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# Asymmetric induction in the nucleophilic addition in the series of aromatic azines

I N Egorov, G V Zyryanov, V L Rusinov, O N Chupakhin

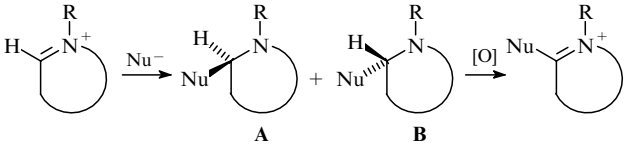
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**Abstract. Stereoselective reactions of nucleophilic addition to the C=N bond in aromatic azines resulting in chiral products are reviewed. Various methods of inducing the optical activity are discussed. The bibliography includes 60 references.**

## I. Introduction

Reactions of nucleophilic substitution of a hydrogen atom ($S_N^H$) in π-electron deficient (hetero)aromatic compounds and azines in particular belong to the abundant class of two-step addition–elimination processes.[1] The initial formation of nucleophilic addition products — $\sigma^H$-adducts of **A** and **B** — as a result of a direct attack of C-, N-, O-, P-, S- and other nucleophiles on a non-substituted carbon atom of the azine ring is a general feature of these reactions. The intermediates **A** and **B** themselves are of great synthetic and sometimes industrial interest.




R = H, Ac, R* (R* is a chiral substituent); Nu is a nucleophile.

The pro-chiral $sp^2$-carbon atom of the C=N bond of the azine ring acquires $sp^3$-hybridisation upon formation of $\sigma^H$-adducts and therefore becomes chiral. In most cases, these intermediates are mixtures of *R*- and *S*-enantiomers.[2] The adducts exist in the form of diastereomeric pairs where a symmetric carbon is present in either the substrate or the nucleophile. The attack of an achiral nucleophile on the chiral substrate should result in stereoselective formation of a new chiral centre. In the ideal case, the addition yields an individual stereoisomer.

Numerous publications (see, for example, reviews [3–7]) on the synthesis of alkaloids and on nucleophilic addition reactions in the series of azines (chiral azines as well) neither specially emphasised nor systematised chiral transformations with asymmetric induction. Nor were stereochemical aspects of the formation of the type **A** or **B** intermediates discussed in the book [1] on the reactions of nucleophilic substitution of the aromatic hydrogen atom. The present review is intended to fill this gap. The results of the studies on stereoselective nucleophilic addition to the carbon atom of the azine C=N bond published over the last 15 years are presented.

## II. Stereochemical effects in the attack of an achiral nucleophile on an optically active azine

In spite of the fact that a pyridine-type nitrogen atom increases the π-deficiency of heterocycles, very few examples of the direct introduction of neutral C-nucleophiles into non-activated azines are known.[1] Activated forms of azine substrates, *viz*., azinium cations, and highly reactive nucleophiles, primarily organometallic compounds, are used as a rule in the induction of chirality upon the nucleophilic attack. In this section, some examples of stereoselective reactions of azines with other C-nucleophiles (cyanide ions, enolates, indoles) as well as with Si- and O-nucleophiles are discussed.

### 1. Reactions of azines with chiral substituents at the nitrogen atom

#### a. The effect of a chiral substituent on the diastereoselectivity of the reaction

The reactions of C-nucleophiles with azinium cations containing nitrogen atoms quaternised with chiral substituents are the best studied. The corresponding salts are usually synthesised by alkylation or acylation (often *in situ*) of an azine substrate with an optically active reagent. The fragments of chiral hydrocarbons, alcohols (including natural ones), amino acids and heterocyclic compounds may be used as the asymmetric inductors. The electrophilicity of the azinium cation depends on the nature of the substituent at the nitrogen atom: less reactive *N*-alkyl-substituted salts react only with carbanions (organometallic compounds), while for *N*-acyl derivatives there is a wide range of potential nucleophiles. The data presented in this Section are ordered according to the type of the nucleophilic agent and in the order of increasing complexity of the azine substrate.

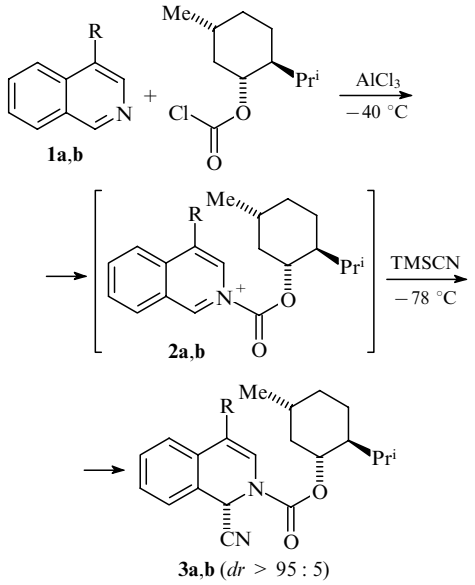
Stereoselective addition reactions of cyanide to chiral isoquinolinium salts have been described.[8] The starting salts have been

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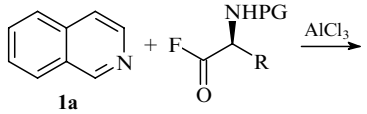
synthesised *in situ* by acylation of isoquinolines with optically active (−)-menthyl chloroformates in the presence of Lewis acids. Trimethylsilyl cyanide (TMSCN) was used as a C-nucleophile.

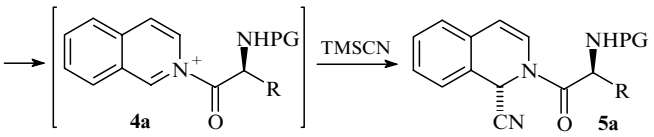
Thus isoquinolines **1a**,**b** in the reaction with (−)-(*R*)-menthyl chloroformate yield optically active salts **2a**,**b**, which add the CN group with high diastereoselectivity. The diastereomeric ratio (*dr*) in the products **3a**,**b** exceeds 95 : 5.[8]




R = H [**a** (98%)], Br [**b** (96%)].

Isoquinolinium salts **4a** obtained from protected amino acid fluorides react with TMSCN in a similar way.[8] In these reactions, the stereoselective formation of Reissert compounds **5a** was observed. The diastereomeric ratio of the reaction products depends on the structure of the original amino acid.




PG is protection group (Z is benzyloxycarbonyl, FMOC is 9-fluorenylmethyloxycarbonyl).

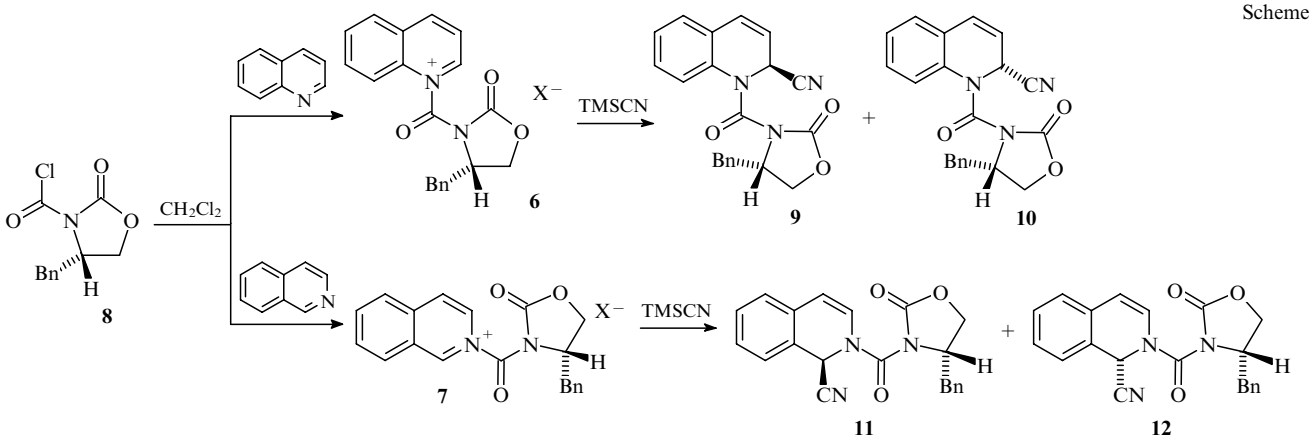
| R | PG | Yield of **5a** (%) | *dr* |
|---|---|---|---|
| Me | Z | 89 | > 95 : 5 |
| Me | FMOC | 44 | 71 : 29 |
| $Pr^i$ | FMOC | 47 | 70 : 30 |
| $CH_2Ph$ | Z | 51 | 82 : 18 |

The chiral *N*-acylazinium salts of the quinoline (compounds **6**) and isoquinoline (compounds **7**) series were obtained by acylation of the corresponding heterocycles with an optically active derivative of 2-oxooxazolidine-3-carbonyl chloride **8**.[9] The study of their reactions with TMSCN has revealed a different diastereomeric ratio of the resulting diastereomeric Reissert compounds **9**, **10** and **11**, **12**. The stereoselectivity of this reaction depends not only on the structure of the anion $X^-$, but on the temperature of the reaction as well (Scheme 1).

It was suggested[9] that the reason for the observed diastereoselectivity of the reaction is that *N*-acylazinium triflates **6** and **7** adopt the most favourable conformation with maximum π−π-interaction between the (iso)quinolinium aromatic ring and the phenyl ring of the acyl substituent. Such a conformation results in shielding of one of the diastereotopic sides of the reacting $C=N^+$ bond. Two possible conformations **A1**, **A2** and **B1**, **B2** can be suggested for the iminium salts **6** and **7**, respectively (Scheme 2). In contrast to the conformers **A2** and **B2**, the *trans*-configuration (relative to the single $N^+-CO$ bond) of the iminium and carbonyl groups in conformers **A1** and **B1** makes the π−π-interaction possible. The attack of the cyanide-ion (the front side is marked by a solid arrow in Scheme 2, the rear side, by dashed one) on the less sterically hindered side of the conformers **A1** (salt **6**) and **B1** (salt **7**) leads to the predominant formation of the diastereomers **9** and **12**, respectively.

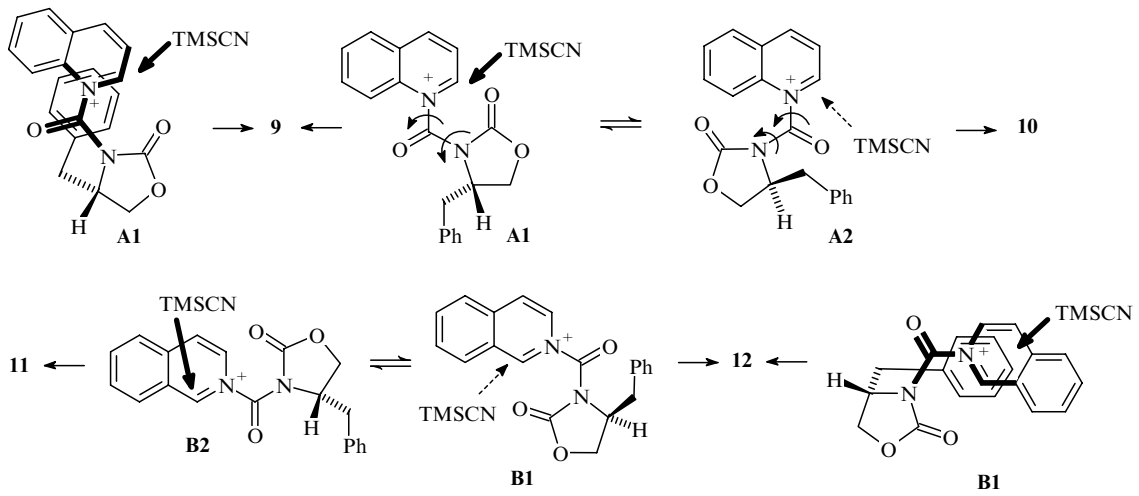
The triflate anion also favours the π−π-interactions in the acylazinium intermediate due to weaker interaction with the iminium part of the molecule than in the case of the chloride

Scheme 1



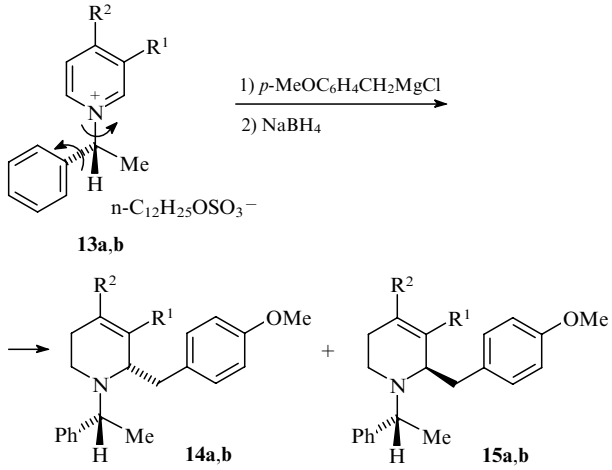

| $X^-$ | *T*/°C | Reagent | Diastereomer ratio | | Total yield (%) | |
|---|---|---|---|---|---|---|
| | | | **9** : **10** | **11** : **12** | **9** + **10** | **11** + **12** |
| $Cl^-$ | 20 | – | 55 : 45 | 60 : 40 | 88 | 76 |
| $TfO^-$ | 20 | TMSOTf | 83 : 17 | 15 : 85 | 70 | 35 |
| $TfO^-$ | 40 | TMSOTf | 84 : 16 | 29 : 71 | 60 | 95 |

Scheme 2




anion. As a consequence, the stereoselectivity of the addition increases.[9]

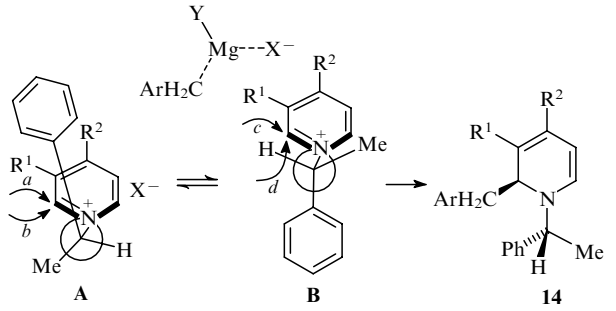
Azines may be quaternised not only by chiral acyl groups, but by alkyl groups as well. Thus chiral *N*-alkylpyridinium salts **13a**,**b** show a high degree of diastereoselectivity in reactions with benzyl-type Grignard reagents.[10] The reduction of the products with sodium borohydride leads to diastereomeric tetrahydropyridines **14a**,**b** (the main product) and **15a**,**b**.



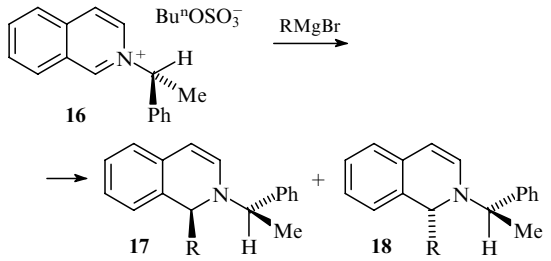

$R^1 = R^2 = Me$ (**a**, *de*† 82%); $R^1 - R^2 = (CH_2)_4$ (**b**, *de* 78%).

Such a relatively high selectivity was rather unexpected for the authors,[10] because the chiral alkyl group in the starting salt **13** is quite mobile and relatively freely rotates around the N–C bond.

The structures **A** and **B**, in which the C–H bond of the chiral group is coplanar to the plane of the pyridine ring, are probably the most energetically favourable conformations of the salts **13**. In such a case, there are several possible directions of the nucleophilic attack: pathways *a* and *b* for the conformation **A** and pathways *c* and *d* for the conformation **B**. But only the pathway *c* leads effectively to stereoisomers **14**, because only in this case is the approach of the nucleophile to the pyridine ring unhindered by the small- (H atom) and medium-sized (methyl group) substituents of the chiral alkyl fragment.[10]



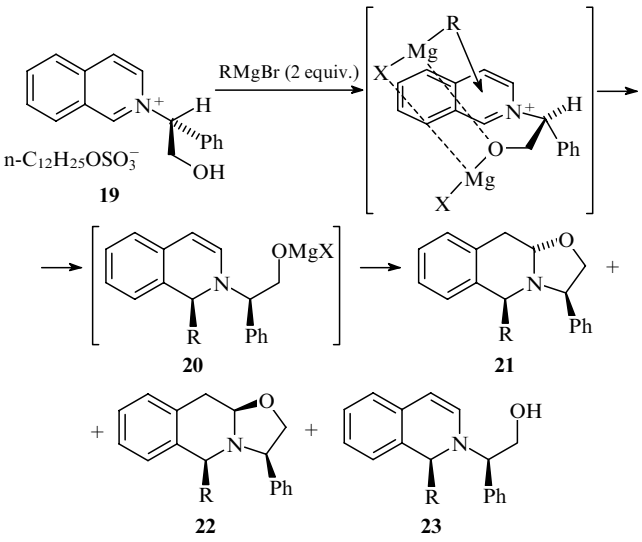

The reaction of the chiral isoquinolinium salts **16** with the Grignard reagents afforded unstable 1-substituted 1,2-dihydroisoquinolines **17** and **18** in good yields (90% – 95%).[11] However, the observed diastereoselectivity of this reaction is lower than that in the case of 3,4-disubstituted pyridinium salts.




| R | Ratio **17** : **18** |
|---|---|
| Me | 64 : 36 |
| Ph | 87 : 13 |
| *m*-$MeOC_6H_4$ | 90 : 10 |
| *m*-$MeOC_6H_4CH_2$ | 62 : 38 |

In a similar reaction of the Grignard reagents with the isoquinolinium salt **19**, which contains a chiral hydroxy(phenyl)ethyl group at the nitrogen atom, the 1,2-dihydroisoquinoline intermediates **20** cyclise spontaneously upon hydrolysis.[11] The main reaction products are tetrahydrooxazoloisoquinolines **21** and **22**. Small amounts of dihydroisoquinolines **23** are also isolated.

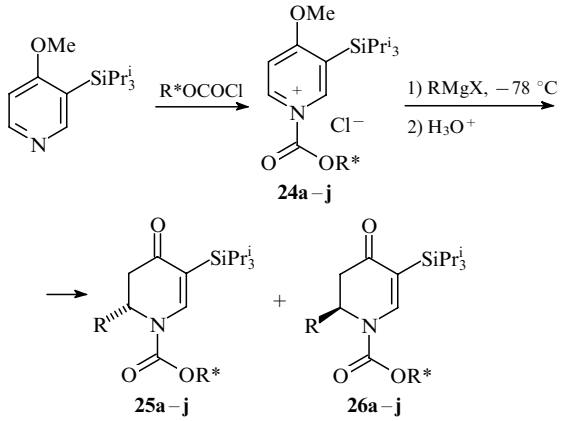
† *de* is diastereomeric excess.




| R | Ratio **21** : **22** : **23** |
|---|---|
| Me | 51 : 37 : 12 |
| Ph | 64 : 29 : 7 |
| Pr$^i$ | 49 : 34 : 17 |
| *m*-MeOC$_6$H$_4$ | 72 : 20 : 8 |

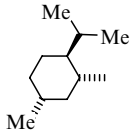
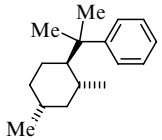
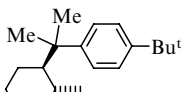
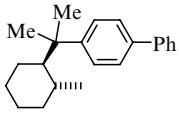
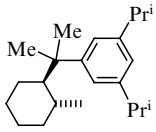
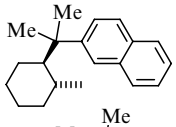
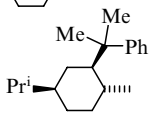
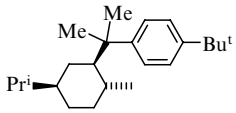
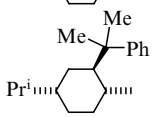
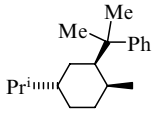
Presumably,[11] the destabilising steric interactions between the phenyl groups of the oxazolidine ring and the substituent R at C(5) are responsible for the preferable formation of the oxazolidines **22** rather than of their stereoisomers **22**.

A series of papers on the influence of chiral substituents at the nitrogen atom of azine substrates on the stereoselectivity of the reactions with organometallic reagents have been published by the Comins group. Thus 1-acylpyridinium salts **24** containing a residue of an optically active alcohol (R*OH) have been studied.[12–16] These salts have been synthesised from 4-methoxy-3-(triisopropylsilyl)pyridine and the corresponding chiral chloroformates. The salts **24a**,**b** react with organomagnesium compounds under very mild conditions.[13] Acid hydrolysis of the reaction mixture yields mainly dihydropyridones **25a**,**b**. The stereoselectivity of the reaction is relatively high, stereoisomers **26a**,**b** are the minor products.



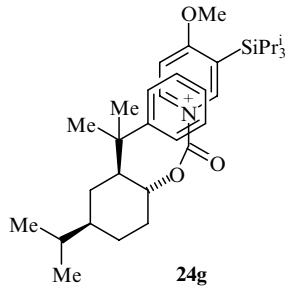

The effect of chiral acyl groups on the stereoselectivity of the addition reaction may be increased by introducing aromatic substituents into the alcohol residue.[14,15] Thus the diastereoselectivities of the reactions of *trans*-2-(α-cumyl)cyclohexyl derivatives of the salts **24c**–**f** with *p*-tolyl- and cyclohexylmagnesium halides were equal to 83% – 93%. Acylpyridinium salts **24g**–**i**, containing an isopropyl group in a similar chiral substituent, appeared to be slightly more effective as asymmetric inductors in this stereoselective synthesis (Table 1).[15]

**Table 1**. Reaction of 1-acylpyridinium salts **24a**–**j** with Grignard reagents.

| Compounds **24**–**26** | R* | R | Total yield (%) | *de* (%) (see [a]) |
|---|---|---|---|---|
| **a** |  [(−)-menthyl] | Ph | 87 | 44 |
| **b** |  [(−)-8-phenylmenthyl] | Me | 92 | 91 |
| | | Bu$^i$ (see [b]) | 95 | 92 |
| | | Cy (see [b]) | 90 | 81 |
| | | Ph | 88 | 94 |
| | | *o*-Tol | 81 | 60 |
| | | *p*-Tol | 90 | 82 |
| | | *p*-MeOC$_6$H$_4$ | 77 | 73 |
| | | *p*-ClC$_6$H$_4$ | 78 | 81 |
| **c** |  | *p*-Tol | 89 | 89 |
| | | Cy (see [b]) | 95 | 82 |
| **d** |  | *p*-Tol | 91 | 93 |
| | | Cy (see [b]) | 92 | 86 |
| **e** |  | *p*-Tol | 93 | 83 |
| | | Cy (see [b]) | 84 | 83 |
| **f** |  | *p*-Tol | 71 | 89 |
| | | Cy (see [b]) | 82 | 86 |
| **g** |  | *p*-Tol | 89 | 92 |
| | | Ph | 82 | 86 |
| **h** |  | *p*-Tol | 64 | 94 |
| | | Cy (see [b]) | 81 | 90 |
| **i** |  | *p*-Tol | 95 | 79 |
| | | Cy (see [b]) | 80 | 85 |
| **j** |  | Ph | 80 | 4 |

[a] Compound **25** is the predominant stereoisomer; [b] in these cases X = Br, in other examples X = Cl; Cy is cyclo-C$_6$H$_{11}$.

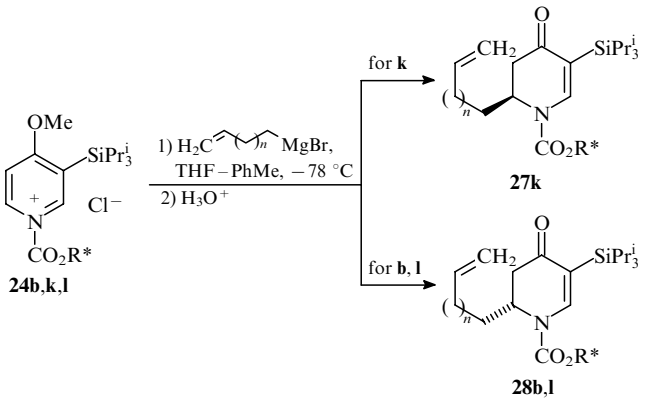
Presumably,[15] it is the steric shielding of one side of the pyridinium ring of salt **24** by bulky chiral acyl groups that determines the predominant direction of the nucleophilic attack. The process is enhanced by aryl substituents in these groups. The π–π-donor–acceptor interaction (further in the text, π–π-interaction) between the substituent and the pyridinium cation stabilises the staggered conformation.[16,17] The positive effect of the isopropyl group of the 8-arylmenthyl moiety on the stereoselectivity of the process is more difficult to rationalise. It was suggested [15,16] that the isopropyl group might affect the ratio of the possible rotamers leading to the optimum π–π-interaction between the aromatic rings.



**24g**

The non-stereoselectivity of the reaction of phenylmagnesium bromide with the salt **24j** where *vic*-substituents in the cyclohexane ring adopt a *cis*-configuration may be explained by the same reason.

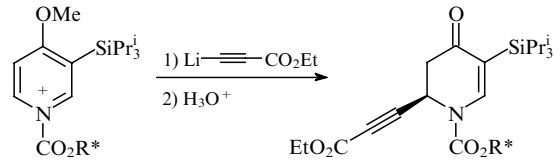
The configuration of the optical centre of the acyl group determines the ratio of the diastereomeric products. Thus the reaction of a homochiral 1-acylpyridinium salt **24k**, obtained by the reaction of chloroformate (as the acylating agent), R* = (+)-*trans*-2-(α-cumyl)cyclohexyl [(+)-TCC], with alkenylmagnesium bromides yielded dihydropyridones **27k**.[18,19] In the case of its optical antipode, *i.e.*, (−)-TCC-chloroformate, the reaction of acylpyridinium salt **24l** leads to the diastereomer of **27**, *i.e.*, dihydropyridone **28l**.[20,21] A similar result has been observed in the reaction of substrate **24b** containing a (−)-8-phenylmenthyl substituent.[22]



**24b**,**k**,**l** — **27k** — **28b**,**l**

| Salt **24** | R* | Reaction product | | | | Ref. |
|---|---|---|---|---|---|---|
| | | compound | *n* | yield (%) | *de* (%) | |
| **b** | (−)-8-Ph-menthyl | **28b** | 2 | 100 | 91 | 18 |
| **k** | (+)-TCC | **27k** | 1 | 91 | 90 | 14 |
| | | **27k** | 2 | 95 | 93 | 15 |
| **l** | (−)-TCC | **28l** | 1 | – | 90 | 16, 17 |

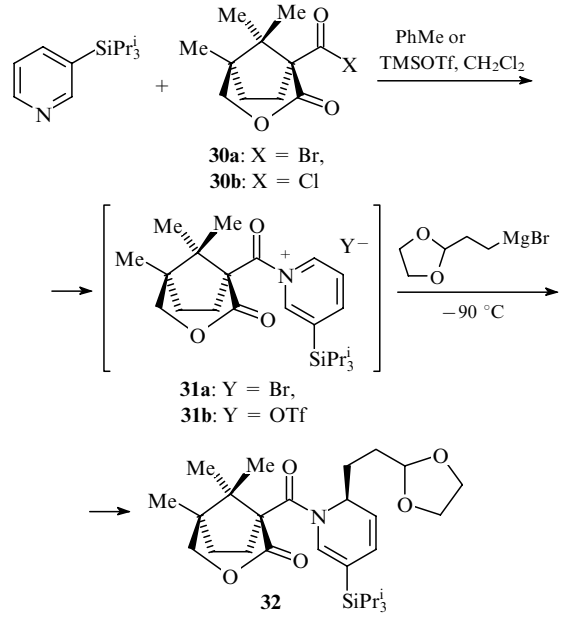
Similar stereochemistry of the addition products was observed with lithium acetylides used as C-nucleophiles instead of alkenylmagnesium bromides. Thus treatment of the salt **24k** with a Li-derivative of ethyl propiolate leads to dihydropyridone **29**.[23]



**24k** — **29k** (68%, *de* > 96%)

R* = (+)-TCC.

The reaction of 3-(triisopropylsilyl)pyridine with chiral bicyclic acyl bromide **30a** in pyridine yields solid *N*-acylpyridinium salt **31a**.[24] The addition of 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide at −90 °C to this heterogeneous system affords 6-substituted *N*-acyl-1,6-dihydropyridine **32**. The reaction is regio- and diastereoselective (yield 41%, *de* 100%). An analogous reaction was carried out with acyl chloride **30b** under homogeneous conditions,[24] which are more suitable for this reaction. In presence of trimethylsilyl triflate (TMSOTf), the addition product **32** is formed *via* intermediate salt **31b**. The yield of the product increased to 62%, but the diastereoselectivity of the process decreased to 88%.

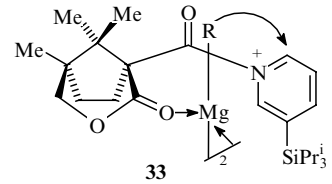


**30a**: X = Br,
**30b**: X = Cl

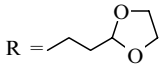
**31a**: Y = Br,
**31b**: Y = OTf

**32**

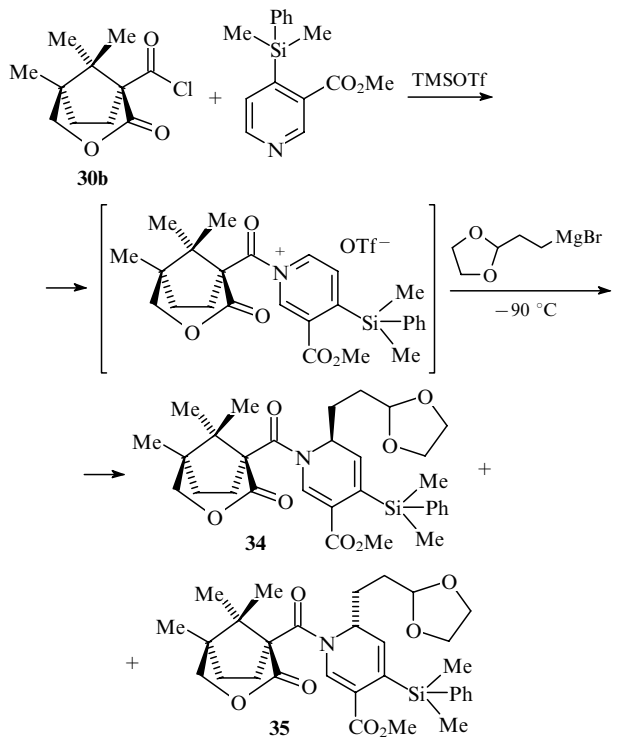
The asymmetric induction in the considered processes may be explained by preliminary complex formation. The reaction mechanism includes the initial coordination and addition of organometallic reagent to the carbonyl group of the chiral acyl substituent with formation of complex **33**. Judging from the stereochemistry of the addition product **32**, the attack of the nucleophilic agent on the iminium moiety proceeds as follows:



**33**

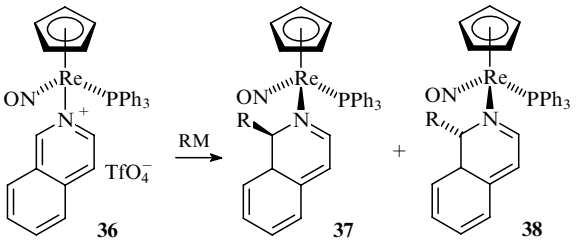


Later, this reaction was extended [25] to methyl dimethyl(phenyl)silylnicotinate in order to avoid addition at position 4. Compound **34** was isolated as the main product, while the stereoisomer **35** was a minor product (ratio **34** : **35** = 87.2 : 12.8).




An example of diastereoselective addition of C-nucleophile to isoquinoline **36**, activated by a chiral rhenium complex, has been described.[26] The reactions of compound **36** with organometallic compounds occur under very mild conditions and start at a temperature as low as −100 °C. The metallocomplex **37** is the main reaction product (*de* 46%–88%); small amounts of the diastereomer **38** were observed [reaction (1)].

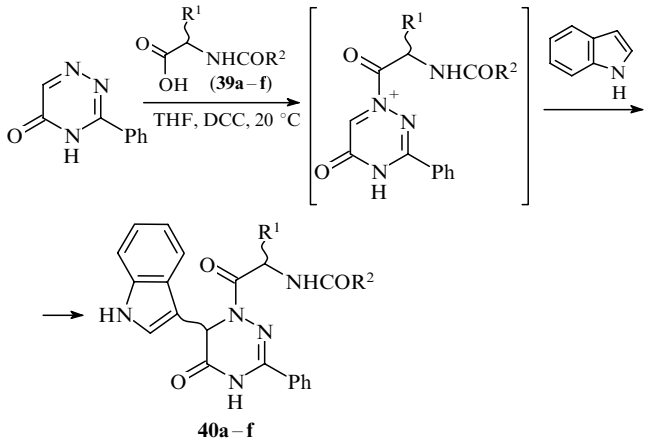
This reaction with $Me_3SiCH_2MgCl$ is significantly slower than that with $Me_3SiCH_2Li$. In the former case, the diastereoselectivity noticeably decreases with an increase in temperature. However, the Grignard reagent containing the secondary alkyl group, *viz.*, $Pr^iMgCl$, reacts with the complex **36** rapidly even at −100 °C. It is worth noting that MeMgCl is the least reactive nucleophile in this reaction.[26]




(1)

| RM | Temperature /°C | Ratio **37** : **38** |
|---|---|---|
| $Me_3SiCH_2Li$ | −55 | 94 : 6 |
| $Me_3SiCH_2MgCl$ | 20 | 80 : 20 |
| $Pr^iMgCl$ | −100 | 89 : 11 |
| EtMgBr | −100 | 89 : 11 |
| $PhCH_2MgCl$ | −100 | 88 : 12 |
| $Pr^nMgCl$ | −100 | 87 : 13 |
| MeMgCl | 20 | 84 : 16 |
| $Bu^nMgCl$ | −100 | 82 : 18 |
| AllMgBr | −100 | 73 : 27 |

π-Electron-donating heterocycles can be used as C-nucleophiles in reactions with azines. Thus 3-phenyl-1,2,4-triazin-5(4*H*)-one was acylated with *N*-protected α-amino acids **39a**–**f** activated by dicyclohexylcarbodiimide (DCC) and reacted with indole.[27] The addition products at the position 3 of indole, compounds **40a**–**f**, were obtained with high diastereoselectivity (*dr* > 95 : 5). The predominant formation of only one pair of diastereomers in this reaction was explained by a significant steric hindrance for the attack of the triazine ring caused by the amino acid residue. However, it is the same circumstances that are the reason for the low yields.[27]

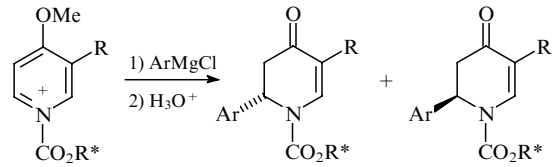



| Compound **40** | Starting amino acid **39** | Yield (%) |
|---|---|---|
| **a** | *N*-Boc-glycine ‡ | 42 |
| **b** | *N*-Bn-D,L-leucine | 26 |
| **c** | *N*-Ac-D-alanine | 28 |
| **d** | *N*-Ac-L-tryptophan | 21 |
| **e** | *N*-Ac-L-valine | 17 |
| **f** | *N*-Ac-D,L-phenylalanine | 22 |

These examples illustrate the significant influence of chiral substituents at the azine nitrogen atom on the stereoselectivity of the reactions with C-nucleophiles.

**b. The effect of an achiral substituent at a carbon atom of the azine ring on the reaction diastereoselectivity**

The most detailed investigation into the effect of the character and size of a 3-substituent in the pyridine ring on the diastereoselectivity of the addition of the Grignard reagents was carried out by Comins *et al.*[14] The authors of the cited paper studied the reactions of a series of optically active 4-methoxy-*N*-[(−)-menthyloxycarbonyl]pyridinium salts **24b**,**n**–**t** with arylmagnesium chlorides leading to 6-substituted compounds **25** and **26** (**25** being the main stereoisomer).




| Compounds **24**–**26** | R | R* | Ar | Yield (%) | *de* (%) |
|---|---|---|---|---|---|
| **b** | $SiPr^i_3$ | (−)-8-phenylmenthyl | Ph | 88 | 94 |
| | | | *o*-Tol | 81 | 60 |
| **m** | H | (−)-menthyl | Ph | 79 | 34 |
| | | (−)-8-phenylmenthyl | Ph | 83 | 30 |
| **n** | $SiMe_3$ | (−)-menthyl | Ph | 88 | 50 |
| | | (−)-8-phenylmenthyl | Ph | 82 | 65 |
| | | | *o*-Tol | 90 | 30 |
| **o** | $SiPr^n_3$ | | *o*-Tol | 88 | 40 |

‡ Boc is *tert*-butyloxycarbonyl.

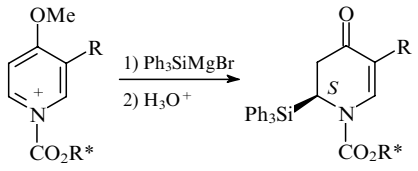
| Compounds **24**–**26** | R | R* | Ar | Yield (%) | *de* (%) |
|---|---|---|---|---|---|
| **p** | $SiBu^i_3$ | | *o*-Tol | 89 | 34 |
| **q** | $SiPh_3$ | | *o*-Tol | 85 | 18 |
| **r** | $SnBu^n_3$ | | Ph | 84 | 60 |
| **s** | $SnPr^i_3$ | | Ph | 80 | 84 |
| **t** | $SnCy_3$ | | Ph | 75 | 80 |

The original idea[14] was to increase the regioselectivity of the reaction by introducing a 3-substituent in the pyridinium ring, which would prevent nucleophilic attack on C(2). However, the substituent also affected the stereochemistry. Although no rigorous regularities were established, some qualitative conclusions could be drawn. The best diastereoselectivity (*de* 94%) was obtained in the reaction of 4-methoxy-3-(triisopropylsilyl)-pyridinium salt **24b** with phenylmagnesium chloride. The use of pyridinium salts with less bulky 3-alkylsilyl substituents in the reactions with aromatic Grignard reagents resulted in a decrease in *de* (in the range of 34%–40%). The triphenylsilyl substituent reduced the diastereoselectivity of the process even more (down to 18%).[14]

### c. The effect of the character of the nucleophile on the stereochemistry of addition reactions of nucleophilic reagents to chiral *N*-acylazinium salts

As was mentioned above, a broad spectrum of addition products have been obtained in reactions of chiral *N*-acylpyridinium salts with Grignard reagents.[13,28,29] Derivatives of indolizine,[21,30] quinolizidine,[31] piperidine[30,32–36] and *cis*- and *trans*-decahydroquinoline[19,22] alkaloids were synthesised from other optically active *N*-acylazinium salts and organometallic compounds. Only one of the possible diastereomers is formed predominantly in these reactions and its stereochemistry depends on the configuration of the chiral acyl group.[13,14,22] Examples of the effect of the character and stereochemistry of the attacking nucleophilic reagent on the product configuration are given below.

**Characteristic features of the introduction of the triphenylsilyl group into chiral *N*-acyl-4-methoxypyridinium salts**. The reaction of triphenylsilylmagnesium bromide (Si-nucleophile) with chiral *N*-acyl-4-methoxypyridinium salt **24b** at −78 °C is stereoselective and results in diastereomerically pure *N*-acyl-2-(triphenylsilyl)-2,3-dihydropyridin-4-one **41b** (yield 73%, *de* 96%).[37] The reaction of this nucleophile with 3-unsubstituted salt **24m** leads to compound **41m** (*de* 96%) in 88% yield. It appeared that the absolute configuration of the newly formed chiral centre C(2) of dihydropyridones **41b**,**m** is opposite to that of the main reaction product of pyridinium salts **1** with arylmagnesium chlorides as C-nucleophiles (see above). In addition, it was shown that the trimethylsilyl group at position 3 of the starting salt did not affect the asymmetric induction in this reaction.[37,38]




**24b**,**m** **41b**,**m**

R = $Me_3Si$ (**b**), H (**m**); R* = (−)-8-phenylmenthyl.

The preferential formation of *S*-isomer is explained[38] by the interaction of the magnesium atom of the Grignard reagent with the carbonyl group of the acyl fragment (Fig. 1). This coordination results in the alteration of the direction of the nucleophilic attack, which was confirmed by quantum-chemical calculations.

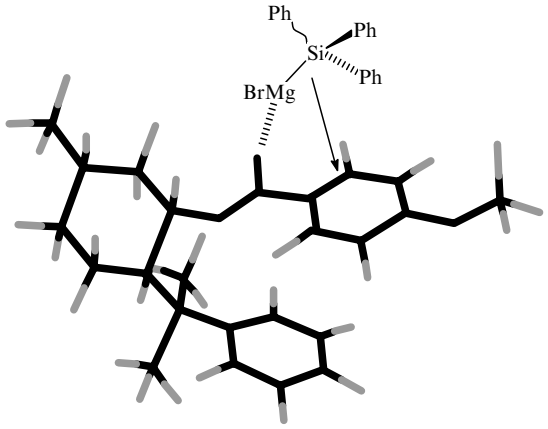
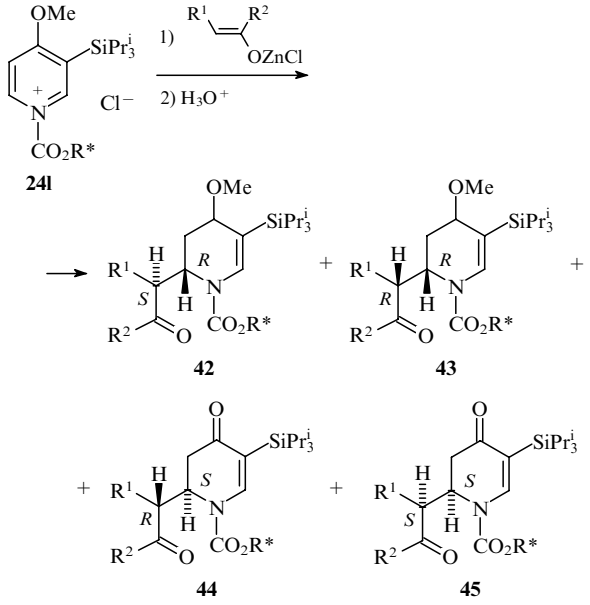



**Figure 1.** The molecular mechanic model of addition of triphenylsilylmagnesium bromide to chiral *N*-acyl-4-methoxypyridinium salts **24**.[38]

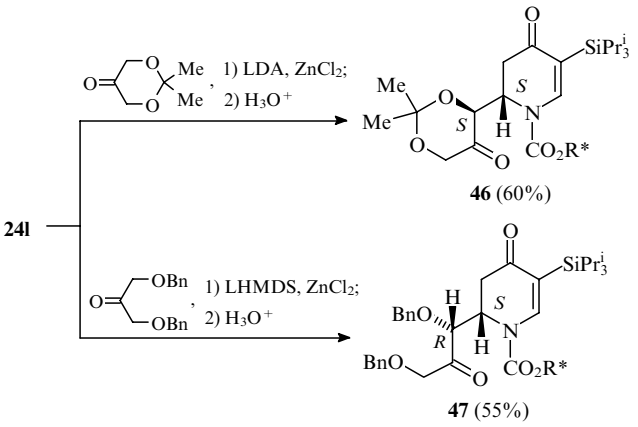
**Characteristic features of the addition of metalloenolates to chiral *N*-acylpyridinium salts** The addition reactions of prochiral metalloenolates of ketones and lactones with salts **24** are highly stereoselective and result in the formation of two new chiral centres.[3,39] The 2*R*,2′*S*-diastereomer **42** is the main reaction product, while (*R*,*R*)-**43**, (*S*,*R*)-**44** and (*S*,*S*)-**45** stereoisomers were obtained in minor amounts.




R* = (−)-TCC.

| $R^1$ | $R^2$ | Ratio **42** : (**43** + **44** + **45**) | Yield of **42** (%) |
|---|---|---|---|
| $-CH_2CH_2CH_2-$ | | 88 : 12 | 82 |
| $-CH_2CH_2CH_2CH_2-$ | | 86 : 14 | 79 |
| Me | Et | 92 : 8 | 83 |

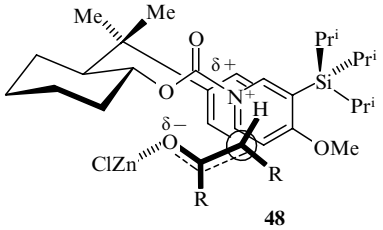
Interestingly, this reaction with the enol form of 2,2-dimethyl-1,3-dioxan-5-one (*E*-isomer) yields compound **46** with (2*S*,2′*S*)-configurations of chiral centres. Compound (2*S*,2′*R*)-**47** with the opposite configuration is formed as the main product in a similar reaction with 1,3-bis(benzyloxy)propan-2-one in the enol form, which exists as *Z*-isomer due to formation of a chelate.[39]




**24l**

R* is (−)-TCC, LDA is lithium diisopropylamide, LHMDS is lithium hexamethyldisilazide.

The selectivity of the addition of *E*-enolate may be explained by the existence of a transition state



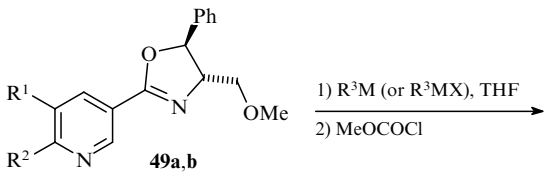
**48**

This transition state is the most probable due to a non-covalent interaction between the pyridinium ring and the phenyl ring of the chiral acyl group (π−π-interaction) and also due to electrostatic attraction between the positively charged nitrogen atom and the negatively charged enolate oxygen atom.[39]

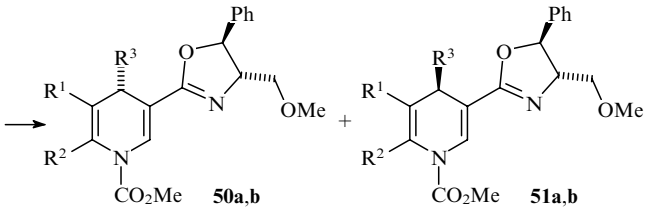
## 2. Reactions of azines containing a chiral atom in the ring

The presence in the azine ring of substituents capable of coordinating the attacking particle is an important factor determining the stereochemical composition of products of a nucleophilic reaction on a carbon atom of a double C=N bond in azines. Thus examples of insertion of functional groups capable of complexation with nucleophiles at the β-position of pyridine and quinoline rings are given in papers[40–42].

One of the first reported reactions of diastereoselective nucleophilic addition to pyridinium and quinolinium salts with initial complexation is the reaction of chiral 2-(3-pyridyl)- (**49a**) and 2-(3-quinolyl)oxazolines (**49b**) with organolithium and -magnesium reagents followed by treatment with methyl chloroformate.[42] This reaction affords the corresponding 1,4-dihydro-derivatives **50a**,**b** and **51a**,**b** in good yields and high diastereomer ratio (*de* > 95%). Replacement of pyridine by quinoline increases the diastereoselectivity of the process. Thus in the reaction of compound **49a** with methyllithium the ratio of the corresponding diastereomers **50a** : **51a** is 93 : 7, while in the case of quinoline derivative **49b** this ratio is equal to 98 : 2.



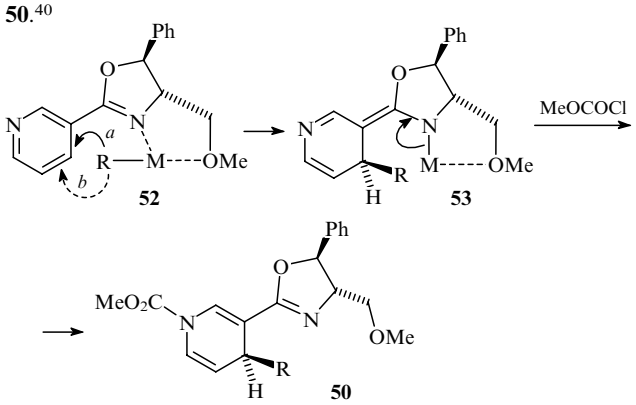

**49a**,**b**



**50a**,**b** **51a**,**b**

| Compounds **49**–**51** | $R^1$, $R^2$ | $R^3M$ or $R^3MX$ | $T$ /°C | Ratio **50** : **51** | Total yield (yield of **50**) (%) |
|---|---|---|---|---|---|
| **a** | H | MeLi | −40 | 93 : 7 | 79 |
| | | | −78 | 94 : 6 | 79 (63) |
| | | MeMgCl | 0 | 91 : 9 | 88 |
| | | EtMgBr | 0 | 92 : 8 | 63 |
| | | $Bu^nLi$ | −78 | 97 : 3 | (92) |
| | | $Bu^nMgCl$ | 0 | 95 : 5 | 98 |
| | | PhLi | −78 | 92 : 8 | 94 |
| **b** | $C_6H_4$ | MeLi | −78 | 98 : 2 | 84 (70) |

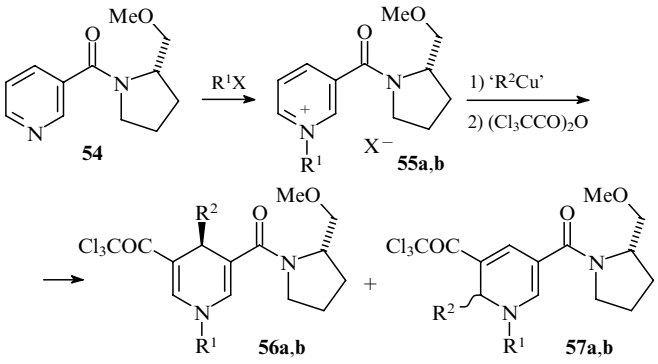
The high stereoselectivity of the addition was explained by initial coordination of an organometallic compound (RM or RMX) to the nitrogen atom and the methoxy group of oxazoline, which leads to the formation of a complex **52** followed by the attack of the group R on the position 4 of the pyridine ring. The addition of RM (or RMX) from different sides of the plane of the ring (paths *a* and *b*) results in products with different stereochemistry. High stereoselectivity of the studied reactions implies that the most common reaction pathway is the path *a*. It was suggested that lithium or magnesium derivatives **53**, formed upon addition of organometallic compound RM (or RMX) to pyridine **49a**, are acylated with methyl chloroformate to afford compound **50**.[40]




**52** **53** **50**

However, an alternative mechanism for the formation of adducts **50** and **52** was suggested:[13] the initial *in situ* formation of *N*-acylazinium salts upon acylation with chloroformate with consequent addition of an alkyl or phenyl group R to the C(4) atom of the pyridine heterocycle. Obviously, the reaction mechanism depends on the order of addition of the reagents.

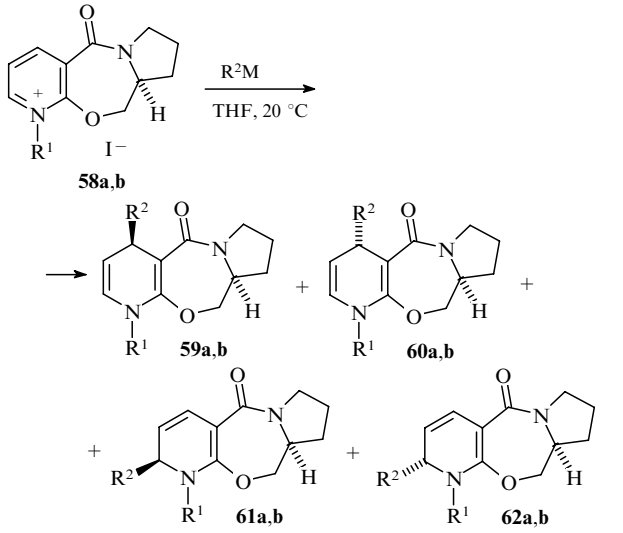
Pyridinium salts **55a**,**b** were obtained by alkylation of nicotinamide **54** with methyl iodide and benzyl bromide, respectively, and then reacted with lithium organocuprates.[43] The expected adducts **56a**,**b** (diastereomer ratio varies from 2.5 : 1 to 9 : 1, only the main product is shown in the Scheme) and **57a**,**b** (*dr* = 1 : 1) were isolated after acylation of the reaction mixture with trichloroacetic anhydride.



$R^1$ = Me (**a**), Bn (**b**); X = I (**a**), Br (**b**); $R^2$ = Me, $Bu^n$, Ph.

| Compound **55** | 'R²Cu' | Reaction products (ratio) | *dr* (for **56**) | Total yield (%) |
|---|---|---|---|---|
| **a** | $Me_2CuLi$ | **56a** + **57a** (2 : 1) | 4 : 1 | 43 |
| | $Bu^n_2CuLi$ | **56a** | 9 : 1 | 62 |
| | $Ph_2Cu(CN)Li_2$ | **56a** + **57a** (4.5 : 1) | 5 : 1 | 50 |
| **b** | $Bu^n_2CuLi$ | **56b** | 4 : 1 | 34 |
| | $Ph_2Cu(CN)Li_2$ | **56b** + **57b** (1.6 : 1) | 2.5 : 1 | 37 |

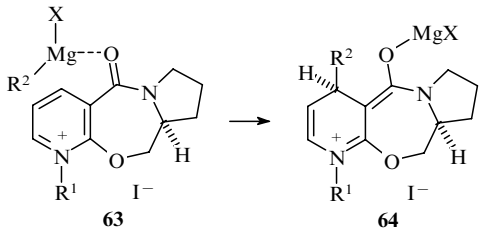
An example of the complexation effect on the stereoselective addition of nucleophiles to pyridinium salts is documented.[41] Reactions of 1-methyl- (**58a**) and 1-benzylpyridoxazepinone (**58b**) salts with alkyl-, alkenyl- and phenyl-magnesium bromide result in the products **59a,b** with high stereoselectivity and in good yields. Stereo- and regioisomers **60a**,**b** – **62a**,**b** are found in minor amounts. The process becomes less selective where organolithium compounds are used instead of the Grignard reagents.



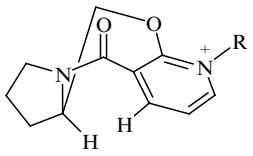
$R^1$ = Me (**a**), Bn (**b**).

| Compounds **58** – **62** | $R^2M$ | Product ratio (**59** + **60**) : : (**61** + **62**) | **59** : **60** | **61** : **62** | Yield of **59** (%) |
|---|---|---|---|---|---|
| **a** | MeLi | 1 : 1 | 3 : 1 | 3 : 1 | – |
| | $Bu^nLi$ | 3 : 1 | 2 : 1 | 1 : 0 | – |
| | MeMgBr | 19 : 1 | 19 : 0 | 1 : 0 | 72 |
| | $Bu^nMgBr$ | 57 : 1 | 57 : 0 | 1 : 0 | 60 |
| | $Bu^iMgBr$ | > 99 : 1 | 99 : 0 | 1 : 0 | 95 |
| | $CH_2=CHMgBr$ | > 99 : 1 | 99 : 0 | 1 : 0 | 74 |
| | $CH_2=CHCH_2MgBr$ | 5.5 : 1 | 4 : 1.5 | 1 : 0 | – |
| | PhMgBr | 98 : 0 | 98 : 0 | 2 : 0 | 88 |
| **b** | MeLi | 1.75 : 1 | 3 : 0.5 | 1 : 1 | – |
| | MeMgBr | 15 : 1 | 75 : 0 | 4 : 1 | 87 |
| | PhMgBr | > 99 : 1 | 99 : 0 | 1 : 0 | 83 |

In this case, the high regio- and stereoselectivity of the reaction is explained by the coordination of the Grignard reagent to the amide oxygen atom, which leads to the formation of complex **63**. The transfer of the organic fragment from the magnesium atom to C(4) of the pyridine ring results in the enolate **64**; its hydrolysis leads to compounds **59** – **62**.[41]

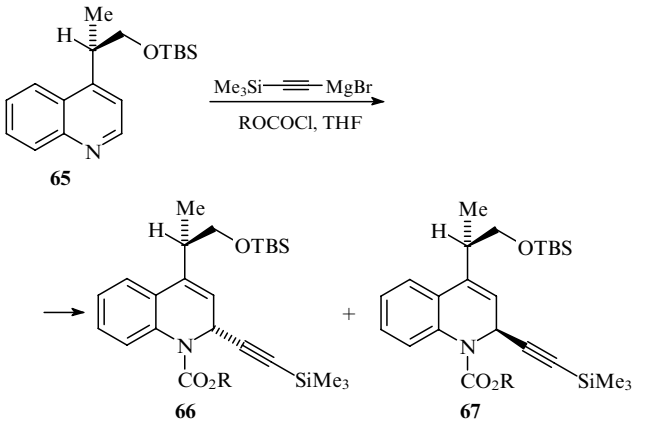


Studies on the conformational behaviour of compounds **58a**,**b** reveal that the seven-membered ring is relatively rigid and only two energetically favourable conformations are possible (only one is shown).[41]



In this conformation, the amide carbonyl group is located above the pyridinium ring plane in an *anti*-position relative to the hydrogen atom in the chiral centre, while in the second conformer the carbonyl group and the pyridinium ring are coplanar. It is remarkable that the conformations of compounds **58** where the carbonyl amide group is arranged under the pyridinium ring are energetically unfavourable. Therefore, the intermolecular shift of the group $R^2$ of the complex **63** through a six-membered transition state can lead predominantly to the isomer **64**.[43]

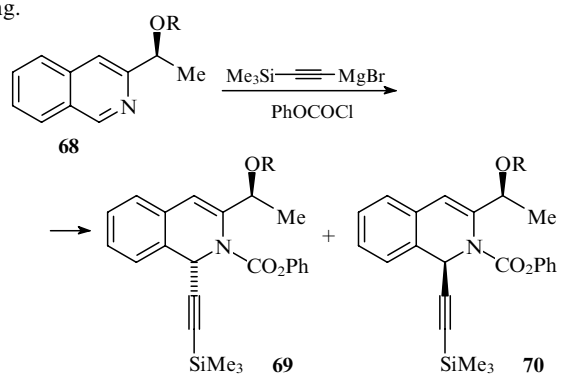
Diastereoselective addition of (trimethylsilyl)ethynylmagnesium bromide to optically active quinolines **65** in the presence of alkyl (or aryl) chloroformates produces compounds **66** and **67** in good yields and moderate diastereoselectivity.[44,45] This is the result of steric hindrance created by bulky substituents at position 4 of the quinoline ring.



| R | Temperature /°C | Total yield (%) | Ratio (±)-**66** : (±)-**67** |
|---|---|---|---|
| Me | 0 | 78 | 66 : 34 |
| Bn | –78 to –2 | 72 | 59 : 41 |
| Ph | –78 to 0 | 87 | 68 : 32 |
| Ph | –78 | 66 | 67 : 33 |

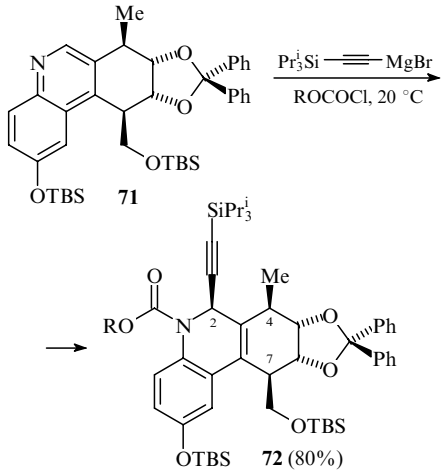
An example of nucleophilic addition to isoquinoline with a chiral substituent at position 3 is known.[46] Diastereoselective addition of (trimethylsilyl)ethynylmagnesium bromide to isoqui-

nolines **68** in the presence of aryl chloroformates yields compounds **69** and **70** with high diastereoselectivities due to the presence of a chiral substituent at position 3 of the isoquinoline ring.



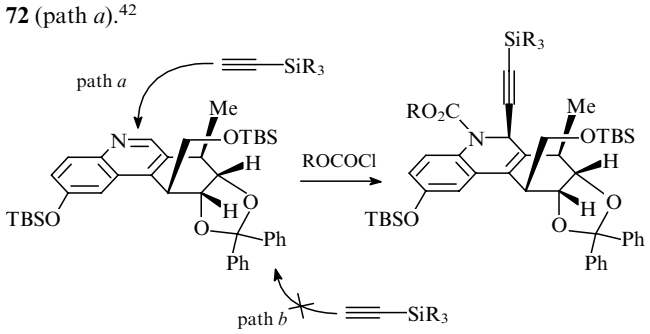

| R | Total yield (%) | Ratio **69** : **70** |
|---|---|---|
| $SiMe_2Bu^t$ | 88 | 87.3 : 12.7 |
| $SiPh_2Bu^t$ | 82 | 94.6 : 5.4 |
| $CPh_3$ (Tr) | 30 | 90.4 : 9.6 |

In the total synthesis of antibiotic dynemycin A, alkyne radicals were introduced into a substituted tetrahydrophenanthridine containing chiral centres in the cyclohexane moiety.[42] A mixture of diastereomers in the ratio of 9 : 1 was obtained upon treatment of compound **71** with chloroformate in the presence of the Grignard reagent, (triisopropylsilyl)ethynylmagnesium bromide. Compound **72** was the main isomer, which was formed as a result of *cis*-addition (relative to the 4- and 7-substituents) of the alkyne fragment to the pyridinium C(2) atom.[42]

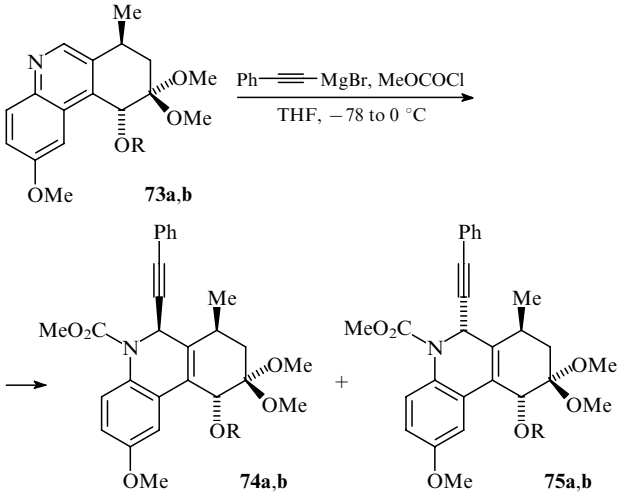



TBS is *tert*-butyldimethylsilyl; R = Me, All.

The starting compound **71** is sterically severely hindered for the attack along the path *b*; therefore, the addition is stereoselective and proceeds with predominant formation of compound **72** (path *a*).[42]

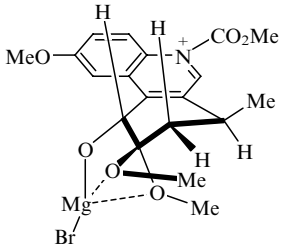



Tetrahydrophenanthridines **73a**,**b** react similarly with phenylethynylmagnesium bromide in the presence of methyl chloroformate. It was found[47] that the non-protected compound **73a** forms predominantly a *cis*-addition product **74a** (relative to the methyl group), the ratio **74a** : **75a** = 11 : 1, while TBS-protected analogue **73b** produces a diastereomer mixture in which *trans*-addition product **75b** is dominant (ratio **74b** : **75b** = 1 : 1.5).

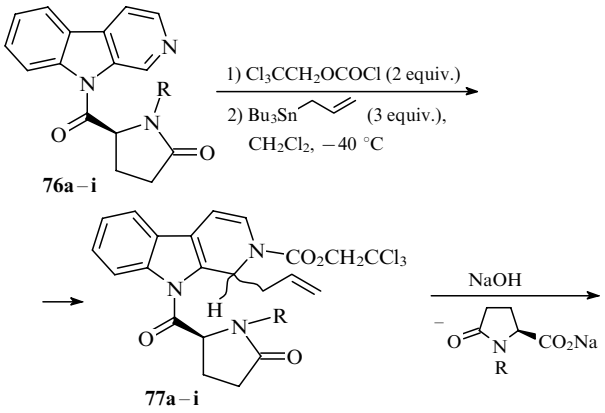


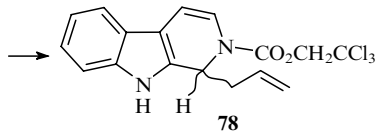

R = H (**a**), TBS (**b**).

This fact was explained by a half-chair conformation of the intermediate alkoxide formed from compound **73a** in which the magnesium counterion is chelated by one or two oxygen atoms of the methoxy groups. This leads to *pseudo*-equatorial orientation of the methyl substituent in compound **74a**. As a result, the axial addition of acetylide at the *cis*-position relative to this Me group is facilitated.[47]




The reaction of 9-acyl-β-carbolines **76a**–**i** activated by 2,2,2-trichloroethyl formate with allyl(tri-n-butyl)tin produces 1,2-dihydroadducts **77a**–**i**; their subsequent hydrolysis occurs with elimination of optically active sodium salt of 5-oxoproline.[48,49] The configuration of the remaining chiral centre in the obtained alkylated dihydro-β-carbolines **78a**–**i** depends on the character of substituent R in the adduct **77**.





**78**

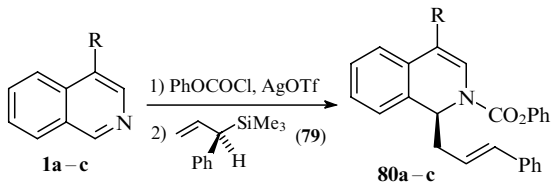
| Compounds **76**, **77** | R | Yield of **77** (%) | Product **78** | |
|---|---|---|---|---|
| | | | configuration | *ee* (%) |
| **a** | Me | 22 | *S* | 7 |
| **b** | Bn | 95 | *S* | 21 |
| **c** | 1-naphthylmethyl | 87 | *S* | 58 |
| **d** | 2-naphthylmethyl | 100 | *S* | 66 |
| **e** | 9-anthrylmethyl | 98 | *S* | 91 |
| **f** | MeCO | 100 | *R* | 89 |
| **g** | PhCO | 92 | *R* | 83 |
| **h** | 9-anthrylcarbonyl | 56 | *R* | 83 |
| **i** | *p*-$NO_2C_6H_4CO$ | 100 | *R* | 88 |

The stereoselectivity of the addition reaction of β-carbolines **76a**–**e** containing *N*-alkylpyroglutaminyl fragments linearly increases with an increase in the size of the substituent R. One side of the β-carboline molecule is shielded, probably due to steric hindrance. In the case of *N*-acylpyroglutaminyl derivatives **76f**–**i**, stereoisomers with opposite configuration of the chiral centre are formed with virtually the same enantioselectivity.[48] One can suggest that in this case another conformation of the adduct **77** is more favourable and therefore the size of the substituent little affects the selectivity of the process.

## III. Stereoselective addition of an optically active nucleophile to an achiral azine

In all previously discussed cases, optically active azine substrates reacted with nucleophilic agents. Steric factors caused by the presence of a chiral azine substituent effectively determined the asymmetric character of the synthesis. Another variant of obtaining optically active azine derivatives where a chiral nucleophile reacts with an achiral amine is rather interesting and much less investigated. In this case, the direction of a nucleophilic attack mostly depends on the structure of the attacking species. It is possible to achieve stereoselective formation of products with the desired configuration by varying the reaction conditions.

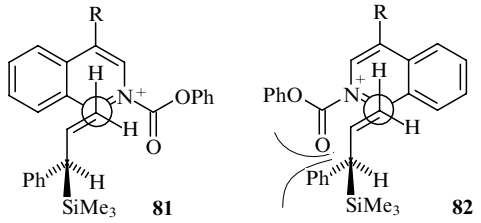
Yamaguchi and co-authors[50] have performed the enantioselective addition of chiral (*R*)-phenyl-3-trimethylsilylprop-1-ene (**79**) with *N*-acylisoquinolinium salts obtained from isoquinolines **1a**–**c**. (*S*)-1-[(*E*)-3-phenylprop-2-enyl]-1,2-dihydroisoquinolines **80a**–**c** are formed in this process with high enantioselectivity.



**1a**–**c** **80a**–**c**

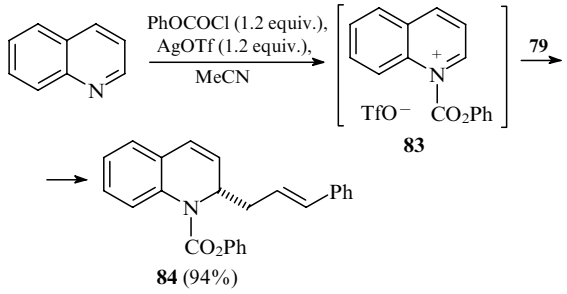
| Compounds **7**, **80** | R | Yield (%) | *ee* (%) |
|---|---|---|---|
| **a** | H | 54 | 95 |
| **b** | Br | 86 | 94 |
| **c** | $CO_2Me$ | 78 | 93 |

The authors suggest[50] that this addition proceeds with formation of an antiperiplanar transition state **81**, which leads to the *S*-adduct. The transition state **82**, which is a precursor of the *R*-adduct, is less energetically favourable.



**81** **82**

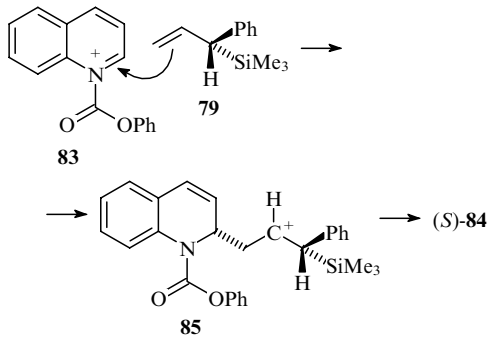
Stereoselective addition of chiral allylsilane **79** to activated quinolines has been described.[51] As a result of the reaction with quinolinium salt **83**, an optically active 2-substituted 1,2-dihydroquinoline **84** (*ee* 77%) is formed.



**83**

**84** (94%)

Several possible reaction pathways have been proposed.[51] The most preferential is believed to be that including the formation of intermediate **85**. Elimination of the trimethylsilyl group yields the product with *S*-configuration of the chiral centre.

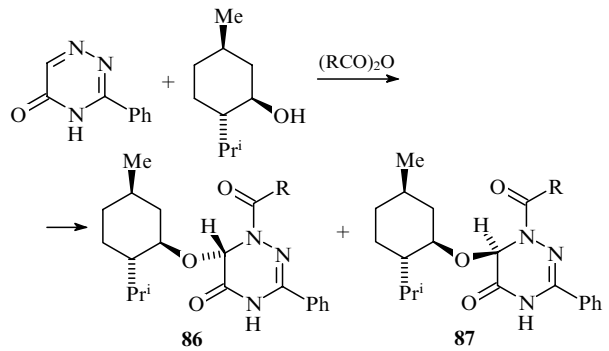


**79**

**83**

**85**

No reactions of stereoselective addition of chiral C-nucleophiles to triazines have been described yet; however, a reaction with an optically active O-nucleophile, *viz*., a natural alcohol L-menthol is known. Thus the addition of enantiomerically pure L-menthol at the unsubstituted carbon atom of 3-phenyl-1,2,4-triazin-5(4*H*)-one activated by acid anhydrides yields a mixture of diastereomers **86** and **87**,[52, 53] the diastereomers **86** being the major products. It was also established that the diastereoselectivity of the reaction depends on the size of the acylating agent. In the case of acetic anhydride (R = Me), the diastereomer ratio **86** : **87** is equal to 60 : 40, while with the more sterically hindered isobutyric anhydride (R = $Pr^i$) this ratio is increased to 85 : 15.[52, 53]



**86** **87**

R = Me, $Pr^i$.

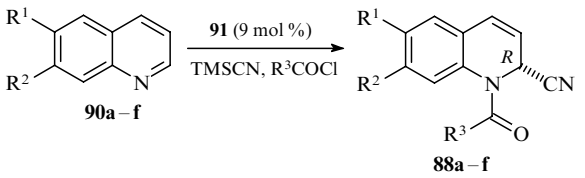
The predominant formation of stereoisomers **86** is explained [53] by steric factors.

## IV. Asymmetric induction in the attack of an achiral nucleophile at an achiral azine

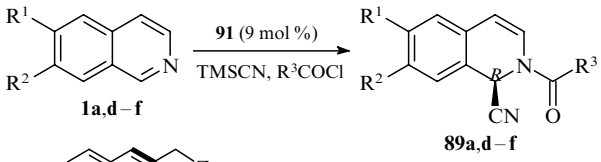
Asymmetric induction in a reaction of an achiral nucleophile with an achiral azine substrate is possible only where optically active solvents, additives or catalysts are used.

Shibasaki *et al.*[54–57] have investigated the formation of Reissert compounds **88a–f** and **89a,d–f** from quinolines **90a–f** and isoquinolines **1a,d–f** catalysed by chiral bifunctional catalysts based on binaphthyl **91**. The enantioselectivity of the reactions (2) and (3) is believed to depend on the character of the substituent $R^3$ in the acyl chloride. For example, in the presence of the electron-rich and, therefore, relatively inert 2-furoyl chloride the reactions are more selective than in the case of acetyl chloride. The polarity of the solvent also strongly affects the enantioselectivity. Thus it was found that the *ee* of the reaction of quinoline with the most reactive benzoyl chloride in non-polar solvents (toluene, benzene) increases from 71% to 78%, although the yield decreases. The use of more polar acetonitrile in this reaction results in a decrease in *ee* down to 37%. The substitution of $P(O)(o\text{-Tol})_2$ for $P(O)Ph_2$ (Z) in the catalyst **91** makes it a stronger Lewis base and as a result the yield and the enantioselectivity of reaction (2) increase.

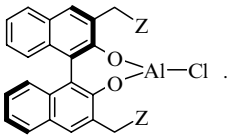
Although the mechanisms of reactions (2) and (3) have not been elucidated so far, it is obvious that the reactions should be accelerated due to double activation of *N*-acyl(iso)quinolinium ion and of TMSCN by the catalyst **91**. Azinium ion is activated by the Lewis acid (an Al atom) and TMSCN, by the Lewis base (an oxygen atom of the P=O group), which are constituents of the structure of catalyst **91**. In a control run with the catalyst **91** where $Z = CHPh_2$, which provides only steric restrictions, the direction of the addition process changes and enantioselectivity decreases significantly. Thus the reaction of quinoline with TMSCN in the presence of benzoyl chloride and catalyst **91** ($Z = CHPh_2$), which is not a Lewis base, leads to the formation of 1-benzyl-1,2-dihydroquinoline-2-carbonitrile mainly with *S*-configuration of the chiral centre (yield 73%, *ee* 24%).




(2)



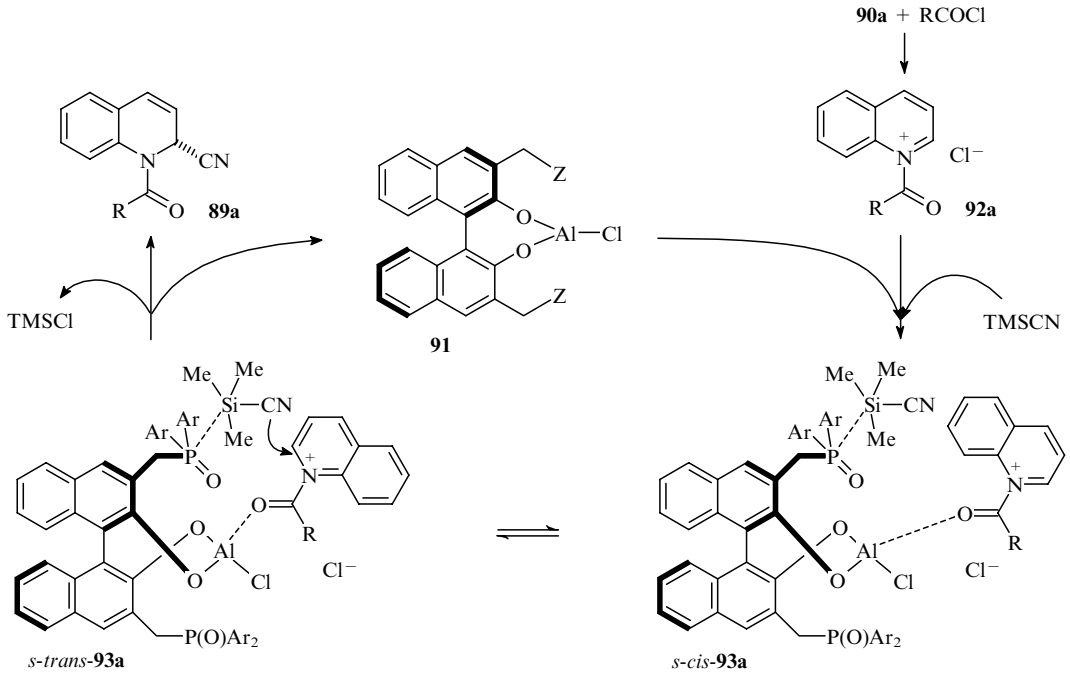

(3)




| Azine | $R^1$ | $R^2$ | $R^3$ | Z | Yield (%) | *ee* (%) |
|---|---|---|---|---|---|---|
| **90a** | H | H | Ph | $P(O)Ph_2$ | 70 | 71 |
| | | | Me | $P(O)Ph_2$ | 42 | 58 |
| | | | 1-naphthyl | $P(O)Ph_2$ | 63 | 46 |
| | | | 2-furyl | $P(O)Ph_2$ | 58 | 73 |
| | | | | $P(O)(o\text{-Tol})_2$ | 91 | 85 |
| **90b** | OMe | H | | $P(O)(o\text{-Tol})_2$ | 74 | 89 |
| **90c** | $NMe_2$ | H | | $P(O)(o\text{-Tol})_2$ | 72 | 89 |
| **90d** | OMe | OMe | | $P(O)(o\text{-Tol})_2$ | 99 | 91 |
| **90e** | $OCH_2O$ | | | $P(O)(o\text{-Tol})_2$ | 77 | 83 |
| **90f** | Cl | H | | $P(O)(o\text{-Tol})_2$ | 57 | 67 |
| **1a** | H | H | Me | $P(O)Ph_2$ | 99 | 71 |
| | H | H | 2-furyl | $P(O)(o\text{-Tol})_2$ | 91 | 85 |
| **1d** | OMe | H | | $P(O)(o\text{-Tol})_2$ | 74 | 89 |
| **1e** | $OCH_2O$ | | | $P(O)(o\text{-Tol})_2$ | 77 | 83 |
| **1f** | Cl | H | | $P(O)(o\text{-Tol})_2$ | 57 | 67 |

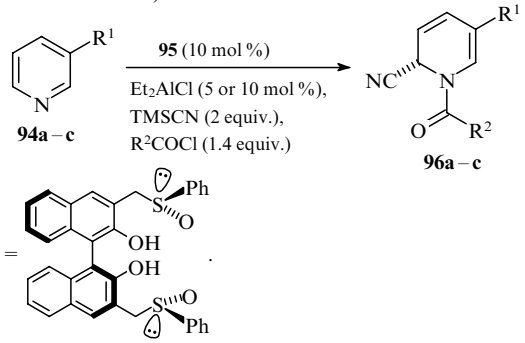
A scheme of the catalytic cycle with unsubstituted quinoline as a model compound has been suggested [54–57] (Scheme 3). In the first step, the reaction of quinoline with acyl chloride results in formation of *N*-acylquinolinium intermediate **92a**. Then the acylquinolinium ion is activated due to complexation of the

Scheme 3



amide oxygen with the Lewis acid (Al atom of chiral catalyst). Two conformers, *s-trans*-**93** and *s-cis*-**93**, exist in equilibrium. However, the reaction will occur with preferable formation of compound *s-trans*-**93** upon activation of TMSCN with the catalyst **91**. The distance between the coordinated TMSCN and the electrophilic carbon atom in the *s-cis*-isomer is too large for successful catalytic reaction. Hypothetical transition state *s-trans*-**93** explains the formation of the product with *R*-configuration.

Later, the asymmetric bifunctional catalyst **91** was modified, which provided the possibility of performing similar reactions with pyridine derivatives **94a**–**c**. Thus the reaction of pyridine **94b** with TMSCN catalysed by chiral binaphthyl **91** [Z = P(O)Ph$_2$] in the presence of carboxylic acid chlorides occurs with low enantioselectivity (*ee* < 9%) to give a mixture of addition products with the cyano group at positions 2 and 6 of the pyridine ring in a ratio of 2.3 : 1.[57] The use of the catalyst **95** increased the regioselectivity of the process. 2-Cyano-substituted pyridines **96a**–**c** with *S*-configuration (*ee* 96%) were predominantly formed (the ratio of 2- and 6-addition products varied from 12 : 1 to 50 : 1 depending on the substituent R$^1$).[54–57]

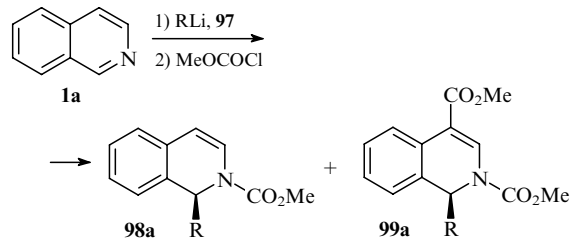


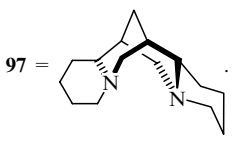




| Compound **96** | R$^1$ | R$^2$ | Yield (%) | *ee* (%) |
|---|---|---|---|---|
| **a** | $NMe_2$ | Me | 98 | 91 |
| | | fluorenylmethyl | 89 | 93 |
| **b** | $NPr^i_2$ | | 98 | 96 |
| | | neo-$C_5H_{11}C(O)$ | 98 | 93 |
| **c** | OMe | fluorenylmethyl | 85 | 57 |

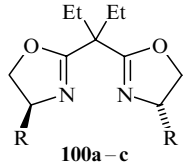
Enantioselective addition of organolithium compounds to isoquinoline under very mild conditions in the presence of a chiral ligand (−)-sparteine (**97**) has been described.[58] These reactions produce either a mixture of chiral dihydroisoquinolines **98a**, **99a** (for R = Me, Bu$^n$) or compound **98a** (R = Ph) alone.



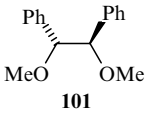

| R | *T* /°C | Yield (%) | Ratio **98a** : **99a** | *ee* **98a** (%) | *ee* **99a** (%) |
|---|---|---|---|---|---|
| Me | −40 | 77 | 75 : 25 | 42 | 48 |
| Bu$^n$ | −80 | 85 | 70 : 30 | 57 | – |
| Ph | −40 | 34 | – | 25 | – |

Later, the reactions of azines with organolithium reagents were studied in detail[59,60] using non-substituted quinoline (**90a**) as a substrate. Not only were the conditions (temperature, solvent) varied, but also a large number of chiral catalysts were used including sparteine (**97**), bisoxazolines **100**, chiral diether **101**, as well as symmetrical (**102**) and non-symmetrical (**103**) 1,2-diamines.

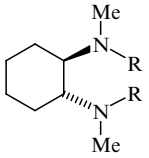



**100a**–**c**

R = Pr$^i$ (**a**), Bu$^t$ (**b**), Bn (**c**)

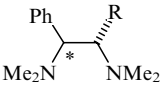



**101**




**102a**–**d**

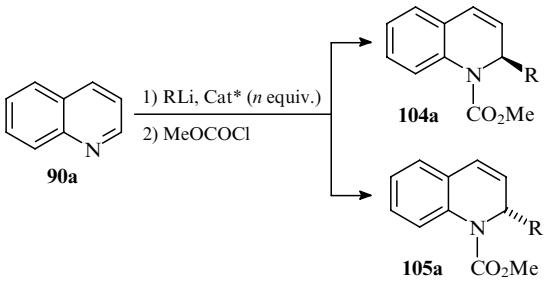
R = Me (**a**), neo-$C_5H_{11}$ (**b**), $(CH_2)_2Bu^t$ (**c**), Bn (**d**)




**103a**–**c**

(*R*)-Ph: R = Me (**a**);
(*S*)-Ph: R = Me (**b**), Ph (**c**)

Treatment of the reaction mixture with methyl chloroformate affords dihydroisoquinolines **104a** or **105a**, the chiral centre formed having *R*- or *S*-configuration depending on the type of the chiral catalyst and the nature of the radical R in the organolithium compound.




(4)

Cat* is a chiral catalyst.

The results of these investigations are listed in Table 2. The following conclusions can be drawn on the basis of data obtained.

(*R,R*)-Dimethoxydiphenylethane (**101**) appeared to be an inefficient chiral catalyst: dihydroquinolines **104a** were obtained in reasonable yields but with low enantioselectivity (*ee* 2%–26%). Dihydroquinolines **105a** with opposite configuration of the chiral centre were prepared using (−)-sparteine (**97**) as the catalyst; the enantioselectivity of this process increased (especially in the reaction with phenyllithium) and in some cases (R = Bu$^n$) the yield of the product was quantitative. Bis(oxazolines) showed the best selectivity as chiral catalysts; in the reaction of quinoline with methyllithium and catalyst **100a**, *ee* was equal to 63%; the resulting dihydroquinolines had *S*-configurations.[59,60]

The use of *N,N′*-tetramethylcyclohexane-1,2-diamine **102a** (TMCDA) was rather successful with 1-naphthyllithium as a nucleophile: the yield of dihydroquinoline **105a** (R = 1-naphthyl) was 75% (*ee* 64%). Replacement of methyl substituents at the nitrogen atoms of the catalyst **102a** by bulkier alkyl groups (compounds **102b**–**d**) resulted in reduction of the yields and a sharp decrease in diastereoselectivity of the reaction (4).[60]

The study of *N,N′*-tetramethylethane-1,2-diamines **103a**–**c** as chiral catalysts gave the following results. Catalysis by the diamine **103a** resulted in virtually racemic product. The reaction in the presence of the diamine **103c** (symmetry $C_2$) produced the addition products with moderate enantioselectivity. And, finally, the catalyst **103b** operated as a pseudo-$C_2$-diamine, because the

**Table 2**. Reaction of quinoline (**90a**) with organolithium compounds RLi in the presence of a chiral catalyst.[59, 60]

| R | Catalyst | Solvent | $T$ /°C | $n$ | Yield (%) | Product | Configuration | *ee* (%) |
|---|---|---|---|---|---|---|---|---|
| Me | **97** | $Et_2O$ | −20 | 1 | 69 | **105a** | *S* | 5 |
| | **100a** | PhMe | −40 | 1 | 47 | **105a** | *S* | 63 |
| | **100a** | PhMe | −40 | 0.2 | 43 | **105a** | *S* | 30 |
| | **100b** | PhMe | −40 | 0.2 | < 5 | **105a** | *S* | – |
| | **100c** | PhMe | −40 | 0.2 | 69 | **105a** | *S* | 21 |
| | **100c** | $Et_2O$ | −40 | 0.2 | 86 | **105a** | *S* | 22 |
| | **101** | $Et_2O$ | −20 | 1 | 67 | **104a** | *R* | 20 |
| | **102a** | PhMe | −20 | 1 | 93 | **105a** | *S* | 13 |
| $Bu^n$ | **97** | PhMe | −40 | 1 | 98 | **105a** | *S* | 18 |
| | **97** | $Et_2O$ | −40 | 1 | 98 | **105a** | *S* | 16 |
| | **100a** | PhMe | −60 | 1 | 63 | **105a** | *S* | 72 |
| | **100a** | PhMe | −70 | 1 | 85 | **105a** | *S* | 79 |
| | **100b** | PhMe | −70 | 1 | 80 | **105a** | *S* | 32 |
| | **100b** | PhMe | −70 | 0.2 | 70 | **105a** | *S* | 37 |
| | **100c** | PhMe | −70 | 1 | 57 | **105a** | *S* | 69 |
| | **100c** | PhMe | −70 | 0.2 | 79 | **105a** | *S* | 41 |
| | **101** | $Et_2O$ | −60 | 0.2 | 86 | **104a** | *R* | 4 |
| | **101** | PhMe | −78 | 0.2 | 53 | **104a** | *R* | 4 |
| | **102a** | PhMe | −78 | 1 | 83 | **105a** | *S* | 10 |
| | **102b** | PhMe | −70 | 0.2 | 53 | see [a] | – | < 4 |
| | **102c** | PhMe | −70 | 0.2 | 67 | **105a** | *S* | 63 |
| | **102d** | PhMe | −70 | 0.2 | 58 | see [a] | – | 5 |
| | **103a** | PhMe | −70 | 0.2 | 55 | **104a** | *R* | 5 |
| Ph | **97** | PhMe | −78 | 1 | 82 | **105a** | *R* | 66 |
| | **97** | PhMe | −78 | 0.2 | 38 | **105a** | *R* | 7 |
| | **97** | $Et_2O$ | −78 | 1 | 55 | **105a** | *R* | 67 |
| | **100a** | PhMe | −78 | 1 | 6 | **105a** | *R* | < 4 |
| | **100a** | $Et_2O$ | −44 | 0.2 | 57 | **105a** | *R* | < 4 |
| | **101** | $Et_2O$ | −78 | 1 | 16 | **104a** | *S* | < 2 |
| | **101** | PhMe | −78 | 1 | 7 | **104a** | *S* | 26 |
| | **102a** | PhMe | −78 | 1 | 29 | **105a** | *R* | 45 |
| Ph | **102b** | PhMe | −70 | 0.2 | 47 | **105a** | *R* | 10 |
| | **102c** | PhMe | −70 | 0.2 | 39 | **105a** | *R* | 17 |
| | **103a** | PhMe | −70 | 0.2 | 68 | see [a] | – | < 4 |
| | **103b** | PhMe | −78 | 1 | 44 | **104a** | *S* | 27 |
| | **103c** | PhMe | −78 | 0.2 | 14 | **104a** | *S* | 23 |
| 1-Naphthyl | **97** | PhMe | −50 | 1 | 37 | **105a** | *R* | 16 |
| | **97** | $Et_2O$ | −78 | 1 | 86 | **105a** | *R* | 28 |
| | **100a** | PhMe | −70 | 0.2 | 20 | **105a** | *R* | 8 |
| | **100a** | PhMe | −50 | 0.2 | 55 | **105a** | *R* | 0 |
| | **101** | PhMe | −50 | 1 | 57 | **104a** | *S* | < 4 |
| | **101** | PhMe | −50 | 0.2 | 45 | **104a** | *S* | 5 |
| | **102a** | PhMe | −78 | 1 | 75 | **105a** | *R* | 64 |
| | **103a** | PhMe | −70 | 0.2 | 46 | see [a] | – | < 4 |
| | **103b** | $Et_2O$ | −70 | 1 | 70 | **104a** | *S* | 58 |
| | **103c** | PhMe | −70 | 0.2 | 35 | **104a** | *S* | 23 |
| 2-Naphthyl | **102a** | PhMe | −78 | 1 | 19 | **105a** | *R* | 28 |

[a] Stereochemical data are unavailable.

results with this catalyst are similar to those obtained with the diamine **103c**.[60]

## V. Conclusion

Thus, the nucleophilic addition reactions with aromatic azines are stereoselective in most cases due to either steric effects of chiral groups in the azine or in a nucleophile, or the presence of optically active catalyst. The stereoselectivity of the process is affected by a number of factors. Among them, the most important are the character and stereochemistry of the nucleophile, the configuration of the chiral centre of the azine, the ability of the nucleophile to form complexes with the substrate and also the possibility of using chiral catalysts in these reactions.

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