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Sparteine Metal Complexes as Chiral Catalyst for Asymmetric Synthesis – A Review

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ABSTRACT

The commercial availability of (2)-sparteine reflects its easy isolation by extraction of papilionaceous plants such as Scotch broom (*Cytisus scoparius*). The aim of this review is to highlight recent advances in the field of asymmetric synthesis that use sparteine as chiral diamine ligand, emphasizing the use of sub-stoichiometric or catalytic amounts of this ligand. Lithium, palladium copper, cobalt, nickel, titanium and zinc chloride complexes with sparteine. It has found widespread use as a chiral ligand for asymmetric reactions. Asymmetric aldol reaction, Sonogashira-type reaction, Henry reaction, oxidative kinetic resolutions of secondary alcohols, Michael addition reaction, asymmetric aerobic oxidative, Wacker cyclization of allylphenol, deprotonation, Mukaiyama aldol reaction are the various asymmetric reactions often lead to highly enantioselective transformations biologically active molecules and natural products.

1. Introduction

Sparteine is a well-known alkaloid from the lupine family with a semirigid bisquinolizidine structure. This cage-like ligand and its isomers of sparteine have been extremely successfully previously used as chiral ligands for lithium in a wide range of enantioselective transformations [1]. However, in most of the reported applications, the reaction requires the use of a stoichiometric amount of chiral ligands [2]. Far fewer applications of sparteine as a chiral ligand to catalysis have been published. The aim of this review is to highlight recent advances in the field of asymmetric transformations that uses sparteine as chiral auxiliary, emphasizing the use of sub-stoichiometric or catalytic amounts of this ligand.

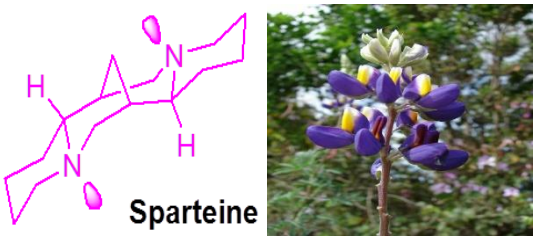


Fig. 1 Structure of Sparteine and its source *Cytisus scoparius*

Sparteine is an extremely useful chiral ligand for a wide range of asymmetric reactions. Its enantiomer, (-)-sparteine (Fig. 1), however, is not commercially available, and therefore the development of a chiral ligand that behaves as (-)-sparteine is of paramount importance. Total synthesis of (-)-sparteine was reported by Aube, but it required 15 steps starting from achiral ketone. Ring A of sparteine was not necessary, whereas rings B–D were essential for high selectivity. A (-)-sparteine surrogate could be prepared from commercially available (-)-cytisine in three steps, and showed approximately equal levels of enantio induction as that achieved with (-)-sparteine [3].

However, in most of the reported applications, the reaction requires the use of a stoichiometric amount of chiral ligands [4]. Far fewer applications of sparteine as a chiral ligand to catalysis have been published. The aim of this review is to highlight recent advances in the field of asymmetric transformations that uses sparteine as chiral auxiliary, emphasizing the use of sub stoichiometric or catalytic amounts of this ligand (Fig. 2) [5].

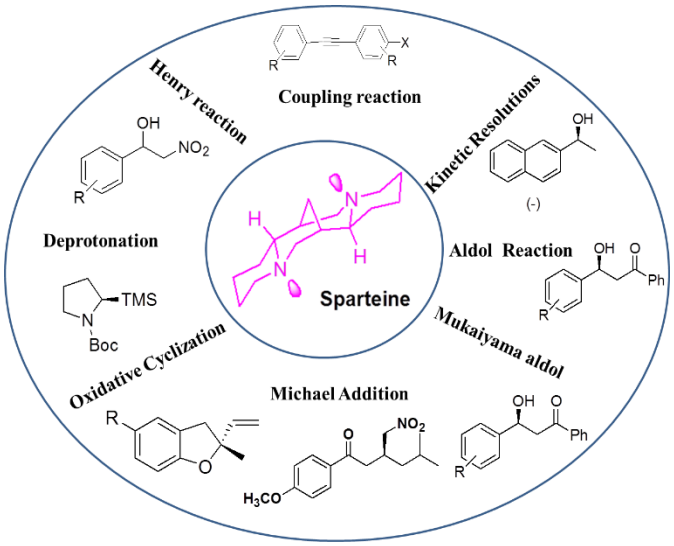
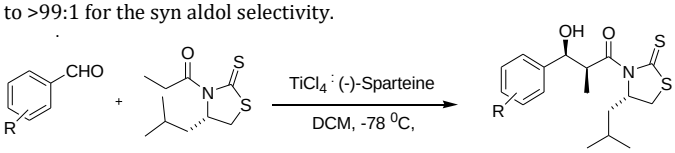


Fig. 2 Application of sparteine in various synthesis

2. Experimental Methods

2.1 Aldol Type Condensation Reaction

Titanium-catalysed aldol type condensation reaction used the Leucine based chiral auxiliary for asymmetric Aldol type condensation reaction [6]. The nature and amount of base is important in order to generated chlorotitanium enolate of thiazolidinethione propionates for which affords the product desired syn diastereoselective formation of the product (Scheme 1). The naturally occurring (−)-Sparteine was used as chiral base. The distereoselectivity was achieved lying in the range of 97:3 to >99:1 for the syn aldol selectivity.



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Scheme 1 Titanium-catalysed aldol type condensation reaction

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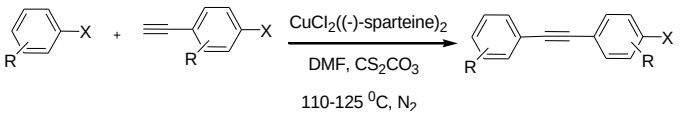
2.2 Sonogashira-Type Reaction

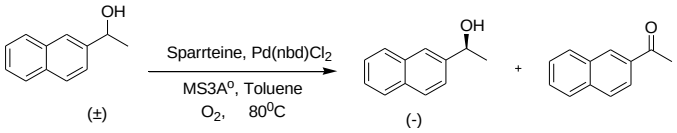
An efficient and cost-effective protocol for the Sonogashira-type cross coupling reactions of phenylacetylenes with a variety of haloarenes including activated aryl chlorides employing the structurally well-characterized bis(μ-iodo)bis((2)-sparteine)dicopper (I) catalyst is described [7]. Bis(μ-iodo)bis((2)-sparteine)dicopper(I) (I) is shown to be a versatile catalyst for Sonogashira-type cross coupling reactions of various phenylacetylenes with diverse aryl halides under palladium and phosphine-free reaction conditions (Scheme 2). This protocol is also applicable to activated aryl chloride substrates.



Scheme 2 Sonogashira-type cross coupling reaction with different aryl halides and alkynes

2.3 Oxidative Kinetic Resolutions of Secondary Alcohol

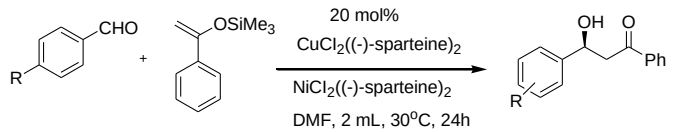
The chiral ligand (−)-sparteine and $PdCl_2$ catalyse the enantioselective oxidation of secondary alcohols to ketones and thus effect a kinetic resolution [8]. The structural features of sparteine that led to the selectivity observed in the reaction were not clear. Substitution experiments with pyridine derivatives and structural studies of the complexes generated were carried out on (sparteine) $PdCl_2$ that indicate the C1 symmetry of (−)-sparteine is essential to the location of substitution at the metal center. Palladium alkoxides were synthesized from secondary alcohols that are relevant steric models for the kinetic resolution (Scheme 3). The solid state structures of the alkoxides also confirmed the results from the pyridine derivative substitution studies. A model for enantioinduction was developed with C1 symmetry and Cl^- as key features. Further studies of the diastereomers of (−)-sparteine, (−)-α-isoand (+)-β-isosparteine in the kinetic resolution showed that these C2-symmetric counterparts are inferior ligands in this stereoselective reaction.



Scheme 3 Oxidative kinetic resolutions of secondary alcohol

2.4 Enantioselective Aldol Reactions

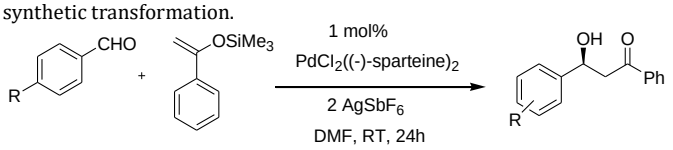
The use of structurally well-defined chiral [$CuCl_2$(sparteine)] and [$NiCl_2$(sparteine)] complexes as catalysts under fluoride anion-promoted double catalytic activation (DCA) conditions cause enantioreversal in the asymmetric Mukaiyama aldol reaction of 1-phenyl-1-trimethylsiloxyethylene with various aromatic aldehydes (Scheme 4) [9]. A similar enantioreversal also occurs in the direct aldol reaction between methyl vinyl ketone and various aromatic aldehydes under Et_3N promoted DCA conditions. Authors have quantitatively analyzed using group theoretical analysis via symmetry deformation coordinates, the molecular structures of catalyst 1 and 2 from the X-ray structural data; the results from the study show that the innate stereochemical differences that are present in their molecular structures form the basis for the enantio-reversal phenomenon in the asymmetric C–C bond-forming aldol reactions.



Scheme 4 Asymmetric mukaiyama aldol reaction of 1-phenyl-1-trimethylsiloxyethylene with various aromatic aldehydes

2.5 (-)-Sparteine) Palladium-Catalysed Enantioselective Aldol Reaction

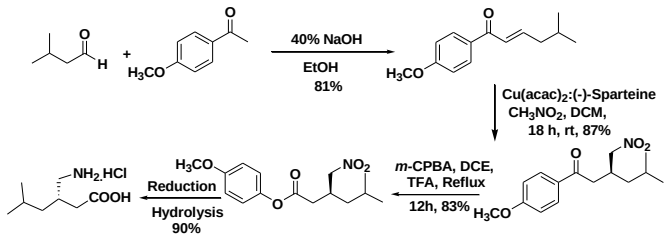
A dicationic (-)-sparteine) palladium complex demonstrated excellent catalytic performance in the enantioselective aldol reaction of aldehydes with 1-phenyl-1-trimethylsilyloxyethene. Starting with (-)-sparteine) PdCl2, the use of (-)-sparteine as a chiral bidentate ligand proved to be highly effective for achieving chiral dicationic palladium-catalyzed enantioselective aldol reactions (Scheme 5) [10]. This system exhibited satisfactory results, showcasing the utility of (-)- sparteine as a suitable chiral ligand for achieving high enantioselectivity in this important synthetic transformation.



Scheme 5 Enantioselective aldol reaction of aldehydes with 1-phenyl-1-trimethylsilyloxyethene

2.6 Cu(acac)₂:Sparteine as a Chiral ligand: Concise Synthesis of Anticonvulsant drug (S)-Pregabalin

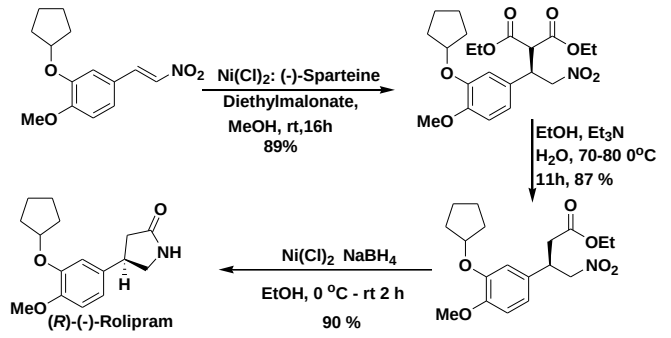
A series of transition Metals-Sparteine as chiral ligand were facilely synthesized and applied for enantioselective Michael addition of nitromethane on chalcones to provide corresponding γ-nitroketone with 88% yield (Scheme 6) [11]. The corresponding adducts were obtained in good yields (80-92%) under simple and clean condition. Herein, we report that asymmetric catalytic methodology for Michael reaction of nitromethane to chalcone. The chiral catalytic system consist of $Cu(acac)_2$ and (-)-sparteine as a naturally occurring chiral ligand. However, authors are demonstrating that the use of sparteine as chiral ligand for Michael addition of nitromethane on chalcone to provide γ-nitro ketone . Authors were also tried as assignment to expand the group of substrates in order to obtain valuable intermediate for synthesis of (S)-Pregabalin. Accordingly, they applied a novel route for synthesis of Anticonvulsant Drug (S)-Pregabalin



Scheme 6 Synthesis of (S)-pregabalin

2.7 NiCl2: Sparteine Catalysed Enantioselective Michael Addition and Concise Synthesis of (R)-Rolipram

An effective and convenient procedure for the asymmetric Michael addition by $NiCl_2$:Sparteine; (10 mol %) as an effective catalyst, catalyses the Michael addition reaction of diethyl malonate on β- nitrostyrene to produce corresponding γ- nitro ester derivatives with good yields (81-90 %) under simple and clean condition (Scheme 7) [12]. Accordingly, Authors applied this synthetic strategy for concise synthesis of (R)-Rolipram. $NiCl_2$:Sparteine novel catalytic methodology for asymmetric Michael addition of malonate esters to substituted β-nitrostyrene to provide good yield (81-90 %) and good enantioselectivity, $NiCl_2$:Sparteine which is readily accessible from commercially available material. This strategy succeeded in the total synthesis of (R)-Rolipram.



Scheme 7 $NiCl_2$: Sparteine catalysed enantioselective Michael addition and concise

2.8 Pd(II)-Catalysed Asymmetric Aerobic Oxidative Wacker Cyclization Of Allylphenol

The Stoltz laboratory has developed an enantioselective Pd(II)-catalysed oxidative phenol cyclisation in nonpolar organic solvents with molecular oxygen using (−)-sparteine as the chiral ligand [13]. Stoltz et al. demonstrated the use of a simple system (Pd catalyst, ligand, PhCH3, O2) for constructing a range of heterocycles by catalytic oxidative cyclization that could be incorporated into a Wacker cyclization. After having optimized their racemic procedure, the system provided a route to enantioselective catalysis using a readily available Pd-sparteine system

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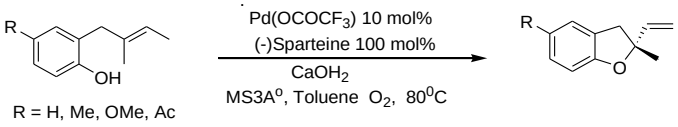
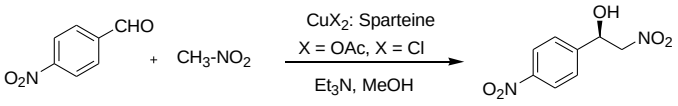
similar to that used in the previously reported enantioselective alcohol dehydrogenation. The best conditions were as follows: 10 mol% of Pd[(–)-sparteine]TFA_2, $Ca(OH)_2$ (2 equiv.), molecular sieves (3 Å), O_2(1 atm.), toluene at 80 °C (Scheme 8). Although the asymmetric results were somewhat limited in scope, the authors established for the first time that aerobic cyclizations of this kind can give high levels of enantioselectivity (57% yield, 90% ee).



Scheme 8 Pd(II)-catalysed asymmetric aerobic oxidative Wacker cyclization of allylphenol

2.9 Enantioselective Nitroaldol (Henry) Reaction using Copper(II) Complexes of (2)-Sparteine

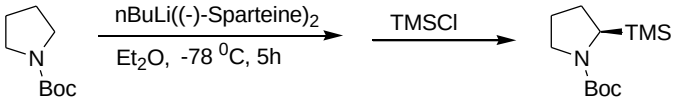
The synthesis of two copper(II) complexes of (2)-sparteine was conducted following a established procedure (Scheme 9) [14]. The reaction involved the combination of sparteine with copper chloride and copper acetate in stoichiometric ratios to form the respective metal-ligand complexes. Specifically, the resulting complexes were diacetatato[(2)-sparteine-N,N9]copper(II) and dichloro[(2)-sparteine-N,N9]copper(II). These complexes in crystalline form were then screened as catalysts for the asymmetric Henry reaction between 4-nitrobenzaldehyde and nitromethane in various solvents at ambient temperature. Dichloro[(2)-sparteine- N,N9]copper(II) is an effective catalyst for asymmetric Henry reaction of nitromethane with various structurally divergent aldehydes. In general, high enantioselectivities were obtained for, most of the substrates, particularly, when reaction is carried out under double catalytic activation (DCA) conditions with Et_3N base in methanol. The chemistry offered here will certainly be useful due to ready availability of (2)- sparteine as well as the (+)-sparteine surrogate as well. Further studies focused on exploring the use of copper(II)-(2)-sparteine complexes for other asymmetric reactions are in progress.



Scheme 9 Enantioselective nitroaldol (Henry) reaction using copper(II) complexes of (2)-sparteine

2.10 Enantioselective Litthiation Reaction using Copper (II) Complexes of (2)-Sparteine

The s-BuLi complex of a cyclohexane-derived diamine is as efficient as s-BuLi/(-)-sparteine for the asymmetric deprotonation of N-Boc pyrrolidine (Scheme 10) [15]. This is the first example of high enantioselectivity using a non-sparteine-like diamine in such reactions. The (S,S)-diamine is a useful (+)-sparteine surrogate and was utilized. With diamines (R,R)- in hand, researchers evaluated them in different asymmetric deprotonation reactions. First, Beak's lithiation-trapping of N-Boc pyrrolidine was used to compare the three ligands. The results are shown in Scheme 10, together with those obtained with (-)-sparteine. (+)-Sparteine is an efficient surrogate for the asymmetric deprotonation of N-Boc pyrrolidine.

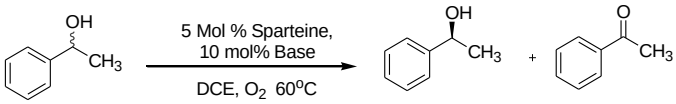


Scheme 10 Asymmetric deprotonation of N-Boc pyrrolidine

2.11 Sparteine in the Palladium-Catalyzed Aerobic Oxidative Kinetic Resolution of Secondary Alcohols

Pd(II)-catalysed aerobic oxidations are a powerful class of transformations for organic synthesis. An excellent example is the simple oxidation of alcohols which provides a practical alternative to high oxidation state metal-mediated oxidation [16]. The development of improved catalysts for Pd(II)-catalyzed aerobic alcohol oxidations would benefit from an understanding of the two distinct processes involved: (a) formation of a palladium alkoxide followed by â-hydride elimination and (b) regeneration of the catalyst using molecular oxygen. Details of the metal-catalysed alcohol oxidation sequence and the precise role of additives are poorly understood.

The first-order (-)-sparteine dependence at low (-)-sparteine suggests that deprotonation is rate-limiting under these conditions. The observed saturation kinetics suggests that another step, either alcohol binding, hydride elimination, or Pd(II) regeneration with O_2, becomes rate-limiting Scheme 11.



Scheme 11 Pd(II)-catalyzed aerobic alcohol oxidations

3. Conclusion

Future direction in this field is to continue expanding and explore the scope of sparteine in the field in enantioselective reaction, enantioselective synthesis of biologically active molecules in pharmaceutical industry and enantioselective reactions through the combination of different types of additives and co catalyst for reactions, the employment of novel chiral catalysts, and apply these powerful strategies to the synthesis of biologically interesting molecules including natural products, and that of novel chiral ligands, and functional materials.

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