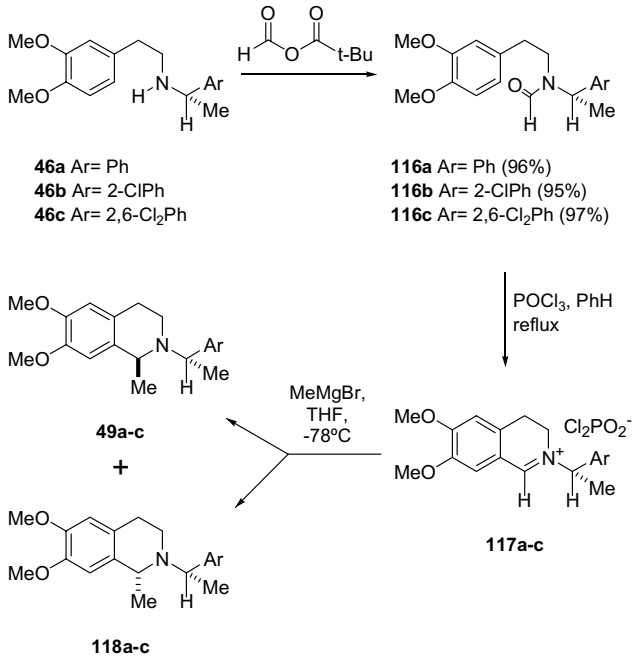
Scheme 21.



Scheme 22.



Scheme 23.



Scheme 24.

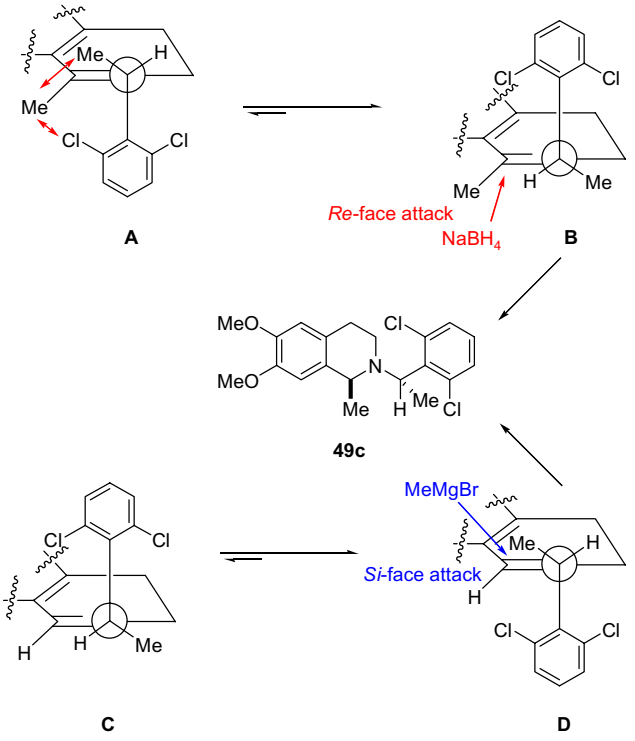
Table 9 compares the results of the addition of MeMgBr to iminium ions **117a**–**c**. In all cases the diastereomer bearing the (1*S*)-stereochemistry **49a**–**c** was found to be the major one. The chiral auxiliary was easily removed by hydrogenolysis with Pd/C in 10% HCl–EtOH, leading to the tetrahydroisoquinoline product.

These authors rationalized the outcome of their diastereoselective hydride reduction of iminium ions and their diastereoselective Grignard addition to activated chiral azomethines, which represent efficient examples of 1,3-asymmetric induction, as shown in Scheme 25.

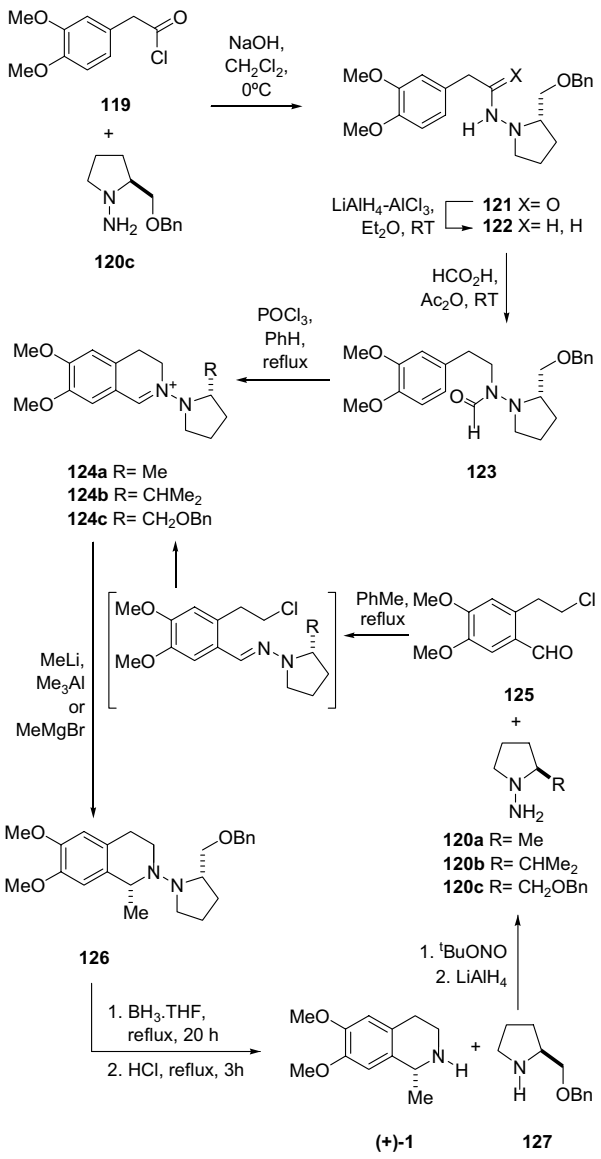
Relative stabilities of the different conformers of **48c** (**A** and **B**) and **117c** (**C** and **D**) were calculated, observing that **B** was more stable than **A** and **D** more stable

Table 9. Addition of MeMgBr to chiral iminium ions **117a–c**

Entry no	Ar	Substrate	**49/118** (De)	Yield (%)
1	Ph	**117a**	58:42 (4)	82
2	2-ClPh	**117b**	54:46 (8)	84
3	2,6-Cl_2Ph	**117c**	85:15 (60)	89



Scheme 25.

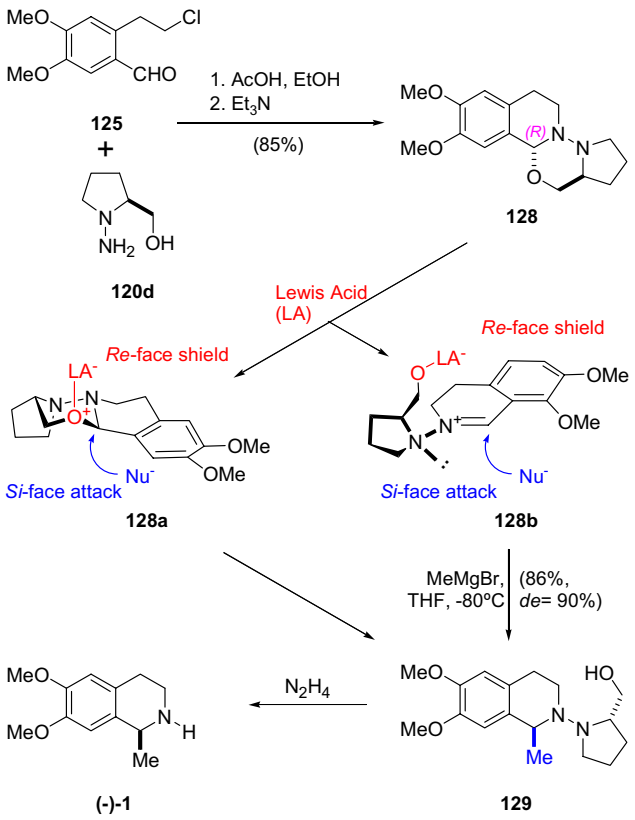


Scheme 26.

than **C**. It was concluded that the structure of the transition state of these addition reactions appeared to resemble the geometry derived from nucleophilic attack on the least hindered face of the more stable reactive conformation of each substrate, where nonbonded repulsions and other strain factors are minimized.

Efficient asymmetric induction also resulted from the diastereoselective addition of carbon nucleophiles to chiral hydrazonium ions, which correspond to a class of activated azomethines, in a methodology developed and exploited by Kibayashi et al.[117] The required hydrazonium derivatives **124a–c** were accessed either by the condensation of the chiral auxiliaries **120a–c** with chloroaldehyde **125** followed by an in situ cyclization of the open iminohydrazine intermediates or by the Bischler–Napieralski cyclization of formyl derivative **123**, easily available in three steps from the acid chloride **119** and hydrazine **120c**, through the intermediacy of hydrazide **121** and its reduction product, the hydrazine **122**. MeLi and MeMgBr were employed as sources of the required carbon nucleophile, providing the addition products in chemical and optical yields in the ranges 71–89% and 88–94%, respectively (Scheme 26). When Me_3Al was employed, 90% ee of **126** was realized; however, the yield dropped to 24%.

The higher levels of diastereoselectivity observed were ascribed to steric control provided by the 2-substituted pyrrolidine moieties, which served as chiral auxiliaries. In this sequence, these were removed in a two-stage process comprising of reductive cleavage and hydrolysis, by sequential treatment with BH_3·THF and refluxing HCl; This allowed the recovery of valuable intermediates **127**, which could be recycled via *N*-nitrosation and reduction,[77] along with the isolation of (+)-**1**. In the further development of their synthetic approach to 1-substituted tetrahydroisoquinolines employing chiral hydrazonium ions, the same Japanese group provided an alternate pathway for generating the chiral hydrazonium ions and a stereochemically complementary route to salsolidine, based on the Lewis acids-assisted preferential cleavage of the C–O bond in cyclic N,O-acetals (Scheme 27).



Scheme 27.

In the context of this strategy, N,O-acetals can be regarded as masked activated azomethine species. The resulting iminium ions produced by treatment with Lewis acids have been extensively employed for the generation of new carbon–carbon bonds;[118a] the reported synthetic sequence preferentially leds to (−)-**1**, the opposite enantiomer of the salsolidine accessed through the hydrazonium-based protocol displayed in Scheme 26.[118b]

When this strategy was applied to 1,3,4-oxadiazine **128**, conveniently synthesized in 85% yield from chloroaldehyde **125** and the proline-derived chiral auxiliary **120d**, 86% yield of the (*S*)-salsolidine derivative **129** was obtained, in 90% de. The reverse stereochemical results observed in the Grignard–Lewis acid combination were explained as being a consequence of S_N1 type attack of the nucleophile to the more exposed *si* face of the hydrazonium ion **128**, as in **128b**. These results are also in agreement with a direct nucleophilic displacement (S_N2) on the Lewis acid–ether complex of **128**, as depicted in **128a**.

In a new variation of this strategy, the authors disclosed an alkylation, which occurs with Me_3Al and displays concentration-dependent reversal of stereochemistry of the stereogenic center. This was based on the observation that, while the addition of MeMgBr in THF at 0 °C to a model 1,3,4-oxadiazine gave rise to a diastereomeric mixture of tetrahydroisoquinolines (61:39) in 68% yield, in the presence of 1.1 equiv of Me_3Al, the diastereomeric ratio of products changed to 19:81 (81% yield), favoring the formation of the opposite diastereomer.

As depicted in Figure 14, cleavage of the N,O-acetal with the organoaluminum reagent leads to the formation of a tight ion pair between the aluminum ate complex and the hydrazonium ion. If the proportion of Me_3Al was low (1.1 equiv of Me_3Al are used), intramolecular delivery of the methyl group from the *re*-face produced the (*R*)-enantiomer; in case an excess amount of Me_3Al being employed, shielding of the *re*-face preferentially produced the (*S*)-enantiomer through an intermolecular *si*-face attack, as also observed with organolithium and Grignard reagents in the presence of Et_2AlCl as Lewis acid.

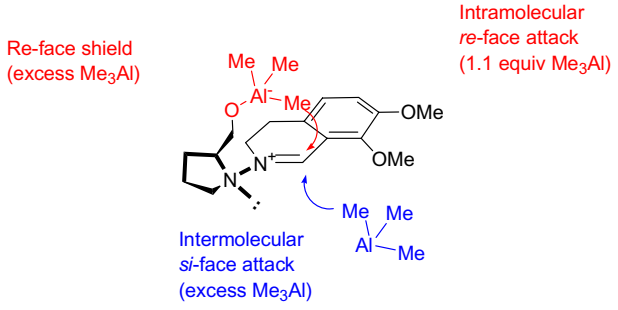


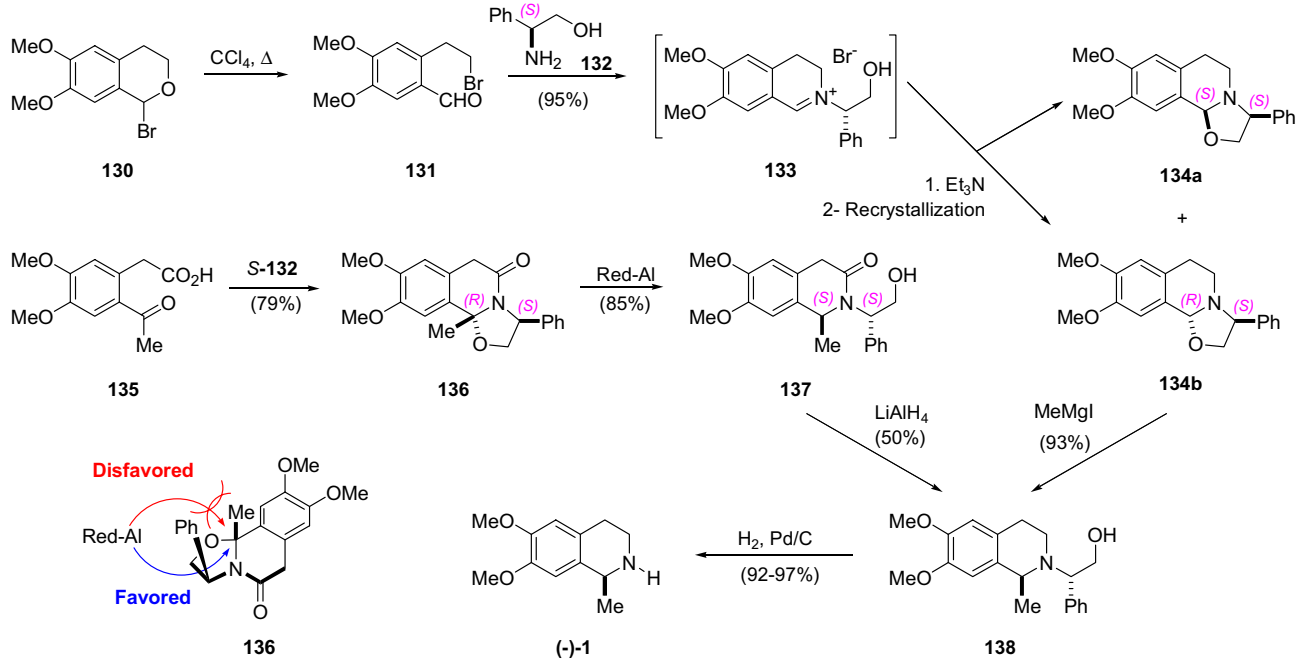
Figure 14.

The enantioselective addition of organometallic compounds to the structurally related chiral oxazolidines **134** as a synthesis of enantiomerically enriched amines has also been explored. Sometime before the results of Kibayashi et al. were published, Yamato et al.[119] synthesized highly selectively diastereomeric chiral oxazolo[2,3-*a*]tetrahydroisoquinolines **134a** and **134b** (de = 90%) by base-assisted intramolecular cyclization of the 3,4-dihydro-isoquinolinium salts **133** derived from (*S*)-phenylglycinol (*S*)-**132** and 1-bromoisochromane **130**, through the condensation of the chiral auxiliary with **131**, the open form of the isochromane.

Upon purification of the major diastereomer **134b** from the 19:1 mixture of tricyclic intermediates, followed by a ring opening of the oxazolidine ring by asymmetric methylation with MeMgI, compound **138** was obtained in 93% yield (Scheme 28).

Removal of the *N*-benzyl moiety was appropriately and efficiently carried out with Pd/C in acidic EtOH, furnishing (−)-**1**. Both enantiomers of the chiral alcohol **132** were submitted to the same sequence of transformations, leading to both enantiomers of salsolidine. In this process, (*S*)-phenylglycinol (*S*)-**132** afforded the (1*S*)-enantiomer of the natural product.

A related chiral oxazolo[2,3-*a*]tetrahydroisoquinoline was also elaborated by Meyers et al.[120] in their most recent enantioselective synthesis of salsolidine, employing *S*-phenylglycinol (*S*)-**132** as the source of chirality.



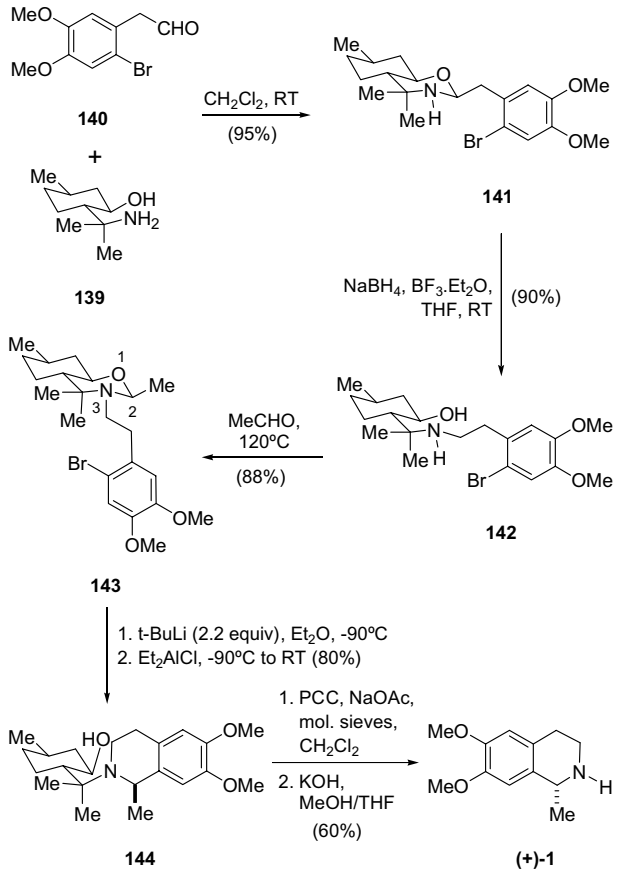
Scheme 28.

As shown in Scheme 28, condensation of phenylacetic acid derivative **135** with (*S*)-**132** afforded tricyclic lactam **136** as a 94:6 separable mixture of diastereomers. Diastereoselective reductive opening of the oxazolidine moiety of **136** with red-Al, followed by lithium aluminum hydride deoxygenation of the resulting lactam **137** in 50% yield and hydrogenolytic removal of the *N*-benzyl moiety of the thus produced **138**, provided (−)-**1** in good overall yield.

Another somewhat related synthesis of salsolidine, leading to the (*R*)-enantiomer involving a diastereoselective ring opening of the N,O-acetal moiety has recently been reported by a Spanish team, and is shown in Scheme 29.[121a] Their strategy consisted of an intramolecular attack of an appropriately substituted aryllithium species to a chiral 1,3-perhydrobenzoxazine derived from (−)-8-aminomenthol **139**.

In this synthetic design, the aryl group is attached to the nitrogen of the N,O-acetal through an ethylene tether. The elaboration of the synthetic intermediate was a straightforward condensation of the polysubstituted phenylacetaldehyde **140** with the chiral auxiliary, followed by reduction of the intermediate N,O-acetal **141** to amine **142**, which was transformed into 1,3-perhydrobenzoxazine **143** via treatment with acetaldehyde at 120 °C in a sealed tube.

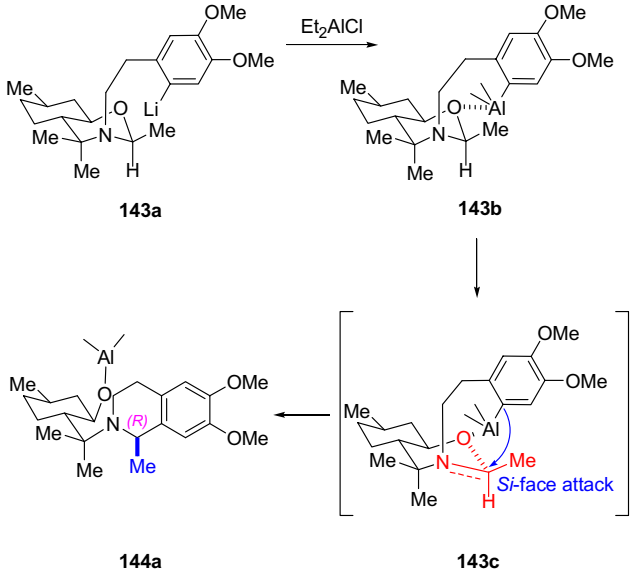
The heterocyclic ring of the tetrahydroisoquinoline **144** was created by intramolecular nucleophilic attack of the aryl metal (formed by low temperature lithium–halogen exchange and transmetallation with diethylaluminum chloride) to C-2 of the N,O-heterocycle, while the stereochemistry and nature of the C-1 substituent in the final product were determined beforehand by the stereochemical outcome of the reaction leading to the



Scheme 29.

starting perhydrobenzoxazine **143**.[121b] The sequence was completed by a retro-Michael process following the PCC-mediated oxidation of chiral alcohol **144**.

The key role of diethylaluminum chloride in the process leading to **144** is explained as shown in Scheme 30. The stereochemical outcome of the intramolecular ring opening of the 1,3-perhydrobenzoxazine is similar to previous findings; the stereodiscrimination is better for organoaluminum derivatives than for their organolithium counterparts because of their comparative greater nucleophilic character.

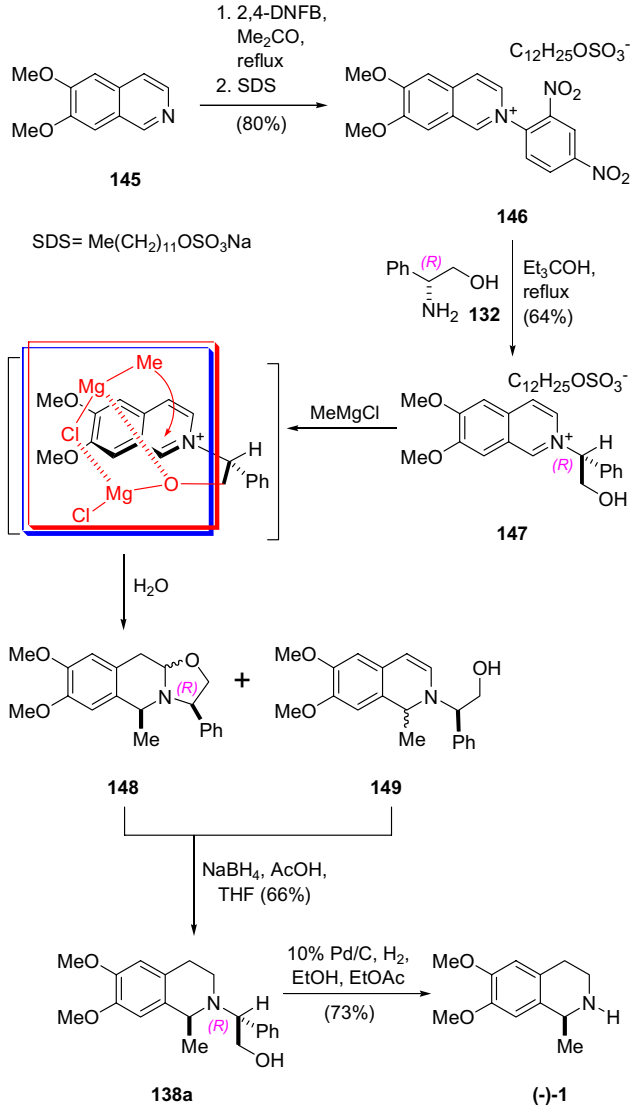


Scheme 30.

Thus, during the reaction, the lithiated intermediate **143a** formed by lithium–halogen exchange of **143** with *tert*-butyl lithium is transformed into the organoaluminum intermediate **143b** via transmetallation with Et_2AlCl; intramolecular transfer of the aryl group to the *si* face of the incipient iminium ion from the aluminum atom while it is still complexed to the oxygen **143b** or by synchronous intramolecular arylation in the early transition state **143c**, would furnish the aluminum species **144a**, which in turn would be transformed into **144** during the work-up.

Optically active isoquinolinium salts are another variety of chiral activated azomethines; these can be practically accessed by a Zincke reaction between chiral primary amines, such as (*R*)-**132**, and *N*-2,4-dinitrophenyl isoquinolinium salts. Potier et al.[122] recently devised a synthesis of salsolidine, which is chirally complementary to those reported by Meyers et al.[120] and Kibayashi et al.[117] The Potier synthesis started with chiral salt **147** (Scheme 31), available from isoquinoline **145** through dinitrophenylisoquinolinium derivative **146**, by the reaction of the latter with (*R*)-phenylglycinol (*R*)-**132**.

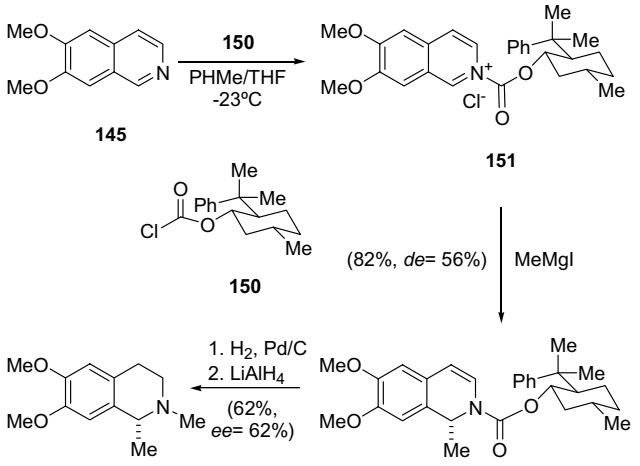
Formally, this sequence can be regarded as the chiral version of Rozwadowska et al. synthesis of salsolidine with a Reissert compound as the key intermediate[43] (vide supra), and is somehow reminiscent of it. Upon



Scheme 31.

reaction with a methyl Grignard reagent, a mixture of the expected 1,2-dihydroisoquinoline **149** (undefined stereochemistry, 20%) and the diastereomeric tetrahydro-10*aH*-oxazolo[2,3-*b*]isoquinolines **148** (80%, 1:1 mixture) was obtained in combined 79% yield. Without separation, these isoquinoline derivatives were reduced in 66% with acidic sodium borohydride to **138a**, the side chain diastereomer of **138** (Scheme 28).

A mixture of diastereomers was produced in a diastereomeric excess of 60%; alternatively, however, chromatographic isolation of **148** in 45% yield followed by catalytic hydrogenation with palladium on carbon, provided (−)-**1** in 38% overall yield from **146** and in much better enantiomeric excess. A somewhat analogous series of transformations was reported by Comins and Badawi in their diastereoselective synthesis of (*R*)-carnegine (Scheme 32).[123] With minor modifications, this sequence could be easily adapted for the enantioselective elaboration of salsolidine.



Scheme 32.

Asymmetric addition of methylmagnesium iodide to 6,7-dimethoxyisoquinoline **145** in the presence of (−)-8-phenylmenthyl chloroformate **150** provided 82% yield of a 78:22 mixture of diastereomeric 1,2-dihydroisoquinolines, in favor of the (1*R*)-diastereomer **152**, probably through the intermediacy of the chiral isoquinolinium salt **151**. Carrying the reaction at −78 °C improved the diastereomeric ratio to 83:17, but caused the chemical yield to be reduced to only 26%. When catalytic hydrogenation of the double bond, followed by the lithium aluminum hydride reduction of the carbamate moiety were carried out, the natural product (*R*)-**7** was accessed in 62% yield and 62% ee.

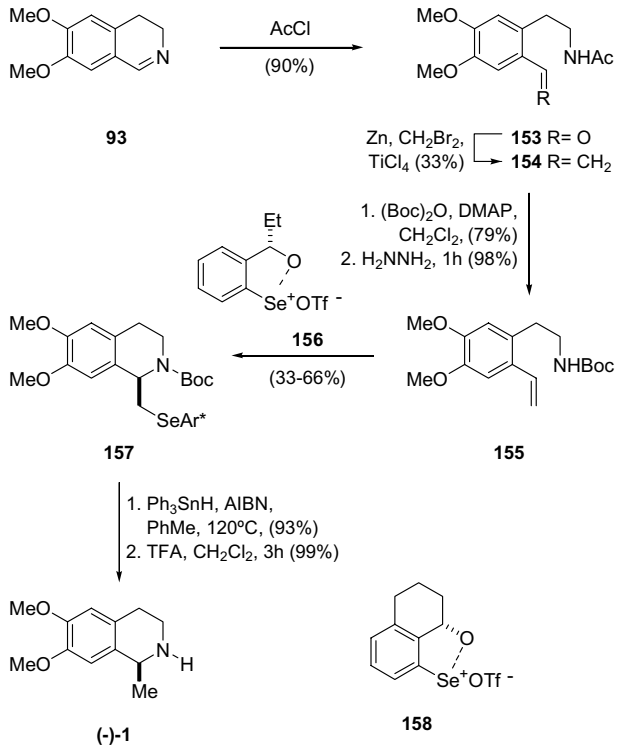
The syntheses of Comins and Badawi, and Potier et al., based on the addition of organometallic reagents to isoquinolinium ions to afford 1,2-dihydroisoquinoline derivatives are complemented by that of Alexakis and Amiot,[113] in which organometallic reagents are allowed to react enantioselectively with isoquinolines in the presence of natural sparteine **88** to yield enantioenriched 1,2-dihydroisoquinolines.

4.5. Syntheses employing organochalcogen derivatives

The involvement of several sulfur species as intermediates during the synthesis of (±)-salsolidine has already been discussed with a synthesis of (+)-salsolidine employing *p*-tolylmethyl sulfinyl carbanion shown in Scheme 21 (vide supra). On the other hand, use of a chiral acetylenic sulfoxide as a two-carbon synthon, leading to 1-arylsulfinyl methyl tetrahydroisoquinolines by way of the related β-aminovinyl sulfoxide has been reported as a strategy for the elaboration of (*R*)-(+)-*N*-methyl salsolidine (*R*)-**7**.[115a,124]

Chiral aryl selenium reagents have been designed for the enantioselective electrophilic addition to C=C double bonds in methanolic medium, resulting in methoxy-selenenylated products in fair to good yield and diastereoselectivities up to 93%.

An intramolecular diastereoselective aminoselenenylation reaction[125] involving these kinds of reagents has been disclosed as a key step in a synthesis of (*S*)-salsolidine from dihydroisoquinoline **93**, as shown in Scheme 33. The substrate for the aminoselenenylation process was acquired in three steps from **93** by acylation to acetamido aldehyde **153** followed by olefination of the aldehyde with Lombardo's reagent (Zn/CH_2Br_2), furnishing **154**, and a protective group change via reaction with Boc anhydride and hydrazinolysis of the acetyl group to yield **155**.



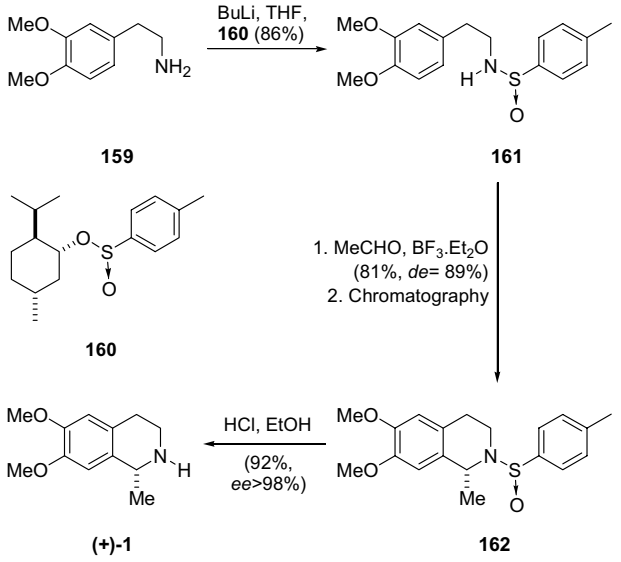
Scheme 33.

With the aid of reagent **156**, 66% of cyclized material in 79% diastereomeric excess was obtained, while an improvement leading to 90% diastereomeric excess of arylselenide **157** in 40% yield from **155** was realized with the more rigid selenium derivative **158**, synthesized in two steps from the related optically active tetralol via *ortho* lithiation.

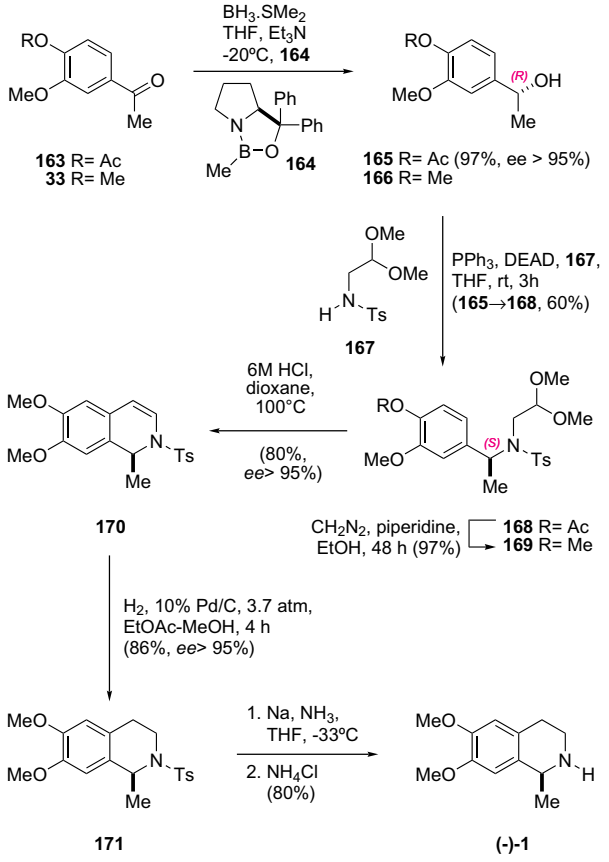
The protecting group change from acetamide to the related carbamate was introduced due to the poor nucleophilicity of the acetamido moiety; this somehow reduced the efficiency of the overall sequence. The arylselenium group was cleanly removed from **157** employing Ph_3SnH and AIBN, leaving (*S*)-Boc-salsolidine, the (*S*)-enantiomer of **21a**,[49a] which was deprotected with trifluoroacetic acid, furnishing (−)-**1**.

An alternative and interesting use of chiral sulfinyl groups for the elaboration of (*S*)-salsolidine has recently been described by Koomen et al.[126] They reported an

efficient variation of the activated Pictet–Spengler condensation, employing a *p*-tolyl sulfinyl group as a chiral inductor and activating moiety (Scheme 34). In their sequence, sulfinylamine **161** was prepared from (*S*)-Andersen's reagent **160** and 3,4-dimethoxy-β-phenethylamine **159** in 86% yield, and this condensed to the corresponding tetrahydroisoquinoline **162** in 81% yield and 89% de with acetaldehyde at −78 °C, under $BF_3{\cdot}Et_2O$ promotion.



Scheme 34.



Scheme 35.

Removal of the chiral auxiliary after chromatographic separation of the diastereomers proceeded without racemization upon treatment with ethanolic HCl at 0 °C, furnishing (*R*)-salsolidine in 92% yield, with an enantiomeric excess superior to 98%, as determined by ^{1}H NMR with (*R*)-1-(9-anthryl)-2,2,2-trifluorethanol as the chiral shift reagent. The (*S*)-enantiomer of the natural product was similarly accessed in 70% yield, employing the commercially available (*R*)-Andersen reagent.

Another example of the use of organochalcogen derivatives for the enantioselective elaboration of salsolidine was provided by Ponzo and Kaufman[127a] (Scheme 35). These researchers coupled chiral alcohol **165** to sulfonamidoacetal **167** through a Mitsunobu sulfonamidation process, which proceeded with complete inversion of configuration of the benzylic center. Acetate **163** derived from acetovanillone had to be used instead of acetophenone **33**, the more straightforward starting material, because the Mitsunobu sulfonamidation of the related alcohol **166** yielded partially racemized **169**.

Thus, an extra step for the transformation of **168** into **169** had to be introduced. Finally, sulfonamidoacetal **168** was cyclized in a refluxing dioxane–6 M HCl mixture and the resulting 1,2-dihydroisoquinoline **170** submitted to catalytic hydrogenation to **171**. Subsequent removal of the sulfonyl moiety via a reductive desulfonylation with sodium in liquid ammonia, as an alternative to photodetosylation[128] furnished (−)-**1** in >95% ee, as determined by ^{1}H NMR with chiral shift reagents. The enantioselective elaboration of **165** and **166** was accomplished through a CBS reduction with chiral oxazaborolidine **164**, a modern and highly improved version of Itsuno's catalyst, developed by Corey et al.[129] This strategy was also employed in the synthesis of other natural products.[127b]

In contrast to the pioneering results of Cho et al., which suggests that oxazaborolidines could hardly be employed for the elaboration of chiral 1-substituted tetrahydroisoquinolines, this strategy, which circumvents the need of a C=N reduction, oxazaborolidine **164** was successfully employed for the elaboration in the C-1 stereogenic center of a 1-substituted tetrahydroisoquinoline.

5. Conclusion

In conclusion, the numerous syntheses of salsolidine published during the last quarter of century are the result of the workings of the fertile minds of many synthetic organic chemists doing research worldwide, and their steady efforts for devising ingenious alternative solutions to this simple but common synthetic target.

They also show the way reactions, reagents, and strategies have been evolving from furnishing low-yield

transformations in their early stages of development, into becoming the key elements of successful and highly priced processes, which cleanly provide their product in high chemical and optical yields. Many of these outstanding and impressive results observed in the synthesis of salsolidine have accompanied the remarkable progress experienced by synthetic organic chemistry over the last 25 years.

A significant body of the group of efficient synthetic procedures, which have been explored and devised to accomplish some of the many syntheses of salsolidine have already found important applications in the development of other interesting targets, including natural products and useful therapeutic medicines, and agrochemicals. They also constitute a fundamental part of the basis for the development of new and more complex synthetic strategies or new synthetic tools, useful for conquering novel, and more demanding synthetic objectives.

The continuous research and discovery of even more practical and powerful hydrogenation catalysts, chiral Lewis acids, and chiral ligands, displaying more versatility and requiring lower catalyst loading, are still formidable challenges for the synthetic organic chemists community and currently constitute highly active areas of research. Therefore, it is expected that new, attractive and more efficient diastereo- and enantioselective syntheses of salsolidine will come to light in the near future.

Acknowledgements

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