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The progress in the chemistry of N-acyliminium ions and their use in stereoselective organic synthesis

Maxim G. Vinogradov, Olga V. Turova, Sergei G. Zlotin

N.D.Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences
Leninsky prosp. 47, 119991 Moscow, Russian Federation

The review summarizes data published in the last decade on the reactions of organic compounds involving N-acyliminium ions, including intramolecular arylation (cyclization), cross-coupling with nucleophiles and some other transformations to form new carbon – carbon and carbon – heteroatom bonds. The stereo- and enantioselective versions of these reactions using chiral auxiliaries and asymmetric catalysts (organocatalysts) are considered. Examples of application of N-acyliminium ions for the synthesis of natural compounds and their analogues are presented.
The bibliography includes 100 references.

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I. Introduction

N-Acyliminium ions (N-acim) play an important role in organic synthesis, first of all, in the chemistry of nitrogen heterocycles, including polycyclic alkaloids and other biologically active compounds.[1,2] Considering the chemical structure, there is a certain analogy between two ionic intermediates, enolate anions and N-acim, as they are characterized by mesomeric charge distribution between the carbon atom and the heteroatom (Fig. 1). In most of chemical reactions, these ionic intermediates behave as species with a reaction centre on carbon, *i.e.*, as C-nucleophiles and C-electrophiles, respectively; this can be illustrated, in particular, by a number of known of enolate anions and N-acim (see below).

N-Acyliminium ions, which are rather unstable, are usually prepared *in situ* from various precursors and used in the subsequent reactions (here and below, for the sake of simplicity, these intermediates are shown in the schemes without square brackets and counter-anions). The typical methods for generation of these ions are shown in Scheme 1 in relation to cyclic N-acim. Most often, the following transformations are involved:

— reaction of hydroxylactams or hydroxy-, methoxy- or acyloxyamides with a protic acid, for example, TFA (trifluoroacetic acid) or a Lewis acid (usually $BF_3 \cdot Et_2O$ or $TiCl_4$) [reaction (1)],[3,4] the initial N,O-systems are often designated in the general form as N,O-acetals;

— protonation of cyclic enamides [reaction (2)];[5–7]

— N-acylation of cyclic imines with acyl halides [reaction (3)];[8,9]

— addition of amides and lactams to aldehydes followed by acid-promoted dehydroxylation of α-hydroxy derivatives [reaction (4)];[10]

— peroxide oxidation[11,12] or hydrogen-transfer oxidation of the carbon adjacent to the amide nitrogen [reaction (5)].[13–15]

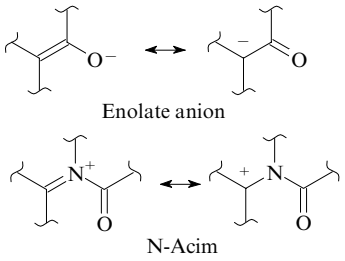


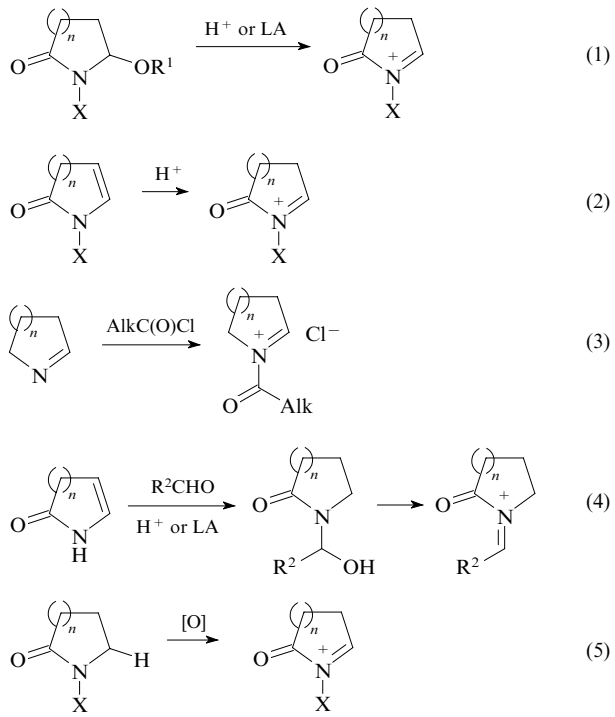
Figure 1. Mesomerism of enolate anions and N-acyliminium cations.

M.G.Vinogradov. Doctor of Chemical Sciences, Professor, Chief Researcher of the Laboratory for Fine Organic Synthesis, ZIOC RAS. Telephone: +7(499)135 – 6431, e-mail: ving@ioc.ac.ru
O.V.Turova. Candidate of Chemical Sciences, Senior Researcher of the same Laboratory. E-mail: turova@ioc.ac.ru
S.G.Zlotin. Doctor of Chemical Sciences, Professor, Head of the same Laboratory.
Telephone: +7(499)137 – 1353, e-mail: zlotin@ioc.ac.ru
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Scheme 1



(1)

(2)

(3)

(4)

(5)

R^1 = H, Me, Ac; R^2 = Alk, Ar; X = H, Alk, Ar, Boc, Cbz, Ts; n = 1, 2;
LA is Lewis acid, Boc is *tert*-butoxycarbonyl,
Cbz is benzyloxycarbonyl, Ts is *p*-tolylsulfonyl (tosyl)

The chemistry of N-acyliminium ions has been discussed in a number of reviews [1, 2, 16 – 18] published before 2005. The present review covers a wider range of reactions and includes more recent data published from 2005 to 2015.

II. Reactions of N-acyliminium ions with π-nucleophiles

II.1. Intramolecular arylation (cyclization)

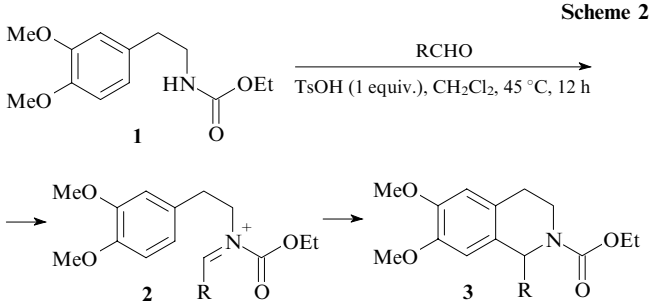
Aminoalkyl-substituted aromatic compounds and their N-acylated derivatives react with aldehydes or acetals in the presence of Brønsted acids to afford polycyclic intramolecular arylation products (the Pictet – Spengler reaction). The key role in this reaction is played, as a rule, by intermediate acyliminium ions, which attack the available *ortho*-position of the aromatic ring (π-nucleophile). In some cases, the reaction can be carried out in the presence of a metal-containing catalyst instead of the acid catalyst.[19]

II.1.a. Cyclization with benzene-type π-nucleophiles

A recent version of the Pictet – Spengler reaction is the transformation of phenethylamine **1** on treatment with aldehydes in the presence of *p*-toluenesulfonic acid.[20] The reaction proceeds through the formation of N-acim **2** to afford cyclization products — *N*-acyltetrahydroisoquinolines **3** in high yields (Scheme 2).

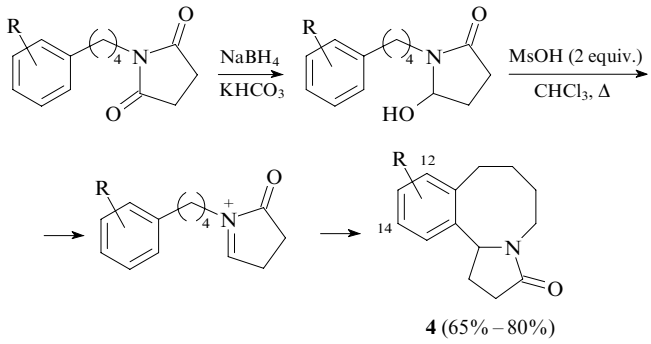
The amine acylation and N-acim cyclization steps can be implemented as a one-pot process, for example, in supercritical CO_2.[10] For generation of N-acim, it is often useful to utilize hydroxylactams, which are prepared, in particular, by reduction of one of the two carbonyl groups in cyclic imides. This method was used to prepare pyrrolobenzazocin-7-ones **4**, which are analogs of known biologically active compounds (Scheme 3).[21, 22]

Scheme 2



R = Pr^n (89% yield), Ph (66%), 2-BrC_6H_4 (90%), 3-$O_2NC_6H_4$ (83%), 3,4-$(MeO)_2C_6H_3$ (88%), 2-Naph (99%); Naph is naphthyl

Scheme 3

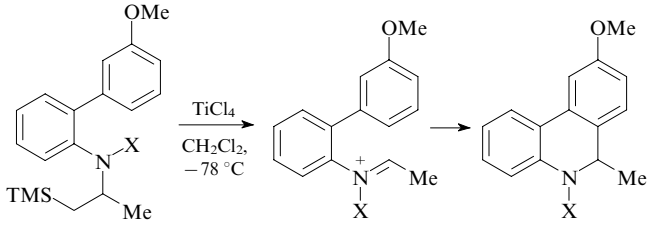


4 (65% – 80%)

R = H, 14-Me, 14-OMe, 14-Cl, 14-Br, 13(15)-Br;
Ms is methanesulfonyl

The cyclization of N-acim **5a – c** was used as an efficient approach to the preparation of phenanthridine alkaloids; in particular, N-substituted 5,6-dihydrophenanthridines **6a – c** (Scheme 4).[23]

Scheme 4



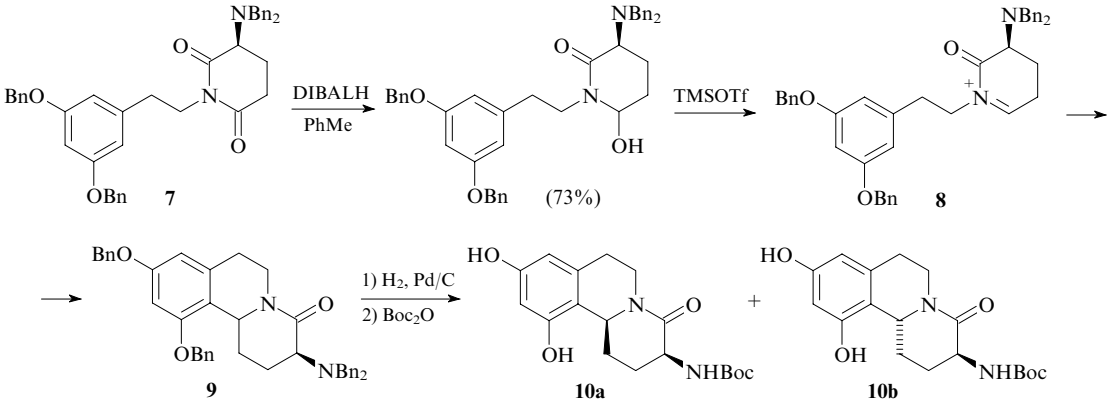
5a – c **6a – c** (98% – 99%)

X = MeO_2C (**a**), Ms (**b**), Ts (**c**); TMS is trimethylsilyl

In recent years, researchers have paid primary attention to the development of stereoselective versions of the Pictet – Spengler reaction, which are based, in particular, on diastereoselective cyclization of N-acim containing a chiral auxiliary and enantioselective cyclization in the presence of chiral organocatalysts.

For example, cyclic glutamic acid derivative **7** was used as a chiral auxiliary,[24] being converted to N-acim **8** to be involved in diastereoselective cyclization. Debenzylation of substituents in the benzene and lactam rings of product **9** followed by acylation of the amino group with Boc_2O furnished a mixture of *cis*- (**10a**) and *trans*-carbamates

Scheme 5

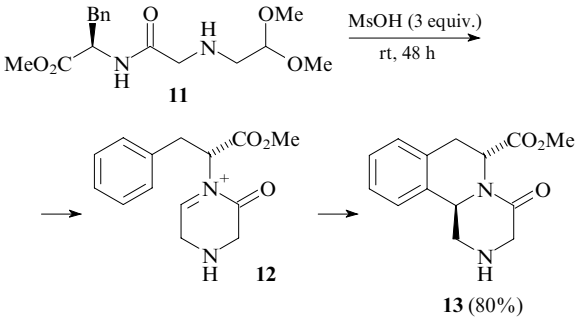


DIBALH is diisobutylaluminium hydride, OTf is trifluoromethylsulfonate (triflate)

(**10b**) in ~3 : 1 ratio and in a total yield of 77 % (Scheme 5). The diastereomers were separated by preparative column chromatography. The configuration of the products was established by NMR techniques (NOESY experiments) and X-ray diffraction.

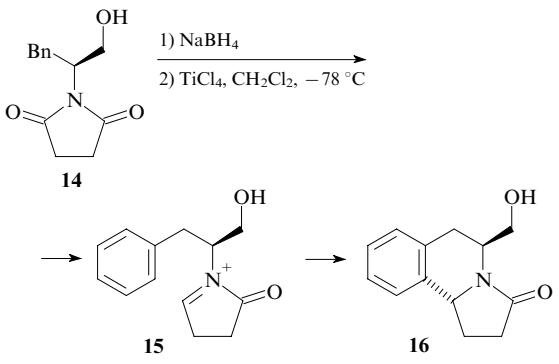
The high diastereoselectivity (formation of virtually a single diastereomer) was achieved by using substrate **11** containing a D-phenylalanine moiety as a chiral auxiliary (Scheme 6).[25] The cyclization proceeds *via* the intermediate formation of N-acim **12** and requires a considerable excess of a strong acid. The final product **13** contains a fused tricyclic chiral hydrogenated pyrazinoisoquinoline system, which is present in the molecules of some biologically active compounds.[26]

Scheme 6



N-Substituted succinimide **14**, incorporating the (*S*)-phenylalaninol moiety as the chiral auxiliary, undergoes ring closure through the intermediate formation of N-acim

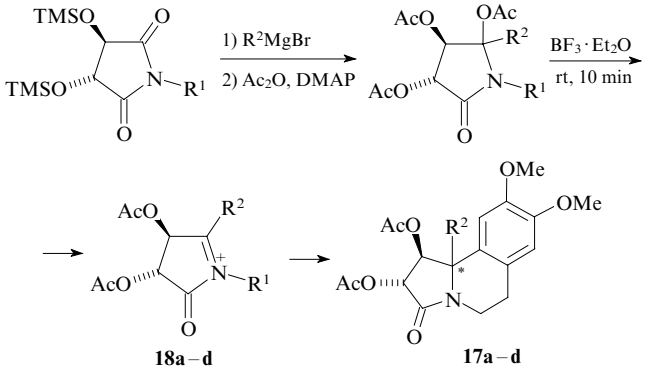
Scheme 7



15 (Scheme 7).[27] The reaction gives only one diastereomer of hydroxylactam **16** in 52% yield after two steps.

Apart from derivatives of natural amino acids, derivatives of chiral hydroxycarboxylic acids, in particular, tartaric and malic acids, are also used as chiral auxiliaries for the diastereoselective cyclization of N-acim. For example, the stereoselective synthesis of hexahydropyrroloisoquinolines **17a – d** has been accomplished by cyclization of N-acim **18a – d** generated from chiral N-substituted tartaric acid imide and appropriate organomagnesium reagents in the presence of DMAP (4-dimethylaminopyridine) in acetic anhydride. The resulting diastereomeric ratio is strongly affected by the structure of the substituent R^2 at the quaternary carbon atom in the N-acim molecule (Scheme 8).[4]

Scheme 8

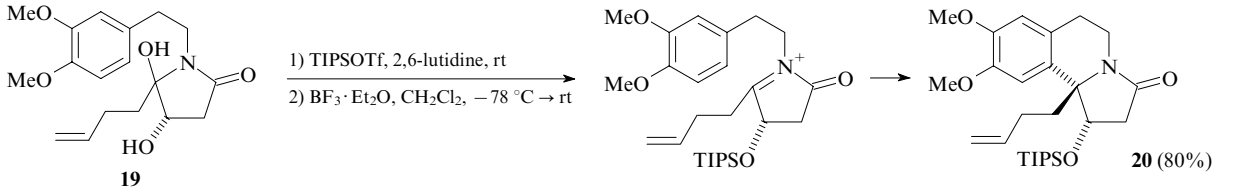


R^1 = 3,4-$(MeO)_2C_6H_3(CH_2)_2$

Compounds **17**, **18**	R^2	Yield of **17** (%)	*S* : *R* ratio
a	Me	85	6 : 1
b	Pr^i	80	1 : 6
c	Ph	82	3 : 1
d	PhC≡C	81	10 : 1

The chiral substrate **19** prepared from malimide undergoes stereoselective ring closure to give lactam **20** with the participation of triisopropylsilane (TIPSH) salt and trifluoromethanesulfonic acid *via* the intermediate formation of N-acim (Scheme 9).[3] The diastereomeric ratio (*dr*) is

Scheme 9



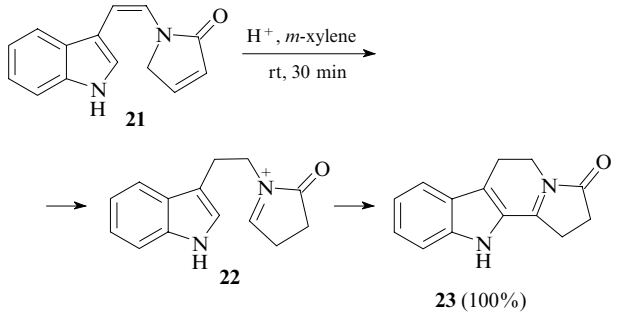
>9 : 1. This reaction was used as the key step in the synthesis of an erythrinan alkaloid.

Later Simpkins and co-workers[28] proposed an alternative approach to erythrinan alkaloids, which also included the formation of N-acim, but was more cumbersome, because additional steps were required to obtain the enantiomerically pure substrate.

II.1.b. Cyclization with heteroaromatic π-nucleophiles

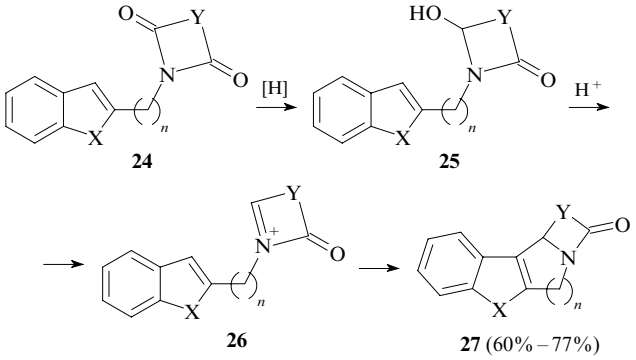
Indole moieties, which are highly reactive towards electrophiles, are often used as heteroaromatic π-nucleophiles in N-acim cyclization. For example, protic acid promotes transformation of tryptamine derivative **21** to N-acim **22** followed by ring closure to tetracyclic product **23** (Scheme 10).[7]

Scheme 10



Grigg *et al.*[29] applied benzofurans and indoles **24**, which were prepared by the Sonogashira reaction from 2-iodophenol and 2-iodo-*N*-tosylaniline, respectively, as initial substrates for the N-acim generation/cyclization reaction sequence (Scheme 11).

Scheme 11

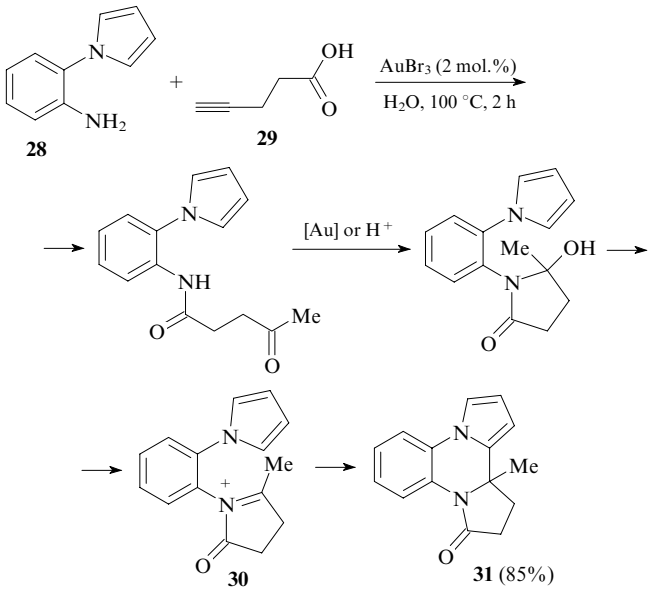


X = O, NTs; Y = $(CH_2)_2$, $(CH_2)_3$, *o*-C_6H_4; *n* = 2, 3

The reduction of the imide group in substrates **24** to give hydroxylactams **25** was carried out by treatment with $LiBEt_3H$ in THF at −78 °C for 20 min. The refluxing of hydroxylactams with TsOH (1 equiv.) in toluene with a Dean – Stark trap resulted in N-acim **26**, which were then cyclized to tetracyclic annulated heterocycles **27**.

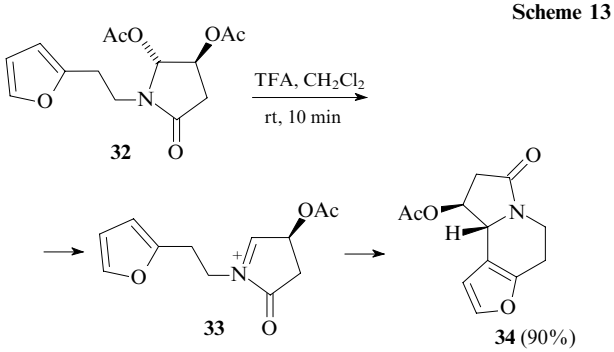
Zhou *et al.*[30] reported an interesting Au-catalyzed domino reaction giving polycyclic structures from simple precursors (Scheme 12). 2-Pyrroloaniline (**28**) and carboxylic acid **29** with a terminal triple bond were used as model substrates. The key role in this process was played by cyclization of N-acim **30**. Product **31** was formed in a high yield; the reaction gave rise to two new C – N bonds and one C – C bond over four steps.

Scheme 12



High diastereoselectivity was attained in the trifluoroacetic acid-induced cyclization of chiral substrate **32** proceeding *via* generation of N-acim **33**; in this case, the furan ring acted as a π-nucleophilic moiety (Scheme 13).[31] This reaction afforded only one of the two possible diastereomers **34** which had the *trans*-configuration. It is noteworthy that the replacement of acetoxy groups in the initial sub-

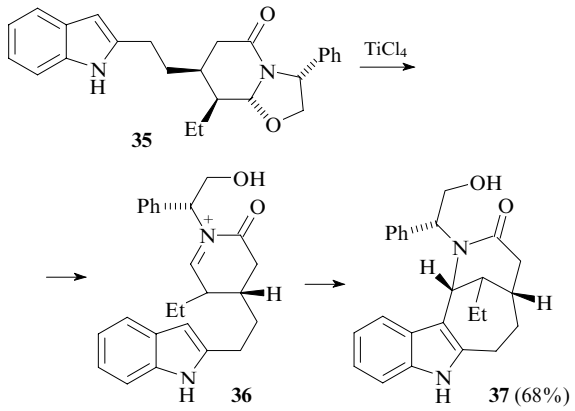
Scheme 13



strate by hydroxy groups induced inversion of configuration at the new chiral centre in the final product, *i.e.*, the *cis*-isomer of compound **34** was predominantly formed.

The diastereoselective cyclization of substrate **35**, which proceeded *via* the formation of N-acim **36** with phenylglycinol-derived chiral auxiliary (Scheme 14),[32] gave tetracyclic compound **37**, a close analogue of the alkaloid ervitsine.

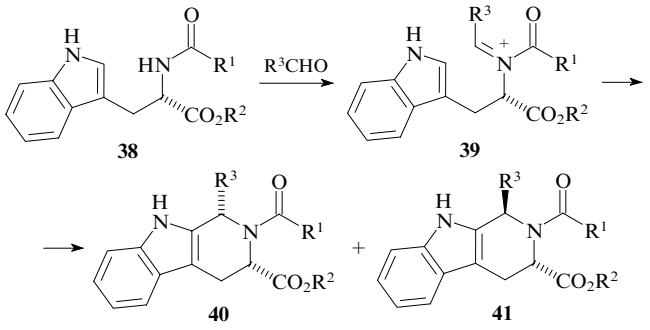
Scheme 14



Tryptophan derivatives are convenient substrates for diastereoselective cyclization of N-acim. These derivatives are readily accessible and, furthermore, they contain both an asymmetric carbon atom and a reactive π-nucleophilic indole moiety.

The classical Pictet – Spengler reaction, that is, the reaction of N-substituted tryptophan ester with aldehyde in the presence of an acid catalyst, results in the formation of a new chiral centre. The reaction of tryptophan derivative **38** with aldehydes carried out under mild conditions (20 – 50 °C) leads to generation of the intermediate N-acim **39**, which is converted to *cis*-diastereomer **40** with high diastereoselectivity. Meanwhile, under more drastic conditions (> 100 °C), the thermodynamically more stable *trans*-diastereomer **41** can become the major product as a result of inversion of configuration at the chiral centre with the substituent R^3 (Scheme 15).[33]

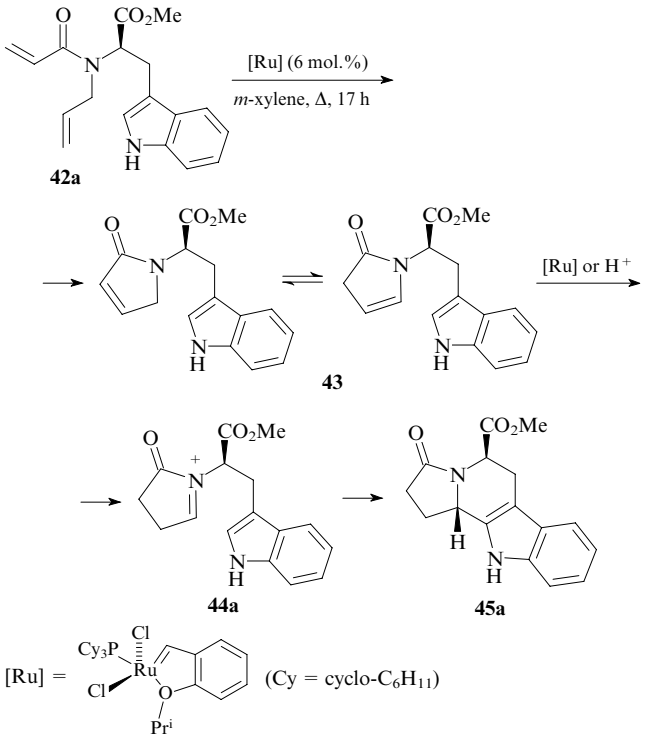
Scheme 15



R^1, R^2, R^3 = Alk

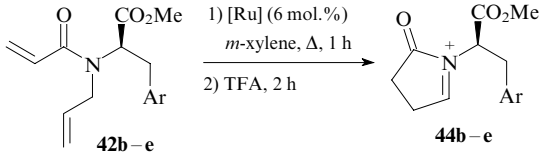
Nielsen's team [7] developed an original tandem process (Scheme 16), the first step being the Ru-catalyzed intramolecular metathesis of chiral tryptophan derivative **42a** to give cyclic enamide **43**. The second step was the transformation of this enamide into N-acim **44a**, which underwent ring closure to give tetracyclic product **45a** with good diastereoselectivity (*dr* = > 10 : 1) and 61% yield (relative to compound **43**).

Scheme16



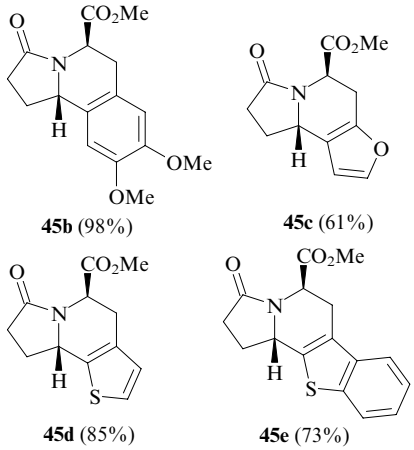
The same approach served for the stereoselective synthesis of similar polycyclic compounds **45b – e** with *dr* = > 20 : 1 from substrates **42b – e** *via* the formation of cations **44b – c** (Scheme 17).[7]

Scheme 17



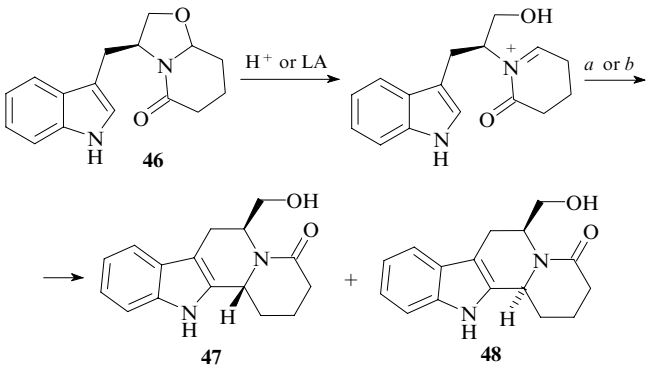
Ar = 3,4-$(MeO)_2C_6H_3$ (**b**), 2-Fu (**c**), 3-Th (**d**), benzothiophen-3-yl (**e**); Fu is furyl, Th is thienyl

Structures 45b – e



The stereochemistry of cyclization of N-acim generated from chiral substrates can be controlled by the nature of acid promoter and the solvent. For instance, the cyclization of compound **46** *via* the generation of acyliminium ion in a 0.5 M HCl solution in EtOH at room temperature gives diastereomeric products **47** and **48** in >95 : 5 ratio (95% yield), while in a solution of $BF_3 \cdot Et_2O$ in CH_2Cl_2, their ratio changes to 10 : 90 (80% yield) (Scheme 18).[34]

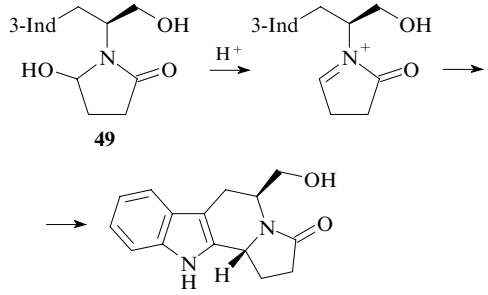
Scheme 18



(*a*) HCl, EtOH; (*b*) $BF_3 \cdot Et_2O$, CH_2Cl_2

The Brønsted acid-catalyzed cyclization of chiral tryptophan derivative **49** proceeds with 90% diastereoselectivity

Scheme 19



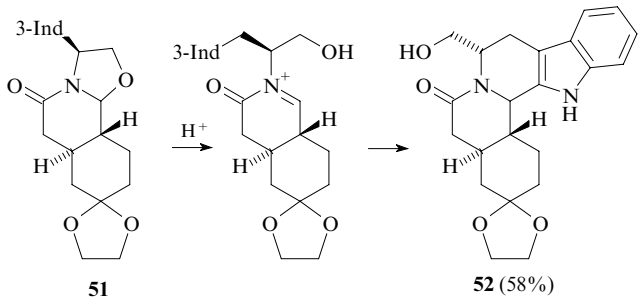
Ind is indolyl

and Allin *et al.*[35] applied this reaction for the synthesis of compound **50**, a precursor of the alkaloid harmicine (Scheme 19).

A similar transformation of compound **51** in a 2 M HCl solution in EtOH (50 °C, 18 h) afforded product **52** as the only diastereomer (Scheme 20).[36] This polycyclic structure is present in the molecules of manadomanzamine alkaloids.

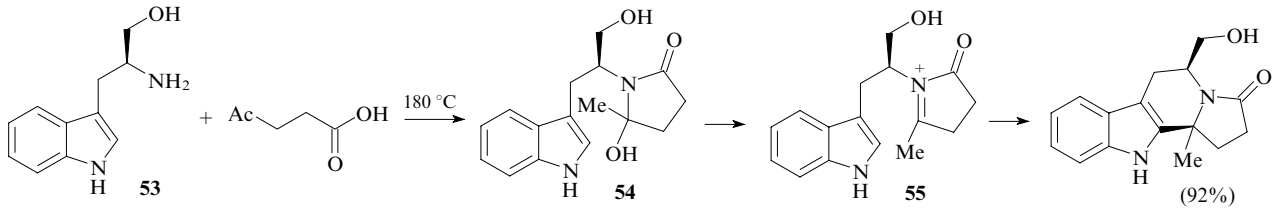
The initial compounds for the synthesis of indole alkaloids by the Pictet – Spengler reaction can be prepared *in situ* by condensation of tryptophanol **53** with γ-oxocarboxylic acids, in particular, under microwave irradiation in the absence of a solvent. Under these conditions, the formation of cyclic species **54** and the subsequent ring closure *via* the generation of N-acim **55** takes only several minutes (Scheme 21).[37] The reaction has an exceptionally high diastereoselectivity (> 99%).

Scheme 20

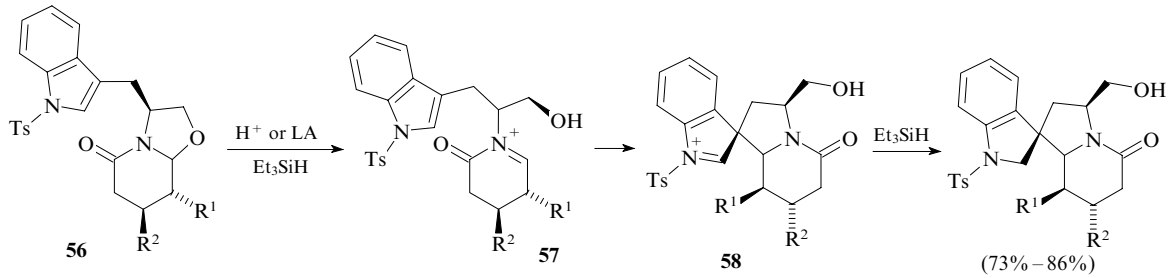


An unusual Pictet – Spengler reaction pathway, giving rise to spiro products, was observed for N-tosylated tryptophanol derivatives **56** in the presence of a Brønsted (TFA) or Lewis ($BF_3 \cdot Et_2O$, $TiCl_4$) acid and Et_3SiH; the reaction was stereoselective (Scheme 22).[38] In the authors' opinion, N-acim **57**, which was initially formed from substrate **56** under the action of acid, was rapidly rearranged to N-tosyliminium intermediate **58**, which, unlike acyliminium ion **57**, was reduced by triethylsilane present in the system.

Scheme 21



Scheme 22

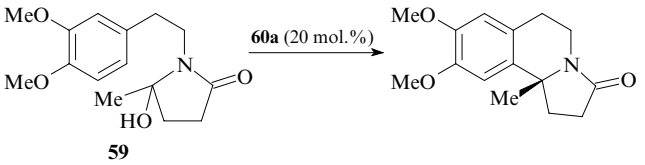


R^1 = H, Et, $MeO_2C(CH_2)_2$; R^2 = H, $MeO_2C(CH_2)_2$

II.2. The use of organocatalysis in the arylation of N-acyliminium cations

After the pioneering publication of Taylor and Jacobsen [39] devoted to the Pictet – Spengler reaction in the presence of chiral organocatalysts involving N-acim as intermediates, a number of papers appeared in which cyclic phosphoric acid diesters with chiral 1,1′-binaphthyl-2,2′-diol (BINOL) derivatives or chiral thiourea derivatives served as organocatalysts for the formation and arylation of N-acim. For instance, series of BINOL-based chiral phosphates **60** have been tested as organocatalysts in the asymmetric cyclization of hydroxylactam **59** in toluene at 110 °C (Scheme 23).[40]

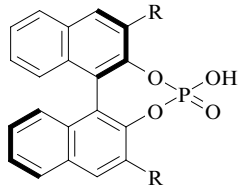
Scheme 23



59

The highest enantioselectivity (74% – 76% *ee*) was achieved with catalyst **60a**; however, the yield of the cyclization product did not exceed 31% even over several days.

Structures 60

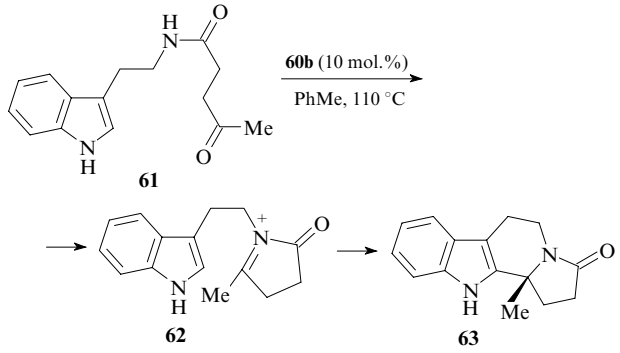


60a – d

R = 2,4,6-$Pr^i_3C_6H_2$ (**a**), Ph_3Si (**b**), 2-Naph (**c**), 3,5-$(F_3C)_2C_6H_3$ (**d**)

The asymmetric cyclization catalyzed by BINOL-containing phosphoric acids occurs much more efficiently with indole derivatives. Dixon and co-workers [41] found that amide **61** containing levulinic acid and tryptamine moieties, which was formed *in situ*, afforded, on heating in the presence of catalyst **60b**, N-acim **62**. The latter cyclized enantioselectively (84% *ee*) to tetracyclic product **63** in a quantitative yield, the reaction being completed within 1 h (Scheme 24).

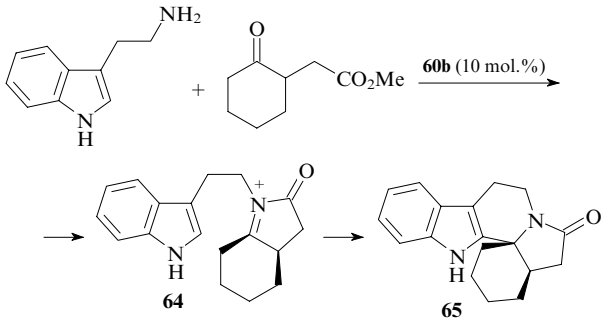
Scheme 24



61 **62** **63**

A similar reaction involving the formation of N-acim **64** resulted in pentacyclic product **65** in a yield of 77% and enantiomeric excess of 81% (Scheme 25). However, in this case, a longer period (24 h) was needed to attain this yield.[42]

Scheme 25



64 **65**

According to the authors, the stereoinduction in the above reactions may be controlled by the chiral counter-ion, which was generated from the catalyst in the transition state depicted in Fig. 2.

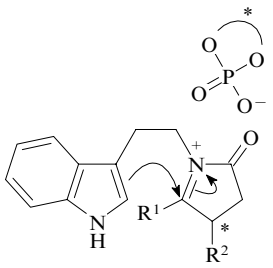
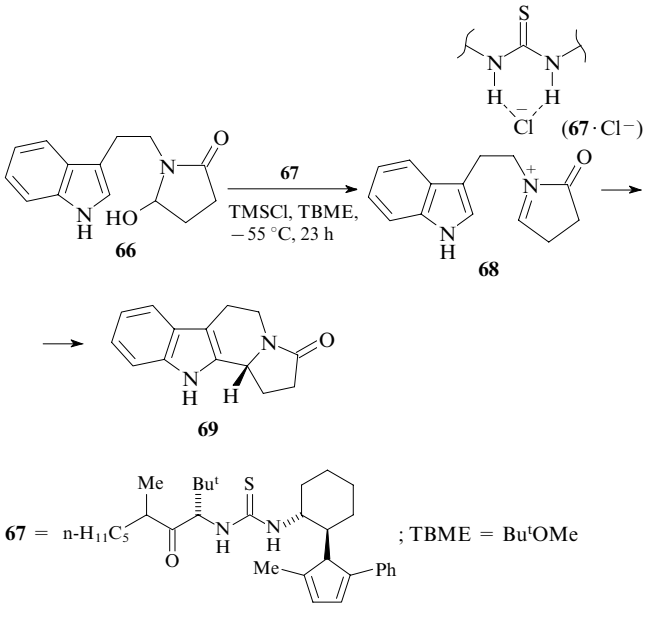


Figure 2. Mechanism of cyclization controlled by chiral counter-ion.

In comparison with BINOL-derived phosphoric acids, the chiral thiourea-based catalysts promote the Pictet – Spengler reaction under much milder conditions and with a better enantioselectivity (Scheme 26).[43] Model substrate **66** is cyclized, in the presence of TMSCl and organocatalyst **67**, at −55 °C over a period of 23 h with high enantioselectivity (97% *ee*) and to a high conversion (80%). In the

Scheme 26



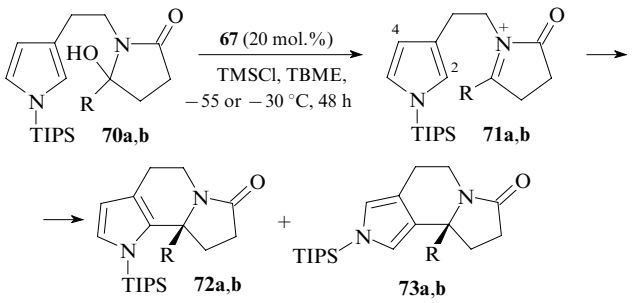
66 **68** **69**

67 = n-$H_{11}C_5$ (Me, Bu^t, S, N, H, O, Me, Ph); TBME = Bu^tOMe

authors' opinion, the asymmetric induction is provided by complex **68** in which the catalyst is enantioselectively coordinated to the chloride anion *via* hydrogen bonding. Product **69** is a precursor of the indole alkaloid harmicine.

Unlike indole substrate **66**, compounds **70a**,**b** are able to react along two pathways comprising cyclization of intermediate N-acim **71a**,**b** at either the C(4) or C(2) atom of the pyrrole ring (Scheme 27).[44] The conversion values are rather high (>95%) in both cases and does not depend on the substituents present in the substrate.

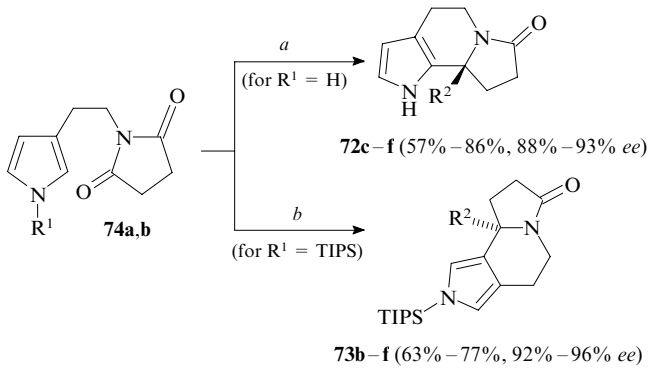
Scheme 27



R = H (**a**), Me (**b**)

Meanwhile, the ratio of regioisomers depends on the presence of the substituent R in the initial compound. In the case of hydroxylactam **70a**, the ratio of products **72a** : **73a** is 1 : 1.7, while for the 5-methyl-substituted analogue **70b**, the ratio is >50 : 1. The product ratio also depends on other structural features of the N-acim precursor (hydroxylactam or acetoxylactam, either a free or substituted nitrogen atom in the pyrrole ring). This makes it possible to control the direction of cyclization of compounds **74a**,**b** by varying the substrate structure (Scheme 28).[44]

Scheme 28

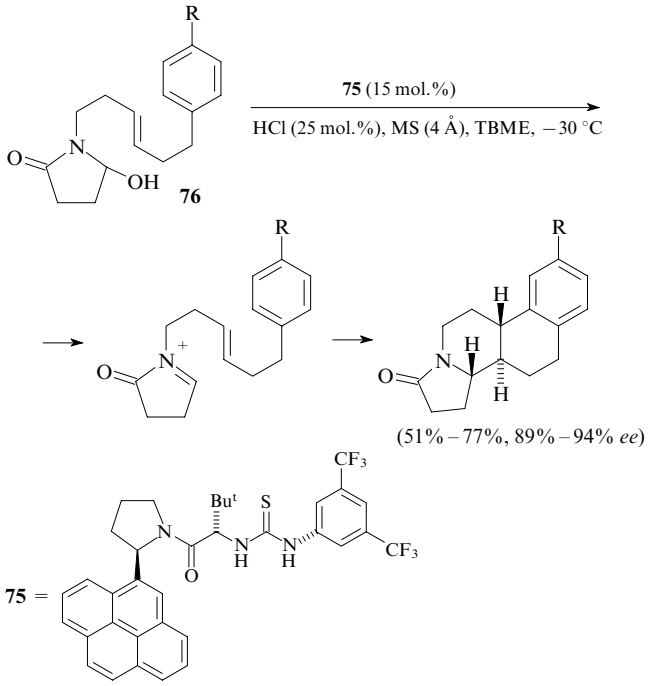


74: R^1 = H (**a**), TIPS (**b**); R^2 = Me (**72c**, **73b**), Pr^i (**72d**, **73c**), Bu^n (**72e**, **73d**), Bu^i (**72f**, **73e**), Ph (**73f**);
(*a*) 1) R^2Li, THF, −78 °C; 2) **67** (20 mol.%), TBME, −78 °C, 24 h;
(*b*) 1) R^2Li, THF, −78 °C; 2) **67** (20 mol.%), TMSCl, TBME, −55 or −30 °C, 48 h

With thiourea derivative **75** as the catalyst, highly enantioselective double cyclization of intermediate N-acim formed from unsaturated hydroxylactams **76** was performed (Scheme 29).[45]

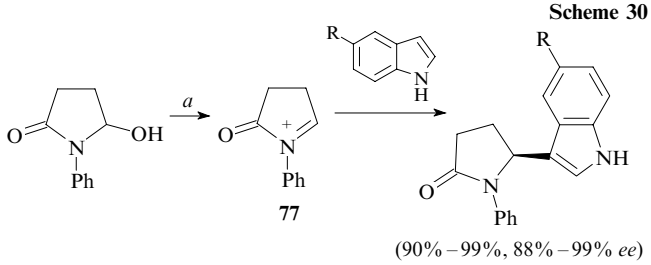
In the presence of organocatalysts, it is also possible to carry out enantioselective intermolecular arylation of N-acim (the Friedel–Crafts type reaction). In these transformations, like in the above intramolecular arylation reactions, the role of π-nucleophile is usually performed by a pyrrole or indole derivative.[46–51] The efficiency of chiral BINOL-derived phosphoric acid organocatalysts was demonstrated in relation to arylation of N-acim **77**–**79** with indole and substituted indoles in 1,2-dichloroethane (DCE),

Scheme 29

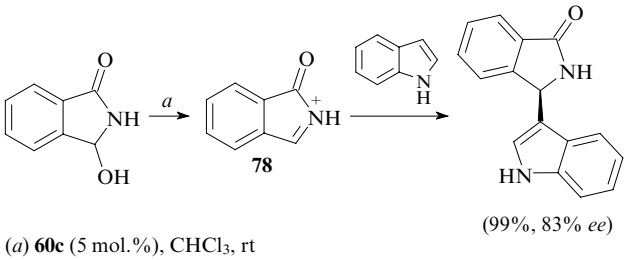


R = H, Me, MeO, Bu^t, Ph; MS are molecular sieves

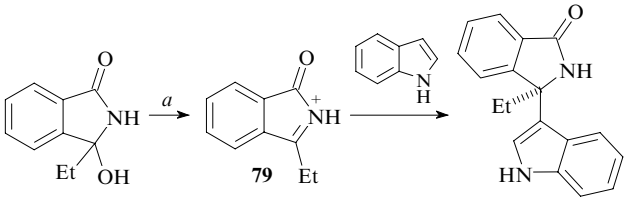
Scheme 30



(*a*) **60a** (5 mol.%), DCE, rt, 18 h; R = H, MeO, Cl, F, NO_2



(*a*) **60c** (5 mol.%), $CHCl_3$, rt

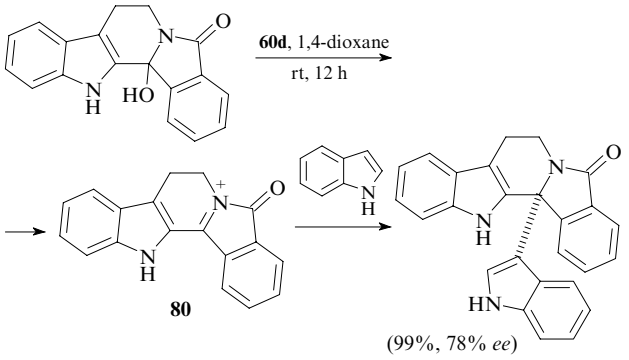


(*a*) **60b** (5 mol.%), MeCN, 20 °C, 11 h

$CHCl_3$ or MeCN (Scheme 30).[47–49] The highest enantioselectivity (88%–98% *ee*) was achieved for catalysts **60a–c**.

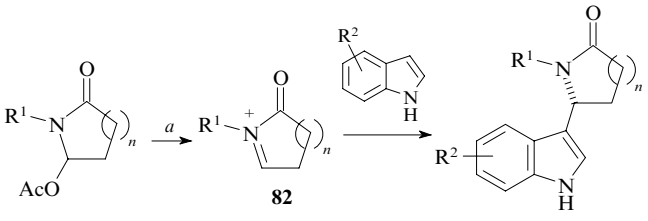
In the intermolecular arylation of polycyclic N-acim **80** with indole, high enantioselectivity (78 % *ee*) was observed with catalyst **60d** containing bis(trifluoromethyl)phenyl substituents (Scheme 31).[50]

Scheme 31



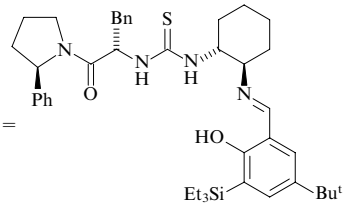
The use of thiourea derivative **81** as the catalyst in the arylation of N-acim **82** with indoles has been reported.[51] A number of nitrogen heterocycles **83** were synthesized in this way with high enantioselectivity under mild conditions (Scheme 32).

Scheme 32



(*a*) **81** (5 mol.%), TMSCl, TMBE, H_2O, −30 °C, 1–2 days;
R^1 = Bn, Me; R^2 = H, 4(5)-Me, 5-CH_2=CH, 5(6)-MeO; *n* = 1, 2;

81 =



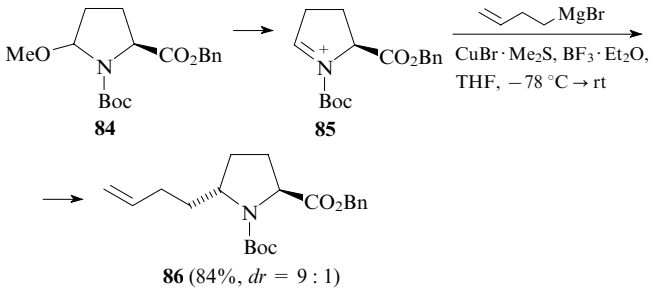
III. Reactions of N-acyliminium ions with C-, O- and N-nucleophiles

III.1. Reactions with C-nucleophiles

III.1.a. Reactions with organometallic and organosilicon reagents

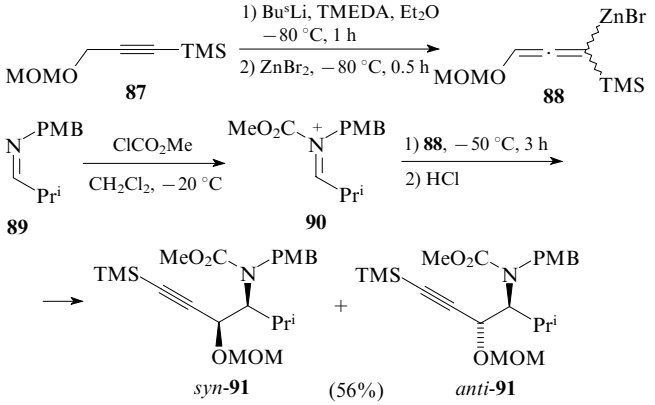
Proline derivative **84**, which can be easily prepared from available L-pyroglutamic acid, reacts with but-3-enylmagnesium bromide in the presence of a Cu^I salt catalyst (Scheme 33).[52] This reaction proceeds *via* intermediate N-acim **85**. The cross-coupling product **86** has predominantly *trans*-configuration. Instead of organomagnesium C-nucleophiles, the complexes $R_2Cu \cdot MgX_2$ can be used for the synthesis of *trans*-5-*S*-proline derivatives.[53]

Scheme 33



An interesting example of a C-nucleophile able to react with N-acim is O-protected allenylzinc bromide **88** prepared in two steps from disubstituted propargyl alcohol **87**. The reaction of **88** with N-acyliminium cation **90** generated from imine **89** furnishes a mixture of isomeric cross-coupling products **91** in which the *syn*-isomer predominated (*syn* : *anti* = 63 : 37) (Scheme 34).[54]

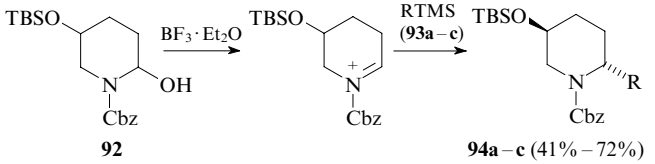
Scheme 34



MOM is methoxymethyl, TMEDA is tetramethylethylenediamine, PMB is *p*-methoxybenzyl

Unlike organomagnesium and -zinc C-nucleophiles, which induce the formation of diastereomer mixtures of products upon the cross-coupling with N-acim precursors **84** and **89** (see Schemes 33 and 34), organosilicon C-nucleophiles react with N-acim stereospecifically. For example, the acyliminium cation generated from precursor **92** reacts with various Si-containing compounds **93a–c** to give only one out of the two possible isomers, namely, *trans*-2-substituted 5-silyloxypiperidines **94a–c** (Scheme 35).[55]

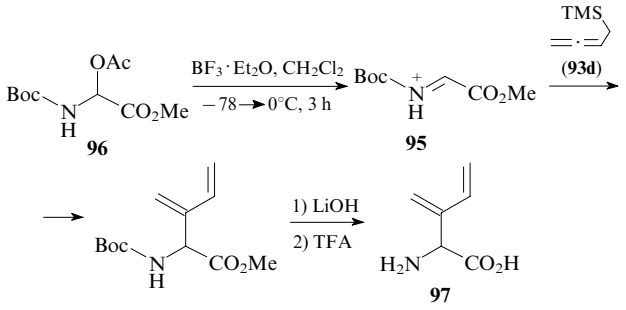
Scheme 35



R = All (**a**), HC≡CCH_2 (**b**), NC (**c**); TBS is *tert*-butyldimethylsilyl

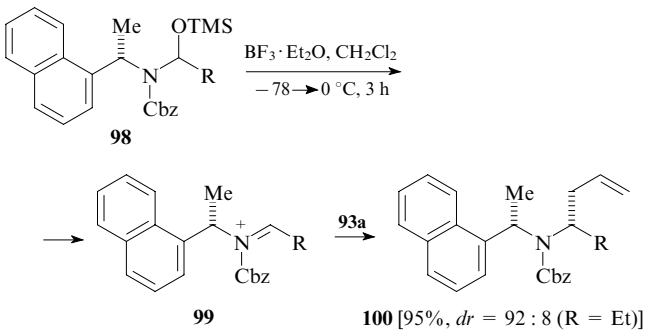
The reaction of N-acim **95**, generated from compound **96**, with silicon-containing C-nucleophile **93d** was used in the synthesis of unusual dienic α-amino acids recently discovered in nature, for example, amino acid **97** in the racemic form (Scheme 36).[56] The product yield over four steps in relation to substrate **96** was 42%.

Scheme 36

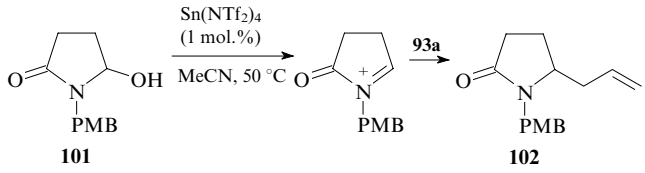


The cross-coupling of enantiomerically pure chiral substrates **98** with allyltrimethylsilane (**93a**) in the presence of a Lewis acid involving the formation of N-acim **99** proved to be convenient for the synthesis of valuable α-allyl-substituted chiral amines **100**. This reaction proceeded under mild conditions to afford products **100** in high yields and with high diastereoselectivity (Scheme 37).[57] Metal triflylimidate-catalyzed allylation of N-protected hydroxypyrrolodinone **101** with the same C-nucleophile produced 5-allylpyrrolidin-2-one **102** *via* the corresponding N-acim formation step. The catalyst $Sn(NTf_2)_4$ showed the highest activity in this reaction.[58 – 60]

Scheme 37

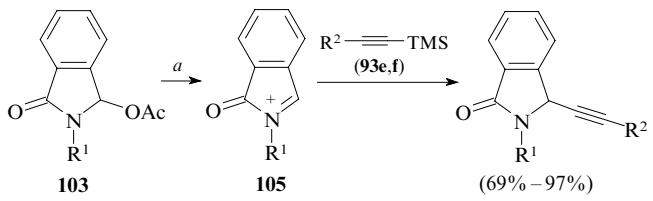


R = Alk, Alkenyl, Alkynyl



Recently Dalla and co-workers[61] have shown that alkynylation of cyclic N,O-acetals **103** with trimethylsilylacetylenes **93e**,**f** [R^2 = Ph (**e**), Bu^n (**f**)] in the presence of gold phosphine complex **104** can proceed under relatively mild conditions *via* N-acim intermediates **105** (Scheme 38).

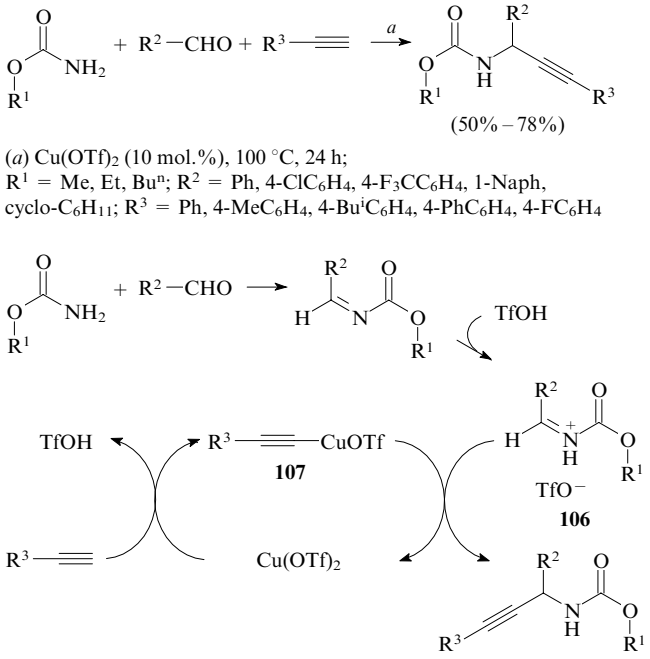
Scheme 38



(*a*) $(Ph_3P)Au$ —≡— Ph (**104**) (3 mol.%), $PhCF_3$, 40 °C;
R^1 = All, Bn, 4-$MeOC_6H_4$, Bu^n, Cbz; R^2 = Ph, Bu^n

Another metal-catalyzed alkynylation comprises the generation of N-acim **106** from aldehyde, carbamate and TfOH (Scheme 39).[62] Cation **106** further reacts with complex **107** formed from alkyne and the $Cu(OTf)_2$ catalyst and functioning as C-nucleophile in the catalytic cycle.

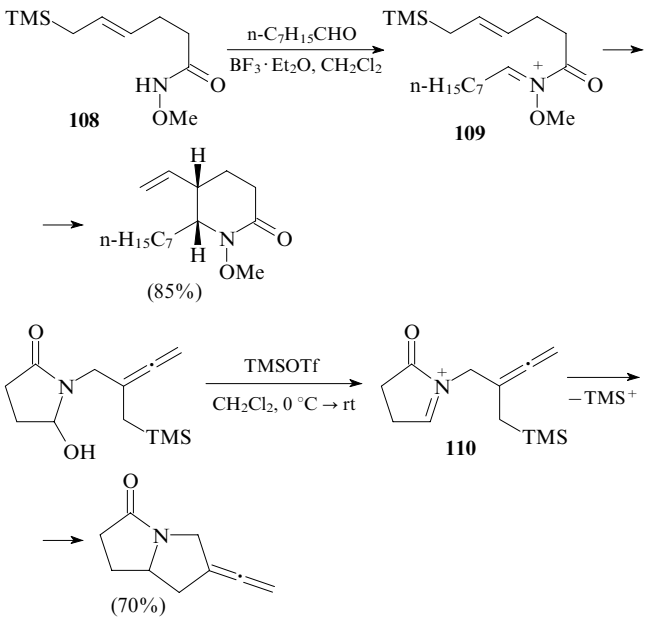
Scheme 39



(*a*) $Cu(OTf)_2$ (10 mol.%), 100 °C, 24 h;
R^1 = Me, Et, Bu^n; R^2 = Ph, 4-ClC_6H_4, 4-$F_3CC_6H_4$, 1-Naph, cyclo-C_6H_{11}; R^3 = Ph, 4-MeC_6H_4, 4-$Bu^iC_6H_4$, 4-PhC_6H_4, 4-FC_6H_4

Apart from the intermolecular reactions considered above, examples of intramolecular cross-coupling of N-acim with organosilicon C-nucleophiles are also known.[63, 64] One such example includes the condensation of silicon-containing acidic N-methoxyamide **108** with aldehyde, resulting in the generation of N-acim **109**, and the subsequent intramolecular alkylation of the N-acyliminium cationic group in compound **109** with the allyl-type C-nucleophilic silane moiety to give a piperidine ring.[63] A similar

Scheme 40

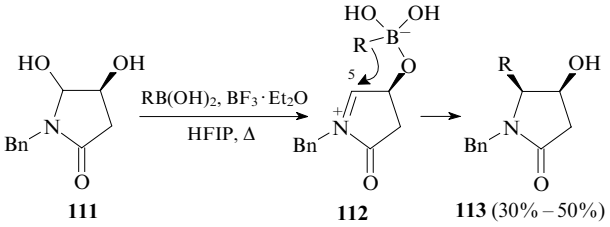


cyclization *via* the C – C bond formation upon the reaction between the cationoid and anionoid moieties, resulting in the pyrrolidine ring, has been observed [64] for N-acim **110** (Scheme 40).

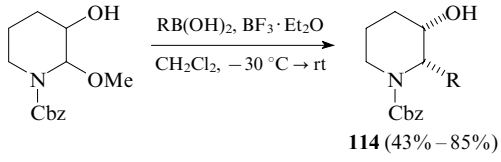
III.1.b. Reactions with organoboron reagents

In recent years, considerable attention has been paid to cross-coupling reactions of N-acim with organoboron nucleophiles such as boronic acids [65–67] and trifluoroboronates.[68] This is attributable to the ability of organoboron nucleophiles to stereoselectively alkenylate or arylate (similarly to Petasis reactions [69]) readily accessible dihydroxy-substituted pyrrolidine and piperidine N-acim to give products with *cis*- or *trans*-arrangements of the incoming substituent and the remaining HO group. *cis*-Substituted heterocycles can be prepared most selectively in this way. The reaction of substrate **111** with $RB(OH)_2$ in hexafluoroisopropyl alcohol (HFIP) in the presence of $BF_3 \cdot Et_2O$ affords products **113** with high diastereoselectivity (*cis* : *trans* = > 20 : 1) (Scheme 41).[65] Presumably, the addition of the C-nucleophile to the C(5) atom of cyclic N-acim **112** is controlled by coordination of boronic acid with the neighbouring hydroxy group. A series of *cis*-substituted piperidines **114** were prepared in a similar way.[66] However, compound **115** containing a protected (and, hence, less prone to coordination to boron) β-hydroxy group [67] reacts with boronic acids to give mainly *trans*-substituted products **116**, although the stereoselectivity is much lower (*dr* ≈ 7 : 3) than that for reactions giving mainly *cis*-isomers.

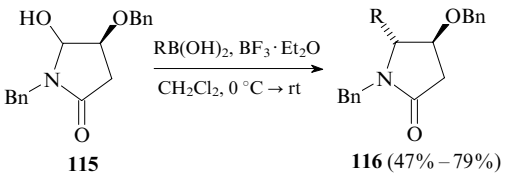
Scheme 41



R = MeCH=CH, Ph, 4-BrC_6H_4



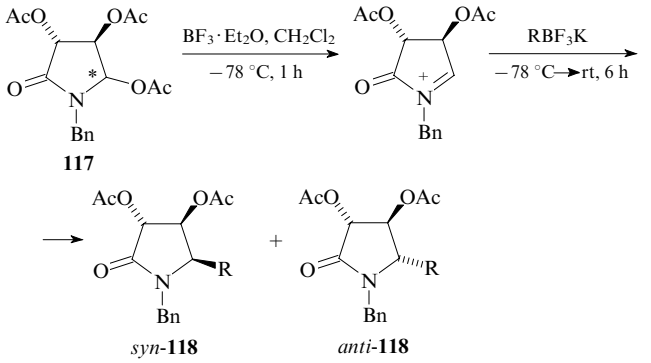
R = 4-$MeOC_6H_4$, 3-PhC_6H_4, 2-Naph, PhCH=CH, 3-Th



R = (*E*)-PhCH=CH (*trans* : *cis* = 91 : 9), 2-Fu (71 : 29), 4-$MeOC_6H_4$ (72 : 28)

Organotrifluoroborates, which are stable on contact with air, including moist air, are more convenient C-nucleophiles than boronic acids. The cross-coupling of tartaric acid derivatives **117** with organotrifluoroborates in the presence of Lewis acid ($BF_3 \cdot Et_2O$) proceeds *via* the formation of the corresponding N-acim and furnishes a mixture of *syn*- and *anti*-5-R-substituted pyrrolidin-2-ones **118** (in a 71% – 87% overall yield) with predominance of the *syn*-isomer relative to the neighbouring acetoxy group (Scheme 42).[68]

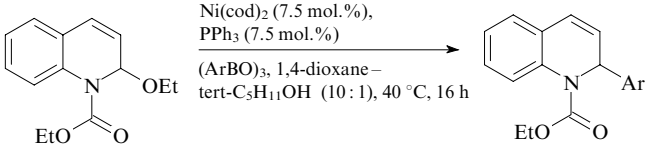
Scheme 42



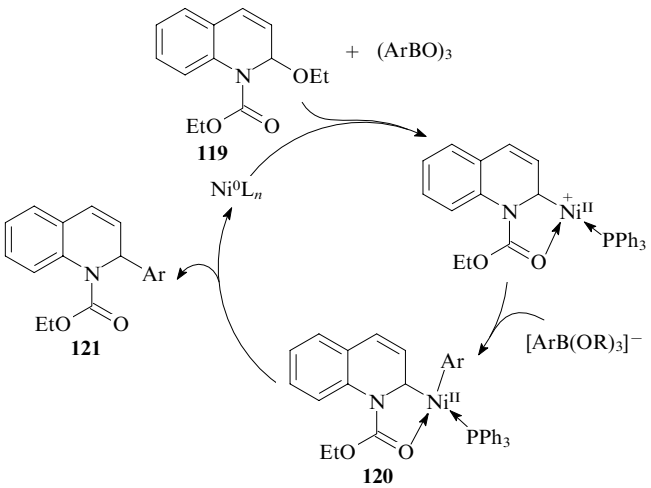
R = Ph (*syn* : *anti* = 90 : 10), 4-$MeOC_6H_4$ (90 : 10), 4-FC_6H_4 (90 : 10), 2-Th (85 : 15), PhC≡C (90 : 10), $MeO_2CC{\equiv}C$ (80 : 20)

It was found [70] that Ni^0-catalyzed cross-coupling of cyclic N,O-acetals **119** with arylboroxines $(ArBO)_3$, which are precursors of anionic *at*-complexes $[ArB(OR)_3]^-$ (R = Et, n-C_5H_{11}), is highly regioselective, yielding 2-aryl-substituted dihydroquinolines **121** (Scheme 43). The authors believe that the catalytic process includes the formation of acyliminium intermediates (not shown in the scheme), which react with Ni^0 according to the oxidative addition mechanism to give Ni^{II} complexes **120** with a metal – carbon bond. Intermediates **120** decompose *via* reductive elimination with regeneration of Ni^0 to give product **121**. The $Ni(cod)_2$ (cod is cycloocta-1,5-diene) is used as the pre-catalyst in this reaction.

Scheme 43

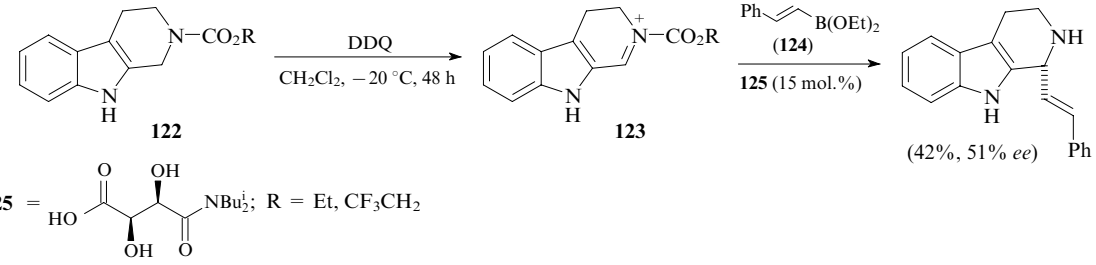


Ar = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4 , 3-$F_3CC_6H_4$, 2-Naph



Recently, attempts have been made to carry out the cross-coupling of N-acim with alkenylboronates in the

Scheme 44

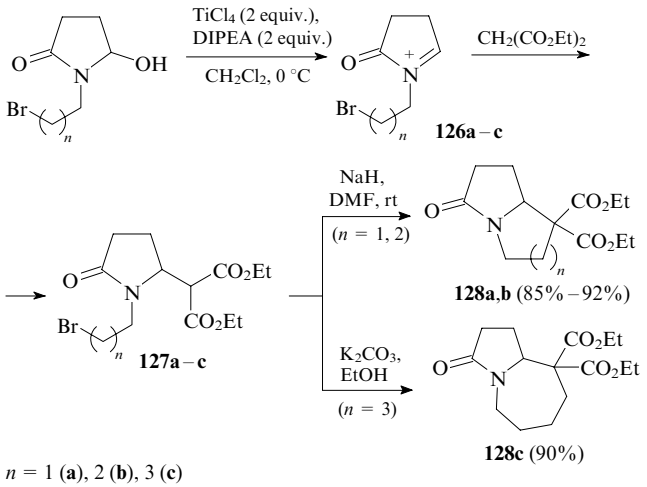


presence of organocatalysts. A reaction of this type has been reported by Liu *et al.*[71] (Scheme 44). The hydrogen atom transfer from indole-containing substrate **122** to the oxidant — 2,3-dichloro-5,6-dicyanoquinone (DDQ) — generates N-acim **123**, which reacts with styrylboronate **124** in the presence of a chiral catalyst. The best results were obtained with organocatalyst **125** (malic acid derivative); however, under standard conditions, the yields and enantioselectivities were moderate.

III.1.c. Reactions with enol-type C-nucleophiles

Cross-coupling of N-acim **126a–c** with diethyl malonate followed by cyclization of adducts **127a–c** was used to develop a convenient method for the synthesis of functionally substituted bicyclic heterocycles: pyrrolizidine (**128a**), indolizidine (**128b**) and hydrogenated pyrroloazepine (**128c**) (Scheme 45).[72] The N-acim **126a–c** were generated from appropriate hydroxylactams in the presence of $TiCl_4$ and diisopropylethylamine (DIPEA).

Scheme 45

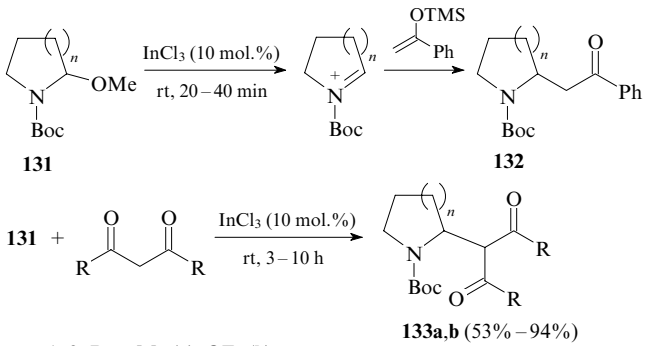


n = 1 (**a**), 2 (**b**), 3 (**c**)

A similar approach was used to prepare tricyclic heterocycles. In particular, the transformation of cross-coupling product **129** to compound **130** can be interpreted as resulting from cationoid cyclization at the benzene ring with the participation of the protonated keto group (Friedel–Crafts reaction) and subsequent dehydration of the corresponding hydroxy derivative (Scheme 46).[73]

Brønsted or Lewis acids needed for generation of N-acim from N,O-acetals can be used not only as reactants, *i.e.*, in equimolar amounts or in excess with respect to the initial substrates (see Schemes 45 and 46), but also as catalysts. It was found that some of the acids such as $InCl_3$,[74] $Al(OTf)_3$,[75] Tf_2NH, TIPSOTf,[76] $Sn(NTf_2)_4$ [59] and AuOTf [77] are efficient catalysts for N-acim generation and cross-coupling of the latter with enol-type C-nucleophiles (Schemes 47–53). Compounds **131** react with activated (for example, trimethylsilyl ether of acetophenone enol) and non-activated nucleophiles (acetylacetone, diethyl malonate) at room temperature in the presence of $InCl_3$ to give the corresponding C–C cross-coupling products **132** and **133a,b** in moderate to high yields (see Scheme 47).[74]

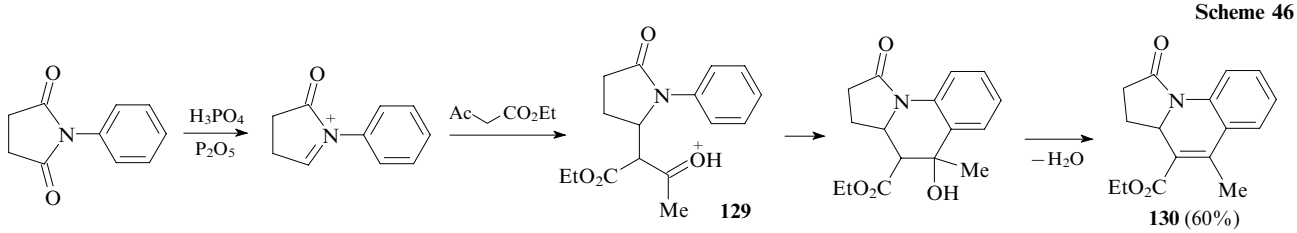
Scheme 47



n = 1, 2; R = Me (**a**), OEt (**b**)

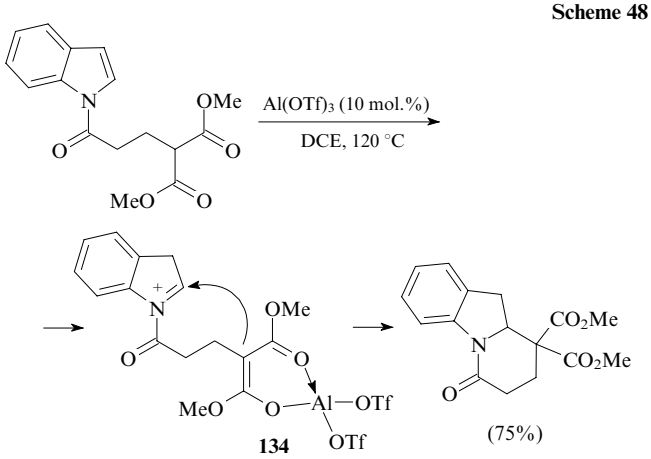
Wang *et al.*[75] described the $Al(OTf)_3$-catalyzed intramolecular cross-coupling of N-substituted indole *via* generation of N-acim **134**. The formation of N-acim in this reaction is probably preceded by complex formation of $Al(OTf)_3$ with the enol form of the substrate with the release of trifluoromethanesulfonic acid, which causes the proto-

Scheme 46



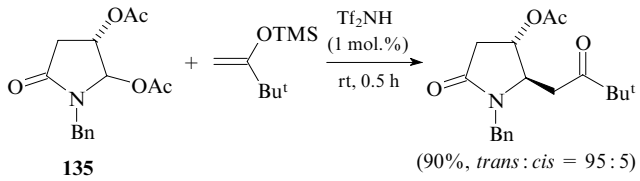
nation of the double bond in the initial enamide (see Scheme 48).

Scheme 48



Dalla and co-workers ascertained that trifluoromethanesulfonimide,[76] its tin-containing derivative[59] and AuOTf[77,78] belong to the most efficient acid catalysts for the cross-coupling of cyclic N,O-acetals of type **135** with enol C-nucleophiles (for example, trimethylsilyl ether of *tert*-butyl methyl ketone enol), which proceeds *via* generation of N-acim. These catalysts exhibit high activity when present in amounts of $\leqslant 1$ mol.% – 2 mol.%, which are several times lower than those needed for the $InCl_3$ and $Al(OTf)_3$ catalysts. Furthermore, Tf_2NH-catalyzed diastereoselective cross-coupling of compound **135** with silyl enolates can be performed under neat conditions (see Scheme 49).[76]

Scheme 49

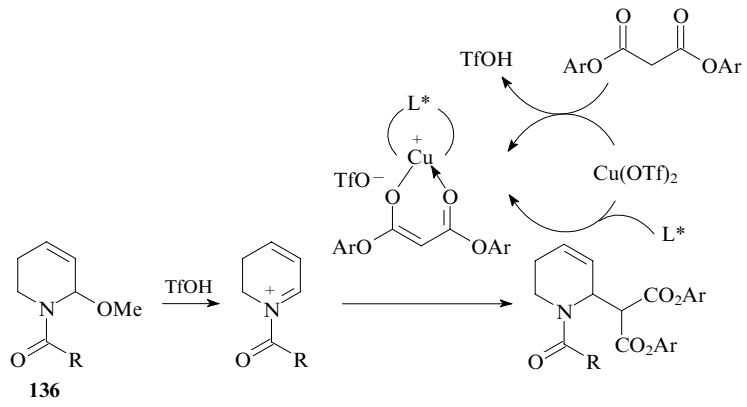


Apart from the N-acim cross-coupling with enol-type C-nucleophiles in the presence of acid catalysts, examples of successful application of metal complexes and organocatalysts in this reaction are also known. Matsamura *et al.*[78] developed an enantioselective method for the introduction of the bis(aryloxycarbonyl)methyl groups into N-acylated tetrahydropyridine ring. The method was based on the reaction of substrates **136** with aryl malonates in the presence of a metal complex obtained *in situ* from $Cu(OTf)_2$ and chiral bis-oxazoline ligand **137** (see Scheme 50). The highest enantioselectivity was attained in the reactions with phenyl- and *p*-chlorophenyl malonates.

Jacobsen's team[79] were the first to carry out the enantioselective cross-coupling of silyl enolates with heterocyclic electrophiles (acyl Mannich reaction) with the participation of N-acim in the presence of organocatalysts — chiral thiourea derivatives **138a – c**. The initial substrates were represented by unsubstituted isoquinoline (see Scheme 51) and isoquinolines with various substituents in positions 3 – 7. The cross-coupling products were obtained with enantioselectivity up to 92% (from 3-methyl-substituted isoquinoline); the highest *ee* value of product **139** was achieved with organocatalyst **138c** containing different substituents (Me and Ph) in the pyrrole ring.

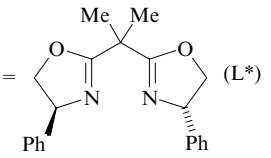
The Mannich-type cross-coupling of N-acim with enol C-nucleophiles plays an important role in multicomponent processes such as the Biginelli reaction.[80 – 83] For example,

Scheme 50

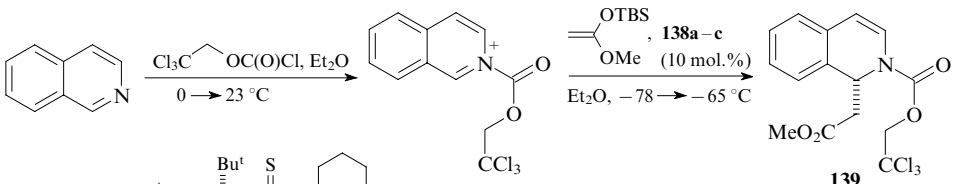


R	Ar	Yield (%)	*ee* (%)
MeO	4-ClC_6H_4	86	68
PhO	4-ClC_6H_4	71	77
Ph	4-ClC_6H_4	51	94
4-$MeOC_6H_4$	Ph	50	89
4-ClC_6H_4	4-ClC_6H_4	71	91

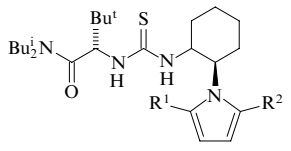
137 =



Scheme 51

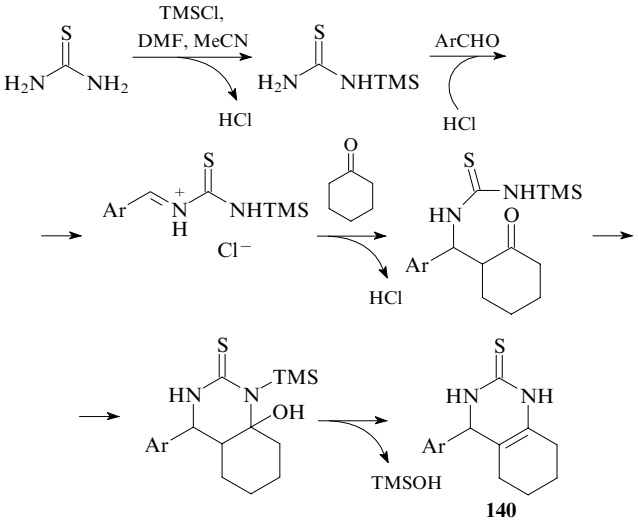


138a – c =



Catalyst **138**	R^1	R^2	Yield of **139** (%)	*ee* (%)
a	Me	Me	60	30
b	Ph	Ph	55	78
c	Me	Ph	55	85

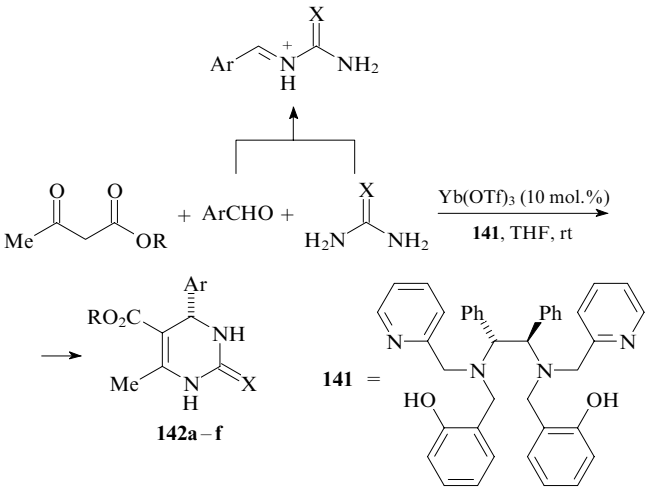
Scheme 52



the one-pot four-component reaction between thiourea, TMSCl (as a Lewis acid), aromatic aldehyde and cycloalkanone taken in a nearly equimolar ratio afforded fused bicyclic pyrimidines **140** in 80% – 97% yield (see Scheme 52).[80]

By using the chiral catalyst (10 mol.%) generated *in situ* from $Yb(OTf)_3$ and chiral ligand **141** in the Biginelli reaction, Zhu and co-workers[82] accomplished asymmetric synthesis of dihydropyrimidinones(-thiones) **142a – f** (up to 99% *ee*) *via* the intermediate formation of the corresponding N-acim (see Scheme 53).

Scheme 53



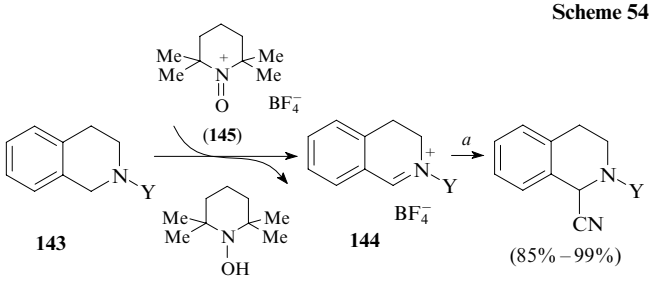
Compound **142**	Ar	R	X	Yield (%)	*ee* (%)
a	Ph	Et	O	87	90
b	Ph	Et	S	81	99
c	3-$O_2NC_6H_4$	Pr^i	O	90	> 99
d	3-$O_2NC_6H_4$	Pr^i	S	88	87
e	3-HOC_6H_4	Et	O	81	91
f	3-HOC_6H_4	Et	S	80	99

High enantioselectivity (up to 97% *ee*) was also attained in the same reaction in the presence of hydrogenated 1,1′-binaphthol-derived phosphoric acid diesters as organocatalysts.[81,83]

III.1.d. Cyanation reactions

Recently, an efficient method was proposed[13] for the cyanation of N-acylated tetrahydroisoquinolines **143** based on cross-coupling of N-acim **144** with TMSCN (**93c**) under mild conditions. Reactive intermediates **144** were generated through hydrogen transfer from compounds **143** to an ionic oxidant — 2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate (**145**) (Scheme 54).

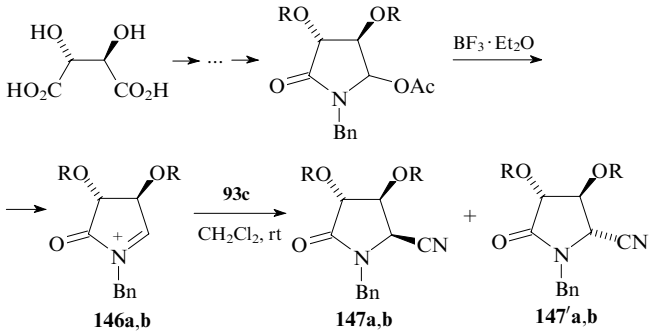
Scheme 54



(*a*) **93c**, MeCN, rt, 2 h; Y = CO_2Et, Cbz, Boc, Ts

A similar approach to the diastereoselective synthesis of 3,4-dihydroxyproline derivatives possessing diverse biological activities includes the cross-coupling of chiral N-acim **146a**,**b**, obtained from natural L-tartaric acid, with trimethylsilyl cyanide (**93c**) (Scheme 55).[84] It is important that the stereochemical outcome of the reaction depends on the protecting group R in the N-acim precursor: when R = TBS, a mixture with predominance of diastereomer **147a** (*dr* = 75 : 25) is formed in a total yield of 91%, while for R = Ac, diastereomer **147′b** predominates (99% yield, *dr* = 20 : 80).

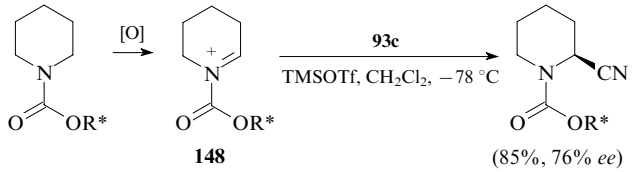
Scheme 55



R = TBS (**a**), Ac (**b**)

Chiral N-acim **148**, formed upon electrochemical oxidation of *N*-(8-phenylmethyloxycarbonyl)piperidine, was used as an intermediate in the diastereoselective cyanation of the piperidine ring (Scheme 56).[85] The enantiomeric excess of a reaction product reached 76%. This process is applicable to the synthesis of the anaesthetic drug ropivacaine[85] and

Scheme 56

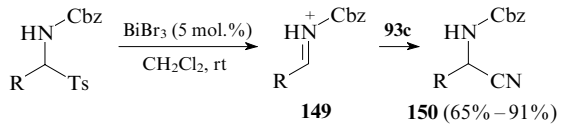


R* is 8-phenylmenthyl

analogues of streptomycin antibiotics containing a piperidinobenzodiazepine ring system.[86]

In the presence of the $BiBr_3$ catalyst, N-acim **149** were generated from α-amido *p*-tolyl sulfones; species **149** were further converted to N-acylated α-aminonitriles **150** — precursors of the corresponding α-amino acids (Scheme 57).[87]

Scheme 57



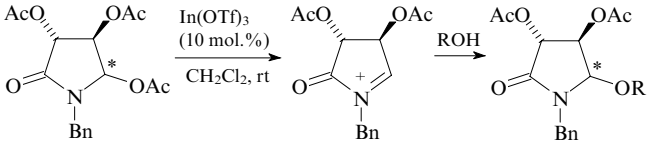
149 **150** (65% – 91%)

R = Ph, 4-$MeOC_6H_4$, 3-FC_6H_4, 3-ClC_6H_4, 2-Th, 2-Py, 2-Naph, cyclo-C_6H_{11}; Py is pyridyl

III.2. Reactions with heteroatomic nucleophiles

Heteroatomic (O- or N-containing) nucleophiles are used in cross-coupling reactions with N-acim much more rarely than C-nucleophiles. Reactions of this type include, in particular, the cross-coupling of chiral N-acim obtained from L-tartaric acid derivative **117** with alcohols in the presence of the $In(OTf)_3$ catalyst.[88] The major reaction products are *syn*-diastereomers of substituted pyrrolidin-2-ones **151**; however, the process diastereoselectivity depends considerably on the nucleophile used (*syn* : *anti* = 10 : 1 for R = All, but 10 : 7 for R = Bn or propargyl) (Scheme 58).

Scheme 58

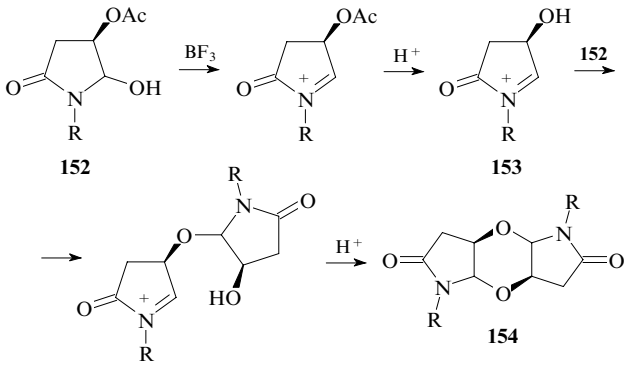


117 **146b** **151** (54% – 78%)

R = n-C_5H_{11} (*syn* : *anti* = 10 : 4), $HO(CH_2)_8$, Bn (10 : 7), All (10 : 1), $HC{\equiv}CH_2$ (10 : 7), Ph (10 : 2), 2-Naph (10 : 2)

Recently, an unusual C – O cross-coupling reaction was reported, in which the accessible substrate **152** functioned as both the C-electrophile and O-nucleophile.[89] This Brønsted acid-catalyzed reaction, which can formally be regarded as cyclodimerization, proceeds *via* the formation of N-acim **153** and leads to symmetrical 1,4-dioxanes **154** (Scheme 59).

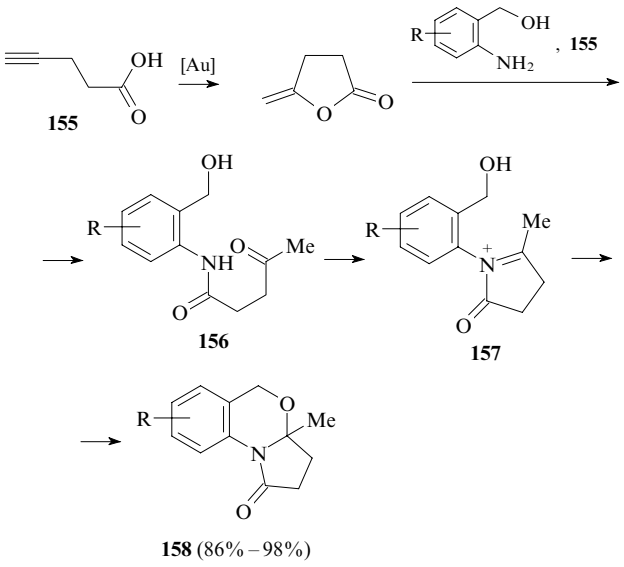
Scheme 59



R = Bn (88% yield), 4-$FC_6H_4CH_2$ (56%), Ph (80%), 4-$MeOC_6H_4$ (62%), 4-BrC_6H_4 (70%), 4-$O_2NC_6H_4$ (55%), $HC{\equiv}CCH_2$ (71%), $HO_2C(CH_2)_2$ (58%), EtC(O) (59%)

The Au-catalyzed tandem process comprising successive amidation of acetylenecarboxylic acid **155** with substituted *o*-aminobenzyl alcohols and cyclization of the resulting ketoamide **156** *via* the formation of N-acim **157** underlay the development of an efficient method for the synthesis of tricyclic pyrrolo[2,1-*b*]benzo[*d*][1,3]oxazinones **158** (Scheme 60; the positions of substituents are indicated for the initial alcohol).[90] It is important that the process is conducted as a one-pot procedure without isolation of intermediate compounds. The best results were obtained in THF in the presence of the catalyst [Au{PBu^t_2(*o*-biphenyl)}(MeCN)]SbF_6 (2 mol.%, 120 °C, 24 h). More recently it was shown that ketoamide **156** obtained *in situ* by an alternative method (from *o*-aminobenzyl alcohol and levulinic acid by the mixed anhydride method) can be converted to heterocycle **158** in 98% yield *via* the formation of N-acim **157** in the presence of a catalyst under milder conditions (THF, 20 °C, 24 h).[91]

Scheme 60



158 (86% – 98%)

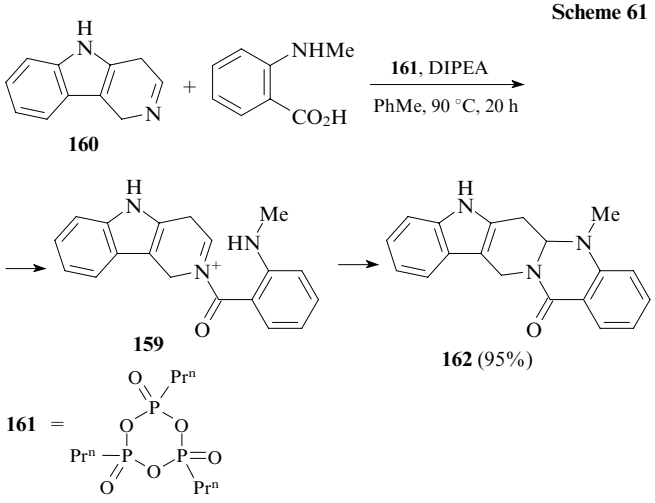
R = H, 4-Ph, 4-Cl, 4-F

Organic amino acids or their amides can serve as nucleophilic components in the cross-coupling reactions with N-acim; the role of N-nucleophile can be performed by either a free[92 – 94] or protected amino group.[95,96] The former option was implemented, in particular, in the intramolecular cross-coupling of N-acyliminium salt **159**, which was formed upon condensation of dihydrocarboline **160** with an anthranilic acid derivative in the presence of anhydride **161**.[92] Intermediate **159** plays a key role in the cascade synthesis of the natural alkaloid evodiamine **162** (Scheme 61), which is a topoisomerase I inhibitor.[9]

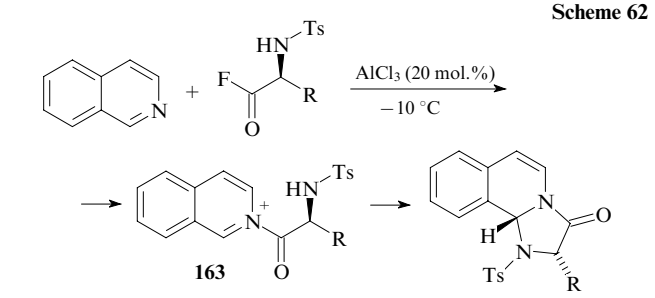
Meanwhile, in the case of isoquinoline N-acim **163**, the protected (tosylated) amino group of the amino acid moiety participates in the intramolecular cross-coupling as the N-nucleophile. In this case, tricyclic products **164** are formed in a moderate yield but with high diastereoselectivity (> 95%) (Scheme 62).[97]

Indole, which is usually utilized in the chemistry of N-acyliminium ions as a reactive π-nucleophile (see Section II.1.b) can act in some cases as an N-nucleophile. In particular, this opportunity was implemented in the enantioselective catalytic cross-coupling of indole derivatives with N-acim activated by acidic organocatalyst (*R*)-**165**-H.

Scheme 61



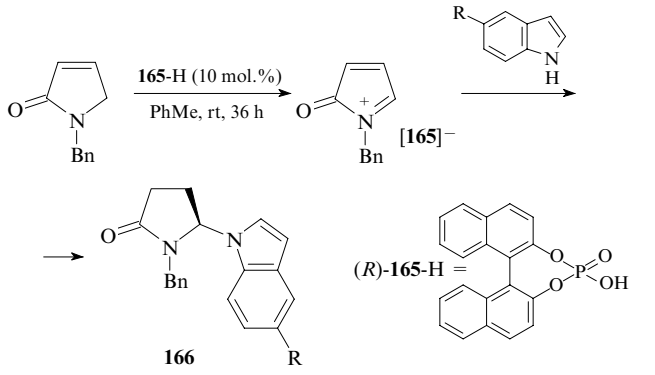
Scheme 62



R = Me, Pr^i, Bu^n

Products **166** are formed under mild conditions in 65% – 87% yield and with enantioselectivity of up to 90% (Scheme 63).[6]

Scheme 63



R = H (90% *ee*), Me (90% *ee*), OMe (90% *ee*), F (86% *ee*), Br (88% *ee*), Cl (90% *ee*)

* * *

The present review demonstrates a significant progress in the chemistry of N-acyliminium ions over the past decade. Novel diastereoselective and enantioselective catalytic methods for the synthesis of nitrogen-containing heterocyclic compounds *via* these reactive intermediates have been developed. Elegant cascade reactions and one-pot multicomponent transformations involving N-acyliminium ions have been elaborated, which are promising as green chemistry processes. Efficient catalytic versions of N-acim-mediated intramolecular arylation (Pictet – Spengler cyclization) and cross-coupling reactions with various nucleophiles have been designed and successfully applied for the synthesis of valuable natural compounds, particularly, alkaloids and their analogues. One can expect that the broad application of novel catalytic strategies, including asymmetric organocatalysis [98] and catalysis by metal complexes,[99] would provide further opportunities to take advantage of high synthetic potential of N-acyliminium ions in novel stereo- and enantioselective processes for the preparation of pharmaceutical drugs and other compounds with practically valuable properties.[100]

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