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ASYMMETRIC REACTIONS OF A SERIES OF AROMATIC AZINES WITH NUCLEOPHILES

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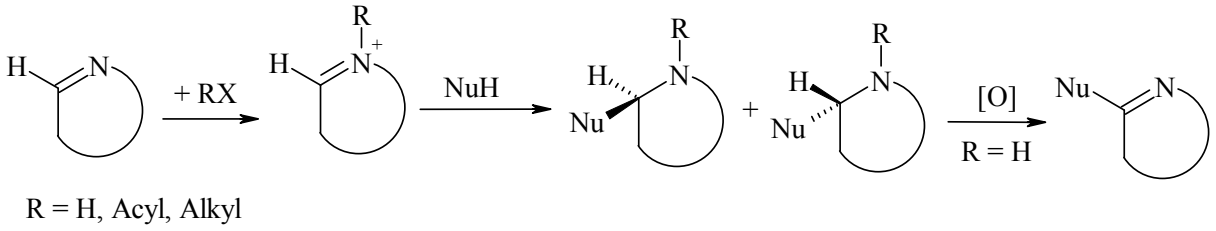
Abstract − Current review is devoted to the reactions of nucleophilic addition in azine series, leading to the stereoselective formation of optically active products. Three types of reactions are reviewed: the reactions of achiral nucleophiles with chiral azines; the reactions of chiral nucleophiles with achiral azines; reactions of achiral nucleophiles with achiral azines in the presence of chiral catalysts.

Dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday

INTRODUCTION

Reactions of nucleophilic substitution of hydrogen (S_N^H) in a series of π-deficient (hetero)aromatic compounds, azines in particular, are known to belong to a wide class of two-stage processes, proceeding via addition-elimination sequence.[1] The general feature of these reactions is the initial formation of nucleophilic addition adducts, i.e. σ^H-adducts, as a result of direct attack of C-, N-, O-, P-, S- and other nucleophiles at the unsubstituted cyclic carbon (Scheme 1). During the formation of σ^H-adducts the prochiral sp^2-atom of carbon at C=N bond of an azine cycle becomes sp^3-hybridizated and thus the whole molecule becomes chiral. In the presence of a chiral catalyst the reaction can give the addition products, enriched by one stereoisomer. When chiral carbon atom presents either in substrate or in nucleophile the reaction also can proceed stereoselectively to afford preferably only one (dia)stereoisomer (Scheme 1). The detailed study of approaches towards azine containing chiral elements is of great practical interest for obtaining enantiomerically pure alkaloids or their analogs.[2]



Scheme 1

The review describes reactions of nucleophilic addition in azine series, afforded the enantiomerically/diastereomerically enriched reaction products. In the first part of the review we report about interactions of achiral nucleophiles with chiral azines, the second part describes interactions of chiral nucleophiles with achiral azines, and the third part describes interactions of achiral nucleophiles and achiral azines, catalyzed by chiral catalysts.

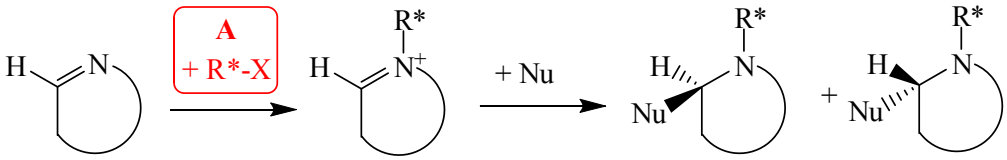
We have considerably modified our previous review[3] published in 2005 with the data described in the literature in last twenty years. In addition, the review summarizes and completes the data, reported in review,[4] which describes in details reactions of pyridinium salts, as well as review,[5] concerning the Reissert reactions, mediated by chiral catalysts.

I. ASYMMETRIC INDUCTION MEDIATED BY THE ATTACK OF ACHIRAL NUCLEOPHILE ON THE CHIRAL AZINE

Pyridine-type nitrogen atom increases the π-deficiency of an azine heterocycles, however only few examples of direct introducing of residues of neutral C-nucleophiles into non-activated azine cycle are known.[1] To induce the chirality during the nucleophilic attack an activated azine substrates, i.e. azinium cations, and/or highly reactive nucleophiles, i.e. organometallic compounds, are commonly used. In current part some typical examples of interactions of azines and other C-nucleophiles (i.e. cyanides, enolates and indoles) and Si-nucleophiles are described.

1. Interaction of azines, containing a chiral substituent next to the nitrogen atom

The reactions of C-nucleophiles with azinium cations containing nitrogen atoms quaternised with chiral substituents have been studied pretty well. The corresponding salts are usually synthesized by alkylation or acylation (often in situ) of an azine substrate with an optically active reagent (Scheme 2).

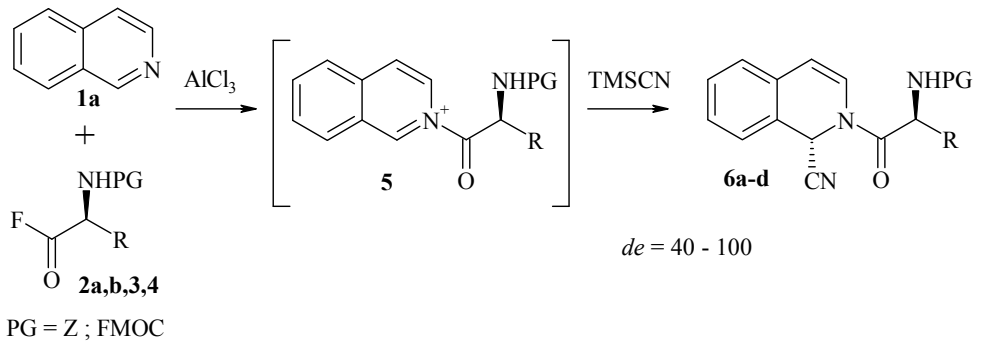


Scheme 2

The fragments of chiral hydrocarbons, alcohols (including natural ones), amino acids and heterocyclic compounds may be used as the asymmetric inductors. The data in this Section are presented according to the type of the nucleophilic agent and in the order of increasing of complexity of the azine substrate.

1.1. Addition reactions of trimethylsylil cyanide (TMSCN)

In publication[6] stereoselective additions of cyanide anion to chiral isoquinolinium salts have been studied. The parent azinium salts were generated *in situ* by the acylation of isoquinoline (**1a**) by chiral amino acids fluoroanhydrides (**2a**,**b**,**3**,**4**) in the presence of Lewis acids. Trimethylsylil cyanide (TMSCN) was utilized as a C-nucleophile.[6] As a result the stereoselective formation of Reissert compounds **6a-d** was observed. The diastereomeric ratio of the reaction products depends on the structure of the original amino acid (Scheme 3).

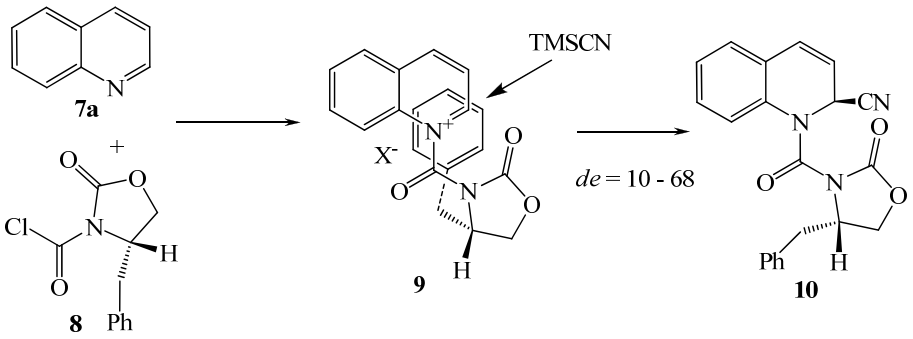


amino acid	R	PG	Product	Yield, %	*dr*
2a	Me	Z	**6a**	89	> 95 : 5
2b	Me	FMOC	**6b**	44	71 : 29
3	Pr^i	FMOC	**6c**	47	70 : 30
4	CH_2Ph	Z	**6d**	51	82 : 18

where Z-benzyloxycarbonyl; FMOC – 9-fluorenylmethyloxycarbonyl

Scheme 3

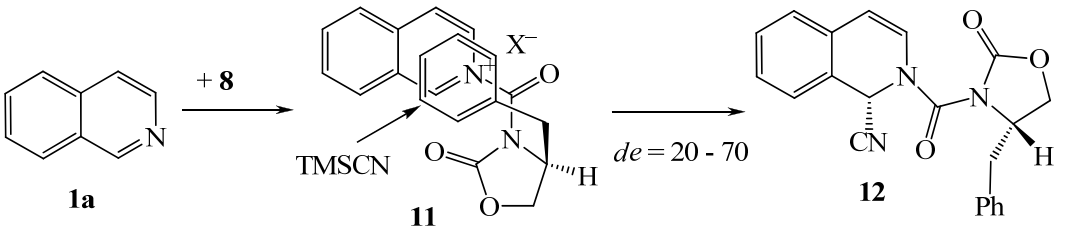
Chiral acylazinium salts **9** or **11** were synthesized by *N*-acylation of quinoline (**7a**) or isoquinoline (**1a**) using (*S*)-4-benzyl-2-oxooxazolydine-3-carbonyl chloride (**8**). The reaction of the salts **9** or **11** with cyanide-anions, generated *in situ* from trimethylsilyl cyanide (TMSCN), has resulted in Reissert compounds **10**, **12** in moderate degree of diastereoselectivity (Schemes 4, 5).[7] According to the authors the possible steric hindrance from the one side of hetarene cation plane, caused by π-π-interaction with benzyl moiety of chiral substituent is the main reason for the observed diastereoselectivity. The triflate anion of acylazinium salt was noticed to facilitate the π-π-interactions in the acylazinium intermediate due to the weaker interaction with the iminium part of the molecule than in the case of the chloride anion. As a consequence, the stereoselectivity of the addition increases.[7]



X^-	T, °C	Yield,* %	*dr***
Cl^-	20	88	55 : 45
TfO^-	20	70	83 : 17
NfO^-	40	60	84 : 16

* Yield of both diastereoisomers as a mixture; NfO^- – nonaflate ($CF_3CF_2CF_2CF_2SO_3^-$)
** *dr* determined by HPLC

Scheme 4

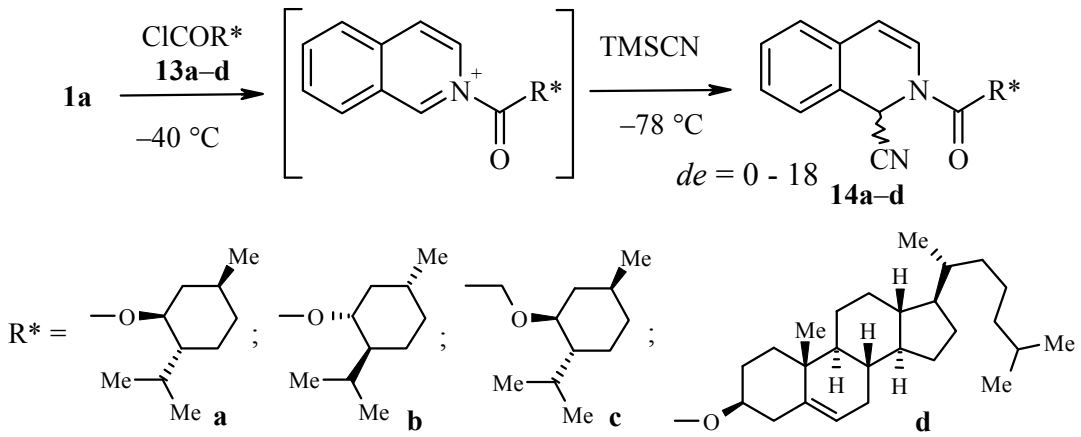


X^-	T, °C	*dr*	Yield,* %
Cl^-	20	60 : 40	76
TfO^-	20	15 : 85	35
TfO^-	40	29 : 71	95

* Yield of both diastereoisomers as a mixture

Scheme 5

Acylation of isoquinoline (**1a**) by (–)-(*R*)-menthyl chloroformate (**13a)**, or by its analogues **13b–d** in DCM followed by the addition of TMSCN has been shown to afford products **14a–d** as racemic mixtures. Low degree of diastereoselectivity was observed only when cholesterol chloroformate was applied (**13d**).[8]



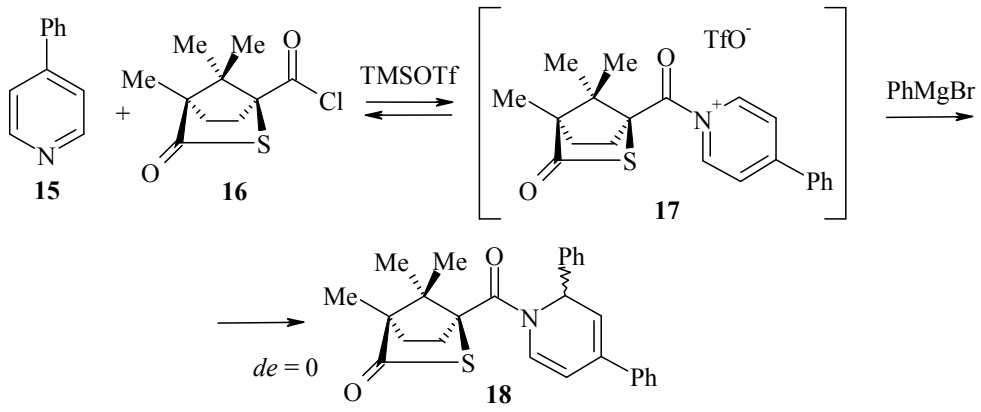
Product	Yield, %	*dr**
14a	96	50:50
14b	98	50:50
14c	67	47:53
14d	91	41:59

* *dr* determined by HPLC

Scheme 6

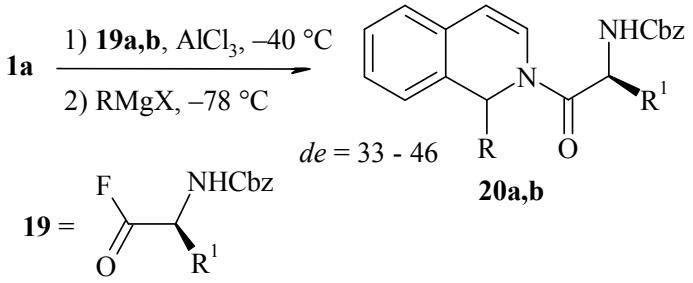
1.2. Addition of organo-Li-, organo-Mg- and organo-Zn compounds as C-nucleophiles

Reaction of 4-phenylpyridine (**15**) and (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-thiabicyclo[2.2.1]heptan-1-carbonylchloride (**16**) *in situ* gave the *N*-acylazinium salt **17**, the latter reacted with phenylmagnesium bromide to form compound **18** in 50% yield. No diastereoselectivity was observed (Scheme 7).[9]



Scheme 7

Isoquinoline (**1a**), acylated by (*S*)-α-Cbz-aminoacyl fluorides **19a,b** in reactions with arylmagnesium bromides resulted in the compounds **20a**,**b** in various degree of diastereoselectivity (Scheme 8).[10]



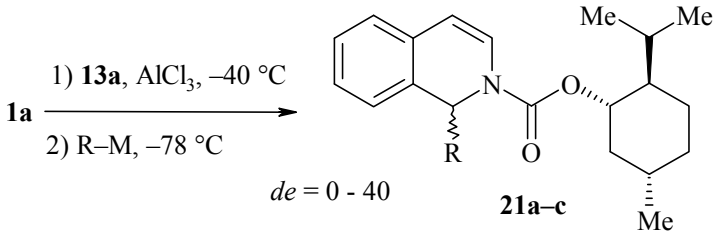
a: R = Ph; R^1 = Me
b: R, R^1 = Bn.

R^1	RMgX	Product	Yield, %	*dr**
Me	PhMgCl	**20a**	50	2.7:1
Bn	$PhCH_2MgBr$	**20b**	69	2:1

* According to NMR ^1H

Scheme 8

Interaction of isoquinoline (**1a**) with (–)-(*R*)-menthyl chloroformate (**13a**) was shown to give isoquinolinium salt, which further reacted with Mg- or Zn-organic arenes to form products **21a–c** in moderate diastereoselectivity (Scheme 9).[10]



21	R–M	Solvent	Yield, %	*dr**
a	PhMgBr	THF	82	55:45
a	Ph_2Zn	THF	76	64:36
a	Ph_2Zn	Toluene	78	70:30
b	4-BrC_6H_4MgBr	THF	62	1:1
c	BnMgBr	THF	55	60:40
c	Bn_2Zn	THF	87	60:40

* *dr* determined by HPLC

Scheme 9

In order to explain the diastereoselectivity in the reaction of isoqinolines with metalloorganic compounds the authors have proposed the plausible pathway for the formation of **21**. According to the pathway R–M interacts with oxygen atom of *in situ* formed *N*-acylazinium salt to result in rigid intermediate state, blocking the unfavorable formation of rotamers along the N–CO bond (Figure 1).[10]

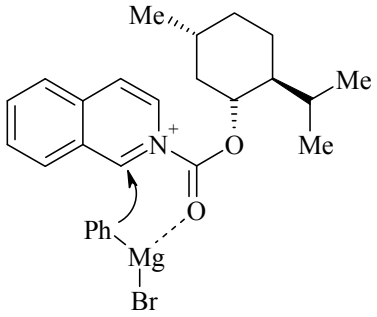
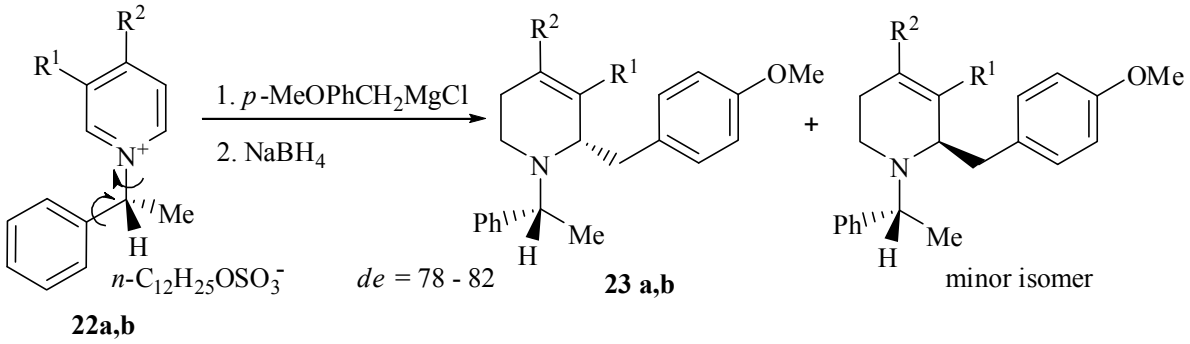


Figure 1

Azines can be quaternised not only by chiral acyl groups, but by alkyl groups as well. Thus chiral *N*-alkylpyridinium salts **22a**,**b** show a high degree of diastereoselectivity in reactions with benzyl-type Grignard reagents.[11] The reduction of the products with sodium borohydride leads to the diastereomeric tetrahydropyridines **23a**,**b** (Scheme 10).

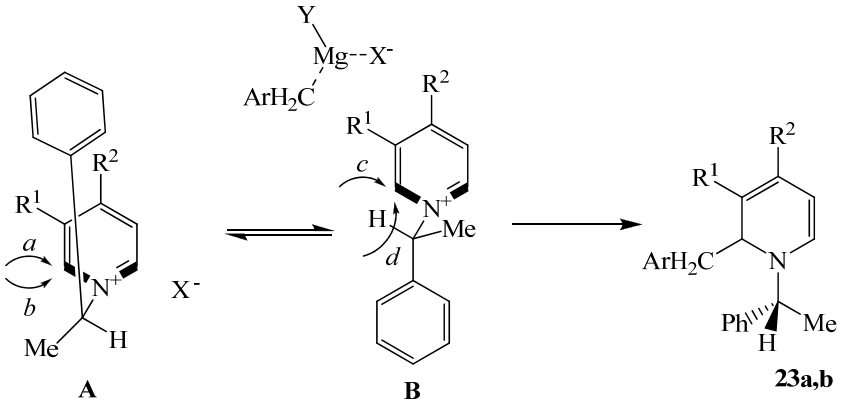


	R^1	R^2	Product	*de*, %
22a	Me	Me	**23a**	82
22b	- $CH_2CH_2CH_2CH_2$-		**23b**	78

Scheme 10

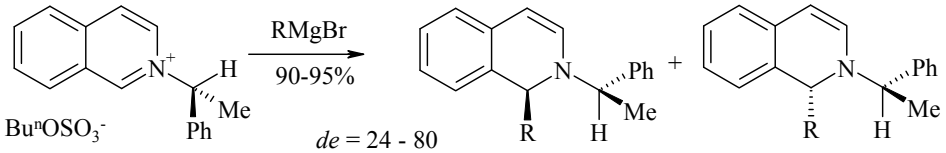
Such a relatively high selectivity was rather unexpected for the authors,[11] because the chiral alkyl group in the starting salt **22a**,**b** is quite mobile and relatively freely rotates around the N-C bond.

The structures **A** and **B**, in which the C-N bond of the chiral group is coplanar to the plane of the pyridine ring, are probably the most energetically favorable conformations of the salts **22a**,**b**. 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 the stereoisomers **23**, because in this case the attack of the nucleophile to the pyridine ring is less hindered by the small- (H atom) and medium-sized (methyl group) substituents of the chiral alkyl fragment (Scheme 11).[11]



Scheme 11

The reaction of the chiral isoquinolinium salts **24** with the Grignard reagents afforded unstable 1-substituted 1,2-dihydroisoquinolines **25** and **26** in good yields (90-95%) (Scheme 12).[11] However, the observed diastereoselectivity of this reaction was lower than that in the case of 3,4-disubstituted pyridinium salts.

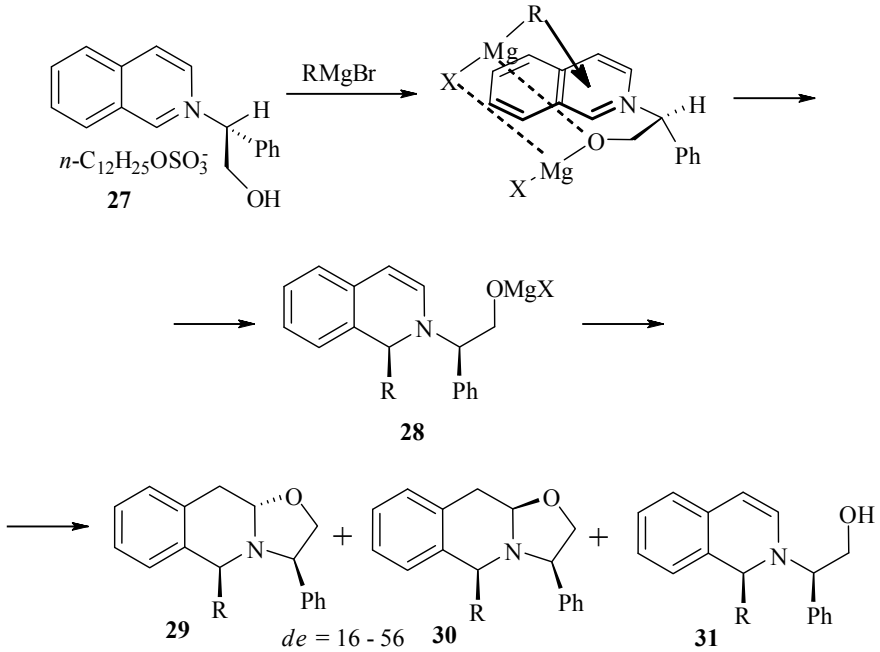


24 **25** **26**

R	**25 : 26**, %
Me	64 : 36
Ph	87 : 13
m-MeOC$_6$H$_5$	90 : 10
m-MeOC$_6$H$_4$CH$_2$	62 : 38

Scheme 12

In a similar reaction of the Grignard reagents with the isoquinolinium salt **27**, containing a chiral hydroxy(phenyl)ethyl group at the nitrogen atom, the 1,2-dihydroisoquinoline intermediates **28** cyclised spontaneously upon hydrolysis.[12] The main reaction products were tetrahydrooxazoloisoquinolines **29** and **30**. Small amounts of dihydroisoquinolines **31** were also isolated (Scheme 13).



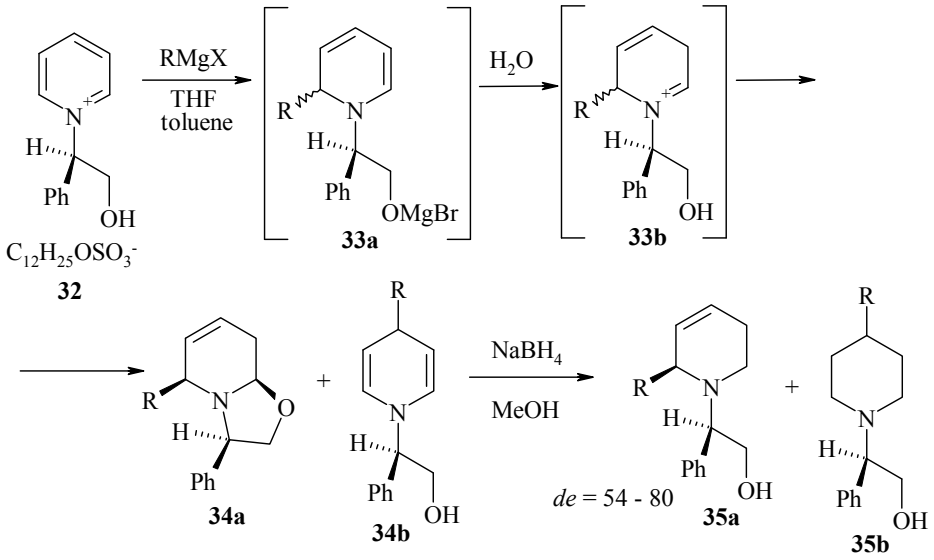
27 **28** **29** **30** **31**

R	**29 : 30 : 31**
Me	51 : 37 : 12
Ph	64 : 29 : 7
Pr^i	49 : 34 : 17
m-MeOC$_6$H$_5$	72 : 20 : 8

Scheme 13

Presumably,[12] the destabilizing 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 **29** rather than of their stereoisomers **30**.

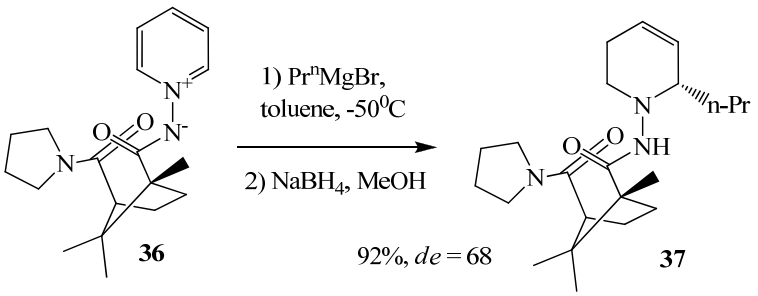
It has been shown, that interaction of the pyridinium salt **32** with Grignard reagents results in unstable addition products **33a**, hydrolyzing further to the compounds **34**, which were reduced to **35** (Scheme 14). There are no data for diastereomeric purity for compounds **34a**,**b**. Their reduction products **35a** were reported to have *de* = 54 - 80.[13]



RMgX	yield **34a**, %	yield **35a**, %	*de* **35a**, %
MeMgCl	70	40	80
$CH{=}CH_2MgCl$	48	27	80
Pr^nMgCl	58	43	70
Pr^iMgBr	40	35	82
BnMgCl	32	21	54

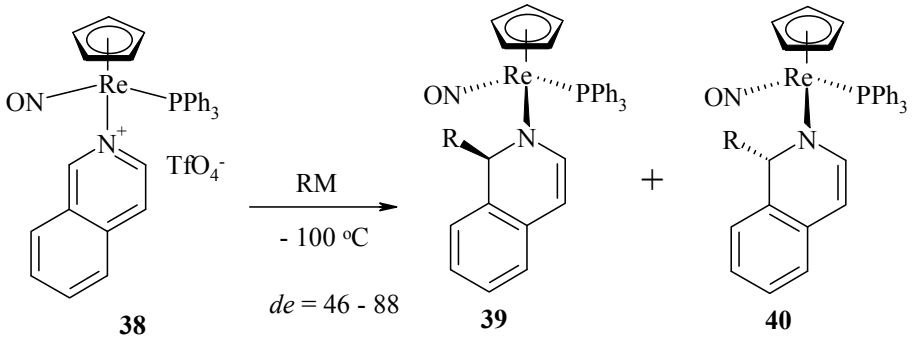
Scheme 14

An example of Pr^nMgBr addition to chiral pyridinium ylide **36**. Reaction proceeds regioselectively and with high degree of diastereoselectivity (*dr* = 84 : 16) (Scheme 15).[14]



Scheme 15

An example of diastereoselective addition of C-nucleophile to isoquinoline **38**, activated by a chiral rhenium complex, has been described.[15] The reactions of compound **38** with organometallic compounds occur under very mild conditions and start at temperature as low as -100 °C. The metallocomplex **39** is the main reaction product (Scheme 16).

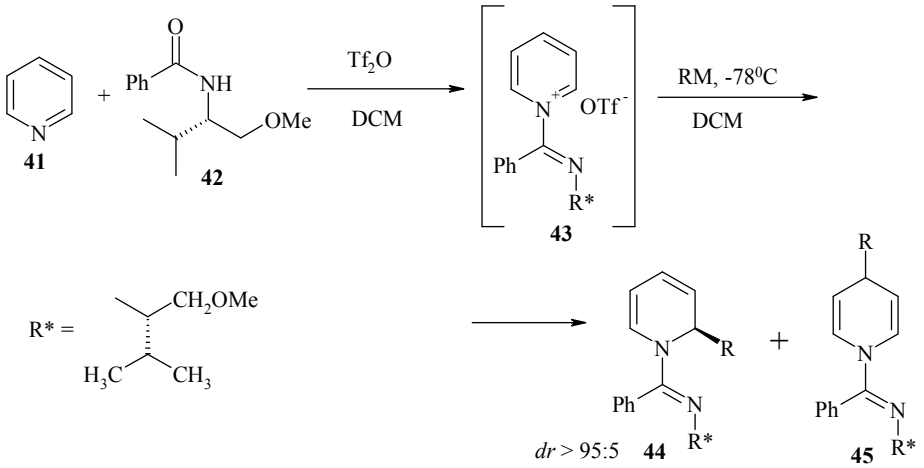


RM	T, °C	**39**:**40**	*de*, %
Me_3SiCH_2Li	-55	94:6	88
Me_3SiCH_2MgCl	20	80:20	60
Pr^iMgCl	-100	89:11	78
EtMgBr	-100	89:11	78
$C_6H_5CH_2MgCl$	-100	88:12	76
Pr^nMgCl	-100	87:13	74
MeMgCl	20	84:16	68
Bu^nMgCl	-100	82:18	64
CH_2=$CHCH_2MgBr$	-100	73:27	46

Scheme 16

The reaction with $(CH_3)_3SiCH_2MgCl$ proceeds much slower in comparison with $(CH_3)_3SiCH_2Li$. In the first case the diastereoselectivity decreases when the temperature increases. Thus, Grignard reagent $(CH_3)_2CHMgCl$ intensively reacts with **38** even at -100 °C. It should be noted that CH_3MgCl was the less active nucleophile in this reaction.[15]

A. B. Charette and co-authors have published a wide scope of works concerning the investigation of reactions of chiral *N*-imidoylpyridinium salts with Grignard reagents. Thus, salt generated from pyridine and (*S*)-valynol amide **42** reacted with Grignard reagents forming the addition products **44** in high degree of diastereoselectivity (*dr* > 95:5).[16] In reactions with PhMgBr the yield and the diastereoselectivity were improved by adding LiBr, and diethyl ether as a solvent (89%, *dr* > 98:2) (Scheme 17).[17]



RM	**44 / 45**	Yield **44**, %
MeMgBr	> 95:5	77
EtMgBr	75:25	79
Et_2Zn	> 95:5	73*
PhMgBr	90:10	74
2-FurylMgBr	> 95:5	68
1-HexynylMgBr	> 95:5	65

* Yield **44**+**45**

Scheme 17

A vacant electron pair of nitrogen atom in imidate **43** effectively governs the nucleophilic attack at the position 2 of pyridine ring. The stereoselective addition to unsubstituted pyridinium salts is complicated by existence of four directions of nucleophilic attack at the pyridine ring (Figure 2). The bulky substituent at R^1 prevents the nucleophilic attack at position 2'. However, neither this substituent, nor the substituent at the imidate nitrogen atom can prevent the formation of (*E*)-imidate. The authors have demonstrated, that the introduction of phenyl group as R^1, as well as the introduction of bidentate auxiliary reagent, derived from valinole, provides excellent regio- and stereoselectivity upon the addition of nucleoplies.[16]

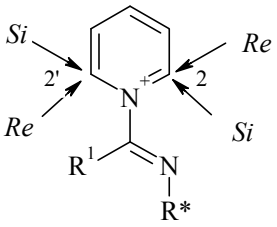
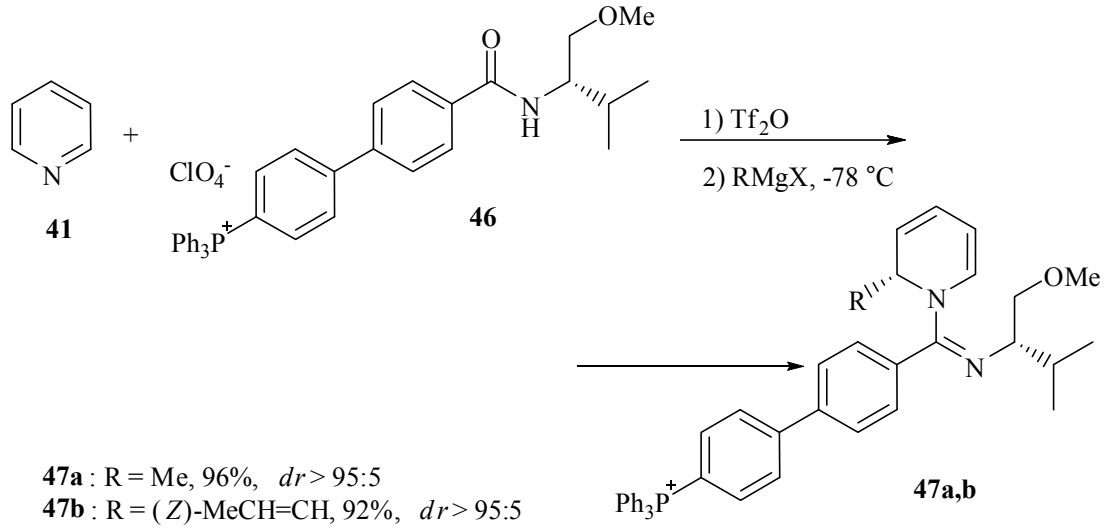


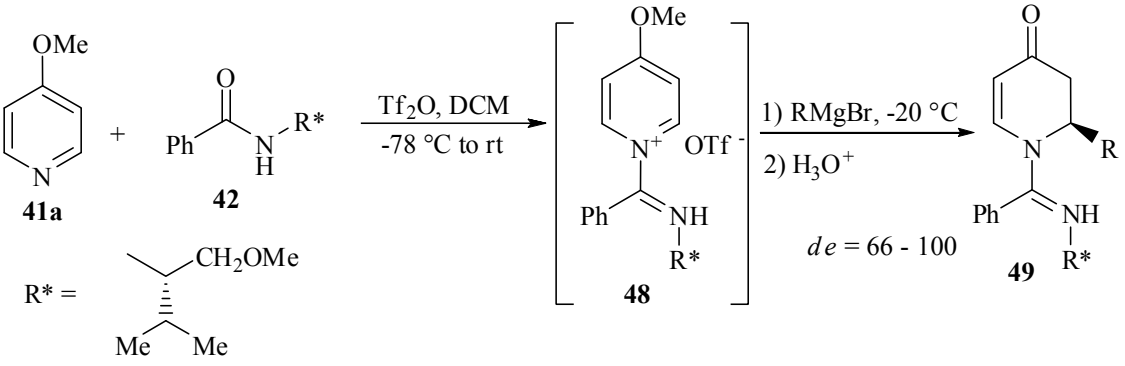
Figure 2

Imidates formation was utilized in a synthesis of derivative of chiral phenylphosphonium salts. As a result the following addition products **47a**,**b** were obtained with high diastereoselectivity (Scheme 18).[18]



Scheme 18

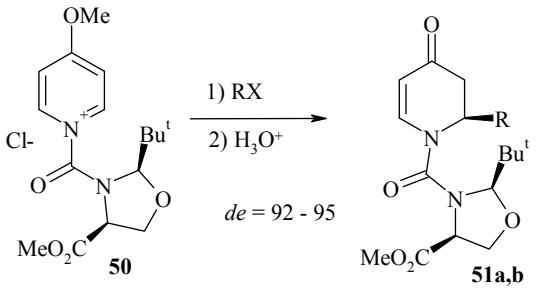
In addition, some reactions of nucleophilic addition to imidates **48** derived from 4-methoxypyridine **41a** and (*S*)-valinole amide **42** were described. It was shown that *N*-imidoylpyridinium salt **48** was attacked by nucleophiles leading to **49** with high diastereoselectivity (Scheme 19).[19]



R	Yield, %	*dr*
Me	85	95:5
Et	76	93:7
Bu^n	71	> 95:5
Bu^t	61	93:7
$(CH_2)_6OTBS$	70	> 95:5
$CH{=}CH_2$	64	92:8
$C{\equiv}CCH_3$	52 + 8	83:17
C≡CPh	65	89:11
Ph	66	91:9
2-Furyl	65	95:5
$CH_2{=}CH(CH_2)_5$	84	93:7

Scheme 19

J. Streith and co-authors have studied the reaction of 4-methoxypyridine (**15**) with Grignard reagents. They found that the introduction of chiral oxazoline into 4-methoxypyridine and the following addition of nucleophiles leads to the products **51a**,**b** with high diastereoselectivity (Scheme 20).[20]



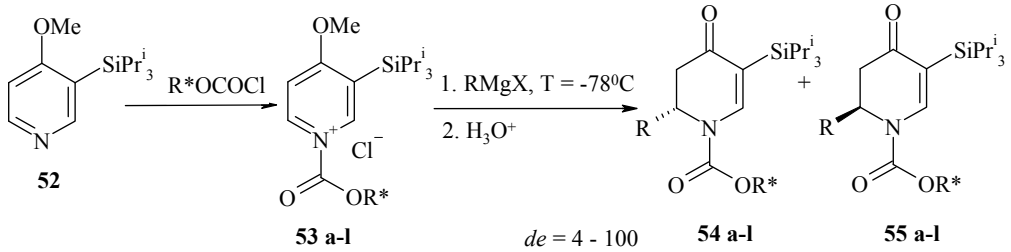
RX	Product	Yield, %	*de**, % (crude, %)
MeMgI	**51a**	74	100 (95)
PhMgBr	**51b**	69	100 (92)

*According to NMR ^{1}H

Scheme 20

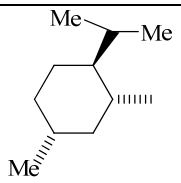
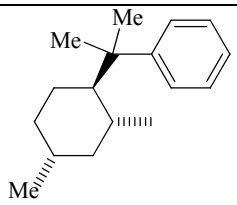
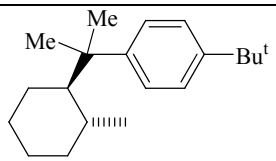
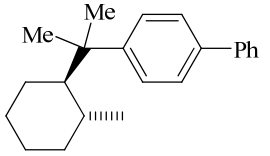
A series of papers studying the influence of chiral substituents at the nitrogen atom of azine substrates on the stereoselectivity of the reactions with organometallic reagents have been published by the Comins group. Thus 1-acylpyridinium salts **53** containing a residue of an optically active alcohol (R*OH) have been studied.[21-25] These salts have been synthesized from 4-methoxy-3-(triisopropylsilyl)pyridine (**52**) and the corresponding chiral chloroformates. The salts **53** react with organomagnesium compounds under very mild conditions.[21] Acid hydrolysis of the reaction mixture yields mainly dihydropyridones **54**. The stereoselectivity of the reaction is relatively high, stereoisomers **55** are the minor products.

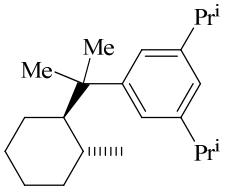
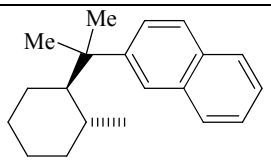
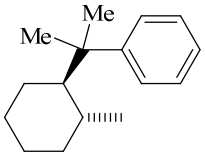
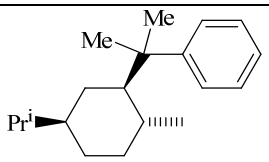
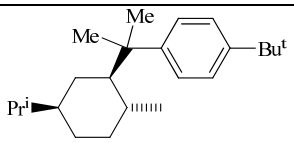
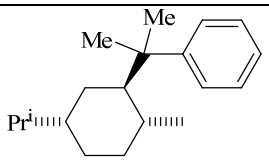
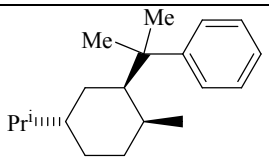
The effect of chiral acyl groups on the stereoselectivity of the addition reaction may be increased by introducing of aromatic substituents into the alcohol residue.[23,24] Thus the stereoselectivities of the reactions of *trans*-2-(6-cumyl)cyclohexyl derivatives of the salts **53c-k** with *p*-tolyl- and cyclohexylmagnesium halides were equal to 83-93%. Acylpyridinium salts **53i-k**, containing an isopropyl group in a similar chiral substituent, appeared to be slightly more effective as asymmetric inductors in this stereoselective synthesis (Scheme 21, Table 1).[21]



Scheme 21

Table 1. Reactions of *N*-acylpyridinium salts **53** with organomagnesium compounds

53	R*	RMgX	Product	Yield, %	*de*, %	Lit.
a	 ((-)-menthyl)	PhMgCl	**54a**	87	44	21
b	 ((-)-8-phenylmenthyl)	MeMgCl	**54ba**	92	91	21
		$Bu^{i}MgBr$	**54bb**	95	92	21
		$CH_3(CH_2)_6MgCl$	**54bc**	79	100	26
		$Hex^{c}MgBr$	**54bd**	90	81	21
		PhMgCl	**54be**	88	94	21
		o-TolMgCl	**54bf**	81	60	21
		p-TolMgBr	**54bg**	90	82	21
		p-$MeOC_6H_5MgBr$	**54bh**	77	73	21
		o-$MeOC_6H_5MgCl$	**54bi**	81	60	21
		p-ClC_6H_5MgBr	**54bj**	78	81	21
		$CH_2=CH(CH_2)_3MgBr$	**54bk**	100	91	22
		$CH_2=CH(CH_2)_5MgBr$	**54bl**	61	97	26
c		*p*-TolMgX [a]	**54ca**	89	89	24
		$Hex^{c}MgX$ [a]	**54cb+55cb**	95 [b]	88	24
d		*p*-TolMgX [a]	**54da**	91	93	24
		$Hex^{c}MgX$ [a]	**54db+55db**	92 [b]	86	24

e		*p*-TolMgX [a]	**54ea+55ea**	93 [b]	83	24
		Hex[c]MgX [a]	**54eb**	84	83	24
f		*p*-TolMgX [a]	**54fa**	71	89	24
		Hex[c]MgX [a]	**54fb**	82	86	24
g	 ((+)-TCC)	PhMgCl	**55g**	90	92	23
h	((-)-TCC)	Pr[n]MgCl	**54h**	98	90	23
i	 (CPC)	*p*-TolMgX [a]	**54ia**	89	92	24
		PhMgX [a]	**54ib**	81	95	24
		BuCH≡CHMgX [a]	**54ic**	76	90	24
		$C_5H_{11}MgBr$	**54id**	95	90	25
j		*p*-TolMgX [a]	**54ja**	64	94	24
		Hex[c]MgX [a]	**54jb**	81	90	24
		VinylMgX [a]	**54jc**	75	90	24
k		*p*-TolMgX [a]	**54ka+55ka**	95 [b]	79	24
		Hex[c]MgX [a]	**54kb**	80	85	24
l		PhMgX [a]	**54l + 55l**	80	4	24

[a] X – authors did not indicate the halogen type; [b] Major product – compound **54**.

Presumably, it is the steric shielding of one side of the pyridinium ring of salt **53** 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 stabilizes the staggered conformation.[27,28] The positive effect of the isopropyl group of the 8-arylmenthyl moiety on the stereoselectivity of the process is more difficult to rationalize. It was suggested[24,27] that the isopropyl group might affect the ratio of the possible rotamers leading to the optimum π-π-interaction between the aromatic rings (Figure 3).

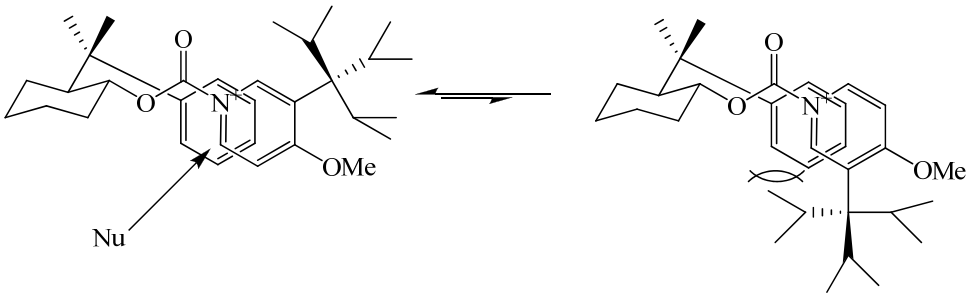
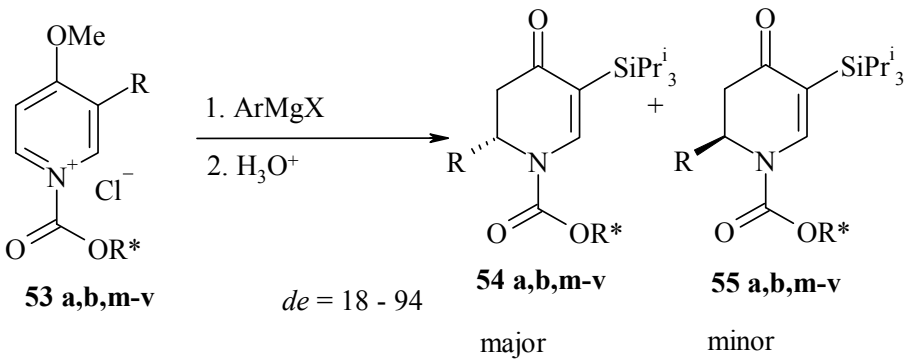


Figure 3

The absence of stereoselectivity in the reaction of phenylmagnesium bromide with the salt **53l** where *vic*-substituents in the cyclohexane ring adopt a *cis*-configuration may be explained by the same reason.

Pyridines are able to attach nucleophiles at various positions. Therefore in order to provide the high regioselectivity Comins and co-authors utilized the pyridine derivatives, substituted in a position C(4) by methoxygroup and in a position C(3) by triisopropylsylil group.

The most detailed investigation of the effect of the character and size of the 3-substituent in the pyridine ring on the diastereoselectivity of the addition of the Grignard reagents was carried out by Comins *et al.*[24] The authors studied the reactions of a series of optically active 4-methoxy-*N*-[(-)-menthyloxycarbonyl]pyridinium salts **53a**,**b**,**m-v** with arylmagnesium chlorides leading to the 6-substituted compounds **54** and **55** (Scheme 22, Table 2).



53 a,b,m-v *de* = 18 - 94 **54 a,b,m-v** major **55 a,b,m-v** minor

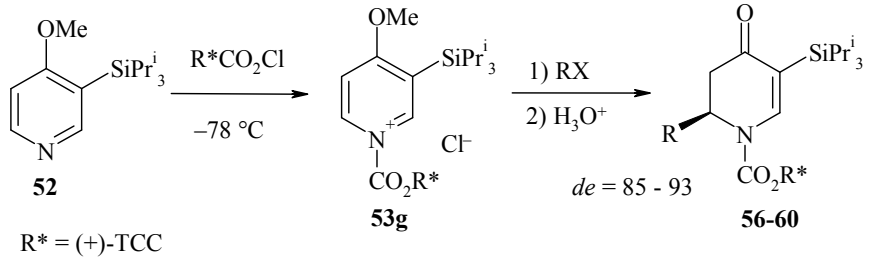
Scheme 22

Table 2. Reactions of 3-substituted pyridinium salts **53** with Grignard reagents

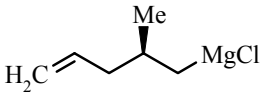
Pyridine	R	R*	ArMgX	Product	Yield, %	*de*, %	Lit.
53m	H	(–)-menthyl	PhMgCl	**54m**	79	34	21, 23
53n	»	(–)-8-phenylmenthyl	PhMgCl	**54n**	83	30	21, 23
53o	$SiMe_3$	(–)-menthyl	PhMgCl	**54o**	88	50	21, 23
53p	»	(–)-8-phenylmenthyl	PhMgCl	**54pa**	82	65	21, 23
»	»	»	*o*-TolMgCl	**54pb**	90	30	21, 23
»	»	»	*p*-TolMgBr	**54pc**	79	42	21
53a	$SiPr^i_3$	(–)-menthyl	PhMgCl	**54a**	87	44	23
53b	»	(–)-8-phenylmenthyl	PhMgCl	**54ba**	88	94	23
»	»	»	*o*-TolMgCl	**54bb**	81	60	23
53q	$SiPr^n_3$	»	*o*-TolMgCl	**54q**	88	40	23
53r	$SiBu^i_3$	»	*o*-TolMgCl	**54r**	89	34	23
53s	$SiPh_3$	»	*o*-TolMgCl	**54s**	85	18	23
53t	$SnBu^n_3$	»	PhMgCl	**54t**	84	60	23
53u	$SnPr^i_3$	»	PhMgCl	**54u**	80	84	23
53v	$Sn(Hex^c)_3$	»	PhMgCl	**54v**	75	80	23

The original idea[23] was to increase the regioselectivity of the reaction by introducing of a 3-substituent into the pyridinium ring, which would prevent nucleophilic attack on C(2). However, the substituent has been shown to affect the stereochemistry. Although no rigorous regularities were established, some conclusions could be drawn. The best diastereoselectivity (de 94%) was obtained in the reaction of 4-methoxy-3-(triisopropylsilyl)pyridinium salt **53b** 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%). In the case of triphenylsilyl substituent the diastereoselectivity of the process fell down up to 18%.[23]

In the most of his works Comins and co-authors utilize the pyridine derivatives, substituted in position C(4) by methoxy group and in position C(3) by triisopropylsylil group, while using the (+)/(-)-TCC as a chiral auxiliary group. Thus, acylation of pyridine **52** by chloroformate of (+)-*trans*-2-(6-cumyl)cyclohexanole ((+)-TCC) resulted in acylpyridinium salt **53g**, which reacted with Grignard reagents RX to form the addition products **56-60** (Scheme 23).[29-33] In the same manner some semi-products for the synthesis of benzomorphane alkaloids,[29] (+)-luciduline,[30] indolyzidin alkaloids (-)-205A, (-)-207A, и (-)-235B[32] and *trans*-decahydroquinoline alkaloid (+)-219A[33] were obtained.

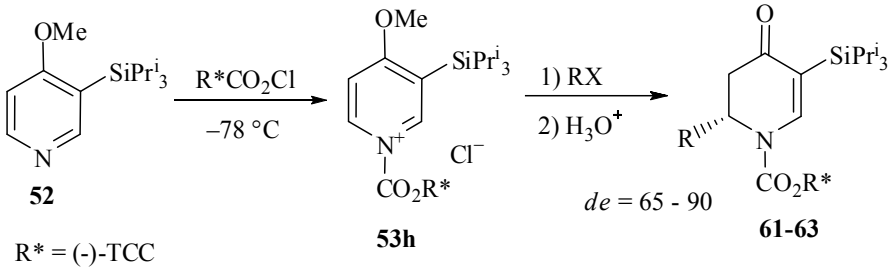


52 R* = (+)-TCC **53g** **56-60**

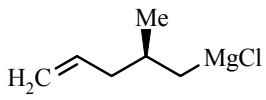
RX	Product	Yield, %	*de*, %	Lit.
$PhCH_2MgCl$	**56**	86	92	29
	**57**	80	85-90	30
p-MeOBnMgCl	**58**	90	90	29, 31
$CH_2=CH(CH_2)_2MgBr$	**59**	91	90	32
$CH_2=CH(CH_2)_3MgBr$	**60**	95	93	33

Scheme 23

Acylation of pyridine **43** chloroformate of (-)-*trans*-2-(6-cumyl)cyclohexanole ((-)-TCC) gave pyridinium salt **44h**, which reacted with Grignard reagents RX to afford the addition products **52-54**, utilized further for the synthesis of such alkaloids, as (−)-septicine,[34] (−)-tylophorine[34] and phlegmarines[35] (Scheme 24).



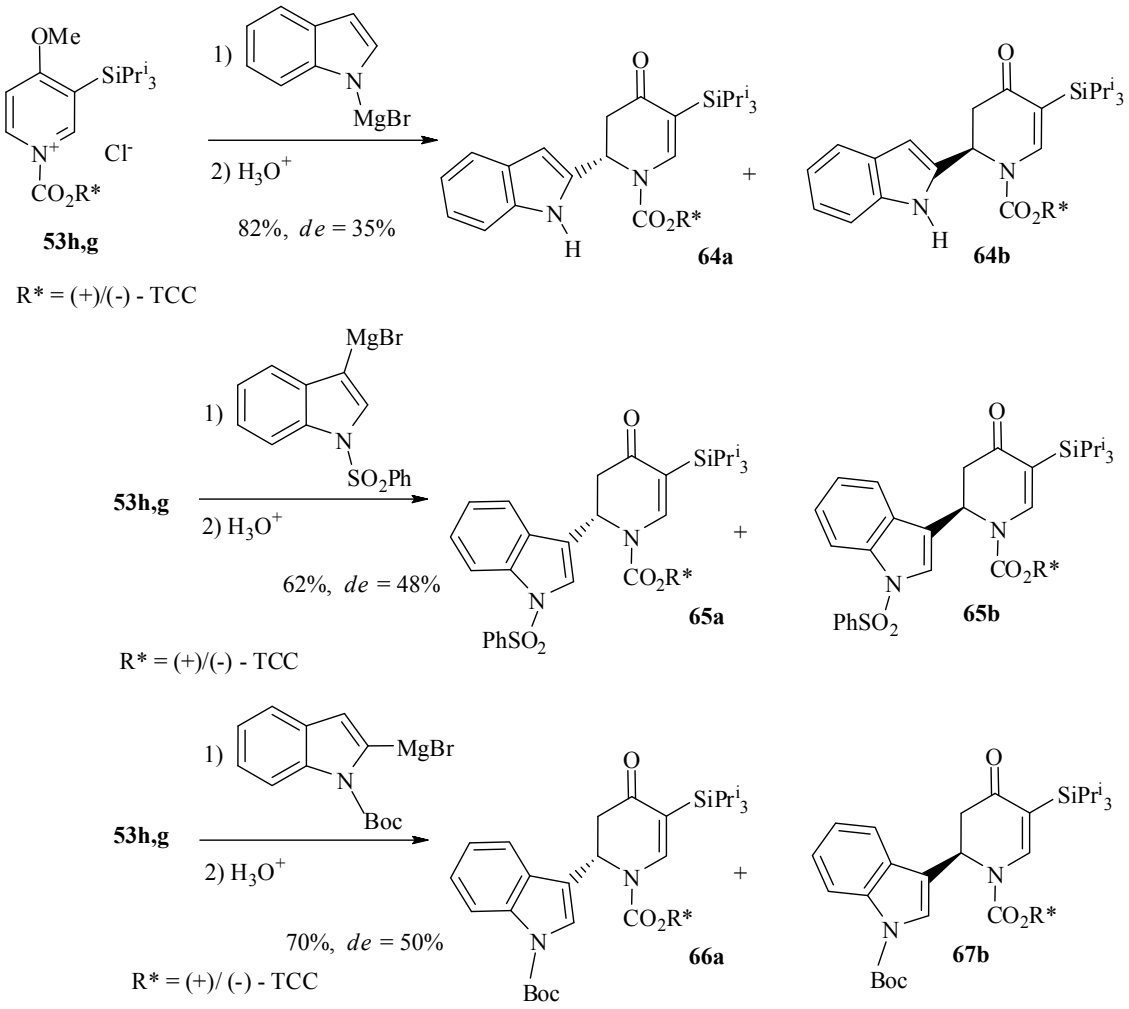
52 R* = (-)-TCC **53h** **61-63**

RX	Product	Yield, %	*de*	Lit.
$CH_2=CH(CH_2)_2MgBr$	**61**	91	90	34
$BnO(CH_2)_3MgBr$	**62** [a]	57	65	34
	**63**	76	88	35

[a] OBn to OH reduction product.

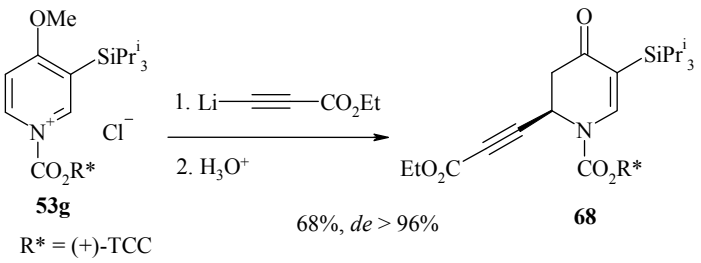
Scheme 24

Unsubstituted indoles proved not to react with 1-(benzyloxycarbonyl)-4-methoxy-3-(triisopropylsylil)pyridine. Organo-Mg derivatives of indole easily reacted with 1-acylpyridinium salts **53h**,**g** (R* = (+)/(-)-*trans*-2-(α-cumyl)cyclohexyl, (+)/(-)-TCC) to form the addition products **64-66a**,**b** with moderate diastereoselectivity (Scheme 25).[36]



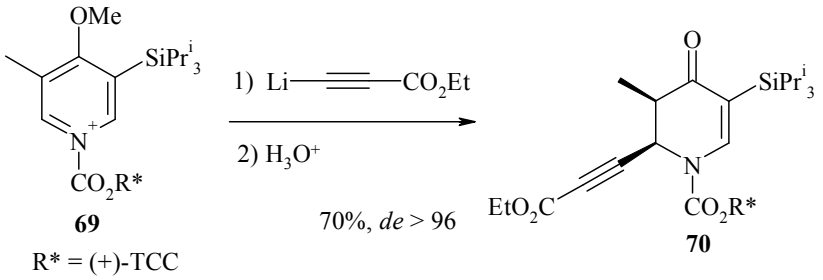
Scheme 25

Application of Li acetylenides instead of alkenylmagnesium bromides results the addition products with the same stereoconfiguration. Thus, treatment of salt **53g** with Li-derivative of ethyl propiolate leads to dyhydropyridone **68** (Scheme 26).[37]



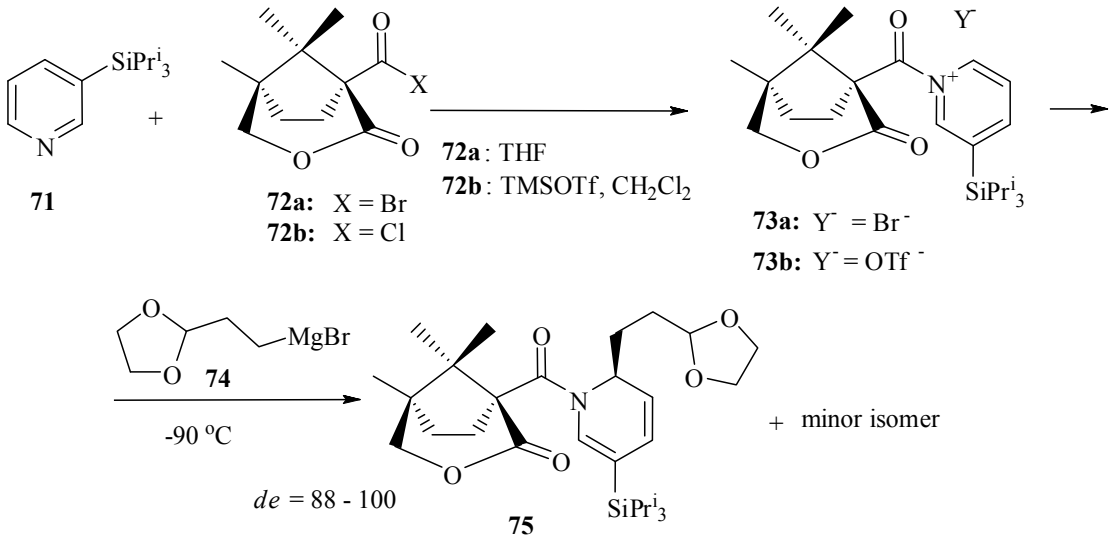
Scheme 26

Introduction of lithium ethyl propiolate in reaction with pyridinium salt **69** results in dyhydropyridone **70**, which was successfully utilized in a synthesis of (+)-allopumiliotoxin 267A (Scheme 27).[38]



Scheme 27

The reaction of 3-(triisopropylsilyl)pyridine (**71**) with chiral bicyclic acyl bromide **72a** in pyridine yields solid *N*-acylpyridinium salt **73a**.[39] The addition of 2-(l,3-dioxolan-2-yl)ethylmagnesium bromide **74** at -90 °C to this heterogeneous system affords 6-substituted *N*-acyl-l,6-dihydropyridine **75**. The reaction is regio- and diastereoselective (yield 41%, *de* = 100%). An analogous reaction was carried out with acyl chloride **72b** under homogeneous conditions, which are more suitable for this reaction. In the presence of trimethylsilyl triflate (TMSOTf), the addition product **75** is formed via intermediate salt **73b**. The yield of the product increased to 62%, but the diastereoselectivity of the process dropped down to 88% (Scheme 28).[39]



Scheme 28

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 (Figure 4).[39]

Judging from the stereochemistry of the addition product **75**, the attack of the nucleophilic agent on the iminium moiety proceeds as follows:

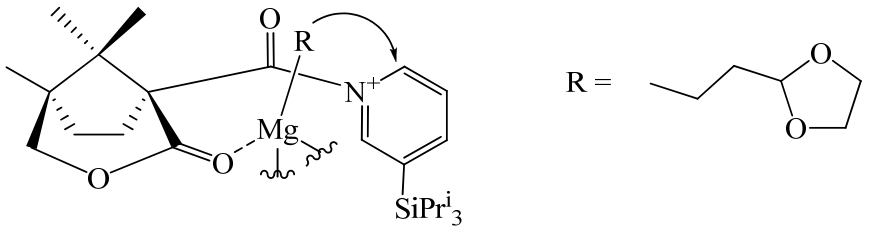
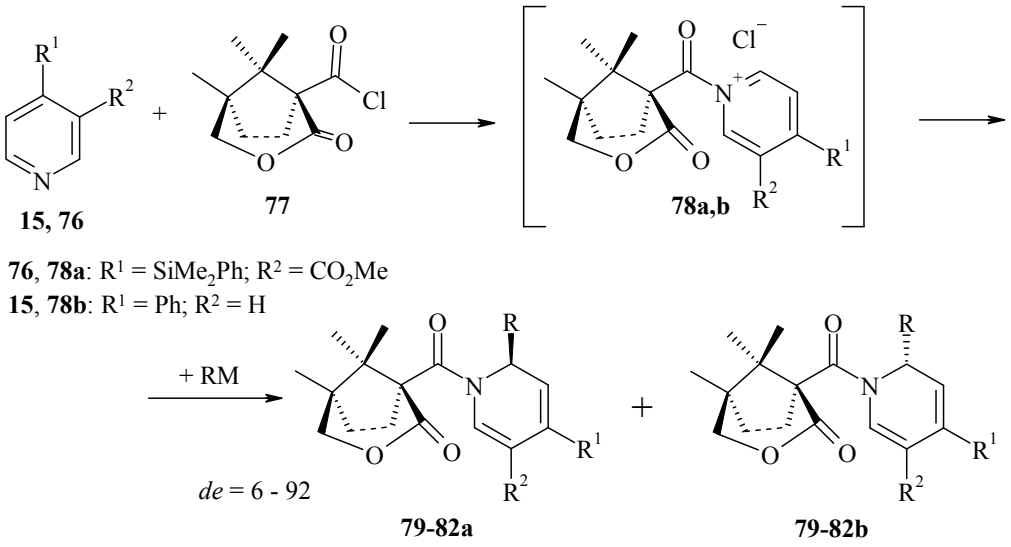


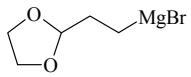
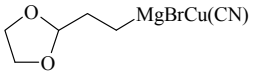
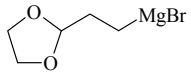
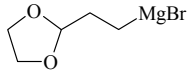
Figure 4

Acylation of pyridines **15, 76** with chloroanhydride of bicyclolactonecarboxylic acid **77** also results in the formation of the corresponding *N*-acylazinium salts **78**. The salts were unreactive to PhMgBr, therefore an additives of various triflates were utilized in order to replace the chloride-anion in **78**. The reactions with Grignard reagents afford the addition products **79-82** in moderate yields and stereoselectivity. The replacement of Grignard regents by organocuprates increases the yield but decreases the diastereoselectivity of the reaction. Introduction of Pr^i_3SiOTf instead of Me_3SiOTf slightly increases the reaction yield. Along with that the increasing of the concentration of salt **78** from 0.1 to 0.2M causes the noticeable growing of the reaction yield either (Scheme 29, Table 3).

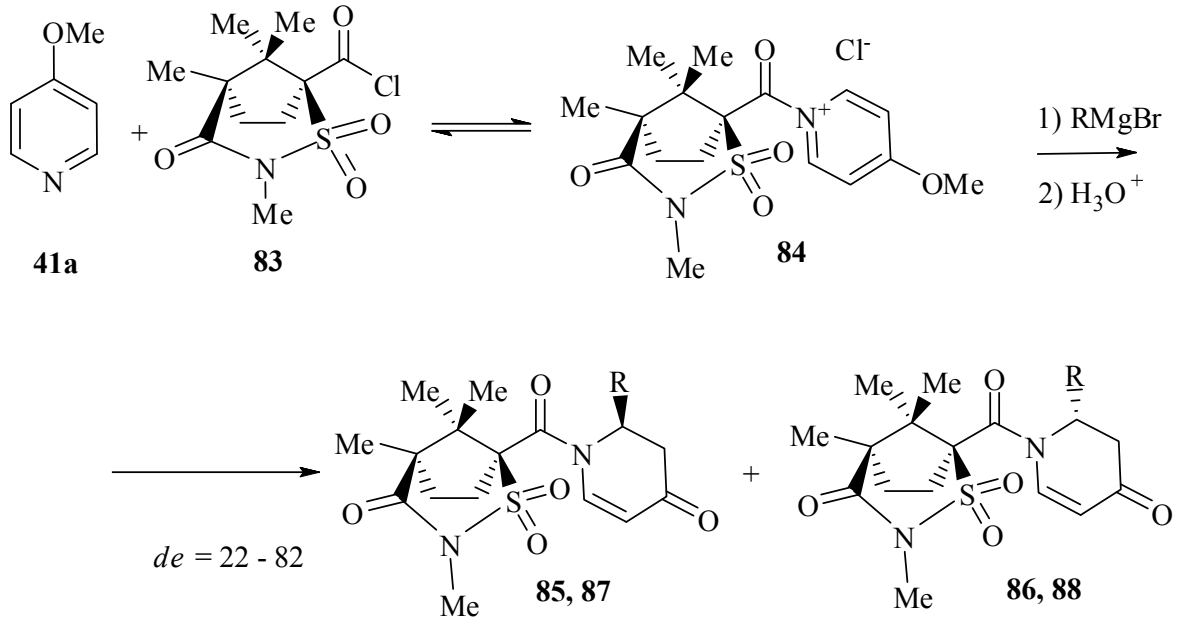


Scheme 29

Table 3. Reactions of *N*-acylazinium salts **68** with Grignard reagents

R^1	R^2	RM	Additive	C, M	Product	Yield **a**+**b**, %	**a**:**b**
$SiMe_2Ph$	CO_2Me	PhMgBr	-	0.1	**79a,b**	0	-
Ph	H	PhMgBr	-	0.1	**80a,b**	1	22:78
$SiMe_2Ph$	CO_2Me	PhMgBr	Me_3SiOTf	0.1	**79a,b**	27	24.0:76.0
Ph	H	PhMgBr	Me_3SiOTf	0.2	**80a,b**	63	47:53
Ph	H	PhMgBr	Pr^i_3SiOTf	0.1	**80a,b**	69	41:59
Ph	H	PhMgBr	Pr^i_3SiOTf	0.2	**80a,b**	89	38:62
$SiMe_2Ph$	CO_2Me	PhCu(CN)MgBr	Me_3SiOTf	0.1	**79a,b**	47	50.5:49.5
$SiMe_2Ph$	CO_2Me		Me_3SiOTf	0.1	**81a,b**	41	87.2:12.8
$SiMe_2Ph$	CO_2Me		Me_3SiOTf	0.1	**81a,b**	62	65.2:34.8
Ph	H		Me_3SiOTf	0.1	**82a,b**	25	96:4
Ph	H		Me_3SiOTf	0.2	**82a,b**	72	93:7

Reaction of 4-methoxypyridine **41a** with sultam chloroanhydride **83** generates *in situ N*-acylazinium salt **84**, which further reacts with Grignard reagents to afford compounds **85–88** (Scheme 30).[41]



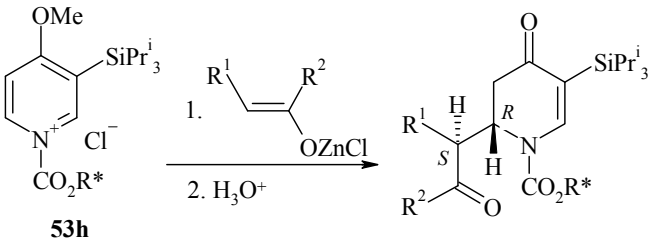
R	X	Compounds	Yield of mixture of compounds, %	*dr**
Et	I	**85** : **86**	59	91:9
Ph	Br	**87** : **88**	74	61:39**

* *dr* determined by HPLC
** The absolute configuration was not determined.

Scheme 30

1.3. Addition reactions of metalloenolates

The addition reactions of prochiral metalloenolates of ketones and lactones with salts **53h** are highly stereoselective and result in the formation of two new chiral centers. The 2*R*,2'*S*-diastereomer **89** was the main reaction product, while (*R*,*R*)-, (*S*,*R*)- and (*S*,*S*)-stereoisomers were obtained in minor amounts (Scheme 31).[42]



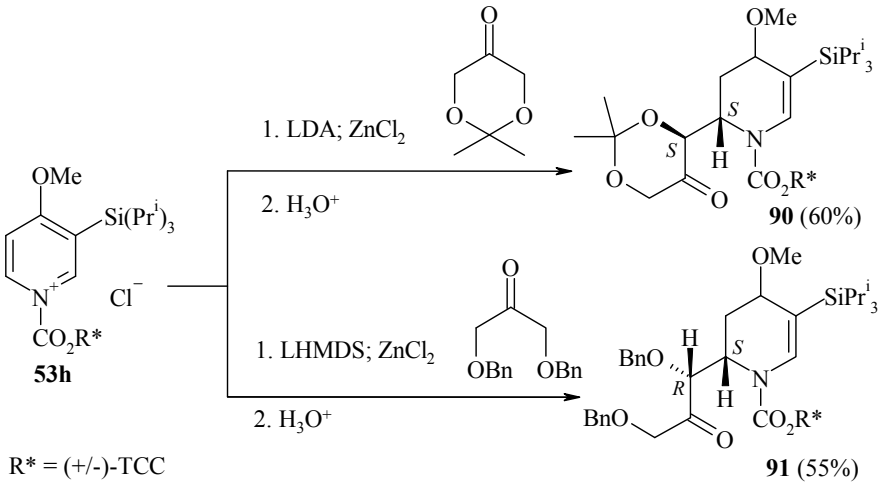
53h
R* = (-)-TCC

de = 76 - 84 **89**

R^1	R^2	Isomeric ratio (2*R*,2'*S*) : (2*R*,2'*R*) + (2*S*,2'*R*) + (2*S*,2'*S*)	Yield **89**, %
-$CH_2CH_2CH_2$-		88 : 12	82
-$CH_2CH_2CH_2CH_2$-		86 : 14	79
Me	Et	92 : 8	83

Scheme 31

Interestingly, the reaction with the enol form of 2,2-dimethyl-l,3-dioxan-5-one (*E*-isomer) proved to yield compound **90** with (2*S*,2'*S*)-configurations of chiral centers. Compound (2*S*,2'*R*)-**91** with the opposite configuration is formed as the main product in the similar reaction with l,3-bis(benzyloxy)propan-2-one in the enol form, which exists as Z-isomer due to the formation of chelate. Dihydropyridones **90** and **91** are formed with enolate facial selectivities of 9/1 and 4/1, respectively (Scheme 32).[42]



Scheme 32

The selectivity of the addition of *E*-enolate can be explained by existence of the transition state (Figure 5).[42]

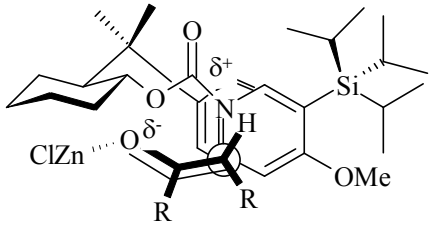
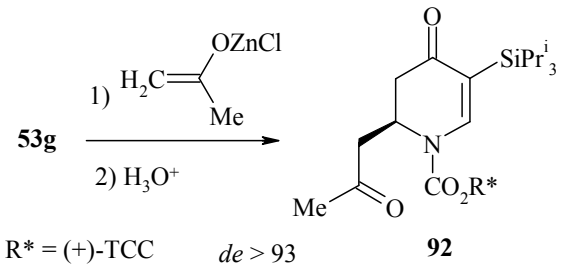


Figure 5

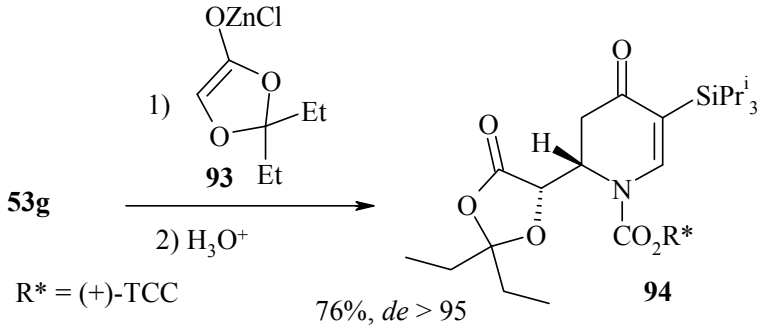
This transition state is the most probable due to the noncovalent interaction between the pyridinium ring and the phenyl ring of the chiral acyl group (π-π-interaction) and also due to the electrostatic attraction between the positively charged nitrogen atom and the negatively charged enolate oxygen atom.[42]

Similar reaction of *N*-acylpyridinium salt **53g** and acetone Zn enolate leads to *N*-acyldyhydropyridone **92** in 72% yield (Scheme 33).[43]



Scheme 33

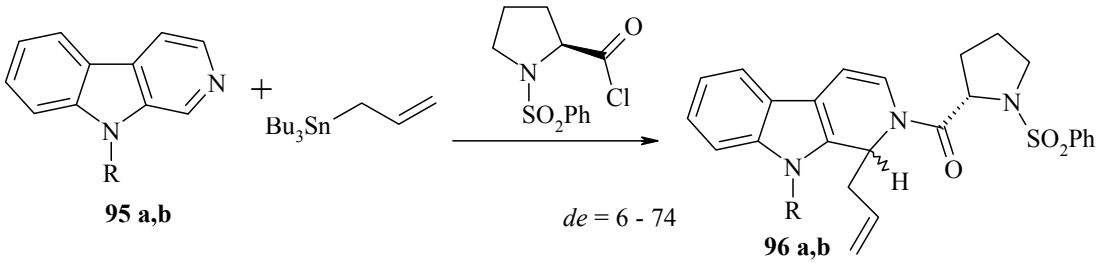
Also the formation of the enantiomerically pure *N*-acylpyridone **94** by the reaction of pyridinium salt **94g** with Zn enolate **93** was described. The *N*-acylpyridone **94** was used as a semi-product in the synthesis of (+)-cannabisativine (Scheme 34).[44,45]



Scheme 34

1.4. Addition reactions of Sn-organic compounds

During the development of asymmetric synthesis of 1-substituted tetrahydro-β-carbolynes the interaction of 3,4-dyhydro-β-carboline **95a** and allylbuthyltin was investigated. As a result the addition product **96a** was isolated in high yield, but in low degree of stereoselectiviry. Upon the introduction of phenyloxycarbonyl moiety at the position C(9) of carbolyne the stereoselectivity of the reaction was improved, but the yield fell down (Scheme 35).[47]

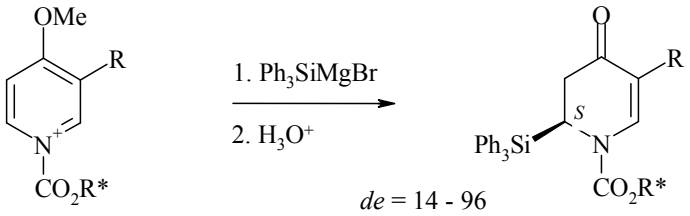


R	Product	Yield, %	*de*, %
H	**96a**	75	6
CO_2Ph	**96b**	18	38

Scheme 35

1.5. Addition reactions of organo-Si compounds

The reaction of triphenylsilylmagnesium bromide (Si-nucleophile) with chiral *N*-acyl-4-methoxypyridinium salts **53** at -78 °C is stereoselective and results in diastereomerically pure *N*-acyl-2-(triphenylsilyl)-2,3-dihydropyridin-4-ones **97** (Scheme 36). The absolute configuration of the newly formed chiral center C(2) of dihydropyridones **97a-f** appeared to be opposite to that of the main reaction product of pyridinium salts **53** with arylmagnesium chlorides as C-nucleophiles (see above[21,23-25,34,35]).[48]



53a,b,m-o,p,t *de* = 14 - 96 **97a-f**

Pyridine	R*	R	Product	Yield, %	*dr*, %
53m	(-)-menthyl	H	**97a**	63	56:42
53o	(-)-menthyl	$SiMe_3$	**97b**	65	63:37
53a	(-)-menthyl	$SiPr^i_3$	**97c**	68	73:27
53b	(-)-8-Ph-menthyl	$SiPr^i_3$	**97d**	65	58:42
53p	(-)-8-Ph-menthyl	$SiMe_3$	**97e**	62	93:7
53t	(-)-8-Ph-menthyl	$SnBu^n_3$	**97f**[a]	40	92:8
53n	(-)-8-Ph-menthyl	H	**97f**	88	98:2

[a] $SnBu^n_3$ was replaced by H by treatment with an acid.

Scheme 36

The preferential formation of *S*-isomer is explained[48] by the interaction of the magnesium atom of the Grignard reagent with the carbonyl group of the acyl fragment (Figure 6). This coordination results in the alteration of the direction of the nucleophilic attack, which was confirmed by quantum-chemical calculations.

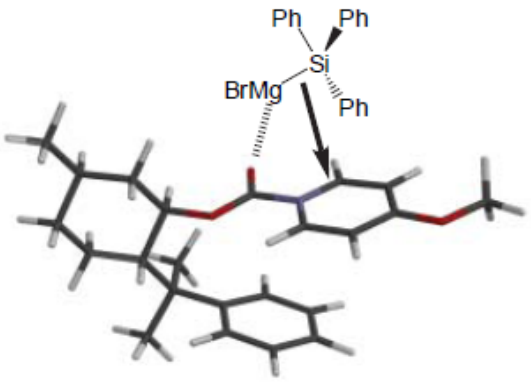
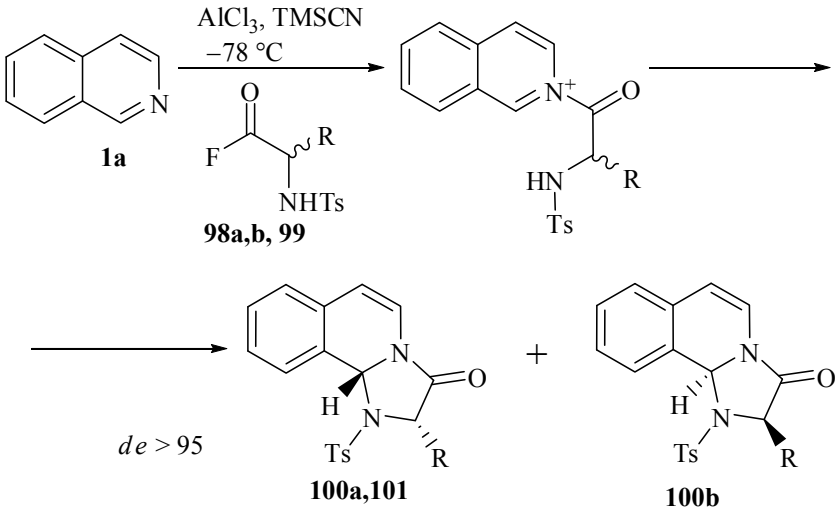


Figure 6. The molecular mechanic model of addition of triphenylsilylmagnesium bromide to chiral *N*-acyl-4-methoxypyridinium salts **97**[48]

1.6. Addition reactions of N-nucleophiles

Acylation of azaheterocycles by carboxylic acids derivatives affords the corresponding *N*-acylazinium salts. Acylation of isoquinoline **1a** by amino acid fluoroanhydrides **98a**,**b**, **99** in the presence of catalytic amounts of $AlCl_3$ and TMSCl leads to the expected *N*-acylation, but the corresponding

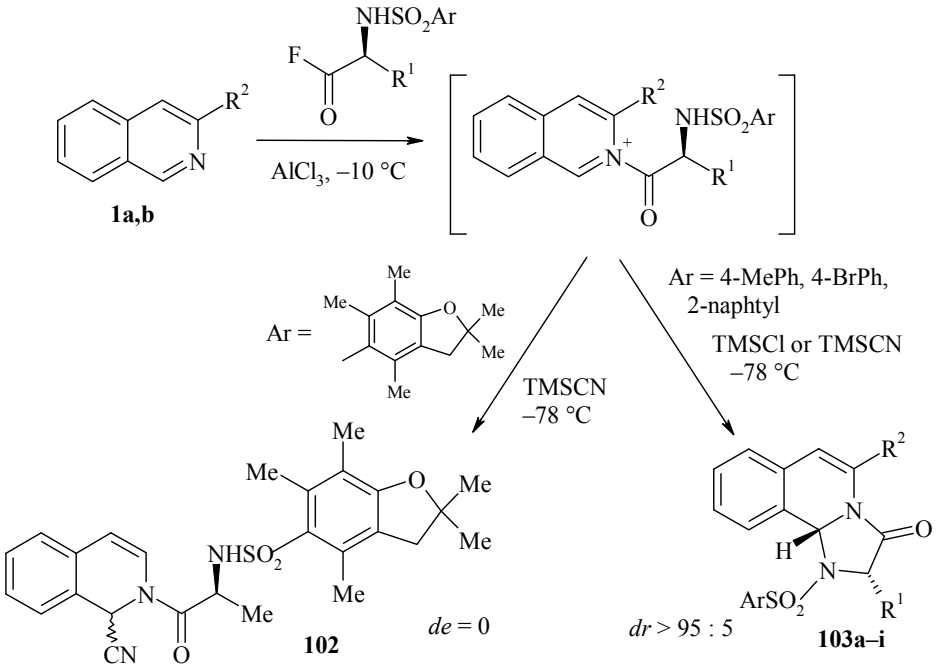
N-(β-aminoacyl)iminium salts do not form. Instead the further cyclisation occurs by the nucleophilic attack of NH-group at the iminium carbon atom, i.e. at the position C(1) of isoquinolinium ring thus to give 1,10-β-dyhydroimidazo[2,1-*a*]isoquinolin-3(2*H*)-ones **100a**,**b**, **101** as enantiopure products (Scheme 37).[49]



Amino acid	R	Configu-ration	Product	Yield, %
98a	Me	*S*	**100a**	47
98b	Me	*R*	**100b**	47
99	Bn	*S*	**101**	46

Scheme 37

Acylation of isoquinolines **1a**,**b** by means of fluoroanhydrides of β-sulphonylamino acids also postulates the formation of acylisoquinolinium intermediates and the following nucleophilic attack is sterically hindered from one side of an azine cycle. Despite the presence of TMSCN, i.e. competitive nucleophile, in the reaction mixture the intramolecular nucleophilic attack of amino group at the position C(1) of isoquinoline generates only products **103a-i**. Only upon the introduction of bulky fluoroanhydride of pentamethylbenzofurylsulphonylalanine, unable to form the cyclization products, the corresponding cyanide-anion addition product **102** was isolated. Substituents at the position C(3), especially at the position C(1) of isoquinoline cycle, cause steric hindrances for the formation of dihydroimidazoisoquinoline **103a–i**. Thus, 3-methylisoquinoline **1b** forms the corresponding reaction product **103i** in lower yield (12%), and 1-methylisoquinolin or 6,7-dimethoxy-1-methylisoquinoline were unable to react at the same conditions (Scheme 38).[50]



isoquinoline	R^1	R^2	Ar	Product	Yield, %
1a	Me	H	4-MeC_6H_4	**103a**	47
1a	Me	H	2-naphtyl	**103b**	46
1a	Me	H	4-BrC_6H_4	**103c**	46
1a	Me	H	benzthiazol-2-yl	**103d***	24
1a	Bn	H	4-MeC_6H_4	**103e**	45
1a	*i*-Pr	H	4-MeC_6H_4	**103f**	44
1a	*i*-Pr	H	2-naphtyl	**103g**	46
1a	*i*-Bu	H	4-MeC_6H_4	**103h**	46
1b	Bn	Me	4-MeC_6H_4	**103i**	12

* *N*-(Benzothiazol-2-yl)alanyl chloride was utilized instead of fluoride.

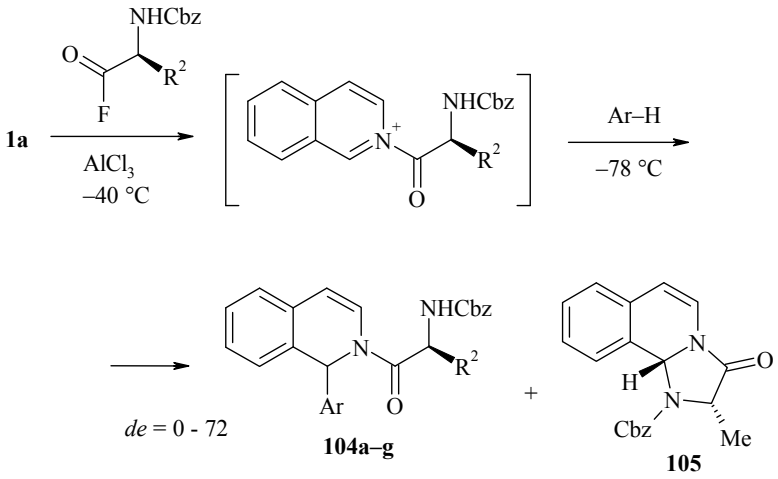
Scheme 38

Investigations of some Lewis acids, utilized for the activation of amino acid fluoroanhydrides in this reaction, demonstrated the higher efficiency of $AlCl_3$ in comparison with $ZnCl_2$, ZnF_2 or Et_2AlCl.[50]

1.7. Addition reactions of CH-active compounds

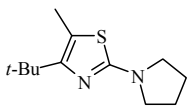
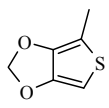
N-Acylazinium salts generated in reactions of aromatic azaheterocycles and chiral carboxylic acids are able to react with CH-active compounds, such as anilines, indoles, pyrroles, thiophenes.

Thus, in reactions of isoquinoline (**1a**), acylated by (*S*)-6-Cbz-aminoacyl fluorides, and π-excessive hetarenes a mixture of 1-aryl-2-acyl-1,2-dyhydroisoquinolines **104a**–**g** and imidazoisoquinolines **105** was obtained. In most cases the reaction proceeds in high degree of diastereoselectivity (*dr* 2:1 – 6:1 according to NMR ^1H data) (Scheme 39, Table 4).[10]



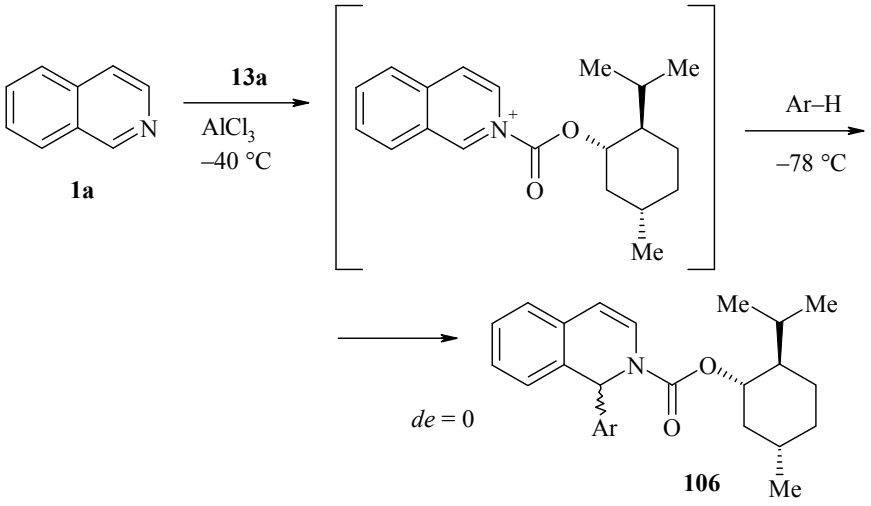
Scheme 39

Table 4. Reactions of isoquinoline **1a**, acylated by (*S*)-6-Cbz-aminoacyl fluorides, and π-excessive hetarenes

R^2	Ar	Product	Yield, %	*dr*
Me	4-$Et_2NC_6H_4$	**104a**	21	6:1
Bn	4-$Et_2NC_6H_4$	**104b**	48	3:1
Bn	4-$Me_2NC_6H_4$	**104c**	44	3.55:1
Me	4-$Me_2NC_6H_4$	**104d**	–*	–
Me	Pyrrol-2-yl	**104e**	47	5:1
Bn	Indol-2-yl	**104f**	63	2:1
Me	Indol-2-yl	**104g**	56	2:1
Me		**105**	55	1:1
Me	Benzofuran-3-yl	**105**	35	2.6:1
Me		**105**	35	3.5:1

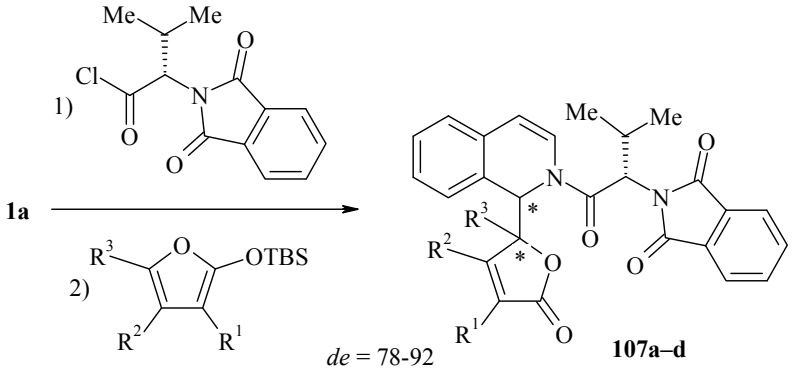
* Mixture of **104d** and **105**, 1:1.6. Yield and *dr* did not determined.

Interaction of isoquinoline (**1a**) with (–)-(*R*)-menthyl chloroformate **13a** followed by the addition of π-excessive hetarenes such as anilines, indoles, pyrroles, thiophenes leads to a corresponding 2-acyl-1-aryl-1,2-dihydroisoquinolines **106** in yields 33–97%. No diastereoselectivity was observed in these reactions (Scheme 40).[10]



Scheme 40

Acylation of isoquinoline (**1a**) by chloroanhydride of *N*-phthaloyl-(*S*)-valine and followed reaction with furan affords compounds **107a–d**. The absolute configuration was not determined by authors (Scheme 41).[51]



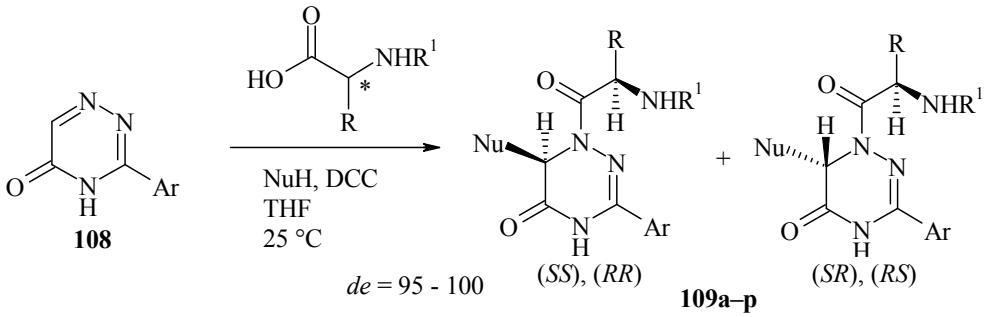
Product	R^1	R^2	R^3	Yield, %	*dr*
107a	H	H	H	99	96:3:<1:<1
107b	Me	H	H	94	89:8:2:1
107c	H	Me	H	88	91:6:2:1
107d	H	H	Me	77	94:3:2:1

* Isomer ratio was determinated by HPLC.

Scheme 41

During the investigations of 1,2,4-triazinone as substrate for an asymmetric synthesis it was found that 3-Ar-1,2,4-triazin-5-one **108** reacted with indoles after acylation by *N*-protected α-amino acids.[21] The interaction results in the addition products **109a-p** in high diastereoselectivity. The preferable formation of one pair of diastereoisomers can be explained by the possible steric hindrances for the nucleophilic

attack of triazine ring by indole, caused by bulky substituents at the α-carbon of amino acid. Besides the steric hindrances is the main reason for low yields in this reaction (Scheme 42, Table 5).[52]



108

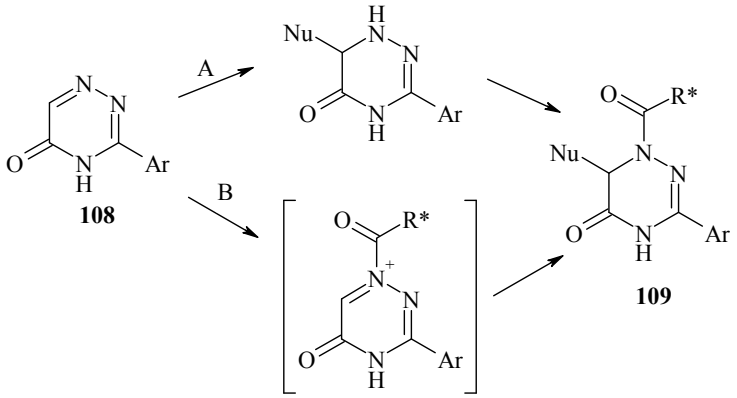
Scheme 42

Table 5. Reactions of 3-Ar-1,2,4-triazin-5-ones **108** with indoles after acylation by *N*-protected α-amino acids

NuH	Ar	*N*-acyl amino acid	Product	Yield, %	*dr**
Indole	Ph	*N*-Boc-glycine	**109a**	48	–
Indole	Ph	*N*- benzoyl-*D,L*-leucine	**109b**	34	> 95 : 5
Indole	Ph	*N*- formyl-*D,L*-alanine	**109c**	28	> 95 : 5
Indole	Ph	*N*- acetyl-*L*-tryptophan	**109d**	21	> 95 : 5
Indole	Ph	*N*- acetyl-*D,L*-phenylalanine	**109e**	22	> 95 : 5
Indole	4-MePh	*N*- acetyl-*L*-valine	**109f**	24	95 : 5
Indole	4-MePh	*N*- acetyl-*D*-alanine	**109g**	15	95 : 5
Indole	4-MePh	*N*- acetyl-*D,L*-phenylalanine	**109h**	22	95 : 5
Indole	4-MePh	*N*- acetyl-*L*-tryptophan	**109i**	18	> 95 : 5
Indole	4-MePh	*N*- acetyl-*D*-tryptophan	**109j**	16	> 95 : 5
Indole	4-MePh	*N*- acetyl-*D,L*-tryptophan	**109k**	25	95 : 5
2-Me-indole	Ph	*N*- benzoyl-*D,L*-leucine	**109l**	36	> 95 : 5
2-Me-indole	Ph	*N*- acetyl-*L*-tryptophan	**109m**	25	> 95 : 5
2-Me-indole	4-MePh	*N*- acetyl-*L*-valine	**109n**	22	> 95 : 5
1-Me-indole	4-MePh	*N*- benzoyl-*D,L*-leucine	**109o**	30	> 95 : 5
1-Me-pyrrol	4-MePh	*N*- benzoyl-*D,L*-leucine	**109p**	14	> 95 : 5

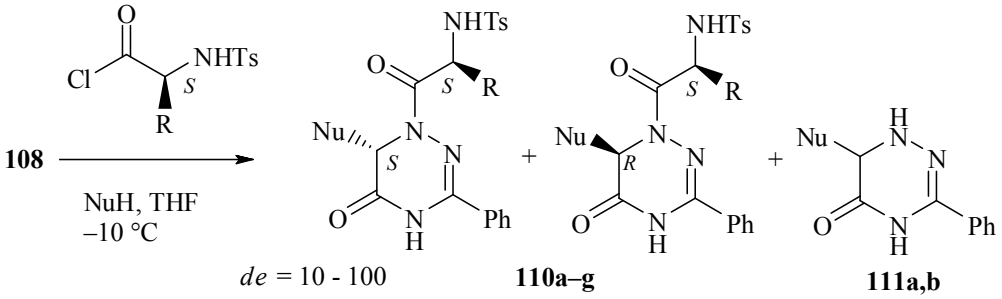
* *dr* determinated by NMR ^{1}H data

It is worth mentioning, that 3-aryl-1,2,4-triazin-5(4*H*)-ones **108**, in contrast to pyridines, quinolines or isoquinolines, which were mentioned above, are able to form the addition products with C-nucleophiles not only in the presence of acylation agents, but in the presence of acids. Authors suppose that from two possible pathways for the formation of compounds **109**, the reaction runs diastereoselectively only in case B (Scheme 43).[52]



Scheme 43

In reactions of triazines **108** and C-nucleophiles at the presence of chloroanhydrides of *N*-Ts-*L*-valine or *N*-Ts-*L*-leucine some 6-aryl-1-(2-tosylamino)acyl-3,4-dyhydro-1,2,4-triazin-5(4*H*)-one **110a**–**g** were obtained in yields from 15 to 77% (Scheme 44). If *N*-Ts-*L*-valine was utilized as an acylating agent the diastereoselectivity of the reaction was the highest. According to NMR ^{1}H the content of *SS*-isomer **110c**,**f** in reaction mixtures was 90–95% (Scheme 44, Table 6).[53]



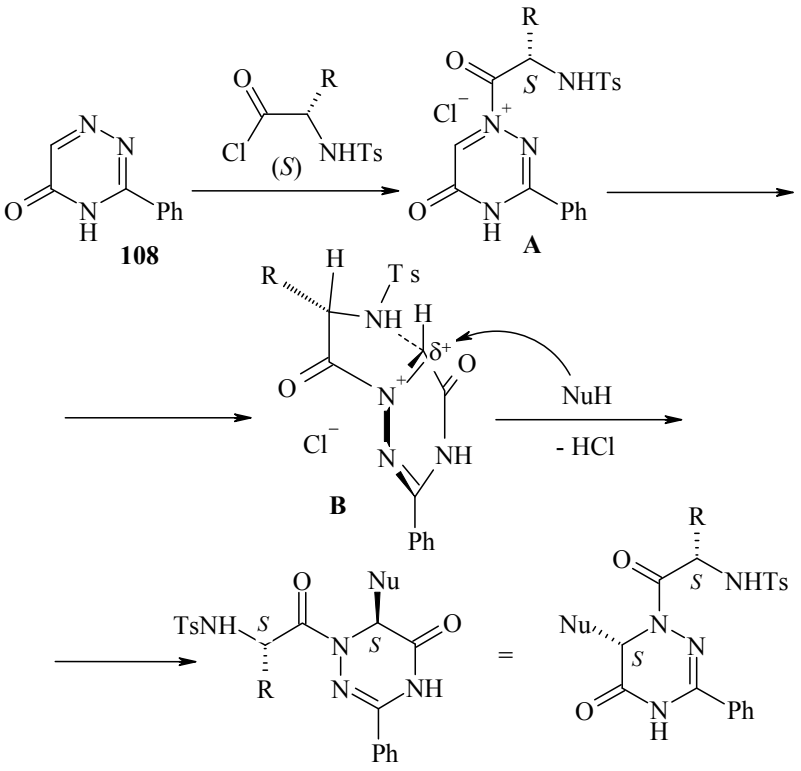
Scheme 44

Table 6. Reactions of 3-Ph-1,2,4-triazin-5-one **99** with indoles after acylation by chloroanhydrides of *N*-Ts-*L*-valine or *N*-Ts-*L*-leucine

NuH	R	**110**, (%)**	*SS*:*SR**	*SS*:*SR***	**111**, (%)
Indole	CH_2CHMe_2	(*S*,*S*)-**110a** (15)	60:40	> 95:5	**111a** (<5)
Indole	CH_2CHMe_2	(*S*,*S*)-**110b**(10), (*S*,*R*)-**110b**(5)	45:55	> 95:5	**111a** (36)
Indole	$CHMe_2$	(*S*,*S*)-**110c** (77)	90:10	> 95:5	–
1-Me-indole	CH_2CHMe_2	(*S*,*S*)-**110d** (65)	55:45	> 95:5	–
2-Me-indole	CH_2CHMe_2	(*S*,*S*)-**110e** (42)	65:35	> 95:5	–
2-Me-indole	$CHMe_2$	(*S*,*S*)-**110f** (32)	> 95:5	> 95:5	–
1-Me-pyrrol	CH_2CHMe_2	(*S*,*S*)-**110g**(15)	60:40	> 95:5	**111b** (7)

* *dr* crude (in reaction mixture).
** *dr* after the separation by means of chiral chromatographic column (NMR ^{1}H data).

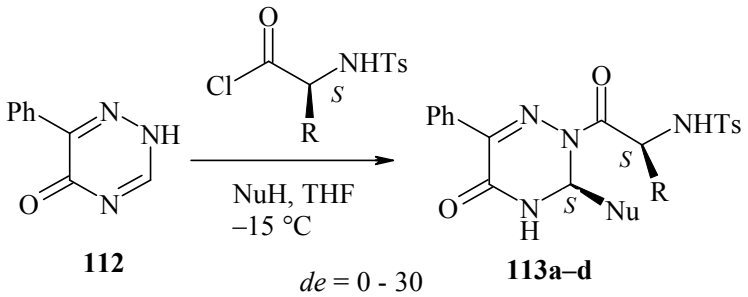
The asymmetric induction can be explained by the formation of *N*-acylazinium salt **A**, there is the dipole-dipole interaction between the nitrogen atom of amino group of amino acid and the electrophilic carbon atom of heterocycle. This interaction forms sterical hindrances for the nucleophilic attack from one side of heterocyclic ring plane (Scheme 45).[53]



Scheme 45

In reactions of triazinone **108** with substituted phenols in the presence of chloroanhydride of *N*-Ts-*L*-valine the formation of products **110** does not occur, the reaction results in the water addition products at the position C(6) of triazine.[54]

In reaction of 6-phenyl-1,2,4-triazin-5(4*H*)-one **112** with C-nucleophiles in the presence of amino acids chloroanhydrides the formation of some 3-substituted 2-(2-tosylamino)acyl-6-phenyl-3,4-dihydro-1,2,4-triazin-5(4*H*)-ones **113a-d** occurs in moderate yields and in low diastereoselectivity (Scheme 46).[53]



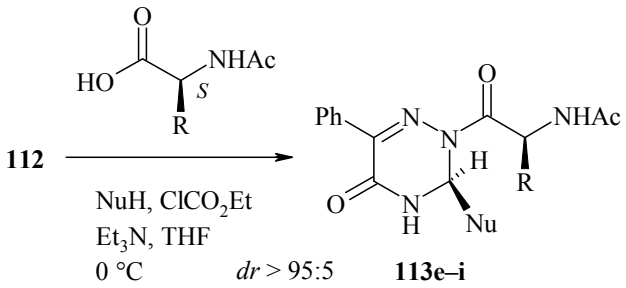
Scheme 46

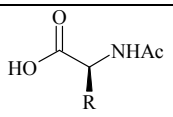
NuH	R	Product	*SS* : *SR**	*SS* : *SR***	Yield **, %
Indole	$CH_2CH(CH_3)_2$	**113a**	55:45	> 95:5	52
Indole	$CH(CH_3)_2$	**113b**	65:35	> 95:5	23
1-Me-pyrrol	$CH_2CH(CH_3)_2$	**113c**	–	> 95:5	15
1-Me-pyrrol	$CH(CH_3)_2$	**113d**	50:50	> 95:5	32

* *dr* crude (in reaction mixture).
** *dr* after the separation by means of chiral chromatographic column (NMR ^{1}H data).

Scheme 46

Reaction of 6-phenyl-1,2,4-triazin-5(4*H*)-one **112** with C-nucleophiles in the presence of *N*-substituted *L*-amino acids and ethyl chloroformate leads to 3-substituted 2-(2-acylamino)acyl-6-phenyl-3,4-dihydro-1,2,4-triazin-5(4*H*)-ones **113e–i** obtained as a pair of (*SS*,*RR*)-diastereomers in moderate yields, but in high diastereoselectivity (Scheme 47).[55]

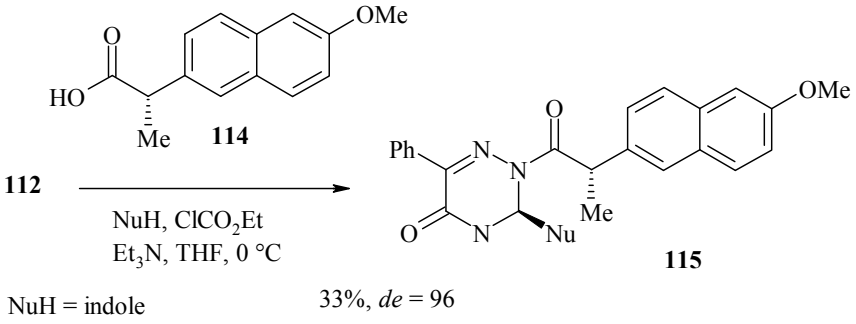


NuH		Product*	Yield, %
Indole	*N*-Ac-*L*-leucine	**113e**	49
Indole	*N*-Ac-*L*-valine	**113f**	76
1-Me-indole	*N*-Ac-*L*-valine	**113g**	40
Indole	*N*-Ac-*L*-tryptophan	**113h**	32
Pyrrol	*N*-Ac-*L*-valine	**113i**	30

**dr* > 95:5 (according to NMR ^{1}H data)

Scheme 47

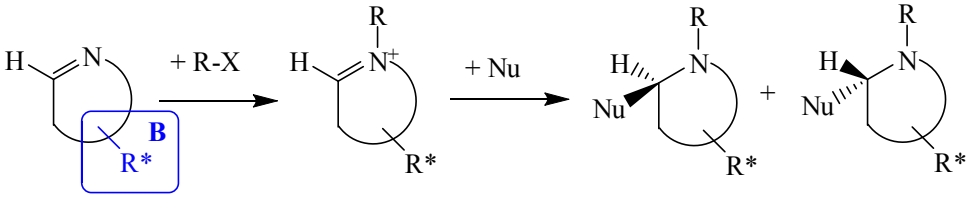
Activation of amino acids via generation of esters leads to racemization therefore the reaction products **113e–i** are racemic mixtures even if enantiopure amino acids are utilized in the reaction. Upon the introduction of naproxen **114** instead of amino acids the reaction affords product **115** (*dr* = 98:2 according to HPLC) (Scheme 48).[55]



Scheme 48

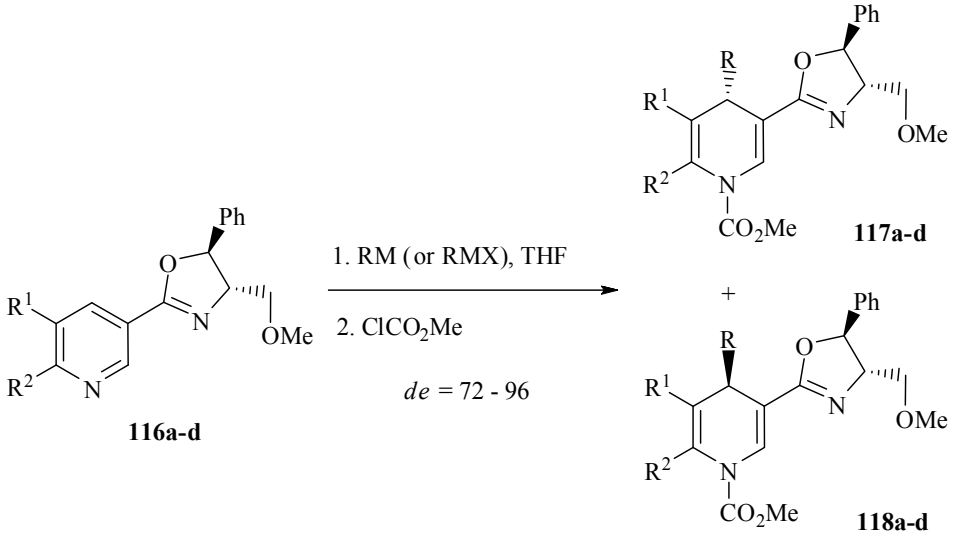
2. Interaction of azines, containing a chiral substituent next to the cyclic carbon atom

The main factor determining the diastereomeric ratio of products of nucleophilic attack at the carbon atom of C=N of an azine, is the presence of any substituents in the azine ring, which can coordinate with the attacking nucleophile. If R* bears chirality it can direct the reaction by the way favoring the formation of one or another possible diastereomeric products (Scheme 49).



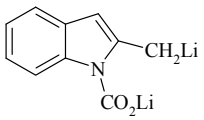
Scheme 49

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)- (**116a**) and 2-(3-quinolyl)oxazolines (**116b**) with organolithium and organomagnesium reagents followed by treatment with methyl chloroformate. This reaction affords the 1,4-dihydro-derivatives **117a-d** and **118a-d** in good yields and high diastereomer ratio (Scheme 50, Table 7).[56-59]



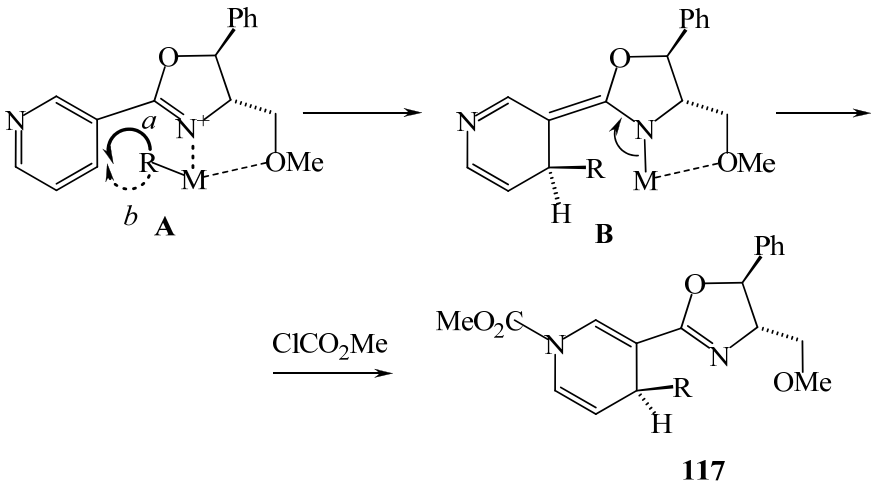
Scheme 50

Table 7. Reactions of oxazolines **116a-d** with organolithium and organomagnesium reagents

116	R^1	R^2	RM	T, °C	**117 : 118**	Total yield **117**+**118** (yield **117**), %	Lit.
a	H	H	MeLi	- 40	93 : 7	79	56
	H	H	MeLi	- 78	94 : 6	79 (63)	56
	H	H	MeMgCl	0	91 : 9	88	56
	H	H	BuLi	- 78	97 : 3	(92)	56
	H	H	BuMgCl	0	95 : 5	98	56
	H	H	EtMgBr	0	92 : 8	63	56
	H	H	PhLi	- 78	92 : 8	94	56
	H	H	PhLi	- 78	89 : 11	78	58
	H	H	*p*-MeOPh	- 78	95 : 5	55	58
	H	H		-	60 : 40	62 [a]	60
b	C_6H_4		MeLi	- 78	98 : 2	84 (70)	56
	C_6H_4		1-NaphthylLi	- 78	88 : 12	(87) [b]	59
	C_6H_4		1-NaphthylMgBr	- 115	14 : 86	(80) [c]	59
c	CO_2Et	H	MeLi	- 78	95 : 5	65	57
d	$CONH_2$	H	MeLi	- 78	98 : 2	78	57

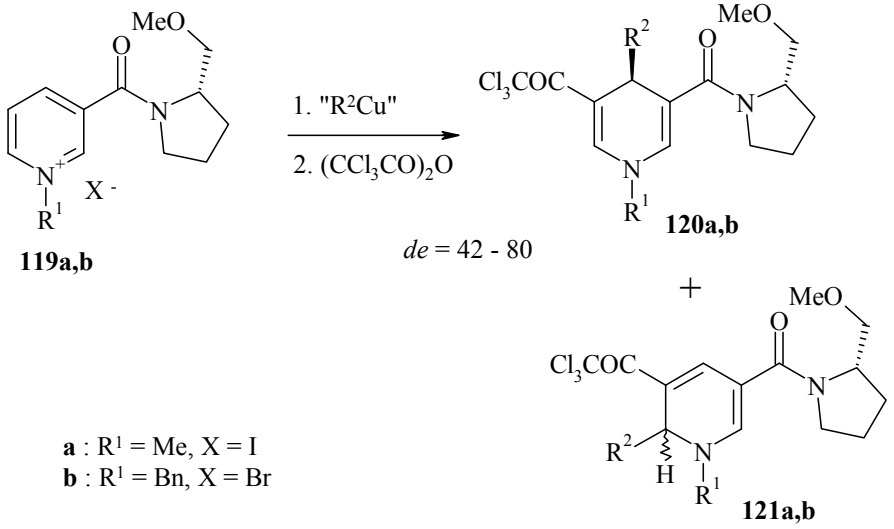
[a] yield of the mixture of 1,4 and 1,2-addition products (9:4);
[b] yield of the oxidation product of **117**;
[c] yield of the oxidation product of **118** obtained using DDQ.

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 complex **A** followed by the attack of the group R on the position C(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 **B**, formed upon addition of organometallic compound RM (or RMX) to pyridine **116a**, are acylated with methyl chloroformate to afford compound **117** (Scheme 51).[56]



Scheme 51

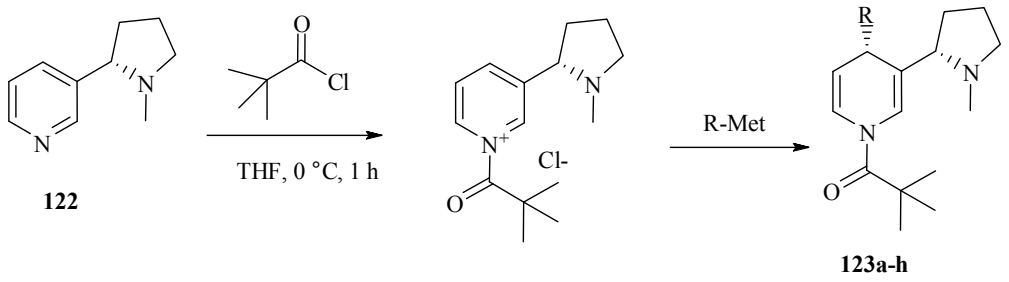
Pyridinium salts **119a**,**b** reacted with lithium organocuprates. After acylation of the reaction mixture with trichloroacetic acid anhydride the expected adducts **120a**,**b** and **121a**,**b** were isolated (Scheme 52).[61] In addition authors consider the possibility of utilizing of such CH-active compound, as 1-Me-2-acetylindole as a nucleophile in this reaction. This indole attacks the position C(4) of pyridine ring by the acetyl group to form the addition product in low yield and diastereoselectivity (yield 30%, *dr* = 2.1:1).[61]

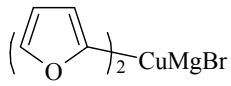
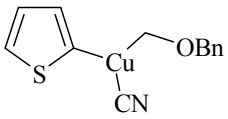


119	«R^2Cu»	R^2	Products	Yield, %	*dr* (**120**)
a	$Ph_2Cu(CN)Li_2$	Ph	**120a** + **121a** (4.5:1)	50	5:1
	$Bu^n{}_2CuLi$	Bu	**120a**	62	9:1
	Me_2CuLi	Me	**120a** + **121a** (2:1)	43	4:1
b	$Ph_2Cu(CN)Li_2$	Ph	**120b** + **121b** (1.6:1)	37	2.5:1
	$Bu^n{}_2CuLi$	Bu	**120b**	34	4:1

Scheme 52

Comins and co-authors have studied the behavior of nicotine **122**, activated by pivaloyl chloride in reactions with nucleophiles. After the addition of organocuprates the addition products **123a-h** were isolated (Scheme 53).[62]

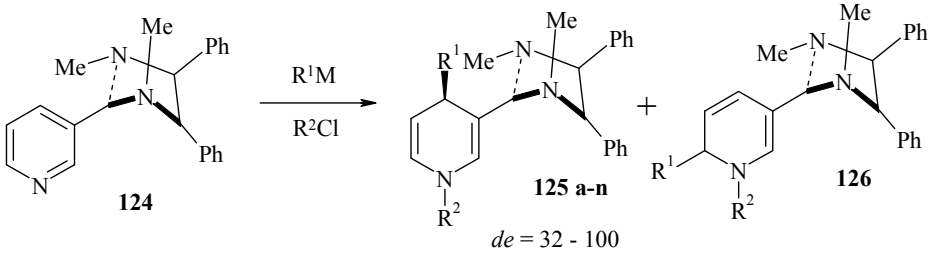


R-Met	Product	Yield, %
MeMgBr, CuBr	**123a**	71
PhMgBr, CuBr	**123b**	79
Bu^nMgBr, CuBr	**123c**	40
BnMgBr, CuBr	**123d**	64
	**123e**	77
	**123f**	76 (*dr* 52%)[a]
$(Bu^tOCH_2)_2CuLi$	**123g**	58
$(PhMe_2Si)_2CuMgBr$	**123h**	81 (*dr* 68%)[a]

[a] *dr* according to NMR ^1H data.

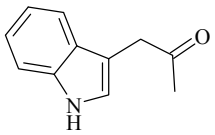
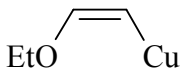
Scheme 53

Pyridines **124** bearing the chiral aminal in position C(3) are able to react with organocuprate with various stereoselectivities. Reaction affords the mixture of 1,4- and 1,2-addition products **125** and **126** respectively (Scheme 54, Table 8).[63,64]



Scheme 54

Table 8. Reactions of pyridines **124** with organocuprates

R-M	R^2	**125:126**	Product	Yield, %	*de*, %	Lit.
MeLi	CO_2Me	-		0	-	63
MeMgBr	CO_2Me	14:86	**125a**	71	93	63
Me_2CuLi	CO_2Me	70:30	**125a**	80	95	63
Me_2CuLi	CO_2Me	100:0	**125a**	90	41	63
$Me_2CuMgBr$	CO_2Me	100:0	**125a**	90	95	63
Et_2CuLi	CO_2Me	81:19	**125b**	79	32	63
$Et_2CuMgBr$	CO_2Me	100:0	**125b**	90	82	63
Et_2CuLi	CO_2Me	100:0	**125b**	90	85	63
Bu_2CuLi	CO_2Me	100:0	**125c**	40	95	63
$(CH_2{=}CH_2)CuMgCl$	CO_2Me	100:0	**125d**	90	95	63
$Ph_2CuMgCl$	CO_2Me	100:0	**125e**	90	95	63
EtCu, 2LiBr		-	**125f**	80	95	64
MeCu	COMe	100:0	**125g**	95	> 95	65
$Me_2CuMgBr$	COMe	100:0	**125h**	90	> 95	65
Et_2CuLi	COMe	100:0	**125i**	70	> 95	65
EtCu	CH_2Ph			0		65
Et_2CuLi	CH_2Ph	100:0	**125j**	95	40	65
	COPh	90:10	**125k**	75	> 95	66
MeCu	$CO(CH_2)_2Cl$	-	**125l**	80	95	67
MeCu	$CO(CH_2)_3Cl$	-	**125m**	92	95	67
MeCu	$CO(CH_2)_4Br$	-	**125n**	89	95	67

In order to explain the observed regio- and stereoselectivity authors supposed the existence of hypothetic transition state in which the organocuprate is linked with either acetyl chloride or methyl chloroformate (Figure 7).[63]

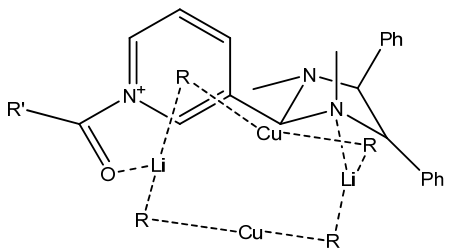
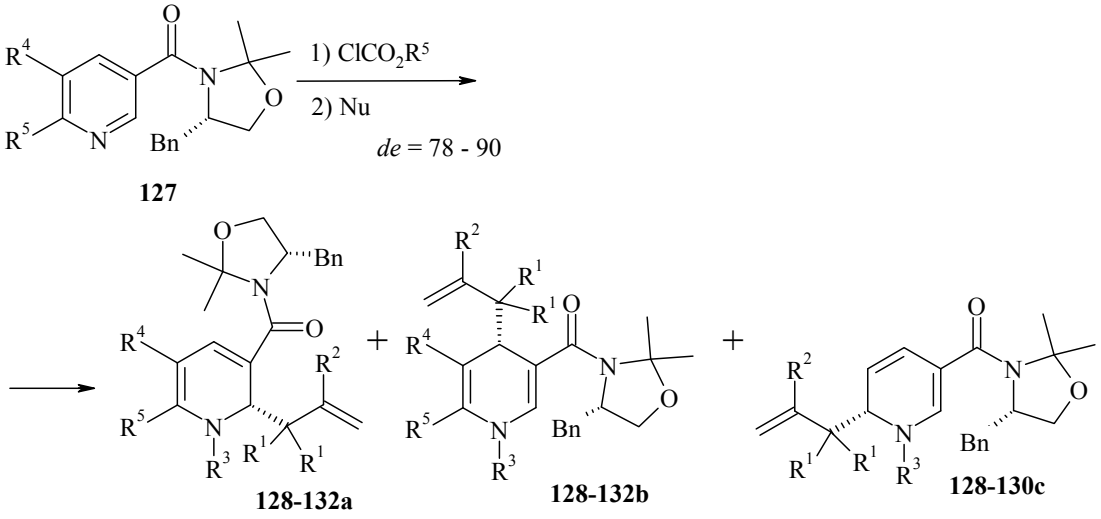


Figure 7

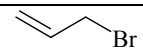
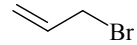
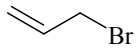
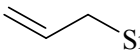
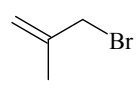
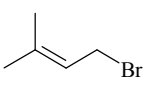
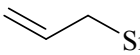
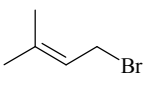
One more example of regio- and stereoselective addition of allylic organometallic compounds to pyridinium or quinolinium π-complexes was described. Allylation of pyridinium or quinolinium salts by

allylindium or allyltin reagents affords 1,2- or 1,4-adducts with high regio- or stereoselectivity. Pyridine **127** acylation and following attack by allylic nucleophile results in a mixture of 1,2-, 1,4- and 1,6-addition products **a**, **b** and **c** correspondingly (Scheme 55, Table 9). It was demonstrated that Zn- and Sn-containing nucleophiles leads to the preferable formation of 1,2- and 1,6-addition products, at the same time organoindium compounds preferably result in 1,4-addition products.[68]

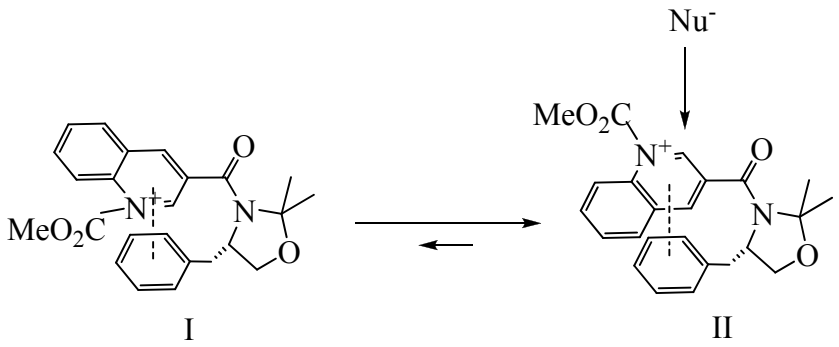


Scheme 55

Table 9. Reactions of allylation of pyridinium or quinolinium salts by organometallic nucleophiles

Nu	R^1	R^2	R^3	R^4	R^5	**a : b : c**	Product	Yield, %	de, %
	H	H	CO_2Me	H	H	72 : 0 : 28	**128a**	64	84
	H	H	CO_2Ph	H	H	70 : 0 : 30	**129a**	78	90
	H	H	CO_2Me	H	H	60 : 0 : 40	**128a**	53	86
	H	H	CO_2Me	H	H	92 : 0 : 8	**128a**	90	84
	H	Me	CO_2Me	H	H	25 : 42 : 33	**129b**	60	84
	Me	H	CO_2Me	H	H	0 : 94 : 6	**130b**	82	84
	H	H	CO_2Me	C_6H_4		100 : 0 : -	**131a**	52	78
	Me	H	CO_2Me	C_6H_4		14 : 68 : -	**132b**	62	78

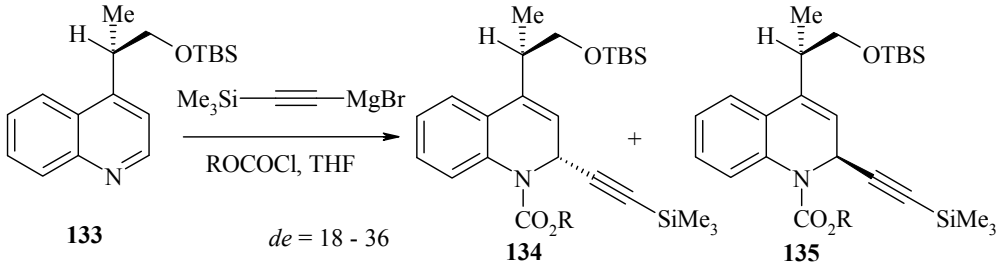
Authors suspect, that π-π-interaction between the aromatic system of azine and its aromatic substituent should block one face of heterocyclic ring plane for nucleophilic attack therefore products of nucleophilic addition will form in a certain stereoselectivity. By means of theoretical calculations it was demonstrated that in the equilibrium between isomers I and II the formation conformer II is preferable (Scheme 56).[68]



I II

Scheme 56

Diastereoselective addition of (trimethylsilyl)ethynylmagnesium bromide to optically active quinolines **133** in the presence of alkyl (or aryl) chloroformates produces compounds **134** and **135** in good yields and moderate stereoselectivity.[69] This is the result of steric hindrance created by bulky substituents at position C(4) of the quinolone ring (Scheme 57).

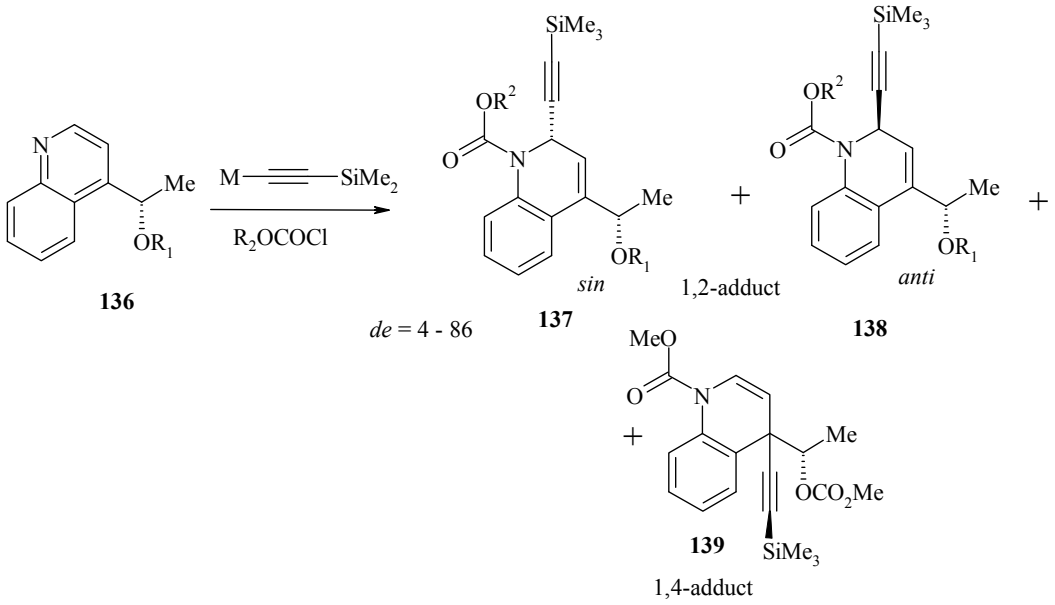


133 **134** **135**

R	T, °C	Total yield, %	ratio (±)**124** : (±)**125**
Bn	-78 → -2	72	59 : 41
Me	0	78	66 : 34
Ph	-78 → 0	87	68 : 32
Ph	-78	66	67 : 33

Scheme 57

During the synthesis of dynemicin A antibiotic it was demonstrated by the example of quinoline **136** that chiral groups at the position C(4) can lead to the stereoselective formation of addition products (Scheme 58, Table 10). Bulky protective groups R^1 for instance phenyl chloroformate (instead of methyl chloroformate) and lower temperature were the most effective factors for improving the stereoselectivity of this reaction.[70]



Scheme 58

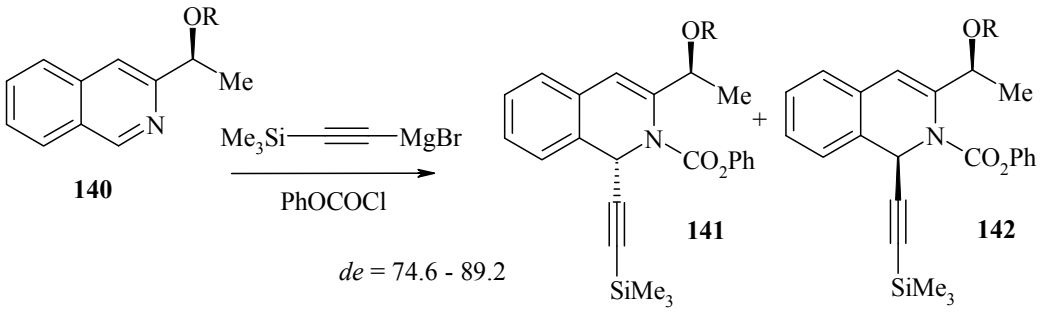
Table 10. Reactions of quinolines **136** with organometallic nucleophiles

R^1	M	R^2	T, °C	Products (1,2-adduct) Yield, %	*Sin:anti*
H	MgBr	Me	0	37 [a]	1:1.7
MOM	MgBr	Me	0	65	1:1.1
MEM	MgBr	Me	0	83	1:1.1
PMB	MgBr	Me	0	85	1:1.3
Bz	MgBr	Me	0	70	1:1.7
TES	MgBr	Me	0	63	1:1.5
TBDPS	MgBr	Me	0	85	1:2.3
TBDPS	MgBr	Bn	0	79	1:2.1
TBDPS	MgBr	Ph	0	100	1:4.9
TBDPS	MgBr	Ph	-20	100	1:5.6
TBDPS	MgBr	Ph	-78	87	1:13
PMB	$SnBu_3$	Ph	0	46	1.6:1
TBDPS	$SnBu_3$	Ph	0	20	2.4:1

[a] Yield of **139** 28%

An example of the reaction of nucleophilic addition to isoquinoline with a chiral substituent at position C(3) is known.[71] Diastereoselective addition of (trimethylsilyl)ethynylmagnesium bromide to isoquinolines **140** in the presence of aryl chloroformates yields compounds **141** and **142** with high

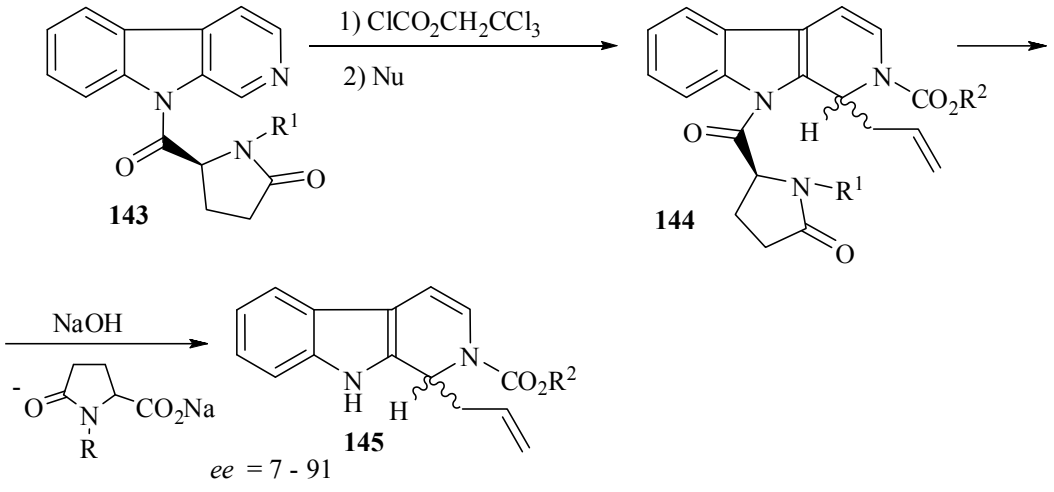
diastereoselectivities due to the presence of a chiral substituent at position C(3) of the isoquinoline ring (Scheme 59).



R	Yield **141** + **142**, %	**141 : 142**
$SiMe_2Bu^t$	88	87.3 : 12.7
$SiPh_2Bu^t$	82	94.6 : 5.4
Tr	30	90.4 : 9.6

Scheme 59

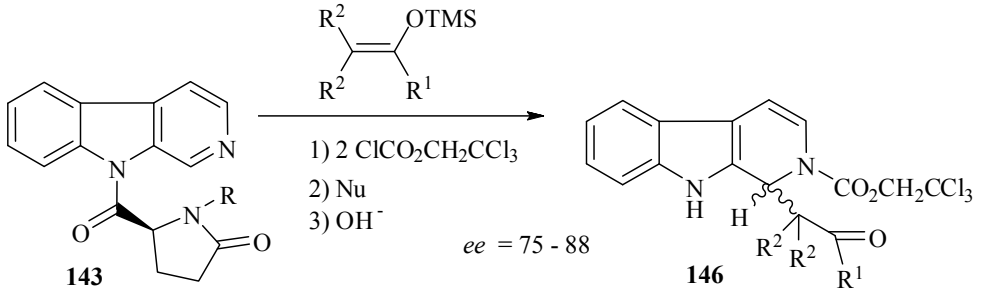
β-Carbolines **143** bearing proline chiral moiety at the position C(9) in the presence of chloroformates are able to react with nucleophiles to form the addition products **144** in high stereoselectivity, the following hydrolysis of **144** affords compounds **145**. In these dihydro-β-carbolynes (**145**) the configuration of an asymmetric center depends on a nature of R^1 substituent of adduct **143**, moreover the size of this substituent does not affect the reaction stereoselectivity of the process (Schemes 60, 61, Tables 11, 12).[47,72,73]



Scheme 60

Table 11. Reactions of β-carbolines **143** with organometallic nucleophiles

R^1	R^2	Nu	Yield **144**, %	Product **145**			Lit.
				Yield, %	configu-ration	*ee*, %	
$PhSO_2$	Ph	$Bu_3SnCH_2CH=CH_2$	53	> 90	*R*	74	47
$PhSO_2$	CH_2CCl_3	»	90	»	*R*	78	47
p-I-$PhSO_2$	»	»	60	»	*R*	73	47
p-Cl-$PhSO_2$	»	»	75	»	*R*	74	47
p-MeO-$PhSO_2$	»	»	70	»	*R*	74	47
p-Me-$PhSO_2$	»	»	74	»	*R*	76	47
p-Pr^i-$PhSO_2$	»	»	63	»	*R*	83	47
p-Ph-$PhSO_2$	»	»	72	»	*R*	77	47
p-PhC≡C-$PhSO_2$	»	»	63	»	*R*	70	47
p-neopentyl-$PhSO_2$	»	»	71	»	*R*	82	47
p-Hex^c-$PhSO_2$	»	»	62	»	*R*	81	47
PhCO	»	»	80	»	*R*	57	47
MeCO	»	»	71	»	*R*	58	47
CF_3CO	»	»	85	»	*R*	76	47
p-Am^t-$PhSO_2$	»	»	98	94	*R*	86	47, 72
p-Am^t-$PhSO_2$	»	$Sn(CH_2CH=CH_2)_4$	-	72	*S*	36	72
PhCO	»	$Sn(CH_2CH=CH_2)_4$	-	71	*S*	9	72
MeCO	»	$Sn(CH_2CH=CH_2)_4$	-	52	*S*	12	72
$PhSO_2$	»	$Sn(CH_2CH=CH_2)_4$	-	54	S	29	72
Me	»	$Bu_3SnCH_2CH=CH_2$	22	-	*S*	7	73
Bn	»	»	95	-	*S*	21	73
1-Naphthylmethyl	»	»	87	-	*S*	58	73
2- Naphthylmethyl	»	»	100	-	*S*	66	73
9-Anthrylmethyl	»	»	98	-	*S*	91	73
MeCO	»	»	100	-	*R*	89	73
PhCO	»	»	92	-	*R*	83	73
9-Anthrylcarbonyl	»	»	56	-	*R*	83	73
p-NO_2-PhCO	»	»	100	-	*R*	88	73
$PhSO_2$	»	»	51	-	*R*	79	73

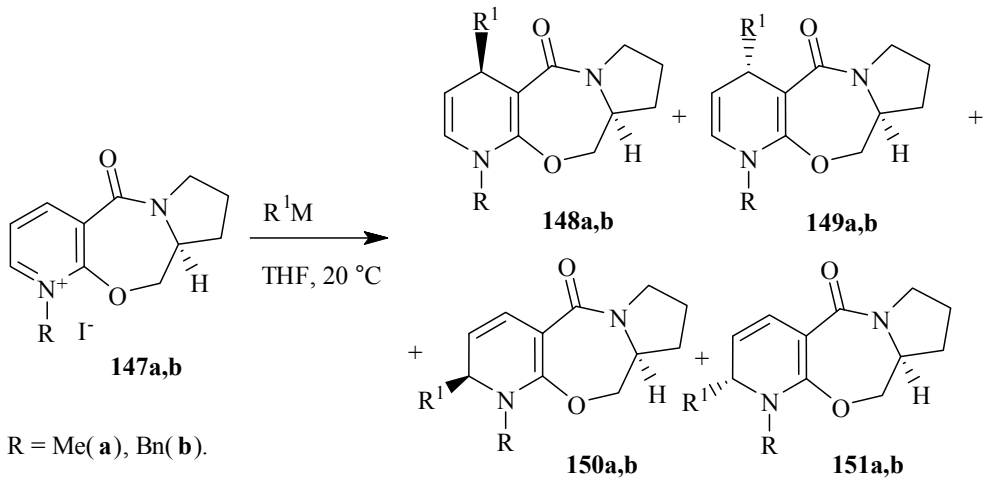


Scheme 61

Table 12. Reactions of β-carbolines **143** with C-nucleophiles

R	R^1	R^2	Yield, %	configu-ration	*ee*, %	Lit.
9- Anthrylcarbonyl	Me	H	40	*S*	79	73
»	Ph	H	79	*S*	86	73
»	OMe	Me	100	*S*	82	73
»	OBn	H	81	*S*	88	73
MeCO	»	H	93	*R*	76	73
PhCO	»	H	100	*R*	76	73
p-NO_2PhCO	»	H	100	*R*	75	73

An example of the complexation effect on the stereoselective addition of nucleophiles to pyridinium salts is documented.[74] Reactions of 1-methyl- (**147a**) and 1-benzylpyridoxazepinone (**147b**) salts with alkyl-, alkenyl- and phenyl-magnesium bromide result in the products 1,2 and 1,4-addition **148a**,**b** with high stereoselectivity and in good yields. Stereo- and regioisomers **149-151a**,**b** are found in minor amounts. The process becomes less selective when organolithium compounds are used instead of the Grignard reagents (Scheme 62, Table 13).

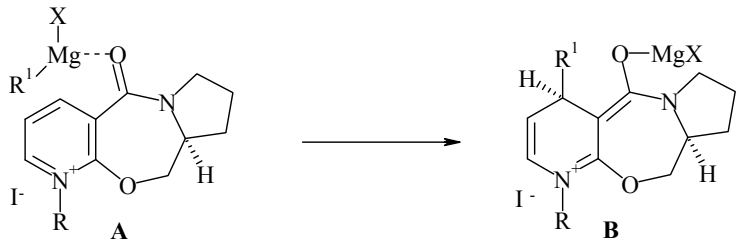


Scheme 62

Table 13. Reactions of pyridoxazepinone salts **147a**,**b** with organometallic nucleophiles

R	R^1M	Ratio of products			Yield **148**, %
		(148+149) : (150+151)	**148:149**	**150:151**	
Me	MeLi	1:1	3:1	3:1	-
CH_2Ph	MeLi	1.75:1	3:0.5	1:1	-
Me	Bu^nLi	3:1	2:1	1:0	-
Me	MeMgBr	19:1	19:0	1:0	72
CH_2Ph	MeMgBr	15:1	75:0	4:1	87
Me	Bu^nMgBr	57:1	57:0	1:0	60
Me	Me_2CHCH_2MgBr	>99:1	>99:0	<1:0	95
Me	$CH_2=CHCH_2MgBr$	5.5:1	4:1.5	1:0	-
Me	$CH_2=CHMgBr$	>99:1	>99:0	<1:0	74
Me	PhMgBr	98:0	98:0	2:0	88
CH_2Ph	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 **A**. The transfer of the organic fragment from the magnesium atom to C(4) of the pyridine ring results in the enolate **B**; its hydrolysis leads to compounds **148-151** (Scheme 63).[74]



Scheme 63

Studies on the conformational behavior of compounds **147a,b** reveal that the seven-membered ring is relatively rigid and only two energetically favorable conformations are possible (only one is shown) (Figure 8).[74]

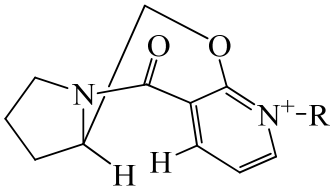
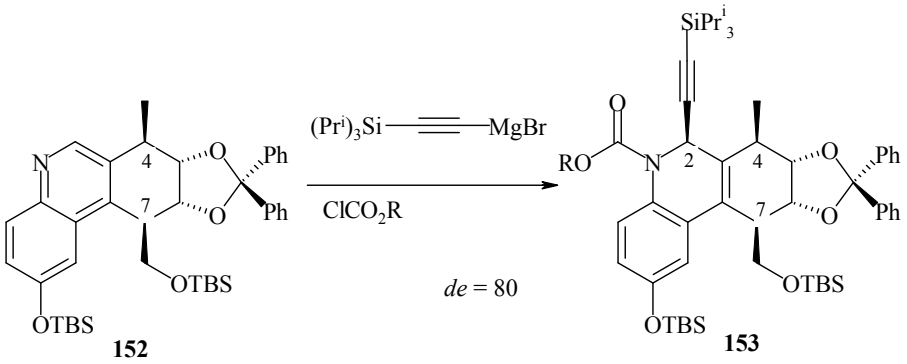


Figure 8

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 center, while in the second conformer the carbonyl group and the pyridinium ring are coplanar. It is remarkable that the conformations of compounds **137** where the carbonyl amide group is arranged under the pyridinium ring are energetically unfavorable. Therefore, the intermolecular shift of the group R^1 of the complex **A** through a six-membered transition state can lead predominantly to the isomer **B** (Scheme 63).[74]

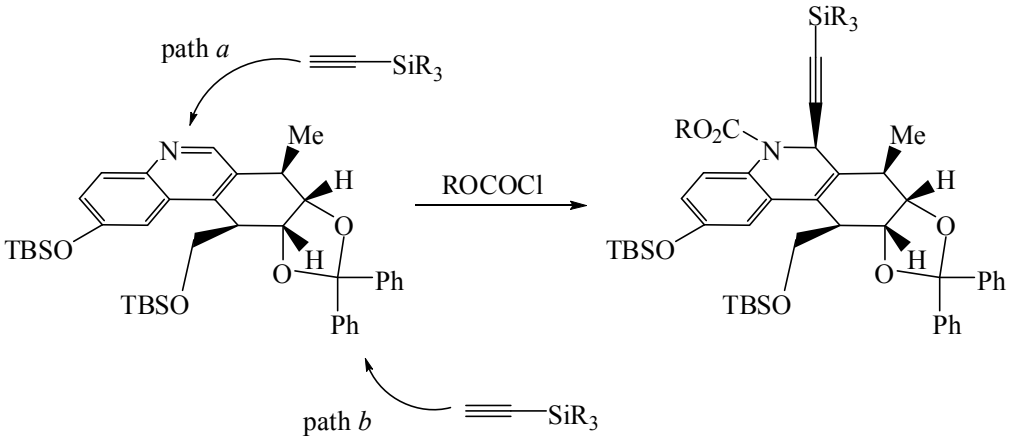
In the total synthesis of antibiotic dynemycin A, alkyne radicals were introduced into a substituted tetrahydrophenanthridine containing chiral centers in the cyclohexane moiety.[75] A mixture of diastereomers in the ratio of 9:1 was obtained upon treatment of compound **152** with chloroformate in the presence of the Grignard reagent, (triisopropylsilyl)ethynylmagnesium bromide. Compound **153** was the major 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 (Scheme 64).[75]



TBS = Bu^{t}Me$_2$Si; R = Me, All.

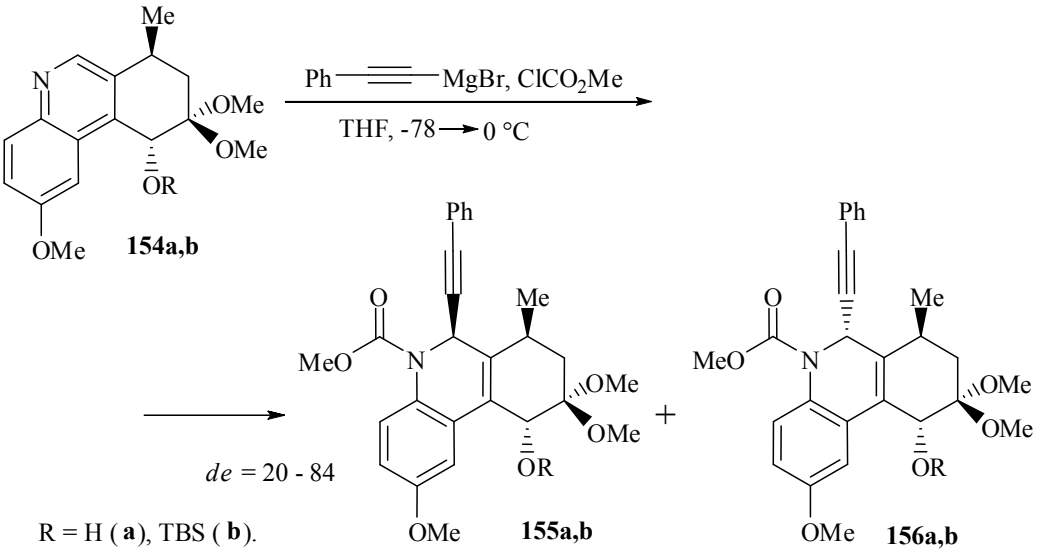
Scheme 64

The starting compound **152** is sterically severely hindered for the attack along the path *b*; therefore, the addition is stereoselective and proceeds with predominant formation of compound **153** (path *a*) (Scheme 65).[75]



Scheme 65

Tetrahydrophenanthridines **154a**,**b** react similarly with phenylethynylmagnesium bromide in the presence of methyl chloroformate. It was found[76] that the non-protected compound **154a** forms predominantly a *cis*-addition product **155a** (relative to the methyl group), the ratio **155b**:**156b** = 11:1, while TBS-protected analogue **154b** produces a diastereomer mixture in which *trans*-addition product **156b** is dominant (ratio **155b**:**156b** = 1:1.5) (Scheme 66).[76]



Scheme 66

This fact was explained by a half-chair conformation of the intermediate alkoxide formed from compound **154a** in which the magnesium counter ion is chelated by one or two oxygen atoms of the methoxy groups. This leads to *pseudo*-equatorial orientation of the methyl substituent in compound **155a**. As a result, the axial addition of acetylide at the *cis*-position relative to this Me group is facilitated (Figure 9).[76]

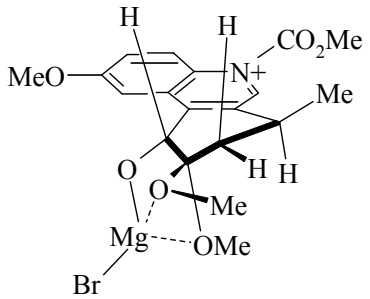
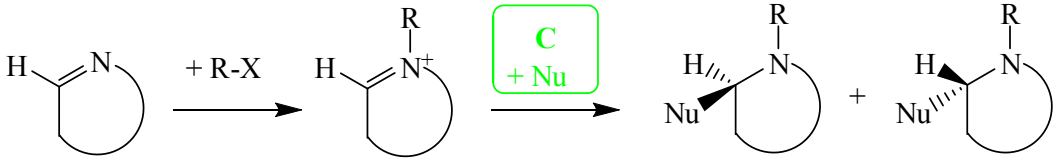


Figure 9

II. Stereoselective addition of an optically active nucleophile to an achiral azine

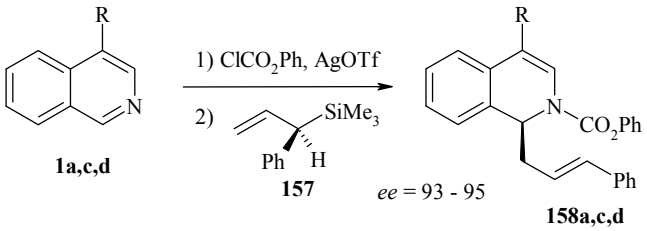
In all previously discussed cases, optically active azine substrates reacted with nucleophilic agents. Steric factors caused by the presence of a chiral azine substituent effectively determined the asymmetric

character of the synthesis. Another variant of obtaining of 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.



Scheme 67

Yamaguchi and co-authors[77] have performed the enantioselective addition of chiral (*R*)-3-phenyl-3-trimethylsilylprop-l-ene (**157**) with *N*-acylisoquinolinium ions obtained from isoquinolines **la**,**c**,**d**. The reaction leaded to formation of *(S)*-1-[(*E*)-3-phenylprop-2-enyl]-1,2-dihydroisoquinolines **158a-c** with high enantioselectivities (Scheme 68).



1, 158	R	Yield, %	*ee*, %
a	H	54	95
c	Br	86	94
d	CO_2Me	78	93

Scheme 68

The authors suggest[68] that this addition proceeds with formation of an antiperiplanar transition state **A**, which leads to the (*S*)-adduct. The transition state **B**, which is a precursor of the (*R*)-adduct, is less energetically favorable (Figure 10).

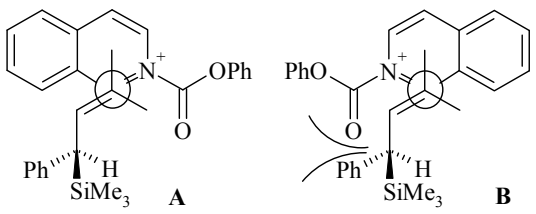
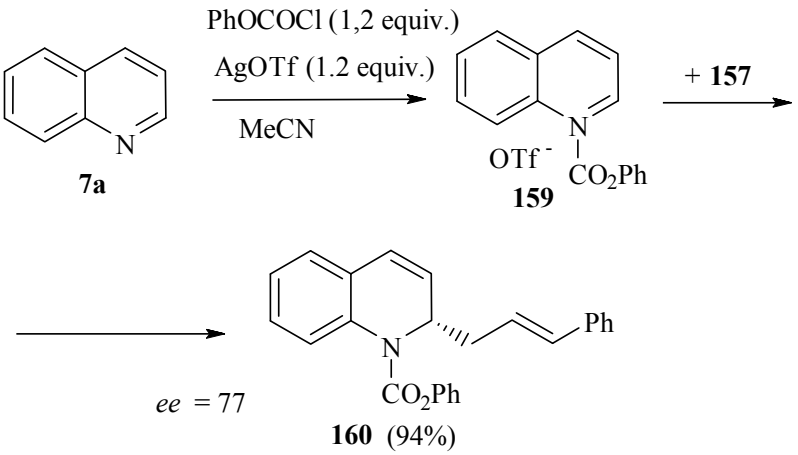


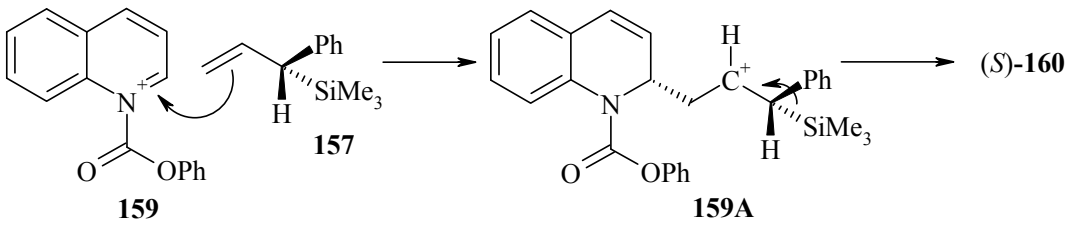
Figure 10. Possible transition states of the enantioselective addition allylsilane **157** with *N*-acylisoquinolinium ions obtained from isoquinoline **la**

Stereoselective addition of chiral allylsilane **157** to activated quinoline has been described.[78] As a result of the reaction with quinolinium salt **159**, an optically active 2-substituted 1,2-dihydroquinoline **160** *(ee* 77%) is formed (Scheme 69).



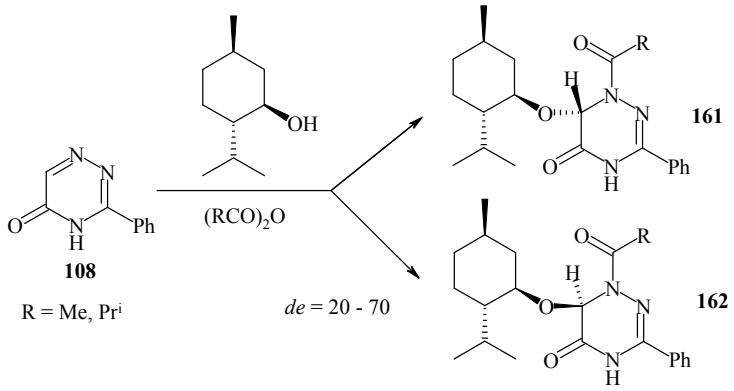
Scheme 69

Several possible reaction pathways have been proposed.[78] The most preferential is believed to be that including the formation of intermediate **159A** (Scheme 70). Elimination of the trimethylsilyl group yields the product with (*S)*-configuration of the chiral center.



Scheme 70

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 (**108**) activated by acid anhydrides yields a mixture of diastereomers **161** and **162**.[79] The diastereomer **161** is the major product. 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 **161**:**162** is equal to 60:40, while with the more sterically hindered isobutyric anhydride (R = Pr^i) this ratio increases to 85:15 (Scheme 71). The predominant formation of stereoisomers **161** is explained[79] by steric factors.

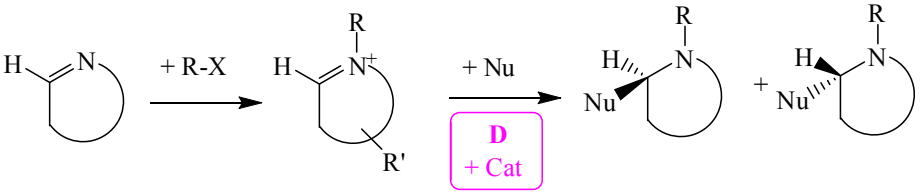


Scheme 71

The addition of chiral alcohols like cholesterol, dihydrocholesterol, borneol and isoborneol to 3-phenyl-1,2,4-triazin-5(4*H*)-one (**108**) in the presence of acetic and isobutyric acid anhydrides runs without diastereoselectivity.[80]

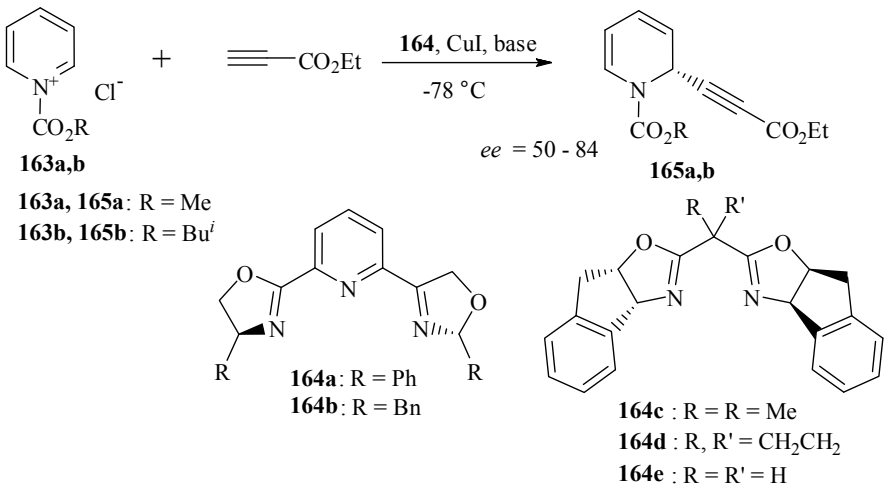
III. Asymmetric induction in the attack of an achiral nucleophile at an achiral azine

Asymmetric induction in a reaction of an achiral nucleophile with an achiral azine substrate is possible only if optically active solvents or catalysts are used (Scheme 72).



Scheme 72

Pyridinium salts **163a**,**b** in the presence of chiral ligands **164a-e** react with ethyl propiolate diastereoselectively. The addition products **165a**,**b** are useful building blocks for the elaboration of a wide range of polysubstituted piperidines and indolizidines (Scheme 73, Table 14).[81]



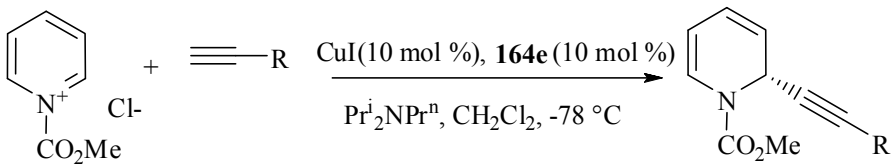
Scheme 73

Table 14. Reactions of pyridinium salts **163a**,**b** in the presence of chiral ligands **164a-e** with ethyl propiolate

R	ligand	base	solvent	product	yield, %	*ee* ,%*
Me	**164a**	Pr^i_2NEt	CH_2Cl_2	**165a**	78	50
Me	**164b**	Pr^i_2NEt	CH_2Cl_2	**165a**	71	51
Me	**164c**	Pr^i_2NEt	CH_2Cl_2	**165a**	67	74
Me	**164d**	Pr^i_2NEt	CH_2Cl_2	**165a**	63	87
Me	**164e**	Pr^i_2NEt	CH_2Cl_2	**165a**	75	88
Me	**164e**	$Pr^i_2NPr^n$	CH_2Cl_2	**165a**	72	94
Me	**164e**	$Pr^i_2NBu^n$	CH_2Cl_2	**165a**	74	65
Me	**164e**	Pr^i_2NEt	$CHCl_3$	**165a**	77	83
Me	**164e**	Pr^i_2NEt	MeCN	**165a**	71	55
Bu^i	**164e**	Pr^i_2NEt	CH_2Cl_2	**165b**	72	86
Bn	**164e**	Pr^i_2NEt	CH_2Cl_2	-	-	-
Me	**164e**	$Pr^i_2NPr^n$	CH_2Cl_2	**165a**	47	69

* Determined by HPLC on chiral stationary phase

The best enantioselectivity was achieved when $Pr^i_2NPr^n$ base and **164e** ligand were used. They were used in the synthesis of addition products of some propiolates (Scheme 74). It was shown, that the substituent size of propiolate dramatically exert on stereoselectivity. The highest *ee* value was recorded using 1-pentyn-3-one (product **165f**). With increasing of the chain length of the ynones, the enantioselectivity gradually dropped. The removing of the carbonyl group leads to practically complete loss of *ee* (compounds **165j-l**) (Scheme 74).[81]



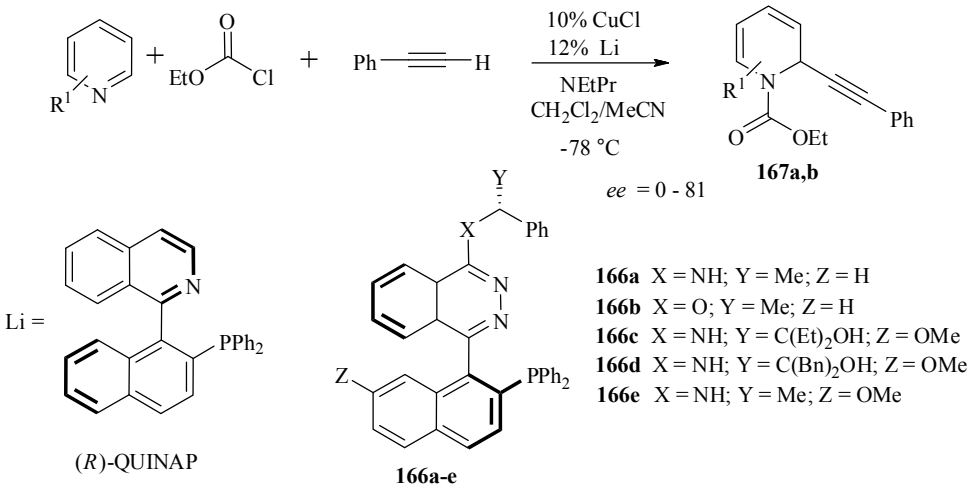
163a *ee* = 1 - 95 **165c-l**

R	Product	Yield, %	*ee*,%
CO_2Me	**165c**	74	95
CO_2Bn	**165d**	81	86
COMe	**165e**	69	93
COEt	**165f**	65	99
$CO(CH_2)_3Me$	**165g**	70	91
$CO(CH_2)_4Me$	**165h**	68	90
$CO(CH_2)_3OBn$	**165i**	70	77
Ph	**165j**	75	1
$(CH_2)_3Me$	**165k**	63	11
CH_2OAc	**165l**	77	3

Scheme 74

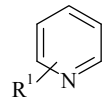
Pyridines, quinolines, and isoquinolines in the presence of ethyl chloroformate participate in copper(I) - catalyzed reactions of nucleophilic addition with alkynes leading to compounds **167** (Schemes 75, 76, Tables 15, 16). This multicomponent reactions running in the presence of CuCl provide a straightforward and regioselective pathway to cyclic propargylcarbamates, widely used as chiral building blocks for synthesis of alkaloids and other biologically relevant molecules.[82]

As shown in table 15, the use of several commercially available chiral phosphorus- and nitrogen-donor ligands in this reaction unfortunately resulted in low to zero enantioselectivity with phenylacetylene. The best result was achieved with (*R*)-QUINAP and the authors tried similar PINAP ligands **166a-e**. The best of used PINAP ligands in investigated type of reactions turned out ligand **166e**.

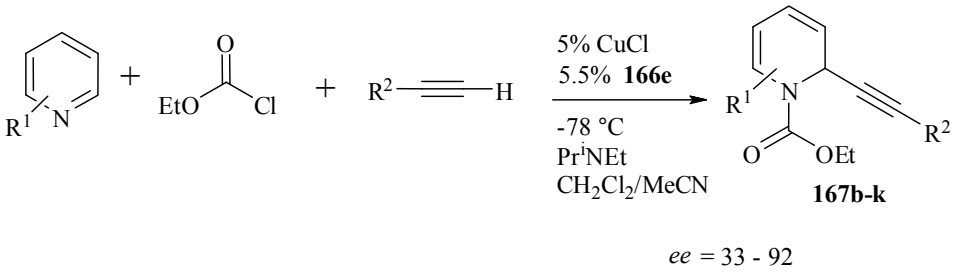


Scheme 75

Table 15. Reactions of pyridine and quinoline with alkynes

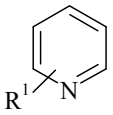
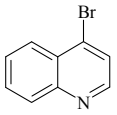
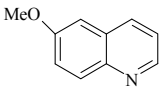
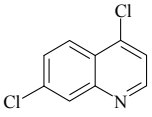
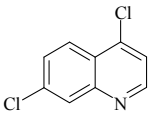
	Li	Product	Yield, %	*ee*, %
pyridine	(*R*)-Tol-BINAP	**167a**	n.d.	2
pyridine	(*R*)-Pr^{i}-PYBOX	**167a**	n.d.	0
pyridine	(*R*)-Bu^{i}-BOX	**167a**	n.d.	1
pyridine	(*R*)-MONOPHOS	**167a**	-	-
pyridine	(*R*)-MOP	**167a**	72	0
pyridine	(*R*)-QUINAP	**167a**	17	49
quinoline	(*R*)-QUINAP	**167a**	86	43
quinoline	**166a**	**167b**	91	53
quinoline	**166b**	**167b**	84	41
quinoline	**166c**	**167b**	86	75
quinoline	**166d**	**167b**	75	66
quinoline	**166e**	**167b**	92	81

n.d. – not detected



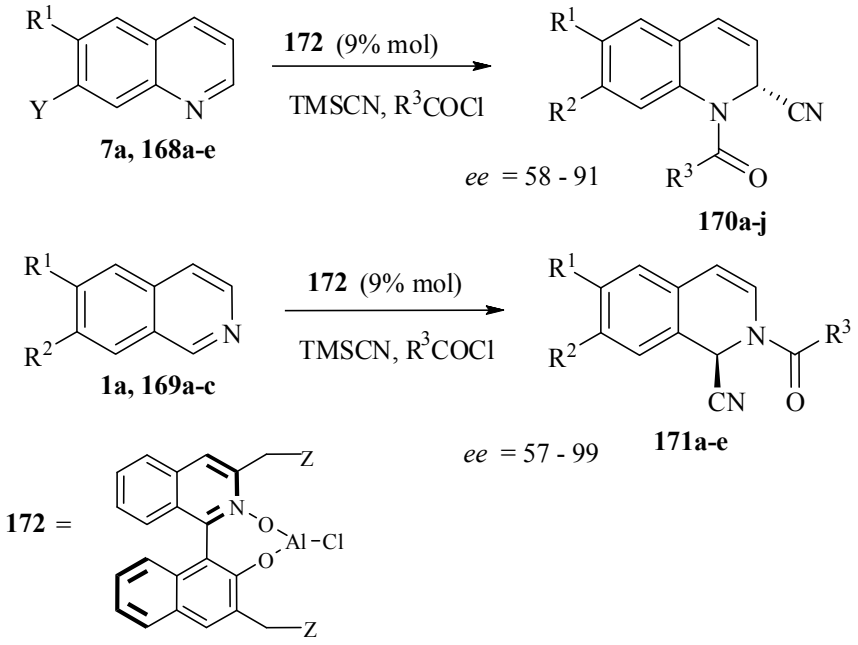
Scheme 76

Table 16. Reactions of pyridine, quinolines and isoquinoline with alkynes

	alkyne	Product	Yield, %	*ee*, %
Quinoline	Ph–C≡CH	**167b**	92	81
Quinoline	TMS–C≡CH	**167c**	72	84
Isoquinoline	Ph–C≡CH	**167d**	88	72
Pyridine	TMS–C≡CH	**167e**	33	80
Quinoline	$ClCH_2$–C≡CH	**167f**	84	75
Quinoline	EtO_2C–C≡CH	**167g**	75	62
	EtO_2C–C≡CH	**167h**	82	78
	Ph–C≡CH	**167i**	92	70
	Ph–C≡CH	**167j**	84	80
	TMS–C≡CH	**167k**	76	81

Shibasaki and co-authors[83-86] studied the synthesis of Reissert compounds **170** and **171** derived from quinolines **168** or isoquinolines **169**, using bifunctional naphthyl catalysts **172**. Authors suggested that enantioselectivity of this reaction depended on the nature of R^3 subsequent at acyl chloride. For example, the more electron-rich and therefore less reactive 2-furoyl chloride gave slightly better enantioselectivity than acetyl chloride. The effect of the solvent's polarity on enantioselectivity is significant. Studding the reaction of quinoline with more reactive benzoyl chloride, it was found that, when the polarity of the solvent was decreased by adding a less polar solvent, the *ee* increased to 78% from 71%, although the

yield of the product became much lower. In contrast, the *ee* decreased to 37% when the more polar acetonitrile was used as a solvent. If changing the Z fragment of catalyst **161** from $P(O)Ph_2$ to $P(O)(o\text{-Tol})_2$, it can give more reactive Lewis base, which increases both *ee* and the yield of the product (Scheme 77, Table 17).



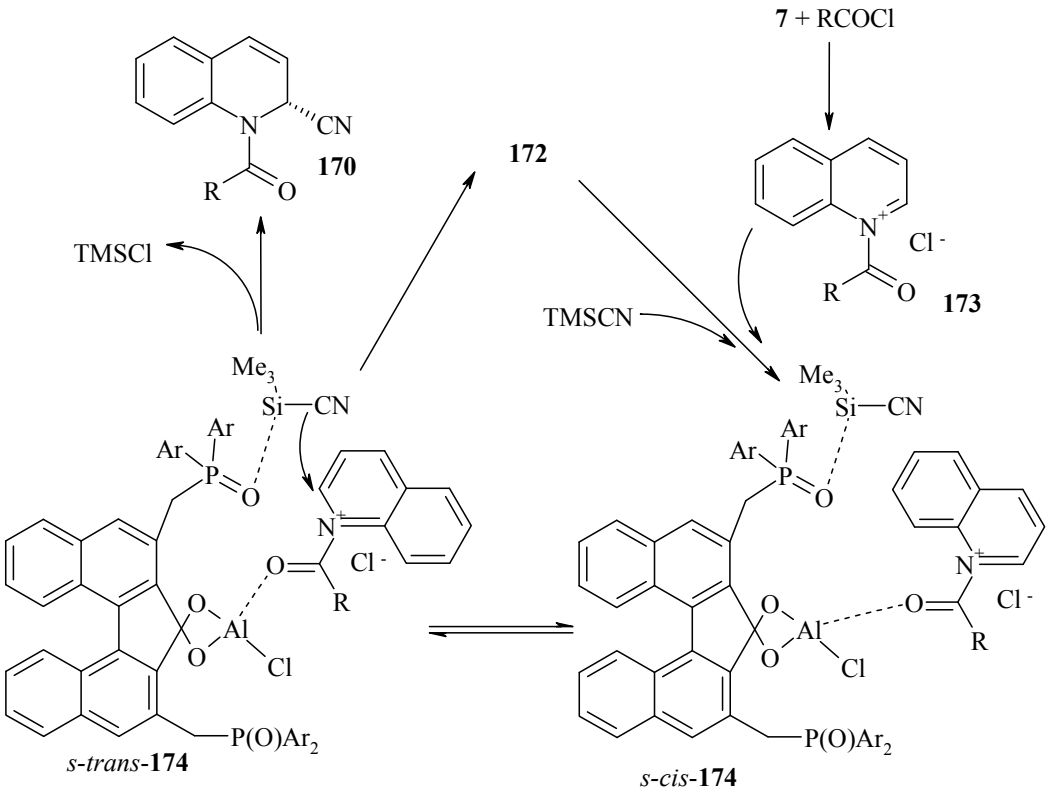
Scheme 77

Table 17. Reactions of quinolines and isoquinolines with TMSCN

azine	R^1	R^2	R^3	Z	product	yield, %	*ee*, %
7a	H	H	Ph	$P(O)Ph_2$	**170a**	70	71
7a	H	H	Me	$P(O)Ph_2$	**170b**	42	58
7a	H	H	1-naphtyl	$P(O)Ph_2$	**170c**	63	46
7a	H	H	2-furyl	$P(O)Ph_2$	**170d**	58	73
7a	H	H	2-furyl	$P(O)(o\text{-Tol})_2$	**170e**	91	85
168a	OMe	H	2-furyl	$P(O)(o\text{-Tol})_2$	**170f**	74	89
168b	NMe_2	H	2-furyl	$P(O)(o\text{-Tol})_2$	**170g**	72	89
168c	OMe	OMe	2-furyl	$P(O)(o\text{-Tol})_2$	**170h**	99	91
168d	OCH_2O		2-furyl	$P(O)(o\text{-Tol})_2$	**170i**	77	83
168e	Cl	H	2-furyl	$P(O)(o\text{-Tol})_2$	**170j**	57	67
1a	H	H	CH_3	$P(O)Ph_2$	**171a**	99	71
1a	H	H	2-furyl	$P(O)(o\text{-Tol})_2$	**171b**	91	85
169a	OMe	H	2-furyl	$P(O)(o\text{-Tol})_2$	**171c**	74	89
169b	OCH_2O		2-furyl	$P(O)(o\text{-Tol})_2$	**171d**	77	83
169c	Cl	H	2-furyl	$P(O)(o\text{-Tol})_2$	**171e**	57	67

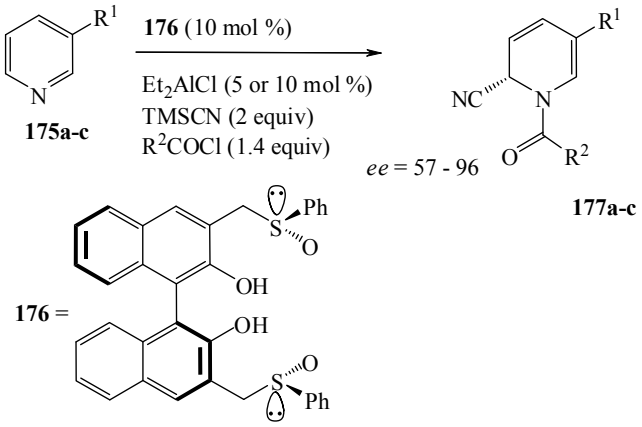
Although a detailed reaction mechanism is still not clear at this moment, the reaction should be promoted by the dual activation of catalyst **172** the *N*-acyl quinolinium or *N*-acyl isoquinolinium ion and TMSCN by the Lewis acid (Al) and the Lewis base (oxygen atom of the phosphine oxide) moieties of the catalyst **172**, respectively. The results using the control catalyst **172** contained diphenylmethyl groups providing only steric bulkiness, leading to decrease of *ee*. Thus, the reaction of quinolinium with TMSCN in the presence of benzoyl chloride and catalyst **172** ($Z = CHPh_2$), which is not the Lewis base, afforded to 1-benzoyl-1,2-dihydroquinolinium-2-carbonitrile with the configuration (*S*) predominantly (24% *ee* in 73% yield).

Authors[83-86] postulated the working model for the catalytic cycle (by the example of substituted quinolinium) (Scheme 78). The first step should be the formation of the reactive *N*-acyl quinolinium intermediate **173** by the reaction of quinoline with the acid chloride. The acyl quinolinium ion should be activated by complexation of the amide oxygen to the Lewis acid (Al atom of chiral catalyst). The two conformers of the amide bond *s-trans*-**174** and *s-cis*-**174** would exist in equilibrium. However, when TMSCN is activated by the Lewis base moiety of the catalyst **172**, the reaction via *s-trans*-**174** would be more favorable than via *s-cis*-**174**. In the *cis*-isomer the distance between the activated TMSCN and the electrophilic carbon would be too far for catalysis. The hypothetical transition state *s-trans*-**174** could explain the absolute configuration *R* of the product (Scheme 78).



Scheme 78

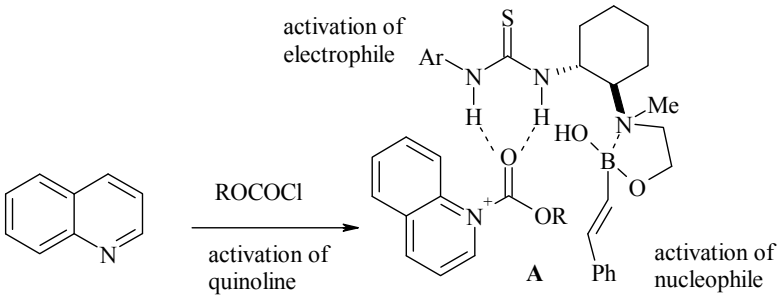
Later, the asymmetric bifunctional catalyst **172** was modified, that allow using pyridine derivatives **175a-c** for this reaction. Thus the reaction of pyridine **175b** with TMSCN, catalyzed by chiral binaphthyl **172** (Z = $P(O)Ph_2$), in the presence of acyl chlorides, leads to the products of cyanide ion addition in positions C(2) and C(6) of pyridine ring in proportion 2.3:1 with low enantioselectivity (*ee* < 9%). The using of catalyst **176** increased regioselectivity. 2-Cyanosubstituted pyridines **177a-c** with (*S*)-configuration were obtained predominantly (ratio of 2- and 6-products changed depending on substituting group R^1 from 12:1 to 50:1) (Scheme 79).[86]



177	R^1	R^2	yield, %	*ee*, %
a	NMe_2	Me	98	91
		fluoromethyl	89	93
b	NPr^i_2	fluoromethyl	98	96
		neopentyl	98	93
c	OMe	fluoromethyl	85	57

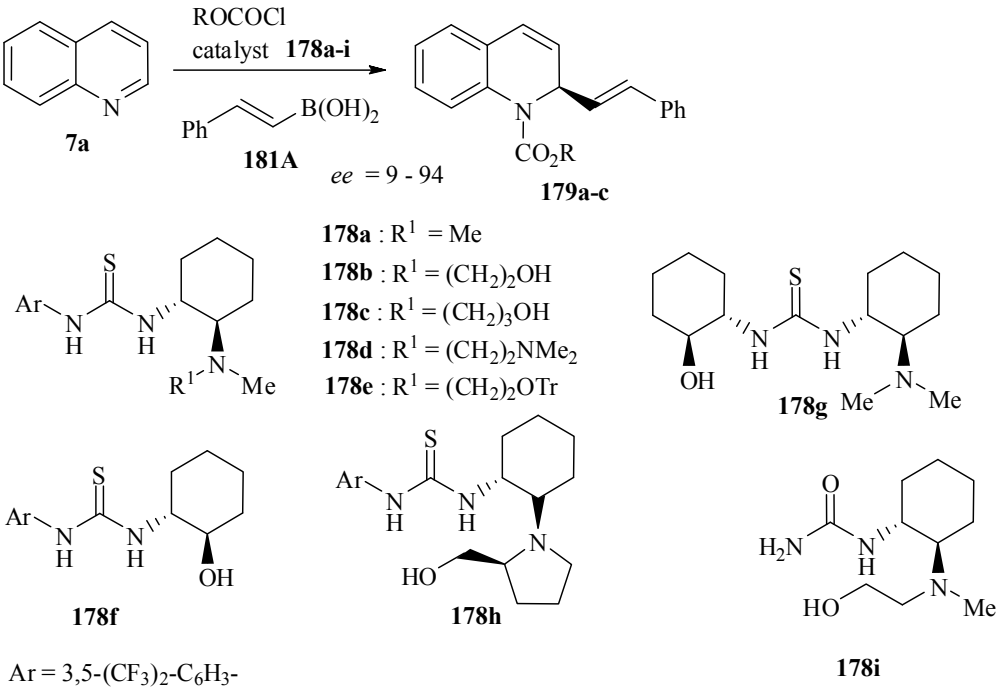
Scheme 79

In 2007 was described the catalytic enantioselective variant of the Petasis transformation of quinolines. On the base of mechanism of Petasis reaction authors created newly designed catalysts that have a chelating functionality, which could activate the boronic acids and direct the stereochemical outcome, as shown for **A** on the Scheme 80.[87]



Scheme 80

For the stereoselective addition of alkynes to quinolines catalysts **178** based on thiourea are useful. In the concept of the authors thiourea moiety could activate *N*-acylated quinolinium salts as a Brønsted acid. Authors firstly probe the utility of new functionalized catalysts in the reactions of quinoline with vinylboronic acid **181A** (Scheme 81, Table 18).[87]



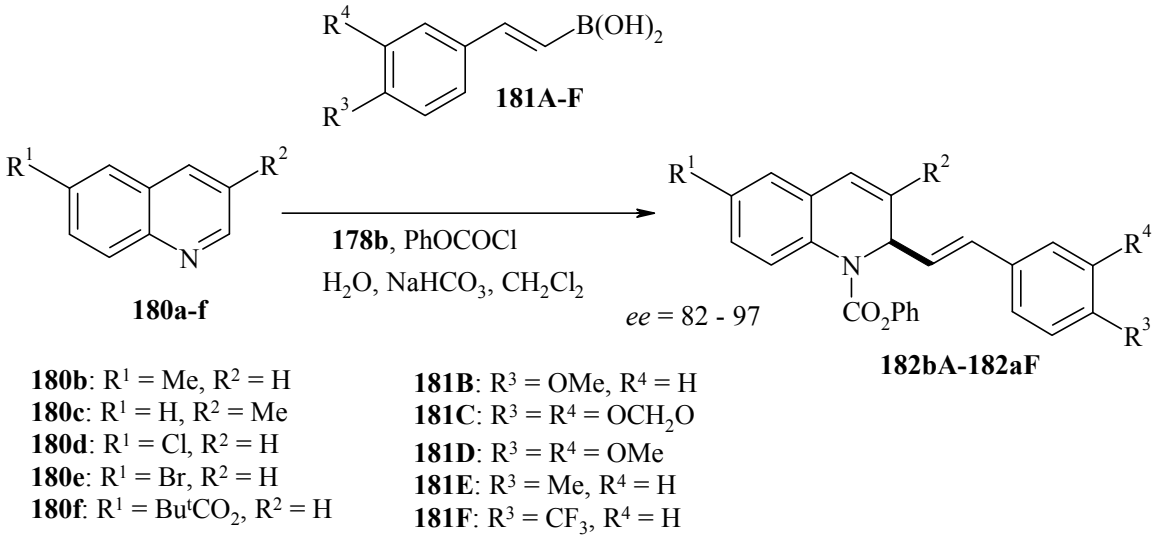
Scheme 81

Table 18. Reactions of nucleophilic addition of alkenes to quinoline in the presence of thiourea catalysts

Catalyst[a]	ROCOCl	Additive	Yield, %	*ee*, %
178a	PhOCOCl	-	34	9
178b	PhOCOCl	-	70	90
178b	EtOCOCl	-	33	42
178b	BnOCOCl	-	44	67
178c	PhOCOCl	-	47	27
178h	PhOCOCl	-	60	68
178i	PhOCOCl	-	70	50
178b	PhOCOCl	H_2O[b]	27	93
178b	PhOCOCl	H_2O, $NaHCO_3$[b]	65	94

[a] Reaction was carried out with catalysts **178a-i** (10 mol %) in CH_2Cl_2 at -65 °C;
[b] $NaHCO_3$ (2 equiv) and H_2O (56 equiv, CH_2Cl_2/H_2O 10:1).

Catalyst **178b** gives better enantioselectivity and was used for the synthesis of compounds **182bA-182aF** (Scheme 82, Table 19).[87]

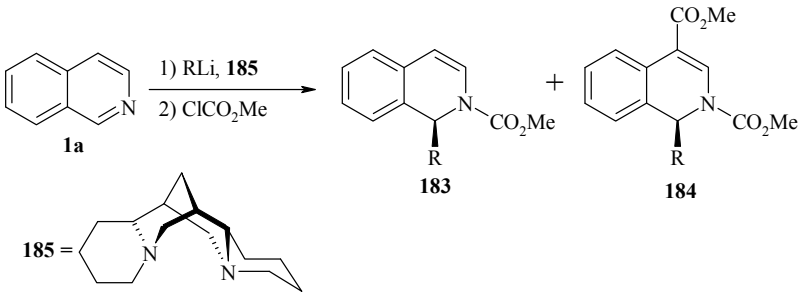


Scheme 82

Table 19. Reactions of nucleophilic addition of alkenes **181A-F** to quinolines **180a-f** in the presence of thiourea catalyst **178b**

Substrate	Boronic acid	T,°C	Product	Yield, %	*ee* (%)
180b	**181A**	-65	**182bA**	75	95
180c	**181A**	-78	**182cA**	70	96
180d	**181A**	-65	**182dA**	63	94
180e	**181A**	-65	**182eA**	78	95
180f	**181A**	-65	**182fA**	61	96
180a	**181B**	-78	**182aB**	70	97
180a	**181C**	-78	**182aC**	59	82
180a	**181D**	-78	**182aD**	60	89
180a	**181E**	-65	**182aE**	60	91
180a	**181F**	-40	**182aF**	28	95

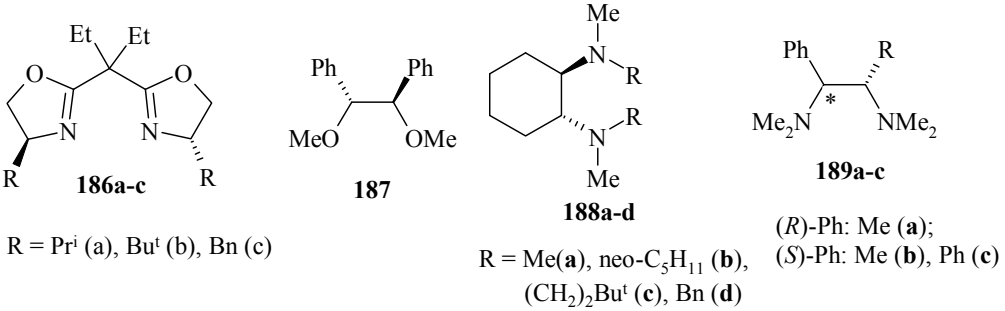
Enantioselective addition of organolithium reagents to the isoquinoline in soft conditions in the presence of chiral ligand (−)-sparteine (**185**) is described.[88] The reaction results in the mixture of chiral dihidroisoquinolines **183**, **184** (for R = Me, Bu^n), or only product **183** (R = Ph) (Scheme 83).



R	T, °C	Yield, %	**183** : **184**	*ee* **183, %**	*ee* **184, %**
Me	- 40	77	75 : 25	42	48
Bu	- 80	85	70 : 30	57	-
Ph	- 40	34	-	25	-

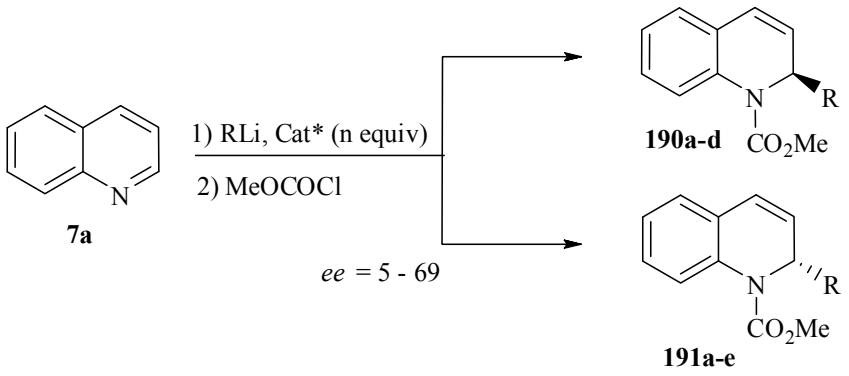
Scheme 83

Hereafter, authors[89,90] studied in detail the reaction of azines with organolithium reagents, using unsubstituted quinoline (**7**) as substrate. They varied the conditions (temperature, solvent) and used the wide range of chiral catalysts, such as sparteine (**185**), bisoxazolines **186**, chiral diether **187**, and also symmetric (**188**) and nonsymmetric (**189**) 1,2-diamines.



Scheme 84

The addition of methyl formate to reaction mixture leads to dihydroisoquinolines **190** or **191**, moreover the configuration of the asymmetrical center depends on the type of chiral catalyst and the nature of R radical (Scheme 85, Table 20).



Scheme 85

Table 20. Reactions of quinoline with organolithium compounds in the presence of chiral catalysts

R	Cat*	Solvent	T, °C	Cat equiv.	Yield, %	product	Configu-ration	*ee*, %
Me	**185**	Et_2O	-20	1	69	**191a**	*S*	5
	186a	PhMe	-40	1	47	**191a**	*S*	63
	186a	PhMe	-40	0.2	43	**191a**	*S*	30
	186b	PhMe	-40	0.2	< 5	**191a**	*S*	-
	186c	PhMe	-40	0.2	69	**191a**	*S*	21
	186c	Et_2O	-40	0.2	86	**191a**	*S*	22
	187	Et_2O	-20	1	67	**190a**	*R*	20
	188a	PhMe	-20	1	93	**191a**	*S*	13
Bu^n	**185**	PhMe	-40	1	98	**191b**	*S*	18
	185	Et_2O	-40	1	98	**191b**	*S*	16
	186a	PhMe	-60	1	63	**191b**	*S*	72
	186a	PhMe	-70	1	85	**191b**	*S*	79
	186b	PhMe	-70	1	80	**191b**	*S*	32
	186b	PhMe	-70	0.2	70	**191b**	*S*	37
	186c	PhMe	-70	1	57	**191b**	*S*	69
	186c	PhMe	-70	0.2	79	**191b**	*S*	41
	187	Et_2O	-60	0.2	86	**190b**	*R*	4
	187	PhMe	-78	0.2	53	**190b**	*R*	4
	188a	PhMe	-78	1	83	**191b**	*S*	10
	188b	PhMe	-70	0.2	53	[a]	-	< 4
	188c	PhMe	-70	0.2	67	**191b**	*S*	63
	188d	PhMe	-70	0.2	58	[a]	-	5
	189a	PhMe	-70	0.2	55	**190b**	*R*	5
Ph	**185**	PhMe	-78	1	82	**191c**	*R*	66
	185	PhMe	-78	0.2	38	**191c**	*R*	7
	185	Et_2O	-78	1	55	**191c**	*R*	67
	186a	PhMe	-78	1	6	**191c**	*R*	< 4
	186a	Et_2O	-40	0.2	57	**191c**	*R*	< 4
	187	Et_2O	-78	1	16	**190c**	*S*	< 2
	187	PhMe	-78	1	7	**190c**	*S*	26

R	Cat*	Solvent	T, °C	Cat equiv.	Yield, %	product	Configu-ration	*ee*, %
	188a	PhMe	-78	1	29	**191c**	*R*	45
	188b	PhMe	-70	0.2	47	**191c**	*R*	10
	188c	PhMe	-70	0.2	39	**191c**	*R*	17
	189a	PhMe	-70	0.2	68	[a]	-	< 4
	189b	PhMe	-78	1	44	**190c**	*S*	27
	189c	PhMe	-78	0.2	14	**190c**	*S*	23
1-Naphthyl	**185**	PhMe	-50	1	37	**191d**	*R*	16
	185	Et_2O	-78	1	86	**191d**	*R*	28
	186a	PhMe	-70	0.2	20	**191d**	*R*	8
	186a	PhMe	-50	0.2	55	**191d**	*R*	0
	187	PhMe	-50	1	57	**190d**	*S*	< 4
	187	PhMe	-50	0.2	45	**190d**	*S*	5
	188a	PhMe	-78	1	75	**191d**	*R*	64
	189a	PhMe	-70	0.2	46	[a]	-	< 4
	189b	Et_2O	-70	1	70	**190d**	*S*	58
	189c	PhMe	-70	0.2	35	**190d**	*S*	23
2-Naphthyl	**188a**	PhMe	-78	1	19	**191e**	*R*	28

[a] *Ee* of products is not determined.

In conclusion, these different studies have shown that (*R,R*)-dimethoxybiphenylethane (**187**) as chiral catalyst was not effective: dihydroquinolines **190** were obtained with moderate yields, but the enantioselectivity was low (*ee* 2-26%). Catalysis with (-)-sparteine (**185**) gave dihydroquinolines **191**, having the opposite chiral center's configuration, herewith the enantioselectivity of the process raised (especially for the reaction with phenyllithium), and the yield of the product was about 99% for R = Bu^n. Bisoxazolines as chiral catalysts allow to get best selectivity for the reaction of quinoline with methyllithium and catalyst **186a** (*ee* 63%), resulting in (*S*)-configuration of dihydroquinolines.[89,90]

N,*N*'-Tetramethylcyclohexane-1,2-diamine **188a** (TMCDA) was the best ligand for the addition of 1-naphthyllithium since the yield of dihydroquinoline **191d** (R = 1-naphtyl) was 75% (*ee* 64%). Replacement of methyl substituents at N-atom of catalyst **188a** to more bulky alkyl groups (compounds **188b-d**) led to the decreasing of yields and diastereoselectivity of reaction (Scheme 1).[89,90]

The experiments on of *N*,*N*'-tetramethylethane-1,2-diamines **189a-c** as chiral catalyst have brought authors to some findings. The catalysis with diamine **189a** led to almost racemic product. The reaction

with diamine **189c**, which has axis of symmetry C_2, resulted in the addition products with medium enantioselectivity. And, finally, the catalyst **189b** operates as diamine with pseudo-C_2-symmetry, because the results with this catalyst are similar to those obtained with the diamine **189c**.[89,90]

CONCLUSION

Comparable analysis of various types of chirality induction in nucleophilic addition reactions in heterocycles indicates that the most common way for the chirality generation based on the introduction of chiral auxiliary groups into azines, the less popular way is the using of various types of chiral catalysts. Possibility for the generation of chirality by the asymmetric center of nucleophile is used very seldom.

The advantage of the method of introduction of chiral auxiliary groups is its generality. Introduction of the same group into various azines is commonly results in generation of asymmetric induction not depending on the type of used nucleophile. The drawback of this method is in difficulty of removing of the auxiliary group afterwards.

The obvious advantage for chiral catalysts methods is in less reaction steps for obtaining the target compound. Moreover as it can be followed in current review in most cases the proper chiral catalyst can be selected only after the screening.

Chiral nucleophiles are extremely short of use in diastereoselective nucleophilic additions, most probably due to their low availability. Therefore investigators prefer to introduce the chirality elements into heterocycles by using another synthetic ways.

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