Chiral Ligands in the Asymmetric Reformatsky Reaction

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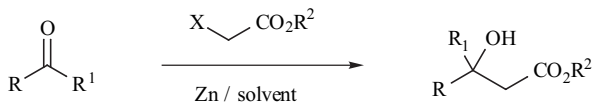
Abstract: Several classes of chiral ligands have been largely used to increase the enantioselectivity of asymmetric Reformatsky reaction, however, chiral diamines and aminoalcohols ligands generally shown better results. Hence, this review describes the results using chiral ligands in the very important Reformatsky reaction.

Keywords: Reformatsky reaction, ligands, zinc, aminoalcohol, diol, diamines.

INTRODUCTION

The Reformatsky Reaction was realized in 1887 [1] and since then it has become one of the most important and useful methods for carbon-carbon bond formation. Reformatsky reactions reviews have been published [2], as well as some less specific reviews have mentioned this reaction [3]. Traditionally this reaction involves the use of α-halocarbonyl compounds, metal zinc, and aldehyde or ketone, resulting in the corresponding β-hydroxy ester, Eq. (**1**).



R; R^1; R^2 = H; alkyl or aryl group.
X= halogen.

Equation 1. Reformatsky reaction.

One of the advantages of the Reformatsky Reaction consists of using neutral conditions in contrast to the Aldol Reaction, for example, which uses a base to produce enolate or acid to activate the eletrophile [2]. Another advantage of this reaction lies in the fact that the halogen reagent determines the reaction site [4]. However, the yield and the stereoselectivity of the Reformatsky Reaction remain lower than those of the Aldol Reaction. Variable parameters, such as the use of other metals including rhodium [5], cadmium [6], nickel [7], indium [3e], cerium [8], lithium [9], samarium [10], tin [11], germanium [12], bismuth [13], manganese [14] and chromium [3c], have been evaluated to mediate the Reformatsky reaction and improve yield. Another alternative would be the activation of the zinc metal. In this feature some research groups have developed methods using of Rieke-Zn [15], Zn-Cu amalgam [16], Zn/Ag-graphite [17], Zn-Ag amalgam [18], trimethylchorosilane [19], ultrasound [20] among others [21]. Benzene, tetrahydrofuran, ethyl ether, toluene have been mostly used as solvents. However, water has been recently investigated as a possible solvent [22].

The structure of the Reformatsky reagent [23] (Zn/halogen-carbonyl compound), which has been discussed in various reviews, constitutes another important aspect of this reaction. Recently, transition structures were reported based on theoretical studies, such as the MNDO-PM3 [24] or by NMR methods [25].

Many important points of the Reformatsky reaction, such as the structure of the reagent, the strategies to improve the yield of the reaction, as well as others parameters, have been described in reviews and papers. Therefore, we decided to focus our attention on the use of chiral ligands in the Reformatsky reaction.

The asymmetric Reformatsky reaction is an interesting methodology to obtain chiral β-hydroxy esters, which can be used to produce synthetic intermediates for synthesis of biological compounds [2, 26]. For this purpose, Reformatsky reagents are added to chiral carbonyl substrates [27] or chiral α-haloesters [28]. Another interesting approach consists of using a chiral ligand to coordinate with the Reformatsky reagent before reaction with the carbonyl compound. As a result, the scope of this review lies in describing the use of ligands in this reaction based on the following functional groups: diamines, aminoalcohols, diols and related examples.

CHIRAL DIAMINES AS LIGANDS IN THE REFORMATSKY REACTION

Guetté *et al.* (1971 and 1973) reported the first version of the Reformatsky Reaction (RR) using a chiral ligand [29]. In these studies, aldehyde (benzaldehyde) and ketones (acetophenone and phenylethylketone) were used as carbonyl compounds (CC), (-)-sparteine (**1**) (Fig. (**1**)), as the chiral ligand (**L***), and α-bromomethyl, ethyl and tert-butylacetate as Reformatsky reagent (RR) to obtain the corresponding α-hydroxyesters. The molar ratio applied in these reactions were 1:1.1:1.1 (CC:**L***:RR), which led from poor to moderate chemical yields (13 – 62%). The enantiomeric excess (*e.e.*) was determined by polarimetry and was 95%, when benzaldehyde was used. The following interesting observations were reported: the enlargement of the alkyl group in the haloester reagent, from methyl to ethyl group,

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increases the enantioselectivity of the reaction. However, when tert-butyl group was used the *e.e.* decreased. The enlargement of the alkyl groups in the carbonyl substrate caused a decrease in the enantioselectivities, and aldehydes are more enantioseletive then ketones. As example, the reaction between benzaldehyde and acetophenone with Zn/α-bromoethylacetate led to 84% and 38% *e.e.*, respectively.

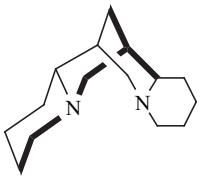

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Fig. (1). (-)-sparteine **1**.

Seebach *et al.* (1979) reported the use of benzaldehyde, bromoethyl or tert-butylacetate and the ligand (+)-DDB **2** [1,4-dimethylamino-2, 3-dimethoxybutane (Fig. (**2**))] to promote a β-hydroxyester in good chemical yield (57% to 90% yield), but with poor reaction enantioselectivity (2% *e.e.* to 24% *e.e.*) [30].

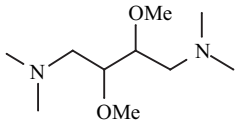

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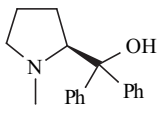
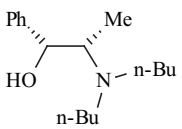
Fig. (2). (+)-DDB.

CHIRAL AMINOALCOHOLS AS LIGAND IN THE REFORMATSKY REACTION

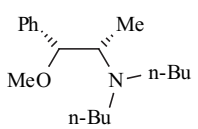
Soai *et al.* reported the use of aminoalcohols in the Reformatsky reaction in 1991 [31] and 1993 [32]. The first work described the use of (S)-(+)-DPMPM **3** [biphenyl (1-methylpyrrolidin-2-yl) methanol], (1R, 2S)-(+)-DBNE **4** and the methoxy derivative **5** as ligands (Fig. (**3**)). The carbonyl compounds applied were benzaldehyde, 2-naphthylaldehyde and butanaldehyde, α-bromot-butylacetate as haloester and THF was used as solvent. The best result was observed when ligand **3** was used to produce the complex with the Reformatsky reagent (RR: Zn/t-butylbromoacetate) and reacted with benzaldehyde and 2-naphthylaldehyde (75 and 78% *e.e.*, respectively). When alkyl aldehydes were used the enantioselectivity of the reaction decreased (56% *e.e.*). When



(*S*)-(+)-DPMPM **3**



(1*R*, 2*S*)-(+)-DBNE **4**

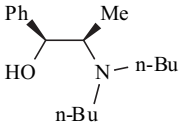


(1*R*, 2*S*)- **5**

Fig. (3). Ligands **3-5**.

4 was used the same observations were reported, but with moderate enantioselectivities. The enantioselectivity was very low (1%) when methoxy derivative **5** was applied, showing that the presence of a free hydroxyl group of the aminoalcohol is an important factor for the enantioselectivity of the reaction. Catalytic quantities of ligands can cause a decrease in the enantioselectivity. The molar ratio 1:1:3 (CC: **L***:RR) presented the best result than the molar ratio 1:0.4:3, 75% *e.e.* and 44% *e.e.*, respectively. Another important observation was the preferential attack from the Reformatsky reagent through the *Si* face of the aldehyde.

The second study involved the use of ligands (-)-**4** and **6** derivated from N,N-dialkylnorephedrine, ketones and tert-butylbromoacetate (Fig. (**4**)). It should be noticed that the best result was reached when β-hydroxyester was obtained in 75% *e.e.* and moderate reaction yield (38% *e.e.*) with ligand **6a**. These results were better than the ones observed for ketones in the Guetté work [29], when (-)-sparteine (**1**) was used.



(-)-**4**

6a: R' = allyl;
6b: R' = Me;
6c: R' = n-Octyl

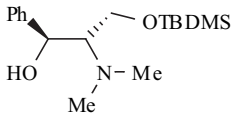
6´a

Fig. (4). Ligands (-)-**4** and **6**.

In both of Soai's work, it was possible to observe that the reaction enantioselectivities were better with aldehydes. The enlargement of the alkyl group, from methyl to allyl group, on the nitrogen's ligand caused an increase in enantioselectivity of the reaction, but larger groups caused a decrease on this effect. The tert-butylhaloesters presented better enantioselectivities than methyl and ethylhaloesters.

Mastantuono *et al.* in a preliminary study [33] have investigated the use of the ligand aminohydroxylated **7** (Fig. (**5**)). Reformatsky reagent was obtained from zinc metal and tert-butylbromoacetate and eight aldehydes were studied. In this example, when benzaldehyde was used the reaction with the reagent molar ratio 1:3:1 (CC:**L***:RR), 65% *e.e.* (100% yield) was achieved. The aromatic aldehyde presented better enantioselectivities than the alkyl aldehyde, as example, 65% *e.e.* to benzaldehyde and 21% *e.e.* to PhCHCHCHO. However, benzaldehyde presented better selectivity than 2- and 1-naphthylaldehyde, 65%, 40% and 33% *e.e.*, respectively. The presence of functional groups in aldehyde decreased the enantioselectivity of the reaction.

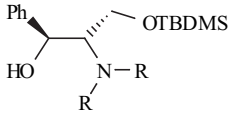
In another study, Mastantuono *et al.* [34] reinvestigated the use of ligand **7** and analogs **8**-**10** with seven aromatic aldehydes and one alkyl aldehyde as carbonyl compounds (Fig. (**6**)). THF was used as solvent and the reagents molar ratio was 1:1:3 (CC:**L***:RR). They observed an increase in the size of the alkyl group on the nitrogen led to a decrease



(1*S*, 2*S*)-**7**

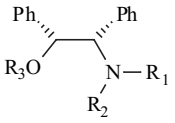
Fig. (5). Ligand **7**.

in the rate of reaction with a similar enantioselectivity. The enantioselectivities were moderate (21 to 70% *e.e.*) and decreased when the steric hindrance of the alkyl group on the nitrogen of the ligand was higher than the one caused by the ethyl group. Similar results were observed by Soai [30, 31].



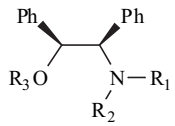
7; R = Me
8; R = Et
9; R = n-Bu
10; R = allyl

Fig. (6). Ligands **7-10**.



(1*R*, 2*S*)-**11**

11a: $R_1 = R_2 = R_3 = H$
11b: $R_1 = R_3 = H$; $R_2 = c\text{-}C_6H_{11}$-
11c: $R_1 = R_3 = H$; $R_2 = C_6H_5CH_2$-



(1*S*, 2*S*)-**11´**

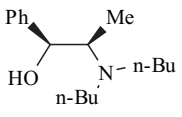
11d: $R_1 = CH_3 = H$; $R_2 = C_6H_5CH_2$-; $R_3 = H$
11e: $R_1 = R_2 = CH_3$; $R_3 = H$
11f: $R_1 = R_2 = CH_3$; $R_3 = C_6H_5CH_2$-

Fig. (7). Ligands **11**.

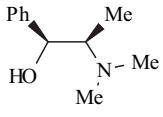
Mi *et al.* investigated the use of aminoalcohols **11a-f** (Fig. (**7**)) [35, 36]. Applying these ligands in Reformatsky reaction between benzaldehyde and Zn/bromoethylacetate [35], the following conclusions were described: catalytic amounts of ligands led to a worse result than stoichiometric amounts, and a linear relationship between *e.e.* values and molar ratios of the ligand to benzaldehyde was not observed. The presence of alkyl groups on the nitrogen's ligand is important to the enantioselectivity of the reaction, as described in the previous papers. The enantioselectivity of the reaction decreased drastically when aminoether **11f** was used. As observed by Soai *et al.*, these reactions showed that the presence of free hydroxyl group is a significant factor [30, 31]. The use of several solvents, as acetonitrile, tetrahydrofuran, chloroform, 1,2-dimetoxyethane, benzene and toluene were also evaluated. Despite the moderate reaction yield, the use of THF led to better *e.e.* in the Reformatsky reaction. Therefore, polar and electron donor solvent are important to achieve a better *e.e.* values.

In another paper, Mi *et al.* [36] reported the use of ligands **11e** and **11´e**. These ligands were used in the reaction between benzaldehyde and ethyl, isopropyl and t-butylbromoacetate, as well as (+)- and (-)-menthylbromo-methylacetate as haloesters. It was possible to observe an increase of the enantioselectivity of the reaction with a bulkier alkyl group of the ester, from 25 % *e.e.* with bromoethylacetate to 46% *e.e.* with bromo-tert-butylacetate. The presence of a chiral auxiliary exerts an influence in the reaction's *d.e.* For example, the reaction between benzaldehyde, (+)-menthylhaloester and **11e** led to the hydroxyester in 97% yield with 60% *d.e.*, when (-)-menthylhaloester were applied the yield achieved was 76% with 24% *d.e.*

Andrés *et al.* described the use of aminoalcohols **4**, **12** and **13** to obtain chiral hydrofluoroesters using several aldehydes (Fig. (**8**)) [37]. This work denoted the importance of the Reformatsky reagent/aldehyde ratio, where an increasing of the ratio from 3/1 to 4/1 caused a marked increase in the reaction yield but caused a small incremental increase in the reaction enantioselectivity. To illustrate this, when 2-naphthylaldehyde was used the reaction yield improved from 34% to 69%, respectively. Others experiments showed that the enhancement in the hindrance of the alkyl group in the nitrogen led to a decrease in the *e.e.* of the products reaction. When benzaldehyde was used as carbonyl compound, the *e.e.* changed from 82% (ligand **12**) to 68% (ligand **4**), with a molar ratio 1:1:3 (CC:**L***:RR).



(-)-4



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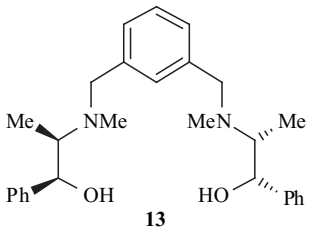

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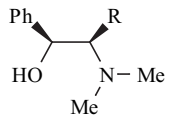
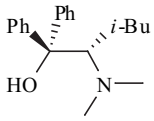
Fig. (8). Ligands (-)-**4**, **12-13**.

In a second study, similar aminoalcohols and bromo-tert-butylacetate were used to lead the Reformatsky reagent (Fig. (**9**)) [38]. Some observations were described using the ligand **14**: a) THF was better solvent than ethylether; b) the relevance of reaction's temperature in the chemical yield (90% yield at 0º C; 43% yield at –78º C to 0^0 C; and 53% yield at 60º C); c) there is a small influence of the temperature in the reaction's enantioselectivities (62% *e.e.* at 0º C; 61% *e.e.* at –78º C to 0º C; 72% *e.e.* at 60º C); d) the



11e: R = Ph
12: R= Me



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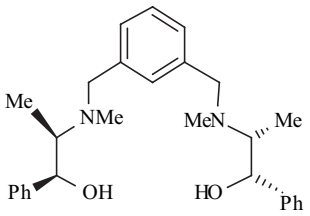

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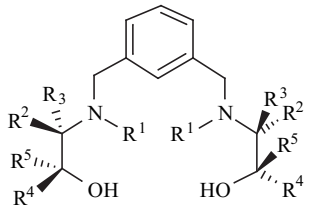

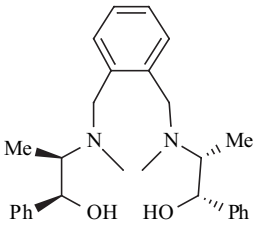

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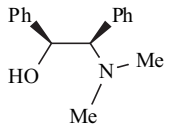
16: R^1=Et; R^2=Me; R^3=H; R^4=Ph; R^5=H
17: R^1=Bn; R^2=H; R^3=Me; R^4=H; R^5=Ph
18: R^1=Me; R^2=Ph; R^3=H; R^4=Ph; R^5=H
19: R^1=Et; R^2=Ph; R^3=H; R^4=Ph; R^5=H
20: R^1=Me; R^2=Ph; R^3=H; R^4=Me; R^5=Me
21: R^1=Me; R^2=H; R^3=*i*-Bu; R^4=Me; R^5=Me
22: R^1=Me; R^2=H; R^3=*i*-Bu; R^4=Ph; R^5=Ph

Fig. (9). Ligands **11-22**.

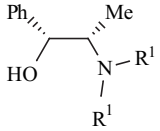
reaction enantioselectivity decreases when catalytic amounts of ligand are used (62% with a molar ratio 1:0.5:3 – CC:**L***:RR; 22% *e.e.* with a molar ratio 1:0.2:3). The results observed in this work also suggest the importance of the hindrance of the alkyl group on ligand's nitrogen, where an increase in the size of the alkyl group causes a decrease in the enantioseletivity of the reaction.

Andrés *et al.* have recently reported the use of α-bromo Weinreb amide [$BrCH_2CONMe(OMe)$] to generate the Reformatsky reagent, and three aromatic and four alkyl aldehydes as carbonyl compound [39]. When ligands **12**, **14** and **18** were used in the Reformatsky reaction type, hydroxyamides were obtained in a moderate yields (25-75%) and enantioselectivities (about 47% *e.e.*). When ligand **14** was used, Reformatsky reaction with haloester led to a better enantioselectivity than with haloamide.

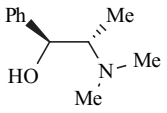
At the same time, Braun *et al.* described the use of ligands (-)-**4**, (-)-**6**, **11e** and **23**-**25** (Fig. (**10**)), in the Reformatsky reaction with three aromatic aldehydes and one alkyl aldehyde, using α–bromo, α,α – difluoroethylacetate as haloester [40]. In this work, the ligand **(-)-6b** afforded the best result in the reaction enantioselectivity (84% *e.e.* with benzaldehyde and the *e.e.* variable between 46-71% with others aldehydes; molar ratio 1:1:3 – CC:**L***:RR). All the same observations presented in previous work were consistent with these results. The importance of the alkyl group in the ligand nitrogen and reagents molar ratio was observed. This work describes also that the presence of the negative oxygen in the ligand causes a decrease in the *e.e.* of the reaction (5% *e.e.* when benzaldehyde were used with ligand **25**, in a molar ratio of 1:1:3 - CC:**L***:RR).



11e



(-)-4: R^1 = n-Bu
(-)-6b:R^1 = Me
23: R^1 = Et



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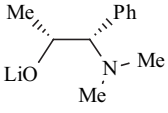

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Fig. (10). Ligands (-)-**4**, (-)-**6**, **11** and **25**.

Ojida *et al.* [41] recently evaluated the use of various commercial ligands in the study of the Reformatsky reaction between ketone I and Reformatsky reagent obtained from tert-butylbromoacetate (Fig. (**11**)). Derivatives **26**-**33** presented the best results, where the *e.e.* of the reaction varied from 65% to 72%. Among the other derivatives, only (-)-sparteine (**1**) gave 19% *e.e.* and 1% yield. To investigate the scope of the molecular rate of ligand several conditions were evaluated. For example, when a catalytic amount of ligand **27** at 0ºC the reaction enantioselectivity achieved at

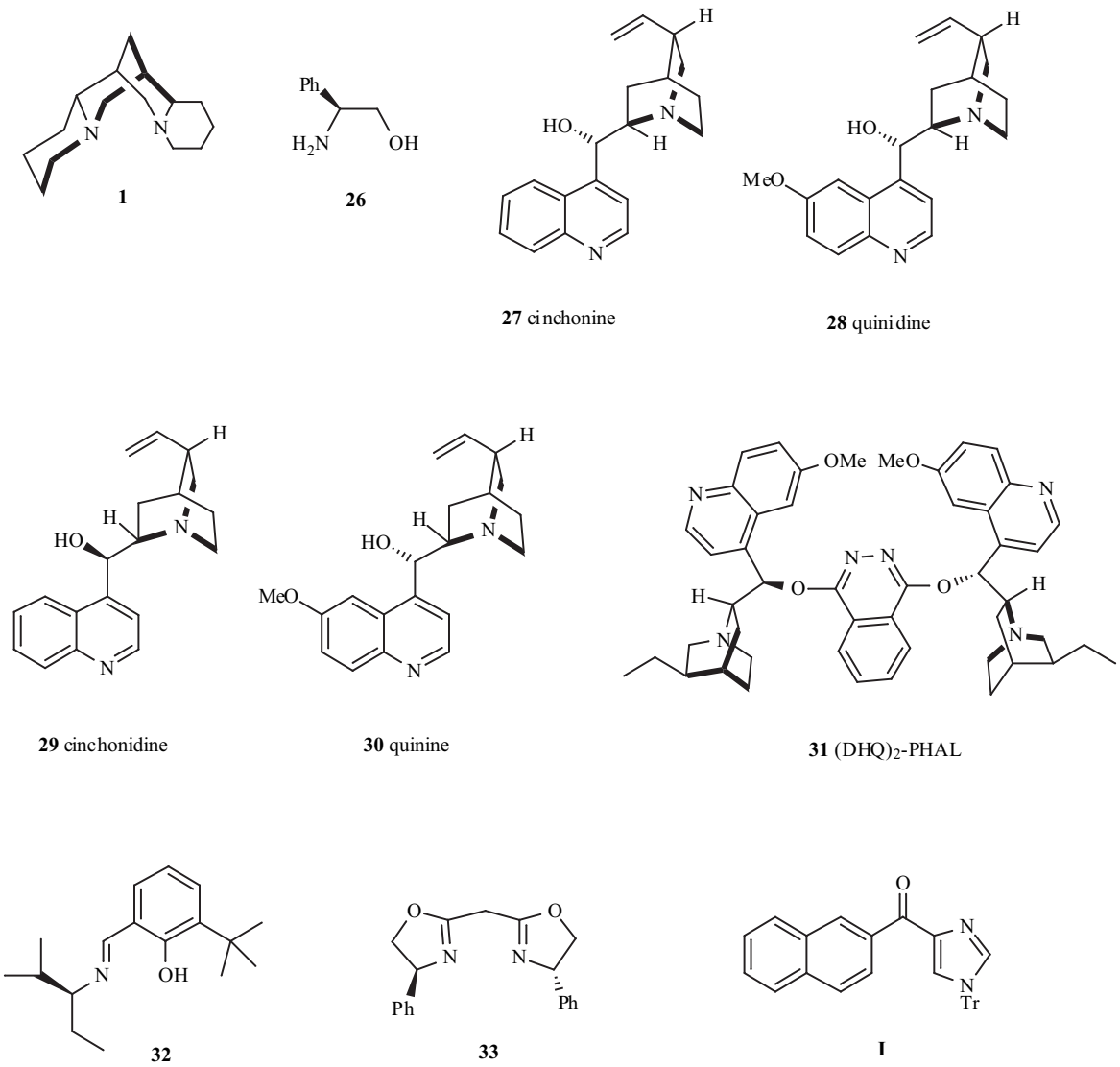


Fig. (11). Ligands **26**-**33** and ketone **I**.

74%, with 1.5 equivalents the *e.e.* was 93%. The temperature also influenced the reaction enantioselectivity, as example, using 1.5 equivalents of ligand **25** at 0ºC the enantioselectivity achieved at 93% and 97% at -40º C. The reaction of ketone **I** with Reformatsky reagent in the presence of the ligand cinchonine (**27**) was investigated in the presence of additives. When pyridine was used as the additive in 1; 1.5; 2; and 4 equivalents, the hydroxyester was obtained in 76; 81; 85 and 85% of enantioselectivity, respectively. When quinoline was used as the additive, the *e.e.* reached 65%, and for isopropylethylamine, the *e.e.* was 70%. However, when DBU was used the *e.e* achieved 6%. In all cases, except when DBU was used, there was an increase in the enantioselectivity.

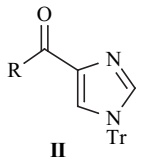
Other ketones II-VI were evaluated in the Reformatsky reaction (1 eq.) using cinchonine (**27**) (1.5 eq.) as the ligand and pyridine as the additive (4 eq.). The results on the enantioselectivity of these reactions are shown in Fig. (**12**). It is possible to observe the importance of the presence of sp^2-nitrogen, from the carbonyl compound, to coordinate with the zinc from Reformatsky reagent to result in a good enantioselectivity of the reaction.

Fujiwara *et al.* [42] recently published the use of some trifluoromethylated aminoalcohols as chiral ligands and bromoethylacetate (Fig. (**13**)). In these studies, the *e.e.* of the reaction remained from 4% to 81%. Several conditions were evaluated and THF was the best solvent used. When the results of ligand **34e** were compared with **35**, the *e.e.* was 78 and 23%, respectively, showing the role of the CF_3 group in enantioselectivity. When iodoethylacetate was used with **34e** in the Reformatsky reaction, the rate of reaction increased and *e.e.* improved to 90%.

CHIRAL DIOLS AS LIGANDS IN THE REFORMATSKY REACTION

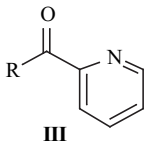
Braun *et al.* [40] has described the use of aminoalcohols in Reformatsky reaction (discussed in the previous sections), but they also applied two hydroxylated ligands (Fig. (**14**)). The enantioselectivity was moderate for **36a** (62% *e.e.*) and for **36b** (55% *e.e.*). When aminoalcohols analogues were employed, the reaction enantioselectivity improved.

Mono and dihydroxy carbohydrate derivatives were recently applied in the Reformatsky reaction by Ribeiro *et*



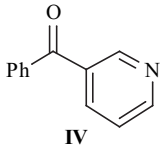
II

a: R = H (84%; 66% *e.e.*); b: R = β-naphthyl (97%; 97% *e.e.*);
c: R = Ph (99%; 97 *e.e.*); d: R = *i*-propyl (73%; 94% *e.e.*).



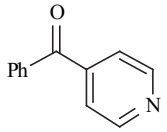
III

a: R = H (94%; 74% *e.e.*);
b: R = Ph (27%; 28% *e.e.*);
c: R = Me (94; 86% *e.e.*).



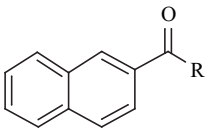
IV

a: 27%; 28% *e.e.*



V

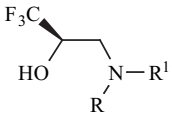
a: 41%; 13% *e.e.*



VI

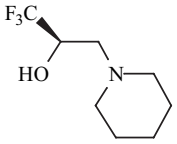
a: R = Me (42%; 15% *e.e.*); b: R = -CH_2NBn_2 (99%; 0% *e.e.*)

Fig. (12). Ketones **II-VI**.

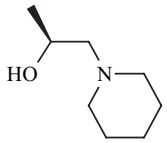


34

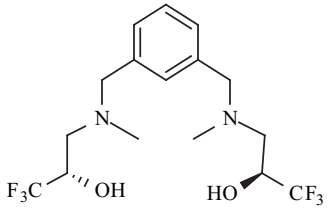
a: R=H; R^1=H; **b:** R=H; R^1=Et
c: R=R^1=Me; **d:** R=R^1=*i*-Pr



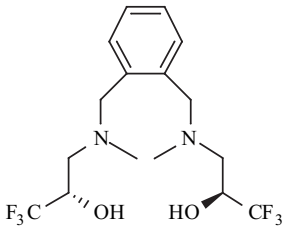
34e



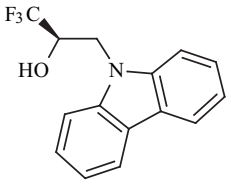
35



34f



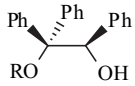
34g



34h

Fig. (13). Ligands **34**.

al. [43] (Fig. (**15**)). The chemical yields observed were moderate (50% yield), but the enantioselectivity of the reactions were not as high as expected, only 30% *e.e.* Therefore, the work showed the importance of the two hydroxyl groups in the ligand, but in some cases the steric hindrance of the monohydroxylated carbohydrate leads to results similar to those observed with diols. A loss in reaction selectivity was also observed with catalytic ligand moieties.



36a: R = H
36b: R = Me

Fig. (14). Ligands **36**.

Miscellaneous

Other asymmetric Reformatsky reactions were evaluated. Soai *et al.* [44] investigated the use the aminoalcohols as ligands, (+)- and (-)-**3**, in the reaction of several aldehydes in THF at –13°C and bromoacetonitrile to prepare the Reformatsky reagent. The yields of the reactions varied between 45 and 82%, with good enantioselectivities (74 to

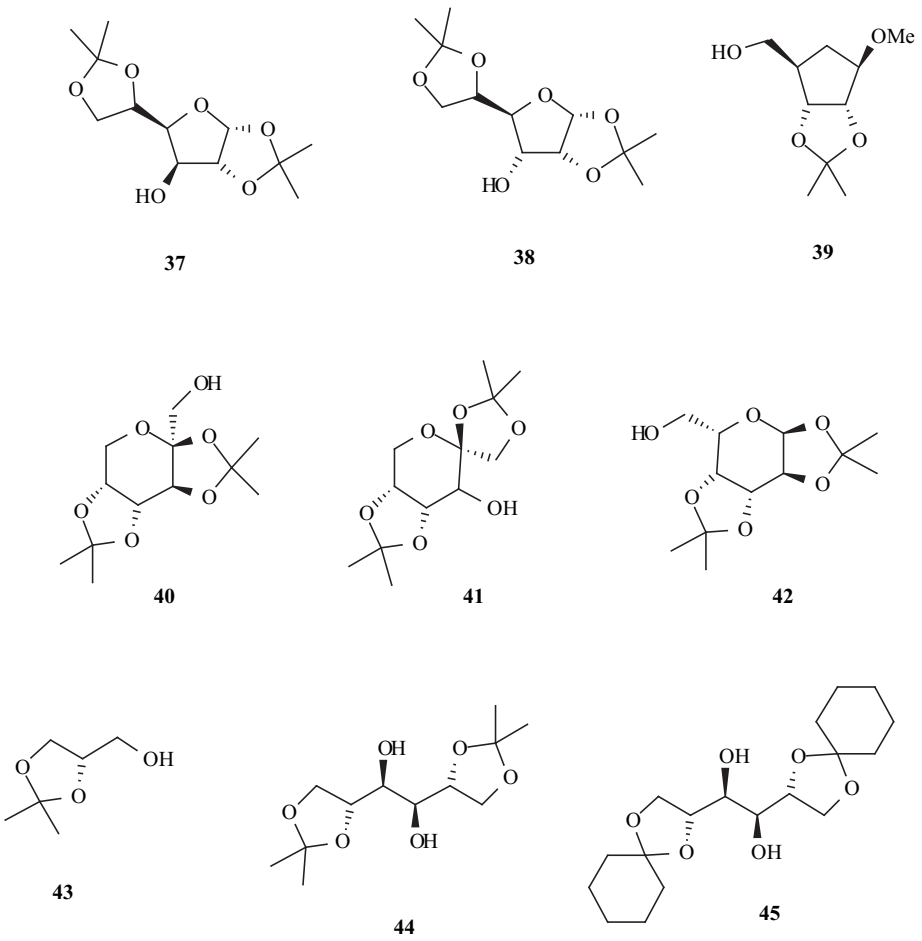


Fig. (15). Carbohydrates derivative ligands **37**-**45**.

93% *e.e.*). Benzaldehyde led to better results. However, no significant changes were observed with others aldehydes.

The synthesis of chiral β-hydroxyesters by indium-induced Reformatsky reaction using ligands **27**-**30** was investigated by Johar *et al.* in 1992 [45]. This work describes the use of seven aromatic aldehydes and ethyliodoacetate. Pentane-THF was used as solvent and the temperature of the reaction changed from –78ºC to 18ºC. Cinchonine (**27**), as ligand, always presented the best results and the *e.e.* of the reaction product achieved 71% level. When electron-withdrawing chloro and nitro groups were present in the aromatic ring of the carbonyl compound the enantioselectivity decreased, but with electron-donor groups no significant difference was observed. (-)-Sparteine (**1**), (-)-norephedrine, (+)-dibutyl tartrate, (+)-1,1´-bi-2-naphthol and (+)-(1-methylpyrrolidin-2-yl) diphenylmethanol were also evaluated. However, the chemical yields and/or the reaction enantioselectivity were modest.

Zhang *et al.* described the use of chiral micelles **46**-**47** as ligands in the enantioselective synthesis of β-hydroxyesters using the Reformatsky reaction (Fig. (**16**)) [46]. Benzaldehyde, 4-chlorobenzaldehyde and 4-methoxybenzaldehyde were used as carbonyl compounds, where ethylbromoacetate and Zn in THF-H_2O led to the Reformatsky reagent. The enantioselectivity was poor to moderate achieving 30% *e.e.* and the chemical yields were similarly modest. The surfactant **47** showed the best selectivity, but no significant differences towards ligands **46**. Among the aldehydes used benzaldehyde present the best results.

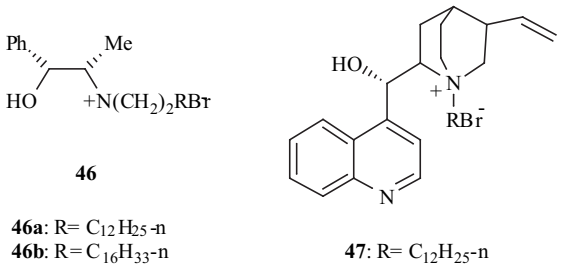
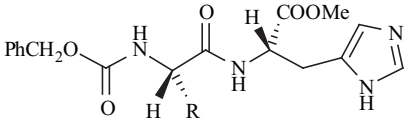


Fig. (16). Chiral micelles **46** and **47**.

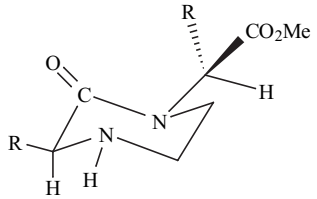
Wang *et al.* [47] have recently studied the use of dipeptides **48**-**50** as ligand in the reaction of benzaldehyde, ethylbromoacetate and zinc (Fig. (**17**)). The β-hydroxyester was obtained with enantioselectivities between 1-22%, and good chemical yields.

Ukaji *et al.* [48] described the use of ethyl tartrate derivative **51** as the chiral ligand in the Reformatsky type to 3,4-dihydroisoquinoline N-oxides derivatives, Eq. (**2**). The reaction enantioselectivity achieved a good *e.e.* value (86% *e.e.*), as well as 99% of yield. No significant differences were observed when the ethyl group was changed to tert-butyl group in the haloester reagent (86 to 76% *e.e.*). The temperature of the reaction exerted some influence on the

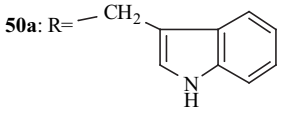


48

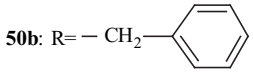
48a: R=CH_3; 74%; **48b**: R=CH_2Ph;
48c: R=$(CH_2)_2SCH_3$



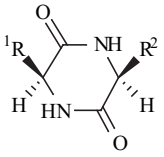
47



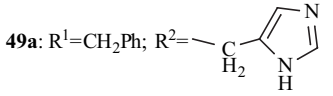
50a: R=



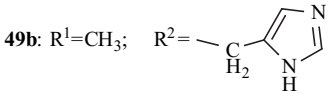
50b: R=



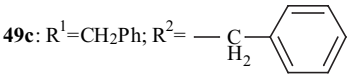
49



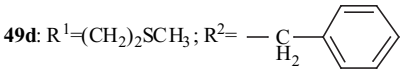
49a: R^1=CH_2Ph; R^2=



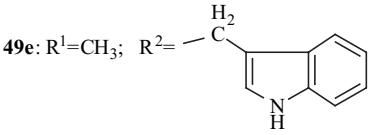
49b: R^1=CH_3; R^2=



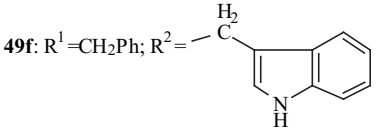
49c: R^1=CH_2Ph; R^2=



49d: R^1=$(CH_2)_2SCH_3$; R^2=



49e: R^1=CH_3; R^2=

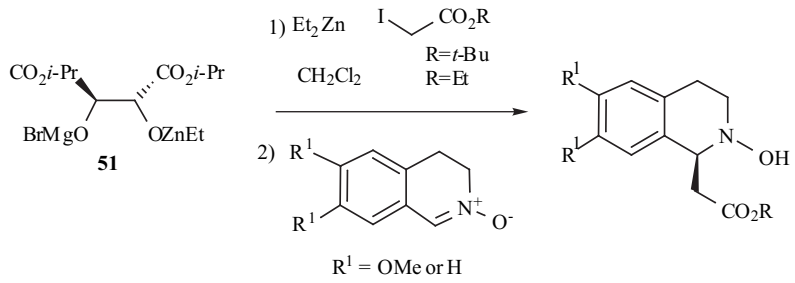


49f: R^1=CH_2Ph; R^2=

Fig. (17). Dipeptides **48**-**50**.

results. For example, a reaction enantioselectivity of 43% (84% yields) was achieved at 0ºC and one of 0% *e.e.* (78% yields) at -50ºC.

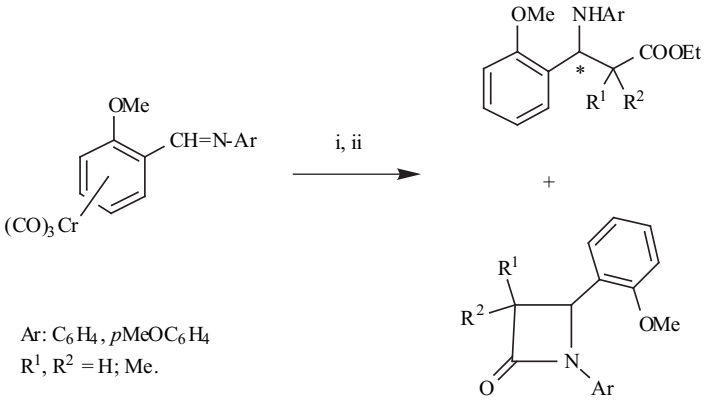
In 1996 [49], Baldoli *et al.* reported the enantioselective synthesis of some β-aminoesters and β-lactams using optically pure tricarbonyl chromium derivatives, Eq. (**3**). The products were obtained from tricarbonyl [N-(2-methoxybenzilidene) aniline] chromium or tricarbonyl [N-(2-methoxybenzilidene)-4-methoxyaniline] chromium and α-bromoesters in the presence of zinc and ultrasound. In these studies, a mixture of aminoesters and lactams was obtained with *e.e.* of 98%.



51

R^1 = OMe or H

Equation 2. Reformatsky reaction using ligand **51**.



Equation 3. Reformatsky reaction using tricarbonyl chromium derivatives.

CONCLUSION

This review presented the state of the art in asymmetric synthesis of β-hydroxyester using ligands in the Reformatsky reaction. Some classes of compounds, as alkaloids, terpenes and carbohydrates with the functions such as diamines, aminoalcohols and diols have been evaluated as ligands in the asymmetric Reformatsky reaction. An interesting analysis of these results was made. For example, the importance of the bulkiness group in the alcoholic moiety of the haloester is clear, as the reaction enantioselectivity increases when methyl group is changed to tert-butyl group. Similarly, when a chiral group is present in the haloester moiety the enantioselectivity of the reaction is enhanced as the result of a double induction. The presence of the free hydroxyl group in the aminoalcohols ligand, as well as, the bulkiness of the alkyl group on the nitrogen atom is usually important to achieve a better enantioselectivity. Diols show moderate enantioselectivities; however, the number of ligands studied was insufficient to provide a definitive conclusion. In analogous derivatives, aminoalcohol affords better enantioselectivity than diols. Ligands used in catalytic quantities have not afforded good results. Hence, despite some improvements, the enantioselectivities of the reactions could be still increased by using new methodologies, which could improve the enantioselectivity of this important reaction. Asymmetric Reformatsky reactions in mild conditions, synthesis of new ligands derivatives and computational chemistry studies for understanding the transition state of the ligand pathway would be excellent tools and strategies to improve this important reaction.

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