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ІНСТИТУТ ОРГАНІЧНОЇ ХІМІЇ НАН УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

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Recent advances in the asymmetric functionalization of *N*-(*tert*-butylsulfinyl)polyfluoroalkyl imines

Abstract

The review covers the latest achievements in the application of *N*-(*tert*-butylsulfinyl)polyfluoroalkyl imines in the asymmetric synthesis and summarizes stereochemical observations of their behavior in different types of reactions (reduction of the C=N bond, addition reactions with organometallic reagents, C-H acids, etc.). Fluorinated *N*-(*tert*-butylsulfinyl) imines are convenient substrates for obtaining enantiomerically enriched derivatives of polyfluoroalkyl amines, amino alcohols, amino acids, and heterocyclic systems. In recent decades, various approaches to their functionalization have been proposed. With this in mind, important aspects of their reactivity, regio- and stereochemistry have been systematized in this paper.

Keywords: *tert*-butylsulfinyl; polyfluoroalkyl imines; asymmetric synthesis; aldimines; ketimines; stereoselectivity

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Нові досягнення в асиметричній функціоналізації *N*-(*трет*-бутилсульфініл)поліфтороалкілімінів

Анотація

Огляд охоплює найновіші здобутки в застосуванні *N*-(*трет*-бутилсульфініл)поліфтороалкілімінів в асиметричному синтезі, а також узагальнює стереохімічні закономірності їхньої поведінки в різних типах реакцій (відновлення C=N зв'язку, приєднання металоорганічних реагентів, C-H кислот тощо). Фторовмісні *N*-(*трет*-бутилсульфініл)іміни є зручними субстратами для одержання на їх основі енантіомерно збагачених похідних поліфтороалкілімінів, аміноспиртів, амінокислот і азотовмісних гетероциклів. За останні десятиліття було запропоновано різноманітні підходи до їх функціоналізації. З огляду на це важливі аспекти щодо їхньої реакційної здатності, регіо- і стереохімії систематизовано в цій роботі.

Ключові слова: *трет*-бутилсульфініл; поліфтороалкіліміни; асиметричний синтез; альдиміни; кетиміни; стереоселективність

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■ Introduction

Since Ellman's group introduced chiral *N*-*tert*-butylsulfinyl amides into synthetic practice [1], the corresponding *N*-sulfinyl imines have also found a wide application in organic synthesis, providing access to a variety of optically active amines [2]. Among different *N*-sulfinyl imines, compounds with a polyfluoroalkyl substituent at the imine carbon atom deserve special attention. On the one hand, the introduction of a powerful electron-withdrawing polyfluoroalkyl group significantly increases the imine electrophilicity, promoting reactions with nucleophilic reagents. On the other hand, the presence of fluorine atoms can lead to significant changes in the physicochemical and biological properties of molecules compared to their non-fluorinated analogs [3–9].

Thus, *N*-(*tert*-butylsulfinyl)polyfluoroalkylimines can be convenient precursors of enantiomerically pure α-polyfluoroalkylamines, important chiral substrates for the preparation of different nonracemic fluorine-containing compounds. Great interest in this type of imines is confirmed by dozens of works in this area over the past decades, which were described, in particular, in reviews by prof. Soloshonok and co-authors in 2016–2018 [10, 11].

In the present review, we attempt to systematize and generalize the regularities of the asymmetric functionalization of *N*-(*tert*-butylsulfinyl) polyfluoroalkyl imines, including the experimental data obtained in recent years, which will allow for an effective prediction of the configuration of the newly created stereocenter and should stimulate the further development of this area of organic chemistry.

■ Results and discussion

1. Reduction of the azomethine bond of *N*-(*tert*-butylsulfinyl)polyfluoroalkyl imines

A stereoselective reduction of non-fluorinated *N*-(*tert*-butylsulfinyl)ketimines with sodium and lithium borohydrides was first determined in the late 2000s in the works of *Ellman et al.* [12, 13]. However, the possibility of involving α-polyfluoroalkyl imines in this reaction was demonstrated only a decade later on the example of α,β-unsaturated *N*-(*tert*-butylsulfinyl)ketimines **1** bearing a trifluoromethyl group (**Scheme 1**) [14].

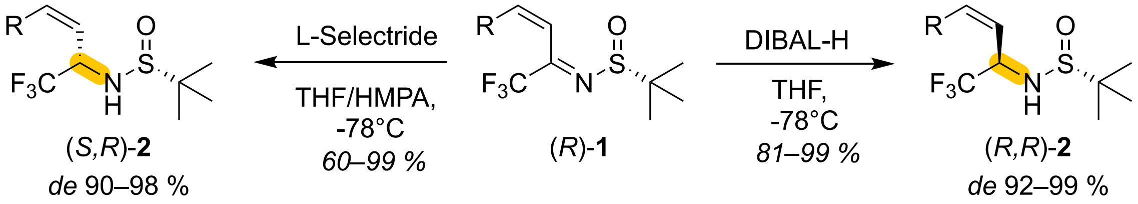
The screening of the spectrum of sodium or lithium borohydrides and aluminum hydrides ($NaBH_4$, $LiBH_4$, $NaBH_3CN$, CatBH, $LiAlH_4$, Red-Al, $LiBHEt_3$, L-Selectride) showed that the highest diastereoselectivity (90–99%) could be achieved when using DIBAL-H in THF and L-Selectride in a mixture of THF/HMPA (5:1) at –78°C.

N-(*tert*-butylsulfinyl)imines of trifluoroacetone and trifluoroacetophenones generated *in situ* were subjected to reduction, skipping the isolation step. According to this procedure, a series of imines of α-trifluoromethyl aryl and alkyl ketones were reduced with sodium borohydrides and L-Selectride with *de* up to 98% (**Scheme 2**, **Table 1**) [15–17].

Most likely, metal hydrides ($NaBH_4$, $LiBH_4$, $NaBH_3CN$, $LiAlH_4$, DIBAL-H) and organoboron compounds (CatBH) coordinate with the oxygen atom of the sulfinyl group, forming a closed transition state ***A***, which results in (*R*,*R*)-diastereomers of sulfinamides **4**. In turn, L-Selectride displays a worse propensity for the coordination and attack over the imine C=N bond occurs through the open transition state ***B***, leading to (*S*,*R*)-stereoisomer of sulfinamides **4** (**Scheme 3**) [15, 18].

The screening of reducing agents for chemo- and stereoselective reduction of the azomethine bond of *N*-*tert*-butylsulfinyl trifluoromethyliminoesters **5** also revealed similar dependence of the stereochemical outcome of the process on the nature of the reductant (**Scheme 4**, **Table 2**). The best results in terms of both chemo- and stereoselectivity were achieved when 9-borabicyclononane (9-BBN) was used as a reducing agent [19].

The hydrolysis of *N*-(sulfinyl)aminocarboxylate **6** gave an optically pure stereoisomer of



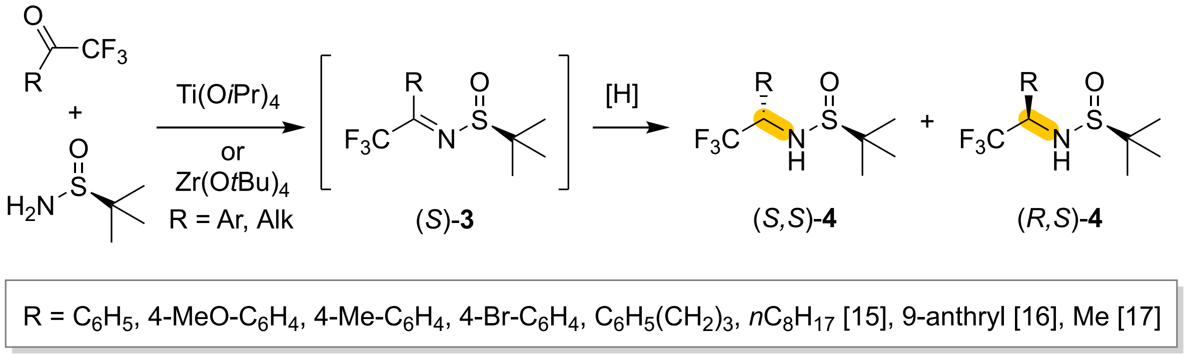
R = C_6H_5, 4-MeO-C_6H_4, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 2-MeO-C_6H_4, 3-Br-C_6H_4, 1-naphtyl, 2-furyl, $C_6H_5C{\equiv}C$, nC_8H_{17}, $C_6H_5(CH_2)_3$

Scheme 1. A stereoselective reduction of α,β-unsaturated *N*-(*tert*-butylsulfinyl)ketimines

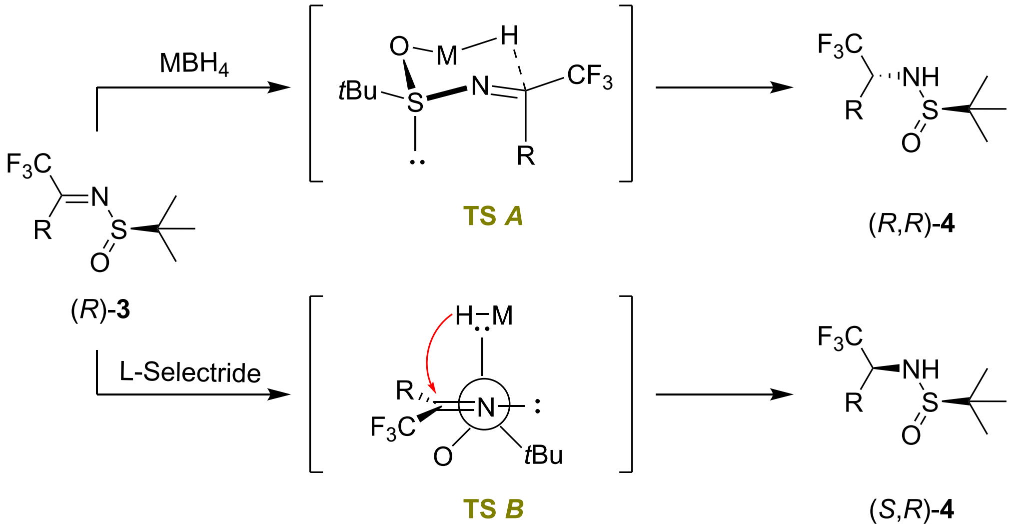
Table 1. The reduction of trifluoromethyl ketimines 3

R	[H]	Yield (%)	Product	*de* (%)
Ar	$NaBH_4$	66–85	(*S*,*S*)-**4**	90–98
	L-Selectride	60–84	(*R*,*S*)-**4**	92–98
Alk	$NaBH_4$	52–79	(*S*,*S*)-**4**	96–98
	L-Selectride	22–84	(*R*,*S*)-**4**	92–98
9-anthryl[a]	$LiBH_4$	71	(*S*,*S*)-**4**	97

Note: [a] The intermediate imine was chromatographically isolated in the individual state before the reduction



Scheme 2. The reduction of aryl- and alkyl trifluoromethyl ketimines

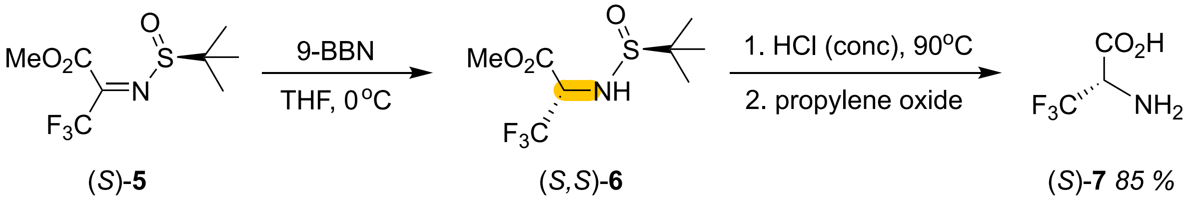


Scheme 3. Possible mechanisms of the reduction of the C=N bond of *N-tert*-butylsulfinyl trifluoromethyl ketimines

3,3,3-trifluoroalanine **7** – a biologically promising α-amino acid. The (*R*)-isomer of trifluoroalanine **7** was obtained similarly from sulfinamide (*R*,*R*)-**6**, the product of imine **5** reduction in (*R*)-configuration.

On the other hand, the reduction of imines **5** with a complex of borane with dimethyl sulfide proceeded with the involvement of the carboxylate function, in addition to the C=N bond [19]. It enabled a stereospecific preparation of synthetically attractive trifluoromethyl aminoethanols with either protected **8** or free amino group **9** (**Scheme 5**).

Thus, the ability to control chemo- and stereoselectivity by selecting the appropriate reducing agent allows for the synthesis of both stereoisomers

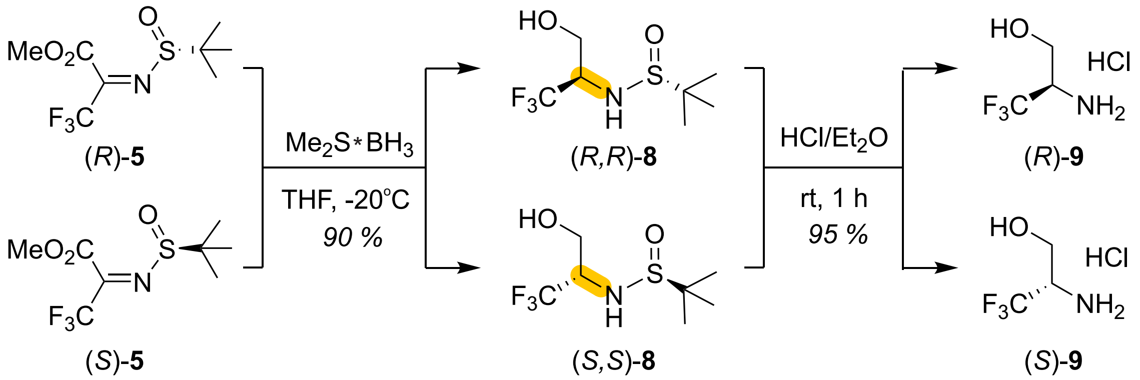


Scheme 4. A stereoselective reduction of the C=N bond of *N-tert*-butylsulfinyl trifluoromethyl iminopyruvates

Table 2. Reaction conditions for the reduction of C=N bond of iminopyruvate (*S*)-**5**

№	[H]	Conditions	(*S*,*S*)/(*R*,*S*)-**6**
1	$NaBH_4$	THF, –78°C	1:1.1
2	$NaBH(OCOCH_3)_3$	THF, rt	1:2
3	$LiBH_4$	THF, –78°C	1:2.4
4	CatBH	THF, –78°C	2.4:1
5	9-BBN	THF, 0°C	>99:1^{a}

Note: ^{a} (*R*,*S*)-**6** is absent according to ^{1}H and ^{19}F NMR data



Scheme 5. The complete reduction of *N*-*tert*-butylsulfinyl trifluoromethyl iminopyruvates

of various β-polyfluoroalkylamines, starting from one enantiomer of *N*-(*tert*-butylsulfinyl)polyfluoroalkyl imines.

2. Reactions of *N*-(*tert*-butylsulfinyl)polyfluoroalkyl imines with organometallic compounds

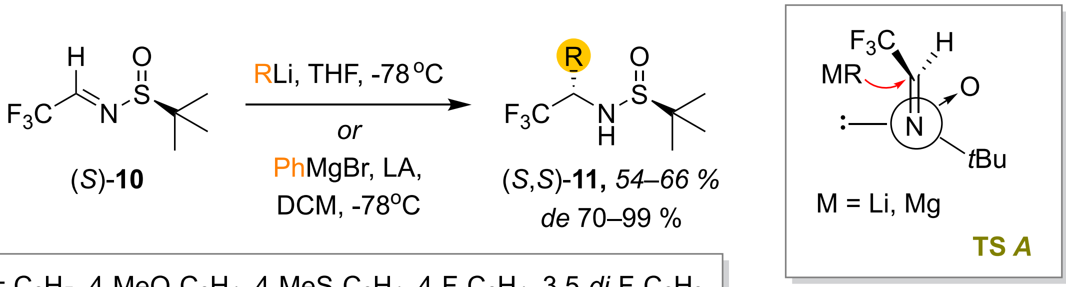
The addition of Li- and Mg-organic compounds to the azomethine bond of imines, including *N*-(*tert*-butylsulfinyl)imines, is a convenient method for forming a new C-C bond with the concurrent generation of a new stereogenic carbon atom. The interaction of imine of fluoral (*S*)-**10** (generated *in situ*) with phenylmagnesium bromide allowed one to obtain amines (*S*,*S*)-**11** with diastereoselectivity of 70% (**Scheme 6**). The selectivity increased with the addition of Lewis acids ($AlMe_3$, $AlEt_3$, $BF_3 \cdot Et_2O$, $TiCl_4$, $Mg(OTf)_2$), but it led to a general decrease in yields [20]. The addition of phenyl lithium (2.5 equiv., 2.5M solution in THF) to trifluoroacetaldimine (*S*)-**10** resulted in the formation of α-trifluoromethyl benzylamine (*S*,*S*)-**11** in the yield of 66% and with a significantly improved diastereomeric ratio (98:2) compared to the reaction with phenyl magnesium bromide. Various aryl lithium reagents were successfully involved in the reaction with imine **10** under optimal conditions (THF, –78°C) (**Scheme 6**). Later, it was shown that *N*-(*tert*-butylsulfinyl) imine of fluoral **10** purified by vacuum distillation demonstrated better yields (83% compared to 64%) in the reaction with PhLi [21]. The authors [20] attributed the stereochemical result obtained in both reactions to the formation of open transition state ***A*** in the course of the reactions (**Scheme 6**).

Similarly to aldimines, α,β-unsaturated *N*-(sulfinyl)ketimines (*R*)-**12** successfully reacted with aryl, alkyl, and alkynyl lithium reagents to provide α-polyfluoroalkyl allylamines (*S*,*R*)-**13** with good yields (48–99%) and diastereoselectivities (70–98%) (**Scheme 7**) [22].

The addition of (trimethylsilyl)ethynyl lithium to trifluoroacetaldimine (*S*)-**10** occurred with sufficiently high diastereoselectivity (*de* 86%), however, the yield of propargylamine (*R*,*S*)-**14** was only 33% [23]. At the same time, when *N*-(*tert*-butylsulfinyl)imine of fluoral (*R*)-**10** interacted with lithium arylacetylides generated in the presence of LiHMDS, the diastereomeric ratio varied from 52:48 to 70:30 (**Scheme 8**) [24].

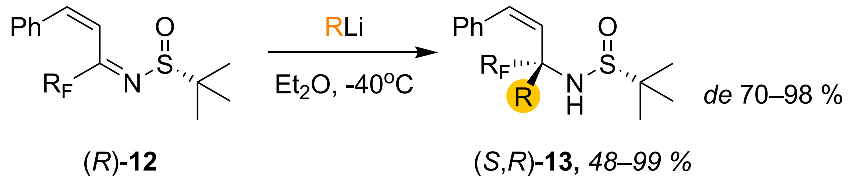
Significantly better results were obtained in the reaction of lithium acetylides (including those with a trimethylsilyl substituent) with α-trifluoromethylketimines **3** in the presence of titanium tetraisopropylate (**Scheme 9**). The corresponding α-trifluoromethyl-α-propargylamines (*R*,*S*)-**16** were obtained with yields from 56 to 97% and the diastereoselectivity of 98% [25].

The stereochemical result of the reaction of polyfluoroalkylaldimines **18** with propargyl



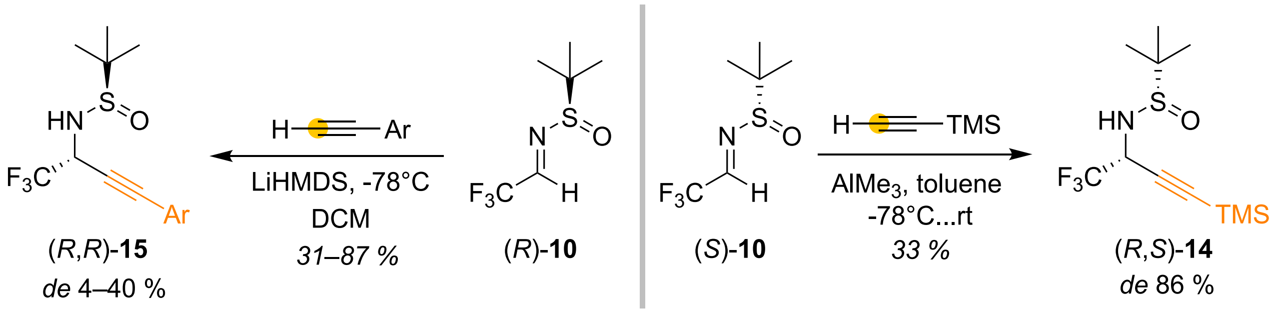
R = C_6H_5, 4-MeO-C_6H_4, 4-MeS-C_6H_4, 4-F-C_6H_4, 3,5-*di*-F-C_6H_3, 2-Me-C_6H_4, pyridin-2-yl

Scheme 6. The addition of propargyl magnesium bromide to N-(*tert*-butylsulfinyl)polyfluoroalkyl imines



R_F = CF_3, CHF_2, $CClF_2$, C_3F_5, C_5F_{11}
R = C_6H_5, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 3-Me-C_6H_4, 2-Me-C_6H_4, naphtyl, PhC≡C, *n*Bu

Scheme 7. The addition of Li-organic reagents to α,β-unsaturated *N*-(sulfinyl)ketimines



Ar = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-EtO-C_6H_4, 3-Me-C_6H_4, 4-Me-C_6H_4, 4-*t*Bu-C_6H_4, 4-(*n*-pentyl)-C_6H_4, 3-F-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 3-Br-C_6H_4, 4-Br-C_6H_4, 3-O_2N-C_6H_4

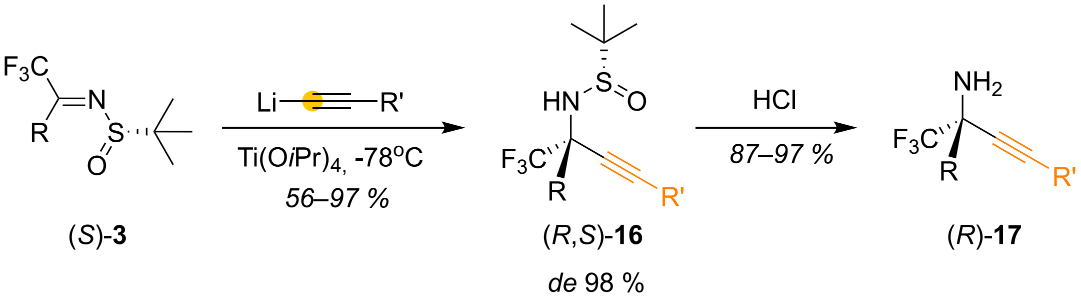
Scheme 8. *N*-(*tert*-butylsulfinyl)imine of fluoral in the reactions with Li-acetylides

magnesium bromide was found to be crucially dependent on the nature of the solvent, variating from *de* 12% (in DCM) to *de* 92–98% (in THF). α-Propargylamines (*S*,*S*)-**19** were used for further transformation into derivatives of terpene alkaloids **21** by the synthesis of enynes **20** and their subsequent cyclization by the Pauson-Khand reaction scheme [26]. Additionally, enynes **20** were introduced into the ruthenium-catalyzed metathesis yielding tetrahydropyridines **22** [27] (**Scheme 10**).

Lithiated thiazoles turned out to be convenient reagents for the nucleophilic addition to the azomethine bond of *N*-(sulfinyl)imine (*S*)-**10**. The optimal conditions (1.1 equiv. of LDA, THF, –78°C) were suitable for thiazoles annulated with an imidazole or 1,2,4-triazole ring and provided reaction products (*R*,*S*)-**23** with the yields of 61–72% and stereoselectivities reaching 99% (**Scheme 11**) [28, 29].

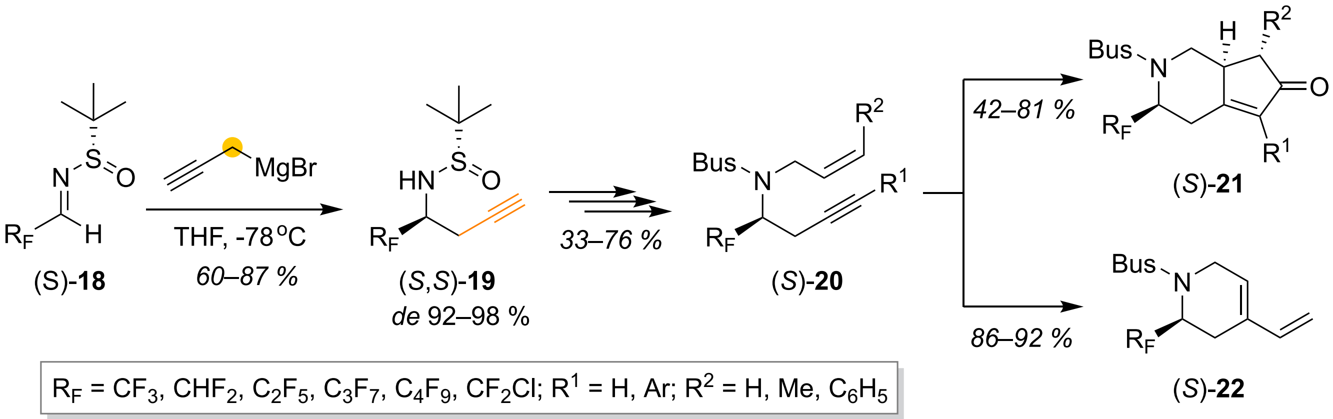
N-Sulfinyl imine of fluoral (*S*)-**10** also undergoes a zinc-initiated reaction with allyl and alkyl bromides to form the corresponding enantiomerically enriched sulfinamides (*S*,*S*)-**24** and (*S*,*S*)-**25** (**Scheme 12**) [21, 30]. The stereochemical result of the reaction is consistent with the open transition state previously proposed, which is similar to reactions with organomagnesium and organolithium reagents.

The interaction of α,β-unsaturated *N*-(*tert*-butylsulfinyl)ketimines (*R*)-**26** with ethyl bromoacetate in the presence of zinc occurred with a high regio- and chemoselectivity (**Scheme 13**) [31].



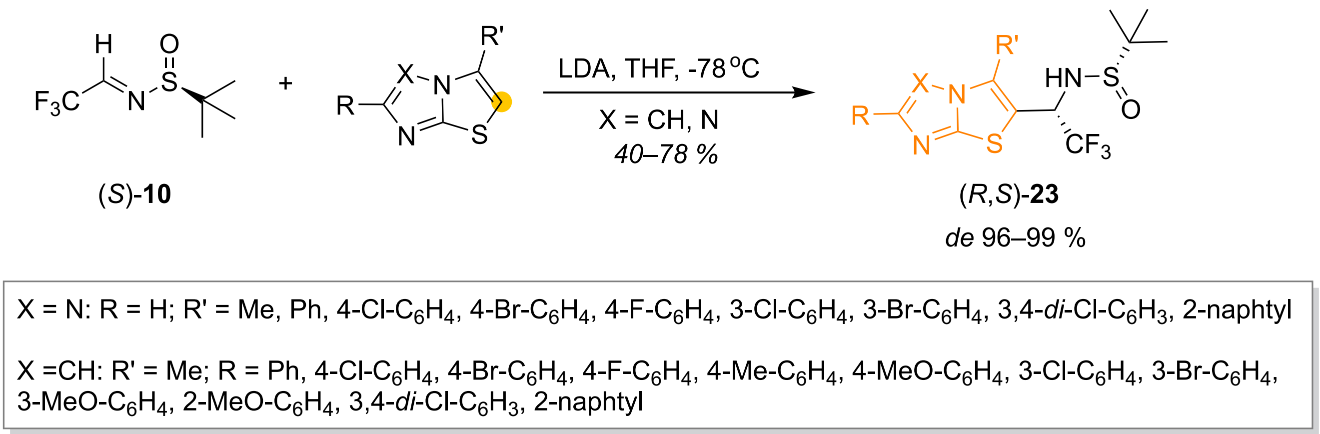
R = C_6H_5, 4-MeO-C_6H_4, 4-Cl-C_6H_4, *n*C_6H_{11}; R' = *n*Bu, *n*Hex, cyclopropyl, TMS, C_6H_5, CF_3

Scheme 9. *N*-(*tert*-butylsulfinyl)trifluoromethyl ketimines in the reaction with Li-acetylides



$R_F = CF_3, CHF_2, C_2F_5, C_3F_7, C_4F_9, CF_2Cl; R^1 = H, Ar; R^2 = H, Me, C_6H_5$

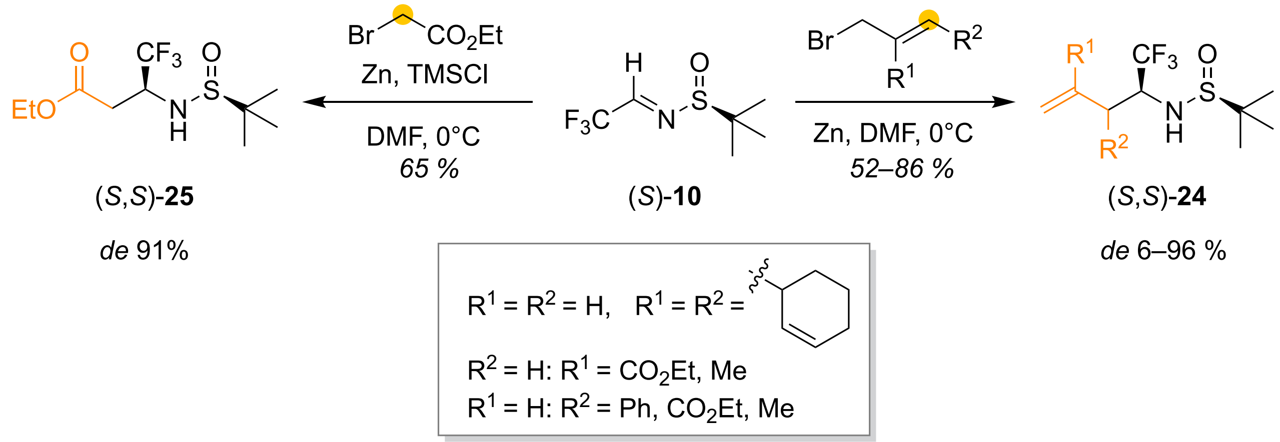
Scheme 10. The addition of propargyl magnesium bromide to *N*-(*tert*-butylsulfinyl)imine of fluoral



X = N: R = H; R' = Me, Ph, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 3-Cl-C_6H_4, 3-Br-C_6H_4, 3,4-*di*-Cl-C_6H_3, 2-naphtyl

X =CH: R' = Me; R = Ph, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 3-Cl-C_6H_4, 3-Br-C_6H_4, 3-MeO-C_6H_4, 2-MeO-C_6H_4, 3,4-*di*-Cl-C_6H_3, 2-naphtyl

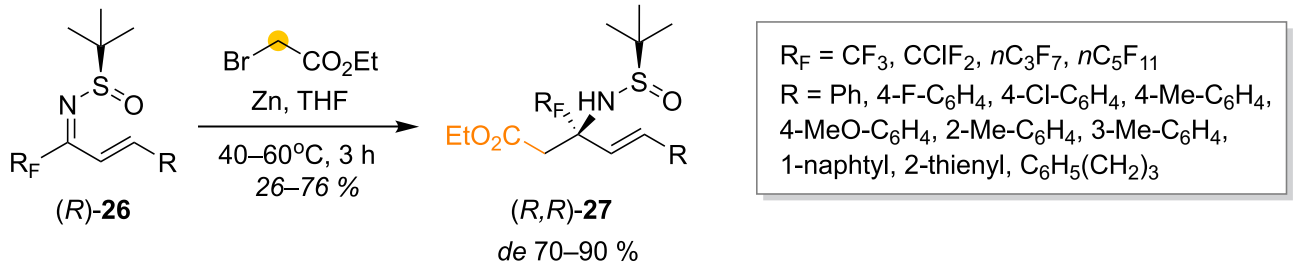
Scheme 11. The reaction of *N*-(*tert*-butylsulfinyl)imine of fluoral with lithiated thiazoles



$R^1 = R^2 = H$, $R^1 = R^2 =$

$R^2 = H: R^1 = CO_2Et$, Me
$R^1 = H: R^2 = Ph, CO_2Et$, Me

Scheme 12. *N*-(*tert*-butylsulfinyl)imine of fluoral in the Zn-mediated reactions with allyl and alkyl bromides



$R_F = CF_3, CClF_2, nC_3F_7, nC_5F_{11}$
R = Ph, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 2-Me-C_6H_4, 3-Me-C_6H_4, 1-naphtyl, 2-thienyl, $C_6H_5(CH_2)_3$

Scheme 13. *N*-(*tert*-butylsulfinyl)trifluoromethyl ketimines in the Zn-mediated reaction with ethyl bromoacetate

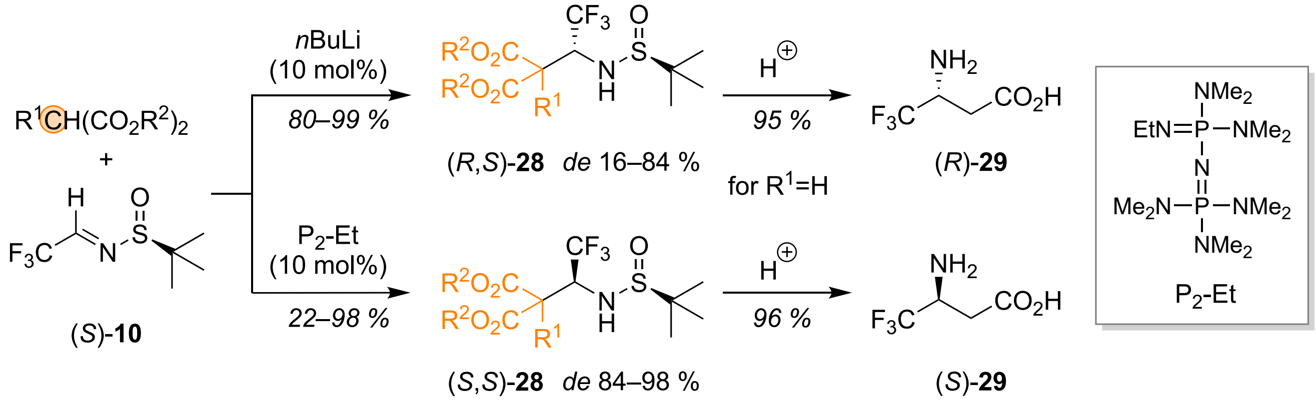
3. Reaction of *N*-(*tert*-butylsulfinyl)polyfluoroalkyl imines with CH-acids

The reaction of polyfluoroalkyl imines with esters of carboxylic acids is a convenient method for the synthesis of fluorine-containing compounds with a β-aminocarboxylic acid fragment. Thus, β-aminomalonates **28** were synthesized by the interaction of *N*-(*tert*-butylsulfinyl)imine of fluoral (*S*)-**10** with a number of dialkylmalonates (**Scheme 14**). The highest stereoselectivities were observed in the presence of *n*BuLi or sterically hindered phosphazene bases (P_2-Et). The products of the Mannich reaction with diethylmalonate were successfully transformed into optically pure β-trifluoromethyl-β-alanine enantiomers (*R*)- and (*S*)-**29** [32, 33].

Esters of β-trifluoromethyl-β-amino acids can be obtained directly, without an additional decarboxylation step, by the reaction of imines with alkyl acetates in the presence of LDA. (*S*,*S*)-diastereomer **30** was formed stereospecifically (*de*>99%). The removal of the sulfinyl group and the subsequent cyclization with a substituted thiourea yielded tetrahydro-6-oxo-pyrimidine (*S*)-**31**, a potential β-secretase inhibitor currently studied as a medicine for the treatment of Alzheimer's disease (**Scheme 15**) [34].

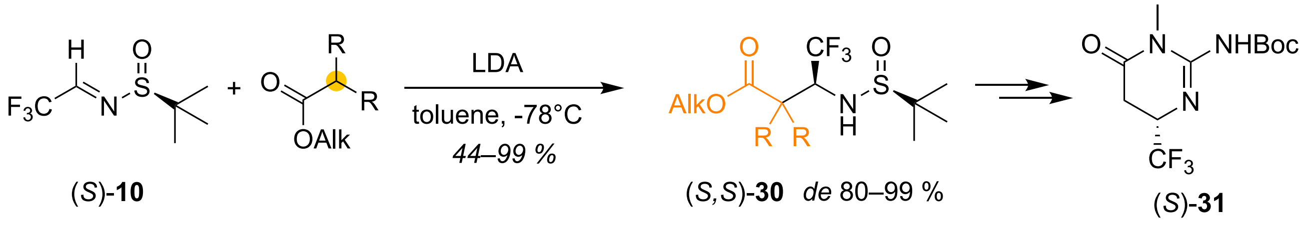
Derivatives of methylsulfonic and phosphonic acids also undergo the reaction with *N*-(*tert*-butylsulfinyl)imines **10** in the presence of strong bases (**Scheme 16**) [35, 36].

N-*tert*-butylsulfinyl polyfluoroalkyl aldimines **18** were successfully involved in the *aza*-Henry reaction with nitromethane under mild conditions. The study of various factors, such as the nature of the base, solvent, temperature and the



R¹ = H, Me, F; R² = Me, Et, *i*Pr, *t*Bu, Bn

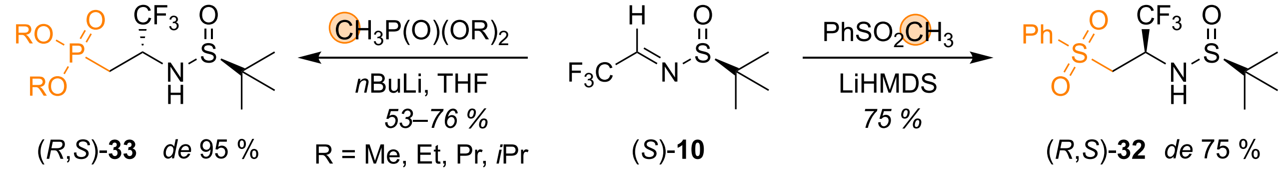
Scheme 14. The reaction of *N*-(*tert*-butylsulfinyl)imine of fluoral with dialkylmalonates



R = H, Me, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2O(CH_2)_2-$, $-CH_2CH{=}CHCH_2-$

Alk = Me, Et, Pr, *i*Pr,Bu, *i*Bu, *t*Bu, CH_2Ph, allyl, $CH_2C_6H_4Me$, $CH_2C_6H_4OMe$

Scheme 15. The reaction of *N*-(*tert*-butylsulfinyl)imine of fluoral with alkyl acetates



Scheme 16. The reaction of *N*-(*tert*-butylsulfinyl)imine of fluoral with derivatives of sulfonic and phosphonic acids

sequence of the reagent addition, showed that the best chemo- and stereoselectivity of the reaction with imine of fluoral were achieved when the reaction was carried out in DMSO in the presence of 0.1 equiv. of Hünig's base (**Scheme 17**) [37].

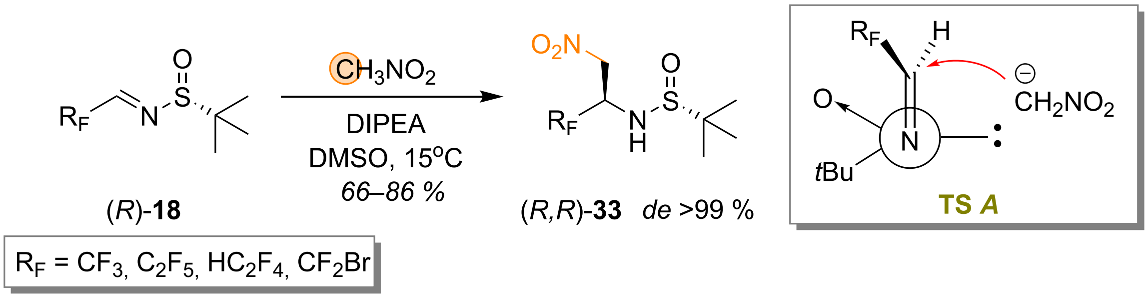
The reaction of *N*-(*tert*-butylsulfinyl)imines of trifluoropyruvate **5** with nitromethane in the presence of quinine allowed for obtaining enantiomerically pure α-trifluoromethyl substituted α-amino-β-nitrocarboxylates **34** (**Scheme 18**) [19].

The study of the effect of the reaction conditions on the stereoselectivity of the process showed that the nature and amount of the base had a crucial impact on the diastereomeric excess of the products. In particular, the transition from stronger (Hünig's base) to weaker (quinine) bases led to a complete reversal of the stereochemical outcome of the reaction explained by the occurrence of two different mechanisms with open and closed transition states (**Scheme 19**).

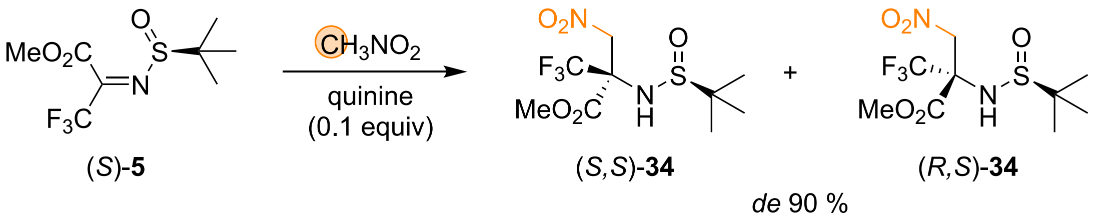
The addition of ketones to fluorinated *N*-(*tert*-butylsulfinyl)imines provides access to another class of optically active compounds – β-amino-ketones **35** – precursors of nitrogen-containing heterocycles, 1,3-diamines, γ-aminoalcohols, and other polyfunctional compounds. However, the yields and diastereomeric excess vary widely depending on the nature of the substituents in the aromatic ring of both imines and ketones (**Scheme 20**) [38].

Recent experimental data have shown that the nature of an organometallic base and a solvent has a significant influence on the result of the addition of ketones to the azomethine. The best results in terms of yields and stereoselectivity in the reaction of trifluoromethyl ketimine (*S*)-**3** with *p*-tolylethan-1-one and methyl acetate were achieved when using KHMDS (**Scheme 21**) [39].

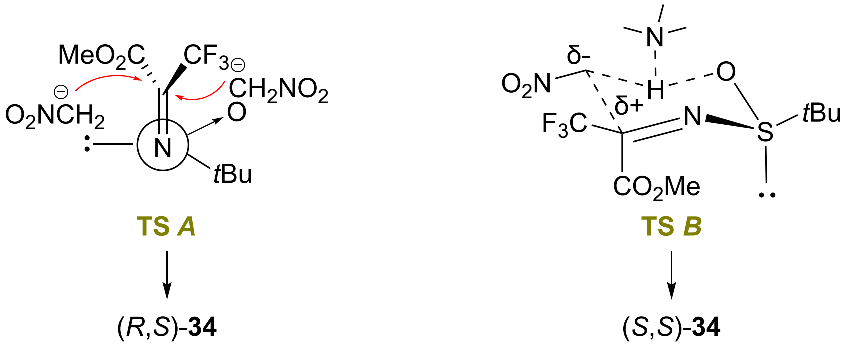
However, it turned out that the addition of *tert*-butyl acetate and *tert*-butyl acetoacetate to *N*-(sulfinyl)-α-fluoromethylaryl imines (*R*)-**38** led to the opposite stereochemical result, and in the case of the reaction with (*R*)-imine **38**, the newly created stereocenter has (*S*)-configuration (**Scheme 22**) [40–42].



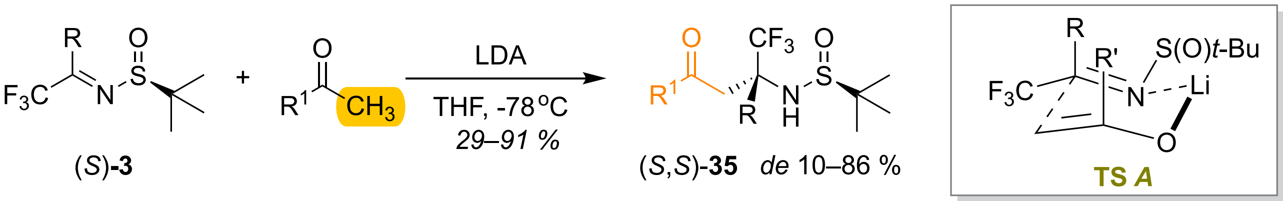
Scheme 17. The addition of nitromethane to *N*-(*tert*-butylsulfinyl)polyfluoroalkyl aldimines



Scheme 18. The addition of nitromethane to *N*-*tert*-butylsulfinyl trifluoromethyl iminoesters

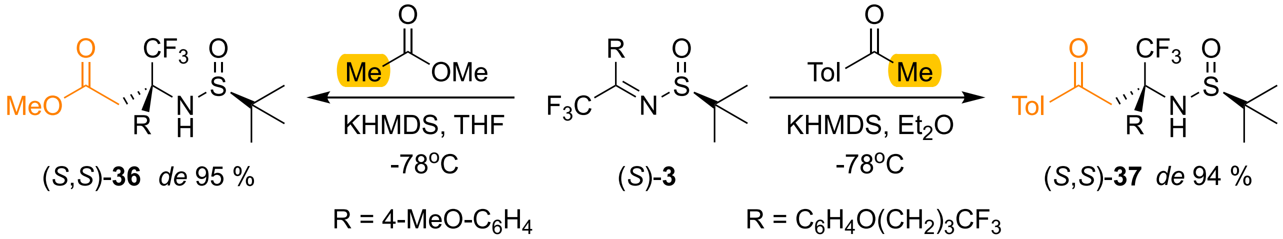


Scheme 19. Possible transition states of the nitromethane addition to N-*tert*-butylsulfinyl imines of trifluoropyruvate

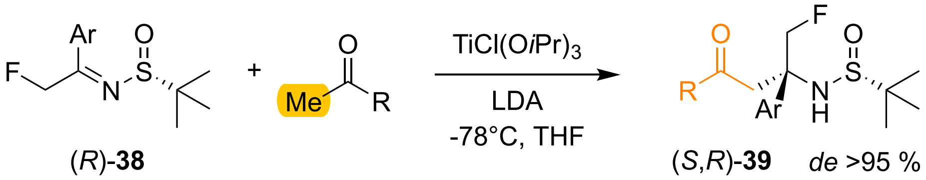


R = Ph, 4-MeO-C_6H_4, 4-Cl-C_6H_4
R^1 = Ph, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 2-Me-C_6H_4

Scheme 20. The reaction of *N*-*tert*-butylsulfinyl trifluoromethyl ketimines with ketones



Scheme 21. The reaction of *N*-*tert*-butylsulfinyl trifluoromethyl ketimines with *p*-tolylethan-1-one and methyl acetate



R = O*t*Bu, CH_2CO_2*t*Bu; Ar = 2-F-C_6H_4, 2-F-4-Br-C_6H_3

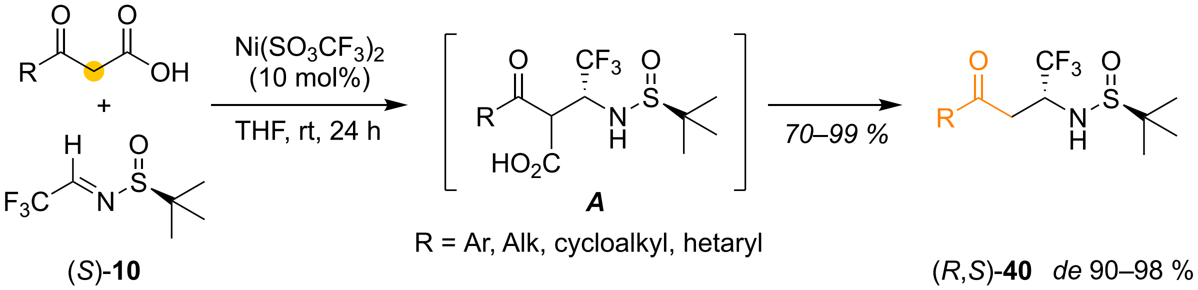
Scheme 22. The reaction of *N*-*tert*-butylsulfinyl fluoromethyl ketimines with ketones and alkyl acetates

The reaction of imine **10** with β-ketoacids in the presence of Lewis acids makes it possible to obtain a wide range of products **40** with alkyl, cycloalkyl, aryl, and hetaryl substituents attached to the oxo-group. The decarboxylation of the intermediate adduct ***A*** at the last step of the process was confirmed by a mass spectrometric study of the reaction mixture (**Scheme 23**) [43].

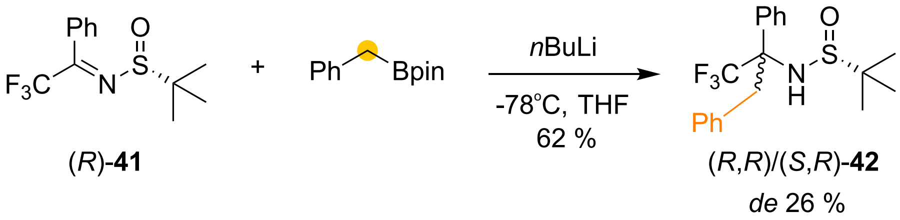
In 2019, the addition of a derivative of boronic acids – benzylboropinacolate – to the C=N bond of *N*-(*tert*-butylsulfinyl)imine of trifluoroacetophenone (*R*)-**41** (**Scheme 24**) was reported for the first time [44, 45]. Similarly to other classes of esters, anion was generated in the presence of a strong base (*n*BuLi) [46]. The reaction proceeded with a good yield, but with a low stereoselectivity (*de* 26%), and unfortunately, the configuration of the major diastereomer was not determined.

The interaction of imine (*S*)-**10** with the lithium enolate of indanone apparently occurred as a nucleophilic attack in the open transition state (**Scheme 25**, TS ***A***), which was consistent with previous observations for aldimines [47].

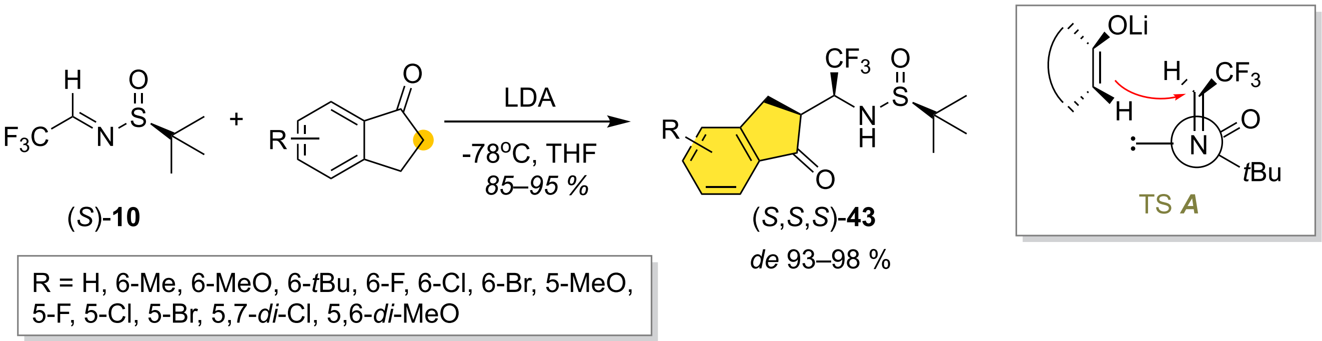
The reaction of aldimine **10** with indanone containing a thiocyanate group led to the formation of both the product of the conventional Mannich nucleophilic addition **44** and the spirocyclic



Scheme 23. The Lewis acids-mediated addition of β-ketoacids to *N*-*tert*-butylsulfinyl imine of fluoral



Scheme 24. Boropinacolates as CH-acids in the addition reaction with *N-tert*-butylsulfinyl trifluoromethyl ketimines



Scheme 25. The addition of ring-substituted indanones to *N-tert*-butylsulfinyl imine of fluoral

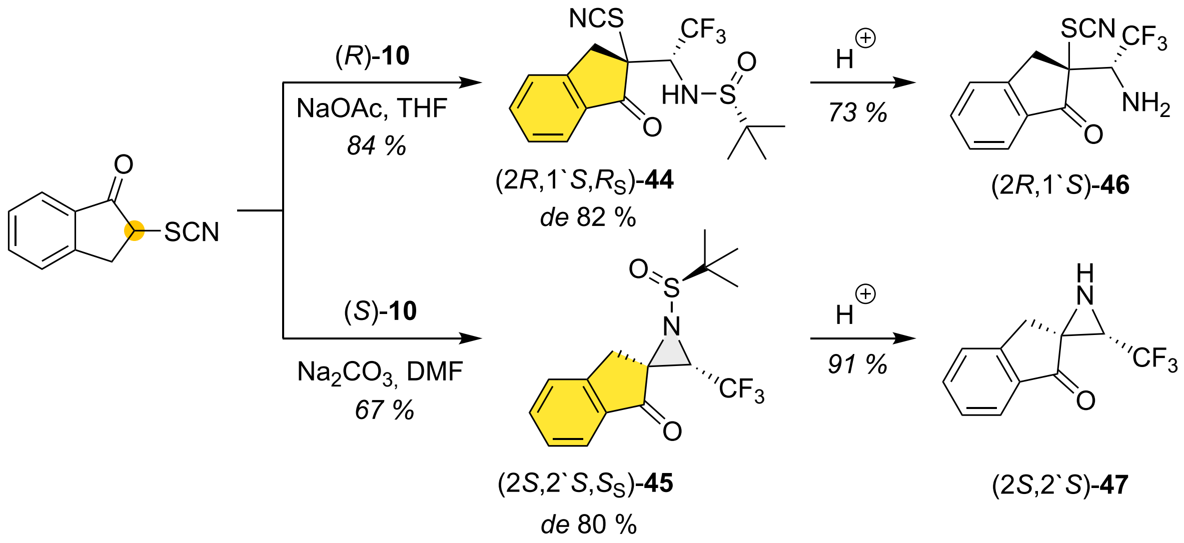
aziridine **45**, which was the result of nucleophilic substitution of the thiocyanate group. The screening of various bases showed that the percentage of aziridine **45** increased with the increase in basicity of the inorganic salt. Replacing the solvent with a more polar DMF facilitating the intramolecular nucleophilic cyclization gave the cyclic product **45** with high chemoselectivity. It is also important that mild conditions for the removal of the sulfinyl group enabled the synthesis of the unprotected aziridine **47** without the destruction of the spirocyclic part of the molecule (**Scheme 26**) [48].

The possibility of using cyclic amides (indol-2-ones) in the Mannich reaction with trifluoroacetaldimine **10** was demonstrated in 2014. The nature of the base has a decisive influence on conversion rates and diastereomeric excess, and lithium bases (LDA, LiHMDS, *n*BuLi) provide the best results (**Scheme 27**) [49].

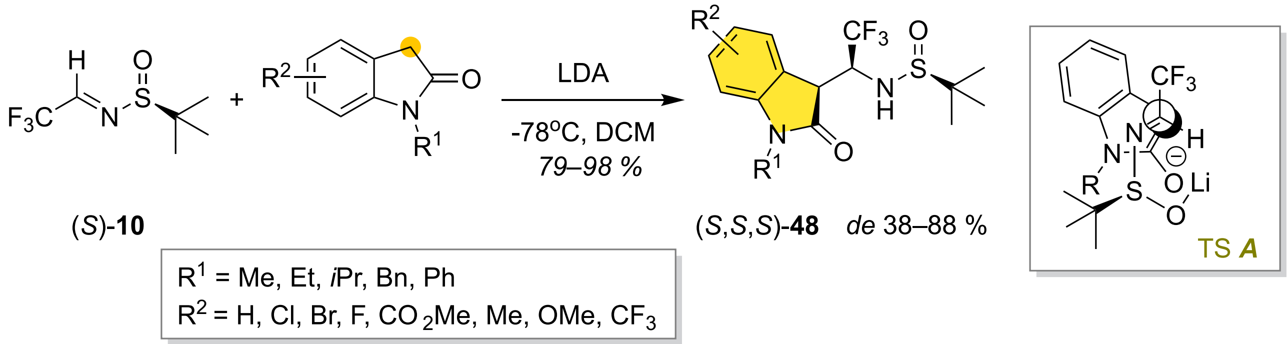
Stabilized α,α-difluoroenolates obtained by the cleavage of the C-C bond of the corresponding α-fluorinated *gem*-diols reacted with imine (*S*)-**10** under mild conditions with a high chemo- and stereoselectivity with the formation of optically active β-amino ketones (*S*,*S*)-**49** (**Scheme 28**) [50, 51].

This method has been proven to be effective for the synthesis of optically pure quaternary α-fluoro-β-ketoamines containing a C-F stereogenic center (**Scheme 29**) [52].

The asymmetric addition of trifluoromethyl *gem*-diols to chiral imines (*R*)-**18** also provided α-difluoroalkyl-β-aminosulfones (*S*,*R*)-**51**. A detailed screening of the reaction conditions showed

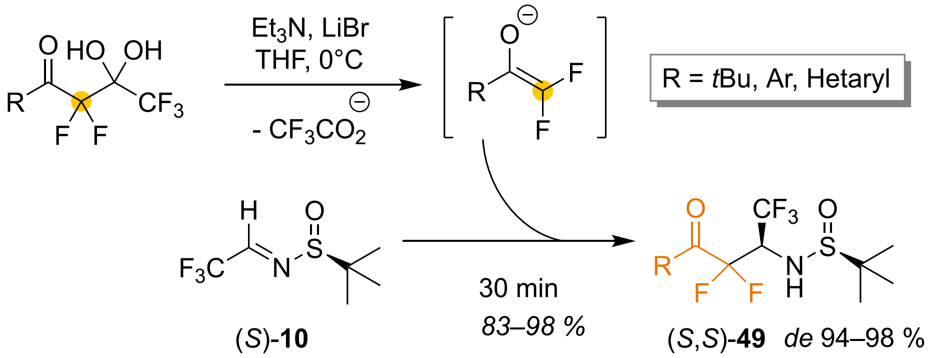


Scheme 26. Different pathways of the *N*-(*tert*-butylsulfinyl)trifluoroacetaldimine reaction with 2-thiocyanoindanone

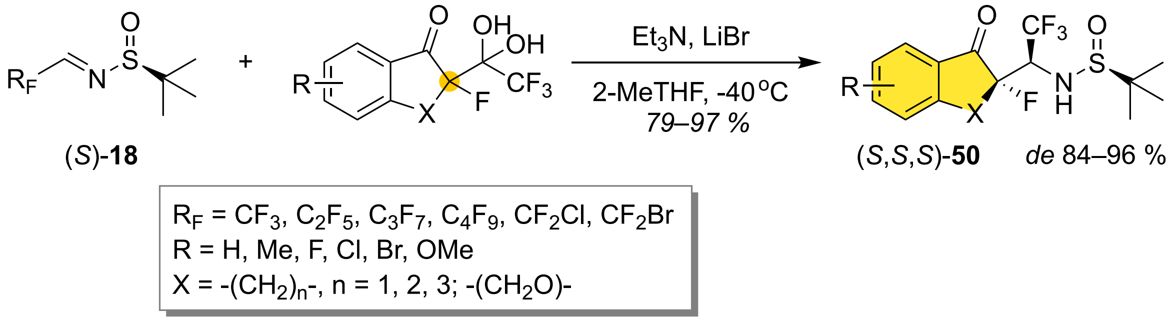


R^1 = Me, Et, *i*Pr, Bn, Ph
R^2 = H, Cl, Br, F, CO_2Me, Me, OMe, CF_3

Scheme 27. The addition of indol-2-ones to *N*-*tert*-butylsulfinyl imine of fluoral



Scheme 28. *N*-(*tert*-butylsulfinyl)trifluoroacetaldimine in the detrifluoroacetylative Mannich reaction



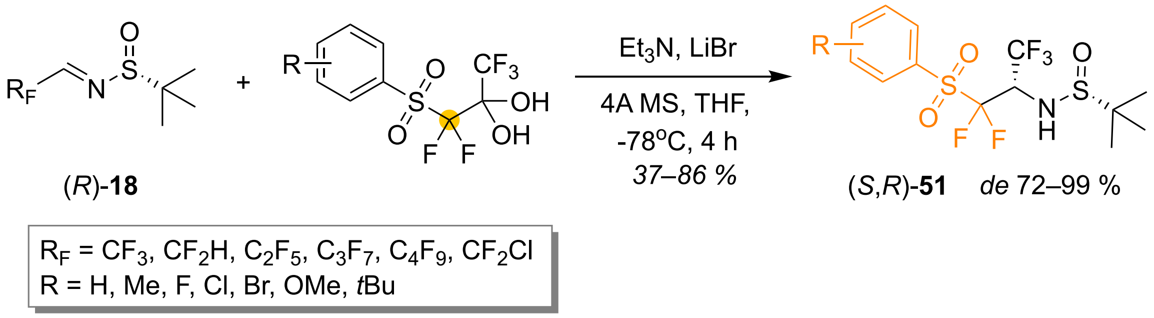
R_F = CF_3, C_2F_5, C_3F_7, C_4F_9, CF_2Cl, CF_2Br
R = H, Me, F, Cl, Br, OMe
X = $-(CH_2)_n-$, n = 1, 2, 3; $-(CH_2O)-$

Scheme 29. The detrifluoroacetylative Mannich reaction in the synthesis of quaternary α-fluoro-β-ketoamines

that the optimal values of yields and diastereomeric excess were achieved only when the reaction time was extended to 4 hours (**Scheme 30**) [53].

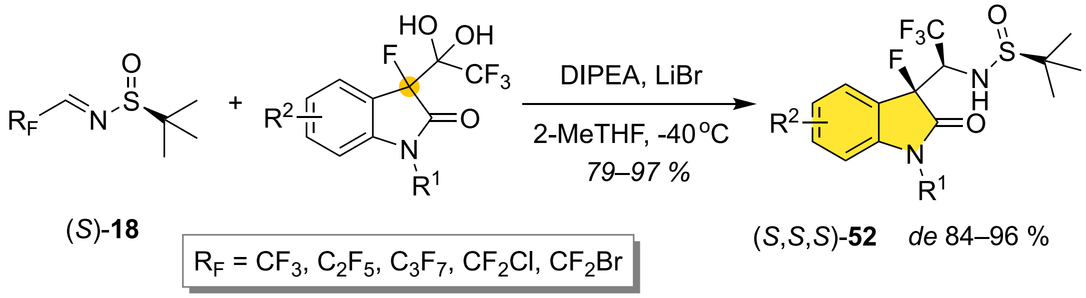
A similar method was applied to 3-fluoroindoline-2-one derivatives, which also formed fluorinated enolates under the action of a mixture of Hünig's base and lithium bromide (**Scheme 31**) [54].

It is known that 2-alkylpyridines can be used as CH-acids in functionalizations with carbonyl compounds and imines under catalysis by Brønsted or Lewis acids [55–57]. The use of optically active *N*-(*tert*-butylsulfinyl)polyfluoroalkyl imines (*S*)-**18** allowed for the preparation of enantiomerically enriched functionalized pyridines (*S*,*S*)-**53** (**Scheme 32**) [58].

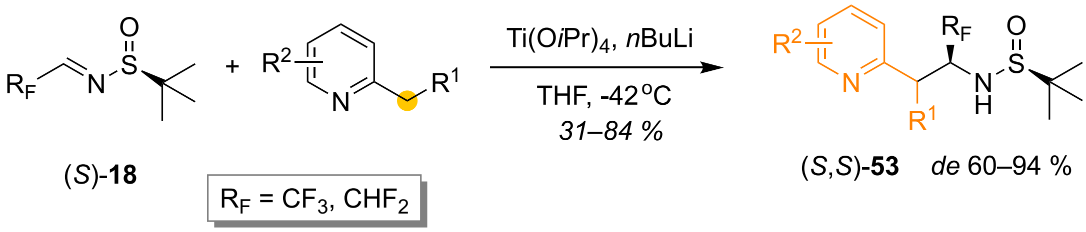


R_F = CF_3, CF_2H, C_2F_5, C_3F_7, C_4F_9, CF_2Cl
R = H, Me, F, Cl, Br, OMe, *t*Bu

Scheme 30. The detrifluoroacetylative Mannich reaction in the synthesis of α-difluoroalkyl-β-aminosulfones



Scheme 31. Fluoroindolinones in the detrifluoroacetylative Mannich reaction with *N*-*tert*-butylsulfinyl polyfluoroalkyl aldimines

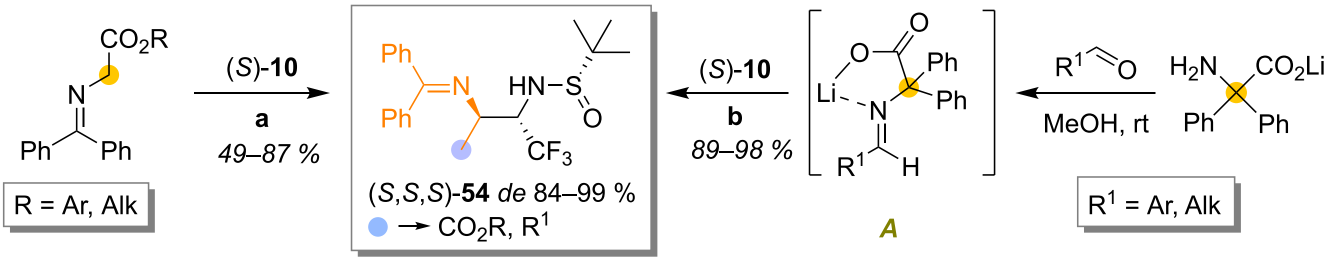


Scheme 32. 2-Alkylpyridines as CH-acids in the addition reaction with *N*-*tert*-butylsulfinyl polyfluoroalkyl aldimines

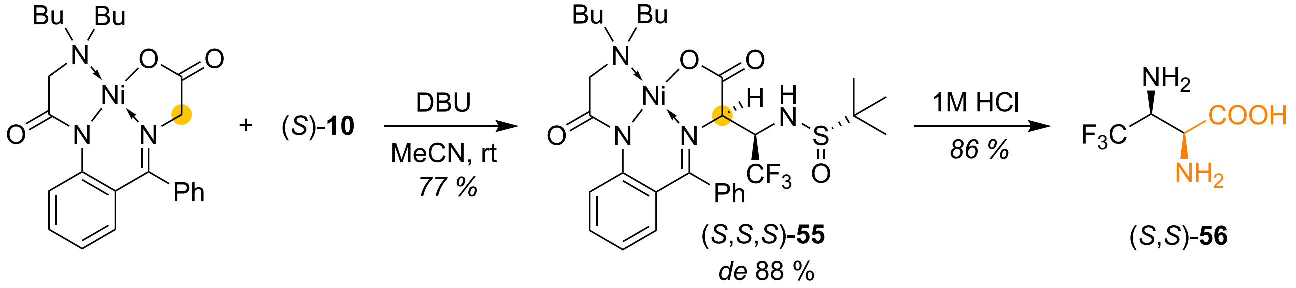
N-(*tert*-Butylsulfinyl)imine of fluoral **10** successfully reacted with enolates of glycine esters in the presence of organic (Et_3N, DMAP, DBU, LiHMDS, *t*BuOLi) and inorganic (K_2CO_3 and Cs_2CO_3, NaOH) bases. The best yields (*49–87%*) and diastereoselectivity (84–98%) were achieved when using 0.1 equiv. of Cs_2CO_3 in THF at room temperature (**Scheme 33**, path **a**) [59]. Another approach to compound **54** involves obtaining Schiff bases *in situ* by the interaction between lithium 2,2-diphenylglycine carboxylate and aldehydes (**Scheme 33**, path **b**). In the next step, intermediate ***A*** reacts with trifluoroacetaldimine **10** under the catalysis by *p*- or *m*-nitrobenzoic acid with the formation of the corresponding diamines [60].

β-Trifluoromethyl-α,β-diamino acid (*S*,*S*)-**56** was synthesized by the reaction of *N*-(sulfinyl) imine of fluoral (*S*)-**10** with the nickel complex of Schiff bases and the subsequent destruction of the resulting complex **55** by hydrochloric acid (**Scheme 34**) [61].

N-(*tert*-Butylsulfinyl)polyfluoroalkylaldimines (*S*)-**18** entered the Lewis acid catalyzed reaction with vinylogous carbonyl compounds – silylated dienolates, and the regiochemistry of the addition depended on the nature of the catalyst. Thus, when $AgBF_4$ was used, the Mannich reaction in the α-position of the enolate occurred, giving β-amino-β-fluoroalkyl-α-vinyl esters (*R*,*S*)-**57**. The stereochemical result of the process can be



Scheme 33. *N*-*tert*-butylsulfinyl imine of fluoral in the synthesis of trifluoromethyl-substitured vicinal diamines



Scheme 34. *N*-*tert*-butylsulfinyl imine of fluoral in the synthesis of β-trifluoromethyl-α,β-diamino acids

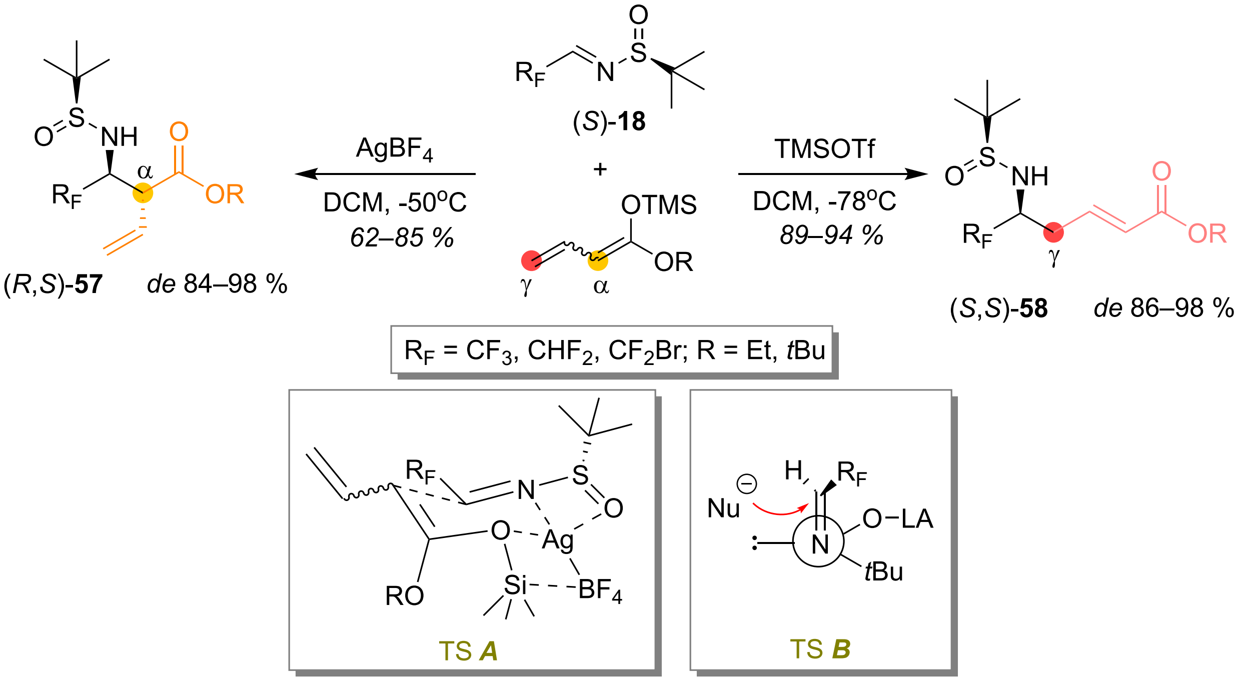
related to the formation of chelated TS ***A***, in which the metal atom is coordinated with two oxygen atoms (of enolate and sulfinyl groups) and a nitrogen atom, and as a result, an "α-product" with the (*R*,*S*)-configuration is formed. In the case of the catalysis by TMSOTf, the γ-addition takes place, resulting in α,β-unsaturated aminoesters (*S*,*S*)-**58**. Assumably, the oxygen atom of the sulfinyl group coordinates with the sterically hindered trimethylsilyl cation forming an open TS ***B*** (**Scheme 35**) [62, 63].

3-Alkenyl-2-oxoindoles reacted with polyfluoroalkylaldimines (*S*)-**18** under the catalysis by organometallic bases (LDA, KHMDS), thus giving γ-addition products **59** in the (*S*,*S*)-configuration (**Scheme 36**) [64].

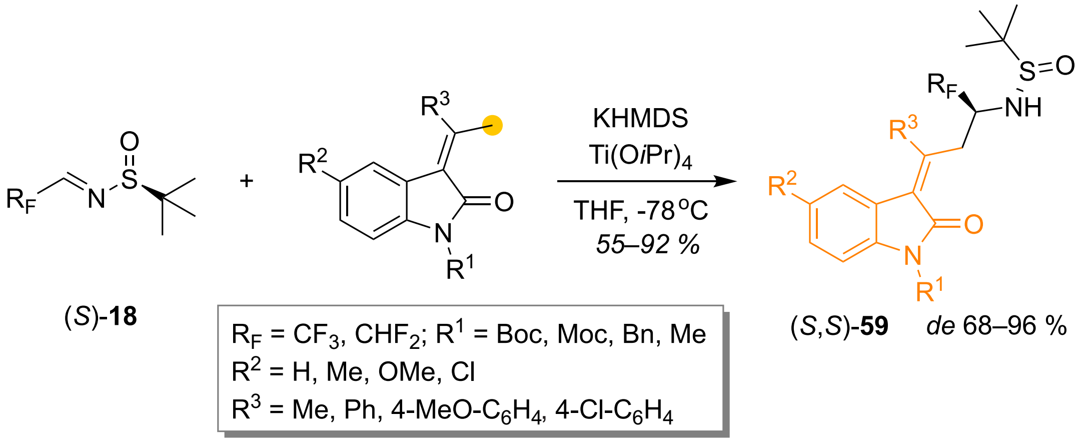
In contrast to reactions with silyldienolates and oxoindoles, the interaction of imines (*S*)-**18** with α,α-dicyanoalkenes led to (*R*,*S*)-isomers of γ-products **60**. This is explained by the formation of TS ***A***, in which the metal atom of the enolate chelates with the nitrogen atom of the aldimine, leading to the *Re*-face addition (**Scheme 37**) [65].

The use of heterocyclic siloxides (furan and pyrrole derivatives) in the addition reactions to imines (*S*)-**18** resulted in non-racemic γ-butenolides **62** and γ-butyrolactams **61** It was found that when the reaction was carried out in a low polar solvent (DCM) in the presence of TMSOTf, the process occurred regio- and stereoselectively (**Scheme 38**) [62, 66].

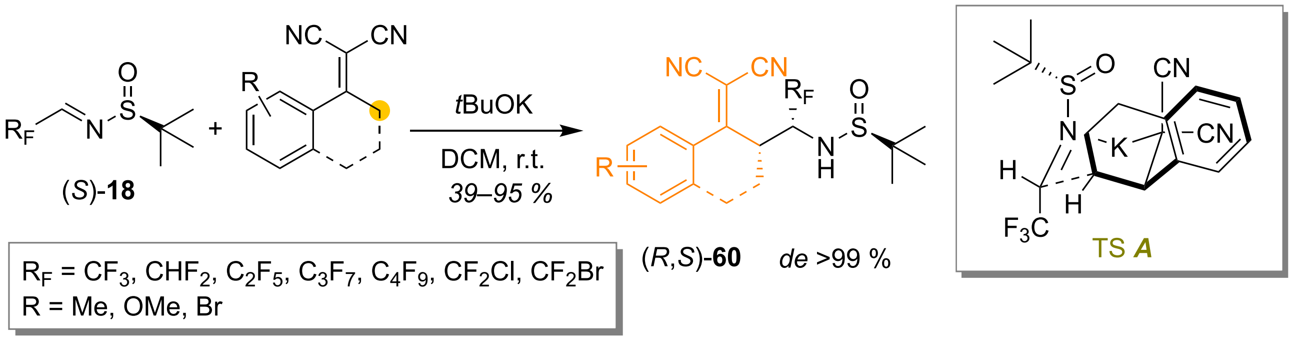
The reaction of aldimines (*S*)-**18** with indoles occurred chemo- and stereoselectively in the presence of $BF_3 \cdot Et_2O$ (in DCM) or LDA (in THF) and led to compounds **63** bearing an indole nucleus and the pharmacophoric 2,2,2-trifluoro-1-aminoethyl function (**Scheme 39**) [67–69].



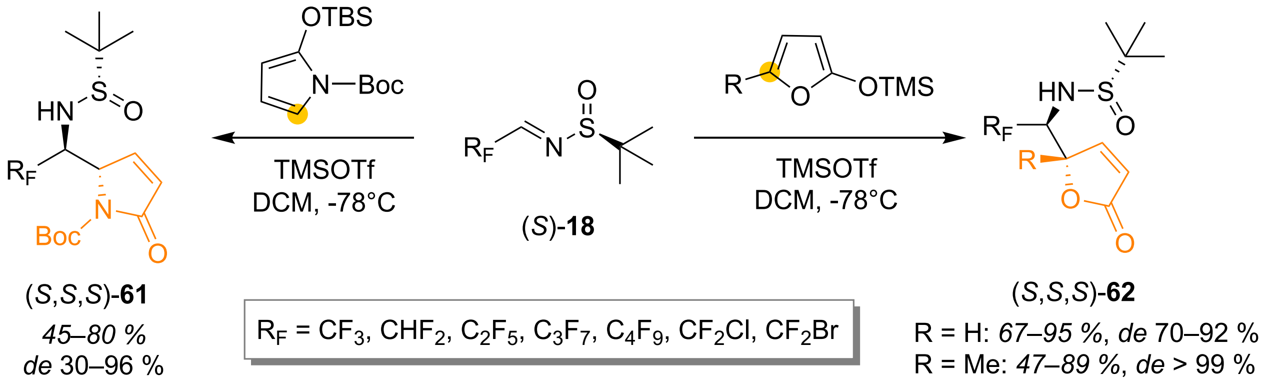
Scheme 35. Different pathways of the silylated dienolates addition to *N*-*tert*-butylsulfinyl polyfluoroalkyl aldimines



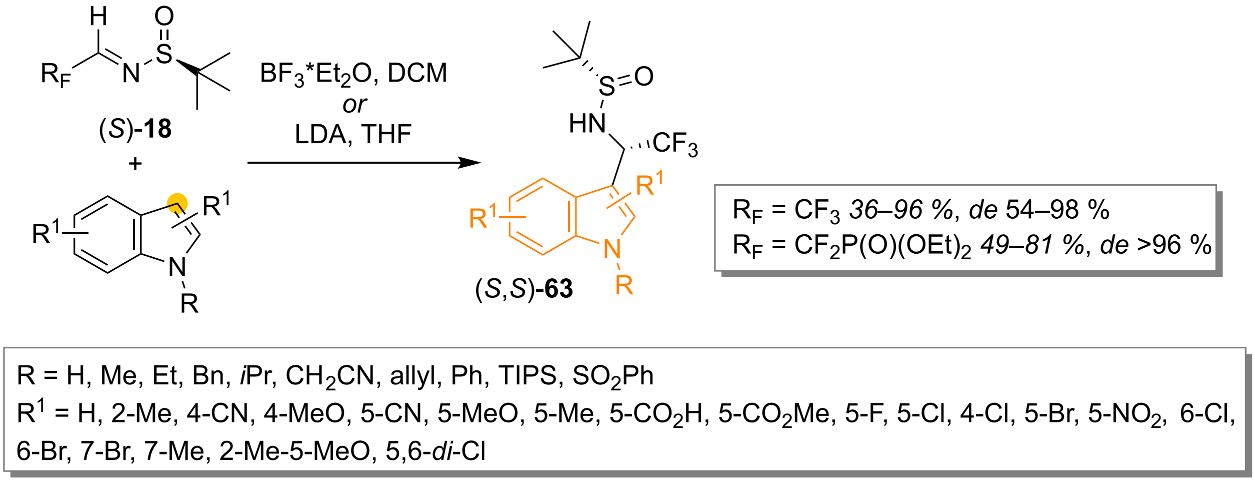
Scheme 36. The vinylogous Mannich reaction of 3-alkenyl-2-oxoindoles with *N*-*tert*-butylsulfinyl polyfluoroalkyl aldimines



Scheme 37. α,α-Dicyanoalkenes in the vinylogous Mannich reaction with *N*-*tert*-butylsulfinyl polyfluoroalkyl aldimines



Scheme 38. Siloxy-derivatives of furan and pyrrole in the addition reaction with *N*-*tert*-butylsulfinyl polyfluoroalkyl aldimines

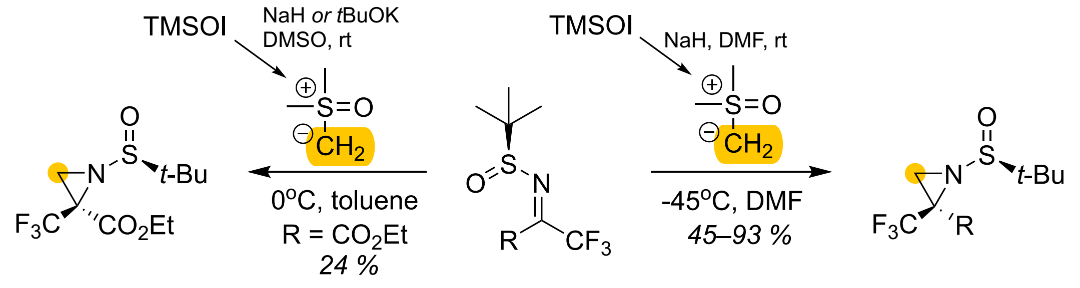


Scheme 39. The reaction of *N*-*tert*-butylsulfinyl polyfluoroalkyl aldimines with functionalized indoles

The *aza*-Corey-Chaykovsky reaction is a convenient method for the construction of an aziridine ring, which is an important moiety in synthetic chemistry. Thus, cyclization of a series of trifluoromethyl ketimines **3** with dimethylsulfoxonium methylide occurred successfully with both alkyl and aryl ketimines, and with a high stereoselectivity led to (*R*,*S*)-2-trifluoromethylaziridines **64** [70]. The introduction of *N*-(*tert*-butylsulfinyl)imine of trifluoropyruvate into the *aza*-Corey-Chaykovsky reaction allowed to synthesize 2-trifluoromethyl-2-ethoxycarbonylaziridine (*S*,*S*)-**65**, an interesting substrate for the synthesis of α-aminocarboxylic acid derivatives (**Scheme 40**) [71].

4. Other types of reactions using *N*-(*tert*-butylsulfinyl)polyfluoroalkyl imines

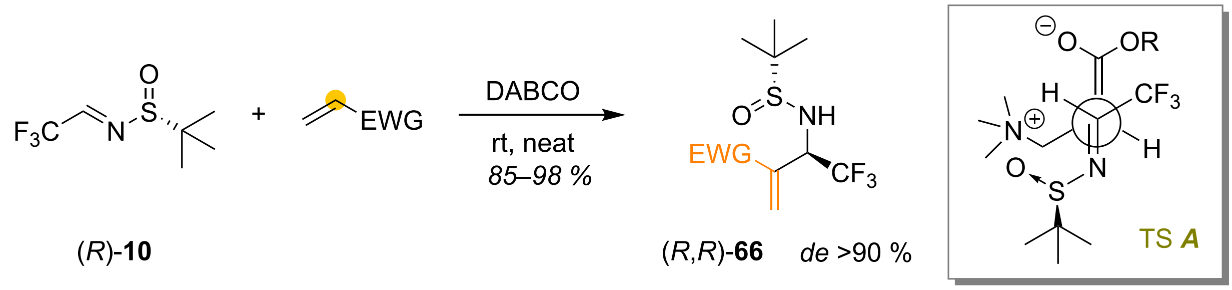
The *aza*-Baylis-Hillman reaction is a convenient method for the preparation of α-methylene-β-amino acids. The introduction of *N*-(*tert*-butylsulfinyl)imine of fluoral (*R*)-**10** in the reaction provided high yields and diastereoselectivity (>90%) even with 10 mol% of a catalyst (**Scheme 41**) [72]. It is worth noting that the stereochemical result, namely the (*R*)-configuration of the new stereocenter, differs from the reaction with non-fluorinated



(S,S)-**65** *de* >99 % (S)-**3** (R,S)-**64** *de* 72–99 %

R = $CH_2(CH_2)_9CH_3$, Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$CF_3C_6H_4$, C≡C-1-(5-MeO)naphtyl, C≡C-1-(3,4-ClC_6H_3)

Scheme 40. The *aza*-Corey-Chaykovsky reaction of *N*-*tert*-butylsulfinyl trifluoromethyl ketimines in the synthesis of 2-trifluoromethylaziridines



(R)-**10** (R,R)-**66** *de* >90 %

EWG = CO_2Me, CO_2*t*Bu, C(O)Me, CN

Scheme 41. The *aza*-Baylis-Hillman reaction of activated alkenes with *N*-(*tert*-butylsulfinyl)imine of fluoral

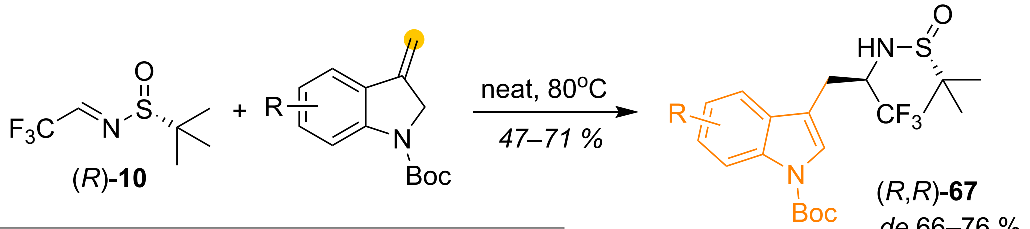
analogs [73, 74], which supports the conclusion that the process proceeds as an attack in the open TS *A* as in most reactions with polyfluoroalkyl aldimines.

Several enantiomerically enriched α-(trifluoromethyl)tryptamines were synthesized by the "ene" reaction with imine (R)-**10**. The reaction proceeded with a high stereoselectivity regardless of the substituents in the indole ring and led to the predominant formation of the (R,R)-stereoisomer **67** (**Scheme 42**) [75].

Lithiated ethyl and butyl vinyl ethers successfully reacted with polyfluoroalkyl aldimines (S)-**18** giving optically enriched amines **68** with a high diastereoselectivity (**Scheme 43**). The configuration of the product was assumed to be (S,S) based on previous observations for these types of interactions [76].

The addition of hydrophosphoryl compounds to optically pure *N*-(*tert*-butylsulfinyl)imines of fluoral or trifluoromethyl ketones leads to derivatives of polyfluoroalkyl-substituted α-aminophosphonic acids. Thus, the reaction of diethyl phosphite and imine (S)-**10** occurred in the presence of potassium carbonate to give products **69** with good yields (65%) and stereoselectivity (*de* 76%). Replacing hydrophosphoryl compounds with their synthetic equivalents, trimethylsilyldialkylphosphites generated *in situ* allowed to significantly improve diastereoselectivity (68–88%), while the diastereomeric ratio increased in the series R = Me < Et ≈ Pr < i-Pr (**Scheme 44**) [77].

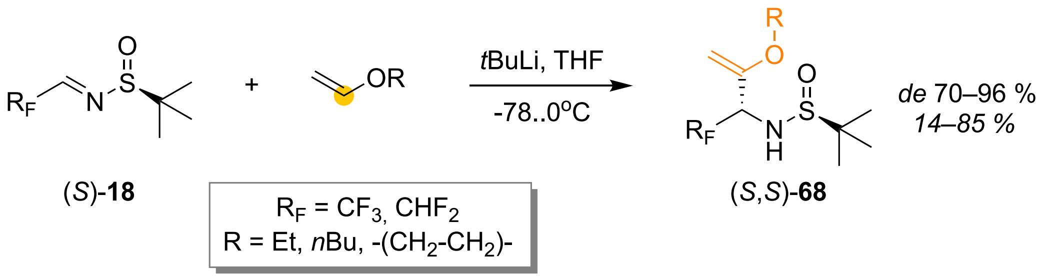
Trifluoromethylketimines (R)-**70** also enter the reaction with phosphites under catalysis by $Ti(OiPr)_4$ [78]. The reaction is effective for both



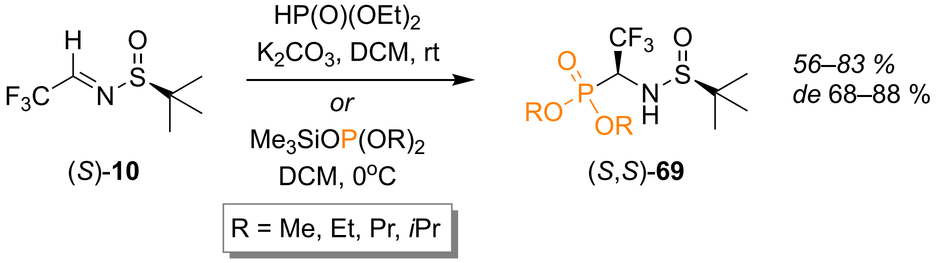
(R)-**10** (R,R)-**67** *de* 66–76 %

R = 5-H, 5-Me, 5-OMe, 5-Cl, 5-F, 5-CF_3, 6-CF_3

Scheme 42. The uncatalyzed diastereoselective "ene" reaction of *N*-(*tert*-butylsulfinyl)trifluoroacetaldimine



Scheme 43. The reaction of lithiated vinyl ethers with *N*-*tert*-butylsulfinyl polyfluoroalkyl aldimines

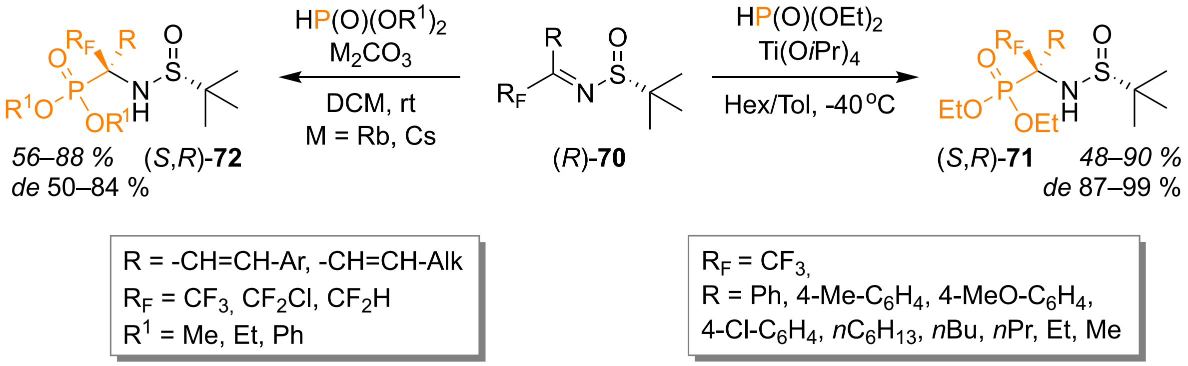


Scheme 44. *N*-(*tert*-butylsulfinyl)imines of fluoral in the asymmetric synthesis of α-trifluoromethyl α-aminophosphonic acids

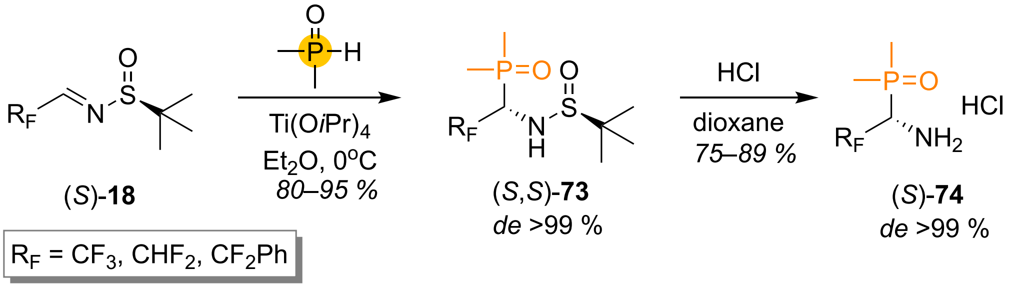
alkyl and aryl ketimines and leads to the formation of α-trifluoromethylaminophosphonates (*S*,*R*)-**71** with a stereoselectivity from 87 to 99%. Although, in contrast to the reaction with imine of fluoral, the use of K_2CO_3 in the reaction with polyfluoroalkyl ketimines did not lead to the desired product, its replacement with stronger inorganic bases, in particular rubidium and cesium carbonates, was proved to be more successful [79]. As a result, non-racemic adducts (*S*,*R*)-**72** were obtained with yields from 56 to 88% and a high diastereoselectivity (**Scheme 45**).

By the addition of dimethylphosphine oxide to imines (*R*)-and (*S*)-**18** in the presence of Ti(O*i*Pr)$_4$, enantiomerically pure α-amino-α-polyfluoroalkyl dimethylphosphine oxides **73** were synthesized in high yields and an excellent stereoselectivity. Upon deprotection, water-soluble optically pure amino-substituted dimethylphosphine oxides **74** were isolated in the form of hydrochloride salts (**Scheme 46**) [80].

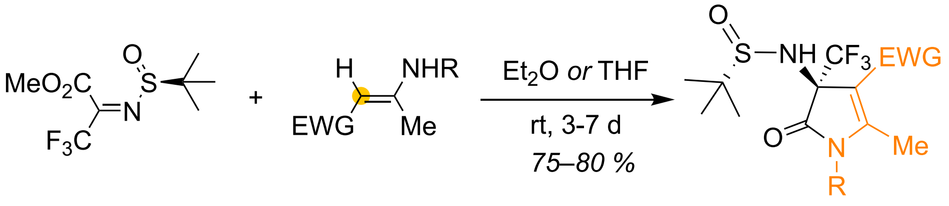
Functionalized pyrrolones (*S*,*S*)-**75** were obtained from the imine of trifluoropyruvate (*S*)-**5** by the cyclocondensation with various push-pull



Scheme 45. The addition of phosphites to *N*-*tert*-butylsulfinyl trifluoromethylketimines



Scheme 46. The Ti-mediated addition of dimethyl phosphine oxide to *N*-*tert*-butylsulfinyl polyfluoroalkyl aldimines

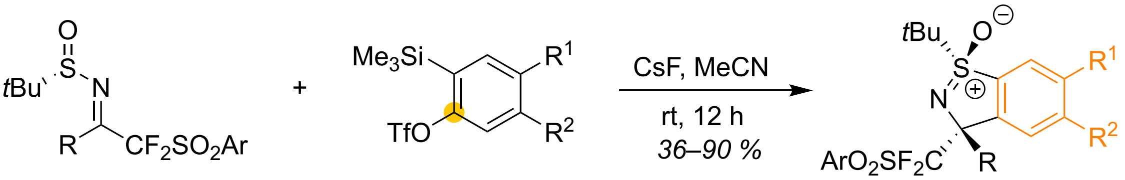


(S)-**5**

(S,S)-**75a–c**
de 70–90 %

a: EWG = CO$_2$Et, R = H; **b**: EWG = CO$_2$Me, R = Me;
c: EWG = CN, R = H

Scheme 47. Push-pull enamines in the reaction with *N-tert*-butylsulfinyl trifluoromethyl iminopyruvates



(S)-**76**

77

(R,S)-**78** *de* >99 %

Ar = Ph: R = Ph, 3-Me-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 3-MeO-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 4-CF$_3$-C$_6$H$_4$, 6-Br-2-naphtyl, (*E*)-styryl, *i*Pr; R^1, R^2 = H, Me, MeO; R^2+R^3 = -(CH$_2$)$_3$-; R^2 = Me, R^3 = H

Ar = 2-pyridyl: R = Ph, 3-Me-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 3-MeO-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 4-CF$_3$-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 4-Ph-C$_6$H$_4$, naphtyl, (*E*)-styryl, *i*Pr; R^1, R^2 = H; R^2 = Me, R^3 = H; R^2 = H, R^3 = Me; R^2+R^3 = naphtyl

Scheme 48. The stereoselective [3+2] cycloaddition of *N-tert*-butylsulfinyl ketimines to arynes

enamines, with diastereoselectivity dependent on the nature of substituents in the enamine molecule (**Scheme 47**) [19].

A series of optically pure cyclic sulfoximines **78** was obtained by the interaction of ArSO$_2$CF$_2$-sulfinyl imines (S)-**76** with trimethylsilylphenyl triflates **77**, the cycloaddition occurred stereospecifically to give diastereomer in (R,S_S)-configuration, meaning that the configuration of the stereogenic sulfur atom was preserved [81, 82] (**Scheme 48**).

■ Conclusions

The analysis of the asymmetric functionalization of the azomethine bond of *N*-(*tert*-butylsulfinyl)polyfluoroalkyl imines allows us to conclude that the stereoresult of the reactions is determined both by the structure and geometry of the imine and by the reaction conditions (the nature of the solvent, the catalyst, and the temperature conditions of the process). The steric and electronic properties of polyfluoroalkyl substituents affect the conformational state of imines (the polyfluoroalkyl substituent is located in the *trans* position relative to the sulfinyl group), as well as the geometry of the transition state (polyfluoroalkyl substituents usually occupy the equatorial position). However, aldimines are more prone to form the open transition state in the addition reactions to the C=N bond, and the result of the process is therefore regulated by steric factors. While polyfluoroalkyl ketimines are more likely to form transition states with a closed geometry. In the latter case, the sulfinyl group usually participates in regulating the direction of the addition due to the ability of the oxygen atom to form coordination bonds.

The review demonstrates that *N*-(*tert*-butylsulfinyl)polyfluoroalkyl imines are versatile substrates, which easily interact with different types of nucleophiles, providing access to a wide range of optically pure derivatives of polyfluoroalkyl-substituted amines, amino alcohols and amino acids.

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Catalytic Performance of Pd Deposited on Various Carriers in Hydrogenation of Quinoline

Abstract

Pd nanoparticles were deposited on two different grades of activated carbon – NORIT and CAW. In addition, these carbons were pre-treated with HNO_3 or covered by polyaniline, and these modified carbons were used as carriers for the Pd deposition. The resulting materials were tested as catalysts for the hydrogenation of quinoline. The best-performing samples were further tested in the hydrogenation of 4-methylquinoline. The structural features of carriers and catalysts were elucidated by the N_2 adsorption studies. The grade of activated carbon was found to be a key factor controlling its performance, and the effect of the surface modification was negligible.

Keywords: hydrogenation; palladium; activated carbon; quinoline; specific surface

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Каталітична ефективність Pd, осадженого на різних носіях, у реакції гідрування хіноліну

Анотація

Наночастинки Pd було нанесено на дві різні марки активованого вугілля – NORIT і CAW. Крім того, ці марки вугілля було попередньо оброблено HNO_3 або покрито поліаніліном і далі використано як носії для осадження Pd. Отримані матеріали випробувано як каталізатори гідрування хіноліну. Найкращі зразки було надалі протестовано в реакції гідрування 4-метилхіноліну. Структурні особливості носіїв і каталізаторів з’ясовано за допомогою адсорбційних досліджень N_2. Виявлено, що марка активованого вугілля була ключовим фактором, який контролював його ефективність, а ефект модифікації поверхні був незначний.

Ключові слова: гідрування; паладій; активоване вугілля; хінолін; питома поверхня

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■ Introduction

Hydrogenation is one of the most important reactions in organic chemistry, and it is widely used for both the fine synthesis and industrial production of chemicals [1, 2]. Among hydrogenation catalysts, Pd-based systems play one of the central roles due to their high efficiency, which includes activity and selectivity, as well as good reproducibility [3, 4]. However, in view of the high price of palladium, searching for ways to reduce the metal consumption is an important task.

In our preliminary studies, it was found that the deposition of Pd nanoparticles on different grades of activated carbon led to the formation of catalysts with a completely different activity.

This difference can be explained by the formation of different particles due to specific surface features (for example, different concentration and activity of "seeding" centers, which act as the growth sites for particles [5]), as well as different influence of the carrier on the electronic structure of Pd particles [6]. Unfortunately, the carbons that give the most active catalysts are the most expensive, and searching for a simple way of modifying the carbon surface to "improve" it is an urgent task.

The aim of this study was to evaluate the role of the activated carbon pre-treatment determining the catalytic performance of Pd/C catalysts. Two samples of activated carbon were chosen for this study: (1) CAW MB240 activated carbon, and (2) NORIT GSX activated carbon. CAW is an activated carbon type, widely used for the purification of wastewater and liquids in different technological processes. Its sorption characteristics depend a lot on the batch; the sample used in this study had $S_{BET} = 49$ m^2 g^{-1}, the total pore volume – $V_T = 0.164$ cm^3 g^{-1}, and contained almost no micropores, according to the data of the N_2 sorption. NORIT is another grade of activated carbon, produced by Norit Ltd., and it can also be manufactured from coconut. The sample used in this study had $S_{BET} = 850$ m^2 g^{-1}, the total pore volume $V_T = 0.604$ cm^3 g^{-1}, and contained a significant quantity of micropores, with $V_{micro} = 0.220$ cm^3 g^{-1} (by Dubinin-Radushkevich); the *Horvath* and *Kawazoe* median micropore diameter was 0.64 nm. Significantly lower sorption characteristics of CAW compared to NORIT may be caused by a simpler activation process used in the production of CAW; consistently, CAW is much cheaper compared to NORIT. The possible use of CAW instead of NORIT after the modification with PANI seemed to be an attractive outlook.

These carbons were oxidized by the treatment with HNO_3, and the oxidized carbons were used as carriers for the Pd deposition. In another series of experiments, a layer of polyaniline (PANI) was deposited on activated carbon to test if the creation of such a "PANI shell" would negate the difference between these materials. The PANI content was chosen at the level of 10% by weight. PANI was chosen as a surface modifier because it was shown that the reduction of Pd^{2+} by PANI led to a very efficient hydrogenation catalyst where PANI served as a carrier for Pd nanoparticles [7]. In addition, the deposition of PANI over activated carbon is a technically accessible task.

The deposition of Pd on the carriers was carried out by the decomposition of the $Pd_2(dba)_3$ complex (dba = dibenzylideneacetone), as previously reported [8, 9]. The decomposition of zero-valent complexes of metals was shown to be an efficient way to obtain hydrogenation catalysts [10–13].

■ Materials and methods

Hydrogen (99.99%) was purchased from Galogas Ltd. (Kyiv, Ukraine) and used without further purification. NORIT GSX activated carbon was purchased from Energochimservise (Kyiv, Ukraine). CAW MB240 activated carbon was purchased from Ecofilter Ltd (Kharkiv, Ukraine). Other starting materials and reagents, except hydrogen, were available from Enamine Ltd. (Kyiv, Ukraine) and UkrOrgSyntez Ltd. (Kyiv, Ukraine).

The N_2 sorption was measured using Sorptomatic-1990 instrument by the volumetric method at 78 K. Prior to the measurements, the samples were heated at 200°C in a 10^{-4} Torr vacuum for 2 hours.

The yield of 1,2,3,4-tetrahydroquinoline was determined by integrating signals of different products in ^{1}H NMR spectra and measuring their ratios. No product is volatile; the total quantity of all products is equal to the quantity of the starting compound. In turn, GC-MS was not used for the quantitative analysis of the mixtures because of the need to calibrate columns. GC-MS was used just for verification of the products (by retention times and MS patterns), as well as to ensure that other products did not form. All quantitative analyses were performed using NMR data. ^{1}H spectra were measured on a Varian Unity Plus 400 spectrometer at 400 MHz. Mass spectra were measured on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and an Agilent 5890 Series II 5972 GC-MS instrument (electron impact ionization (EI)).

The deposition of Pd on the carriers was carried out, as previously reported [8, 9]. In all cases, the quantity of Pd-containing starting material, $Pd_2(dba)_3$, was chosen to ensure the 1% Pd content in the final product.

The oxidation of activated carbons was performed by treating the carbon sample with boiling diluted (30%) nitric acid for 4 hours [14, 15].

The deposition of PANI on activated carbons was performed as described [8]. Since the deposition was carried out in the acidic medium, the samples that were formed contained protonated PANI (hereinafter denoted as PANI(H^+)).

For the conversion of these materials into those containing neutral PANI, samples were treated with an excess of 1% solution of ammonia.

The hydrogenation of quinoline was performed in the high-pressure vessels as previously described [8, 10].

■ Results and discussion

Two types of activated carbons, CAW and NORIT, were used as starting materials for further modification and deposition of PANI. The aim of the surface oxidation with HNO_3 was to unify the surface, i.e., to eliminate specific functional groups (if any) and convert them into hydroxy- or carboxy-groups. The aim of the PANI deposition was to create a uniform layer of organic polymer, and make the conditions of the Pd nanoparticles deposition closer, regardless of different grades of activated carbon.

The deposition of Pd on all carriers, i.e., NORIT and CAW, treated by HNO_3 or covered by PANI (in protonated and neutral forms), was performed by the decomposition of $Pd_2(dba)_3$. The scheme of the catalyst formation, along with their abbreviations, is shown in **Figure 1**.

The hydrogenation of quinoline was chosen as a benchmark reaction for comparing the catalytic properties of the materials. In all cases, 1,2,3,4-tetrahydroquinoline (THQ) was the only hydrogenation product. The yields of THQ achieved in the presence of the catalysts studied are presented in **Table 1**.

It was found that the NORIT-based catalysts possessed high catalytic performance, and the quantitative hydrogenation of quinoline was achieved in the cases of Pd-NORIT and Pd-NORIT-Ox in the presence of 0.1 mol% of Pd at $p(H_2) = 30$ bar, $T = 50$ °C for 4 hours in methanol. At 0.025 mol% Pd loading, the yield of THQ was not quantitative,

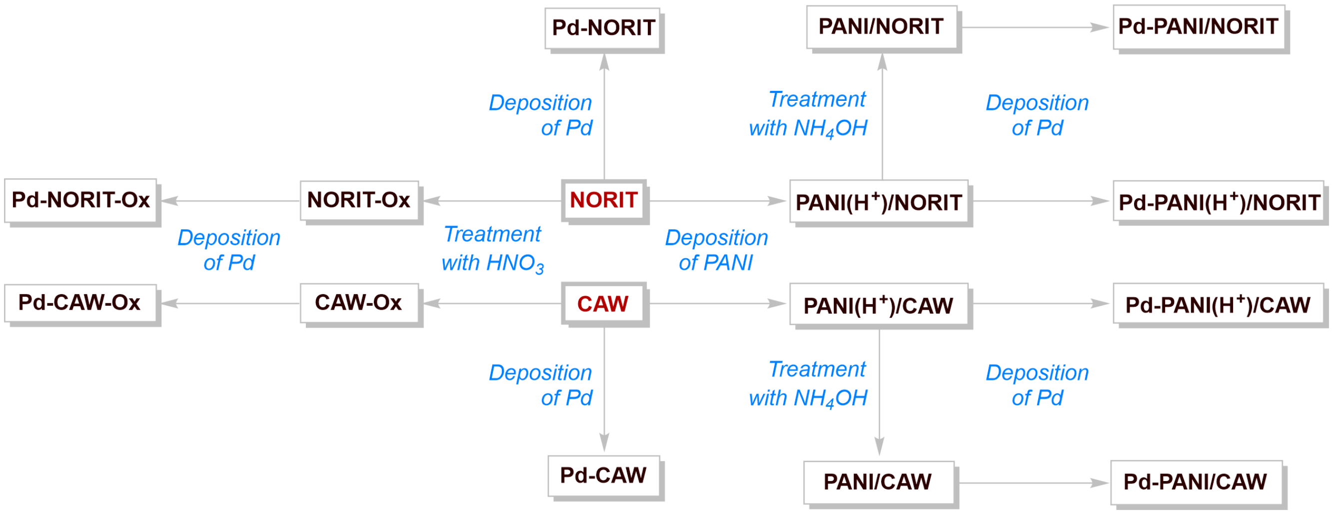

Figure 1. The preparation of Pd-containing catalysts

Table 1. The yields of 1,2,3,4-tetrahydroquinoline upon the hydrogenation of quinoline in the presence of Pd-containing catalysts under conditions $p(H_2) = 30$ bar, $T = 50$ °C, 4 h, methanol

Catalyst	Pd loading, mol. % per 1 mol of quinoline	Yield of THQ, %	Ref.
NORIT series			
Pd-NORIT	0.1	100	this work
Pd-NORIT	0.025	92	this work
Pd-NORIT-Ox	0.1	100	this work
Pd-NORIT-Ox	0.025	74	this work
Pd-PANI(H^+)/NORIT	1[1]	100	8
Pd-PANI/NORIT	1[1]	61	8
CAW Series			
Pd-CAW	0.2	0	this work
Pd-CAW-Ox	0.2	0	this work
Pd-PANI(H^+)/CAW	0.2	0	this work
Pd-PANI/CAW	1	0	this work

Note: [1] The Pd content on the catalysts was different from 1 %, but the weights of the catalysts were adjusted to ensure 1 % of Pd in the reaction mixture

Table 2. The yields of 4-methyl-1,2,3,4-tetrahydroquinoline upon the hydrogenation of 4-methylquinoline in the presence of Pd-containing catalysts in conditions $p(H_2)$ = 30 bar, T = 50 °C, 4 hours, methanol

Catalyst	Pd loading, mol% per 1 mol of quinoline	Yield of THQ, %	Ref.
NORIT series			
Pd-NORIT	0.2	98	this work
Pd-NORIT	0.1	27	this work
Pd-NORIT-Ox	0.2	55	this work
Pd-NORIT-Ox	0.1	26	this work

and it could be found that the performance of Pd-NORIT was better compared to Pd-NORIT-Ox (the yields of THQ were 92% and 74%, respectively). Anyhow, the catalytic performance of these materials was superior compared to those containing PANI since in these conditions, the quantitative conversion of quinoline to THQ was not achieved in the case of Pd-PANI/NORIT at 1 mol% Pd loading.

It was previously shown that the catalysts containing Pd nanoparticles on the carriers made of PANI and NORIT had better performance compared to "classical" Pd-charcoal systems where Pd was deposited on the BAU activated carbon [8]. From the results of the present study, we must conclude that the high performance of such systems was due to NORIT, and not because of the PANI "shell".

In contrast to NORIT-based systems, catalysts made using CAW activated carbon did not possess any catalytic activity in the conditions used herein, i.e., $p(H_2)$ = 30 bar, T = 50 °C, 4 hours in methanol. Their performance could not be improved by the surface oxidation with HNO_3 or the deposition of a PANI layer. We have to admit that the idea of cheap activated carbon transformation into analogues of expensive, but active ones, is not so simple and cannot be implemented by covering with a PANI layer.

The catalytic performance of the best catalysts considered herein, i.e., Pd-NORIT and Pd-NORIT-Ox, was checked in the hydrogenation of 4-methylquinoline. It was found that the yields of 4-methyl-1,2,3,4-tetrahydroquinoline were higher in the case of Pd-NORIT both at 0.2 and 0.1 mol% Pd loading. These yields were expectedly lower compared to the hydrogenation of non-substituted quinoline, but the tendency was the same (**Table 2**).

It was previously shown that the treatment of activated carbon with HNO_3 led to the enhancement of its sorption capacity in the processes of the sorption of heavy metal ions [16], the catalytic thermal decomposition of pentachlorobenzene [17], and in the case of the use as a carrier for hydrogenation catalysts [18]. In contrast, in our case, the treatment of NORIT with HNO_3 prior to the deposition of Pd nanoparticles led to the formation of a less active catalyst, and a similar procedure had no effect on the catalyst properties in the case of CAW.

To determine changes in the structural properties of carriers and catalysts during various treatments, and to assess their possible effect on the catalytic performance of Pd-containing samples, N_2 adsorption experiments were carried out for the NORIT series. The results are presented in **Table 3**.

The oxidation of NORIT with HNO_3 led to a *ca.* 2% decrease in S_{BET}. However, the deposition of PANI resulted in abrupt, about 50%, growth of S_{BET}. In addition, the pore volume also significantly increased. This effect can be explained by the formation of new roughness and folding

Table 3. Structural properties of the NORIT-based carriers and catalysts determined from N_2 adsorption isotherms

Catalyst	S_{BET}, m^2 g^{-1}	Pore volume (Gurvich) at p/p^0 = 0.95, cm^3 g^{-1}	Median micropore diameter by *Horvath* and *Kawazoe*, nm	V_{micro} (by Dubinin-Radushkevich), cm^3 g^{-1}
NORIT	850	0.604	0.64	0.220
Pd-NORIT	605	0.572	0.83	0.202
NORIT-Ox	830	0.588	0.74	0.284
Pd-NORIT-Ox	750	0.553	0.68	0.265
PANI(H^+)/NORIT	1310	0.948	0.75	0.452
Pd-PANI(H^+)/NORIT	1080	0.759	0.74	0.384
PANI/NORIT	1280	0.857	0.71	0.450
Pd-PANI/NORIT	1115	0.802	0.76	0.390

of the surface, including new pores, due to the PANI layer.

The deposition of Pd in all cases led to some decrease in the specific surface probably due to the fact that Pd particles filled the asperities of the surface. Similarly, the total pore volume and the volume of micropores decreased upon the deposition of Pd, indicating the localization of Pd nanoparticles in pores. However, 1% of Pd could not ensure such a significant decrease in the pore volume, and probably Pd nanoparticles blocked some part of the pores, making them inaccessible for N_2 probe molecules. It should be noted that a 1% decrease of the specific surface should have been due to the "addition" of a heavy metallic phase to the porous carrier.

The efficient pores diameter determined using the *Horvath* and *Kawazoe* model, did not change regularly upon the deposition of Pd nanoparticles (for example, it increased in the case of NORIT or decreased in the case of NORIT-Ox), and such irregular variation could be an argument in favor of the pore blocking by Pd nanoparticles, instead of filling the pores volume by Pd in full.

■ Conclusions

The main conclusion from this study is that the grade of activated carbon governs the properties of the deposited Pd-containing hydrogenation catalysts, and the performance of the catalyst cannot be significantly changed by the simple treatment of the carbon. In other words, the use of suitable activated carbon as a carrier is a key point, and the transformation of cheap activated carbon (which acts as a carrier for the catalysts of low activity) into a "good carrier" cannot be achieved by the oxidative treatment with nitric acid or the polyaniline layer formation. In addition, PANI is a good carrier for Pd nanoparticles for creating hydrogenation catalysts only if one compares PANI and a "non-active" carbon, such as CAW. PANI can be an alternative to cheap carbons, but the performance of activated carbon like NORIT is superior (though it is much more expensive). The deposition of a PANI layer on the surface of activated carbon does not improve its performance as a catalyst carrier, despite some reports about the formation of highly active catalysts based on PANI.

The nature of activated carbon itself is a key factor, which controls the performance of the catalysts, containing Pd nanoparticles, at least in the series where Pd was deposited in the same way. Thus, the activated carbon grade should be carefully selected for the preparation of Pd catalysts for the hydrogenation.

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A Competitive Substitution of the Difluoromethoxy Group in Aminodehalogenation Reactions of Aromatic Nitro Compounds

Abstract

The interaction of substituted nitrobenzenes containing activated halogen atoms (fluorine or chlorine) and the difluoromethoxy group with an aqueous solution of ammonia at high pressure and temperature of 80–160 °C was studied. It has been found that under the conditions studied, the difluoromethoxy group can be replaced by the amino group as a pseudohalogen. It has been shown that the reactivity of the difluoromethoxy group in the same positions is lower than that of the fluorine atom, but significantly higher than that of the chlorine atom.

Keywords: difluoromethoxynitrobenzenes; difluoromethoxy group; amination; nucleophilic substitution

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Конкурентне заміщення дифторметокси групи в реакціях амінодегалогенування ароматичних нітросполук

Анотація

Досліджено взаємодію заміщених нітробензенів, що містять активовані атоми галогенів (фтору або хлору) і дифторметокси групу, з водним розчином амоніаку за високого тиску та температури 80–160°С. З'ясовано, що за досліджуваних умов дифторметокси група може поставати як псевдогалоген і її можна замінити аміногрупою. Виявлено, що реакційна здатність дифторметокси групи в тих самих положеннях нижча, ніж в атома фтору, але значно вища, ніж в атома хлору.

***Ключові слова*:** дифторметоксинітробензол; дифторметокси група; амінування; нуклеофільне заміщення

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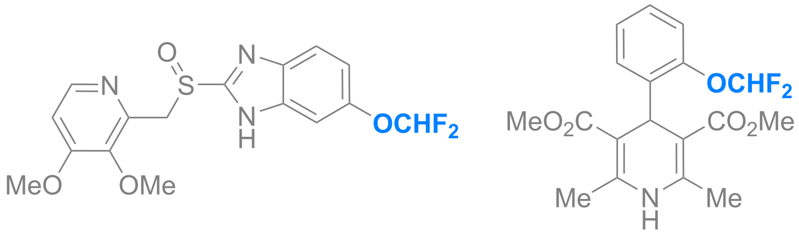
■ Introduction

The difluoromethoxy group has recently become quite readily available, and compounds containing it are often considered as promising bioactive agents [1]. Prominent examples include approved drugs Pantoprazole and Foridon containing the $OCHF_2$ group in their molecules (**Figure 1**).

In previous studies, the difluoromethoxy group in aromatic compounds was considered relatively stable, and no cases of the nucleophilic substitution of this group were described. Interestingly that the cases of the nucleophilic substitution of a closely related trifluoromethoxy group in an aromatic ring are known [2], and even cases of the methoxy group substitution were described [3].



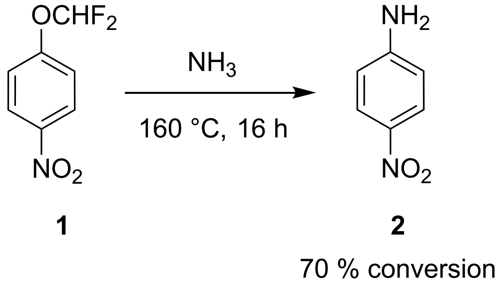
Pantoprazole

Foridon

Figure 1. Drugs with a difluoromethoxy group

During nucleophilic substitution reactions involving halogenated benzene rings bearing a difluoromethoxy group, we repeatedly observed impurities resulting from the substitution of the difluoromethoxy group rather than the halogen atom. The reaction of the model compound, 4-nitrodifluoromethoxybenzene (**1**), with 25% aqueous ammonia at 160 °C for 16 h led to the formation of *para*-nitroaniline (**2**) with an approximate conversion of 70%. Simultaneously, other reaction products, such as 4-nitrophenol or 4-difluoromethoxyaniline, were not observed (**Scheme 1**).

Therefore, we considered a systematic study of the behavior of the difluoromethoxy group as a potential leaving group during the nucleophilic substitution of activated halogens in aromatic rings to be a relevant and important task for synthetic organic chemistry.



Scheme 1. The substitution of the $OCHF_2$ group in the model compound

Results and discussion

The starting compounds selected were halonitrobenzenes containing a difluoromethoxy group in the *para*-position to the nitro group, namely 2-chloro-4-(difluoromethoxy)-1-nitrobenzene (**3**), 1,4-dichloro-2-(difluoromethoxy)-5-nitrobenzene (**4**) and 1-chloro-2-(difluoromethoxy)-4-fluoro-5-nitrobenzene (**5**), as well as halonitrobenzenes containing a difluoromethoxy group in the *ortho*-position, namely 4-chloro-2-(difluoromethoxy)-1-nitrobenzene (**6**), 2-(difluoromethoxy)-4-fluoro-1-nitrobenzene (**7**), 1-chloro-3-(difluoromethoxy)-2-nitrobenzene (**8**) and 1-(difluoromethoxy)-3-fluoro-2-nitrobenzene (**9**) (**Figure 2**). Aqueous 25% ammonia was chosen as a model nucleophile.

Compounds **3**, **6**, and **8** were previously reported [4–6]. Nitroarenes **4** and **5** were synthesized *via* the nitration of the corresponding haloaryldifluoromethyl ethers **10a** and **10b** (**Scheme 2**, *A*). Compounds **7** and **9** were obtained through the difluoromethylation of phenols **11** and **12** using chlorodifluoromethane (**Scheme 2**, *B, C*). Due to the presence of an activated fluorine atom, these substrates could not be difluoromethylated under standard strongly basic conditions at 60–70 °C, as described in [7]. Therefore, we employed milder reaction conditions, performing the transformation at 30–35 °C in a THF/water

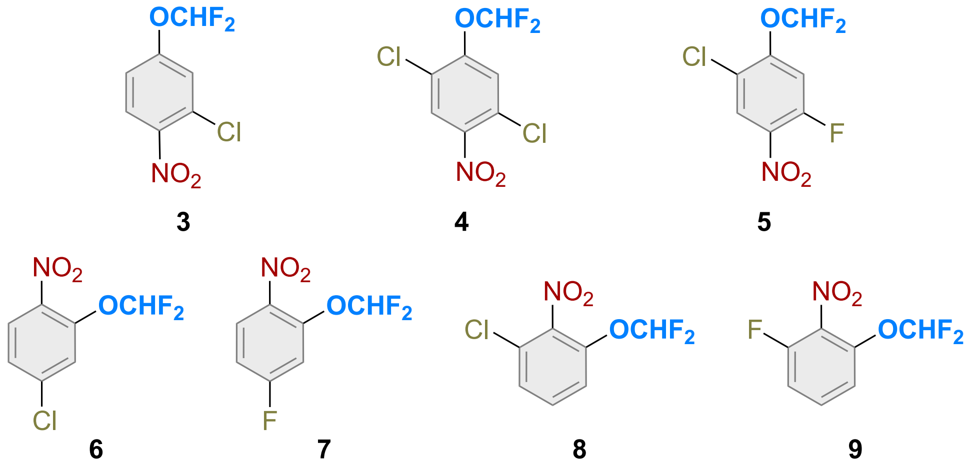
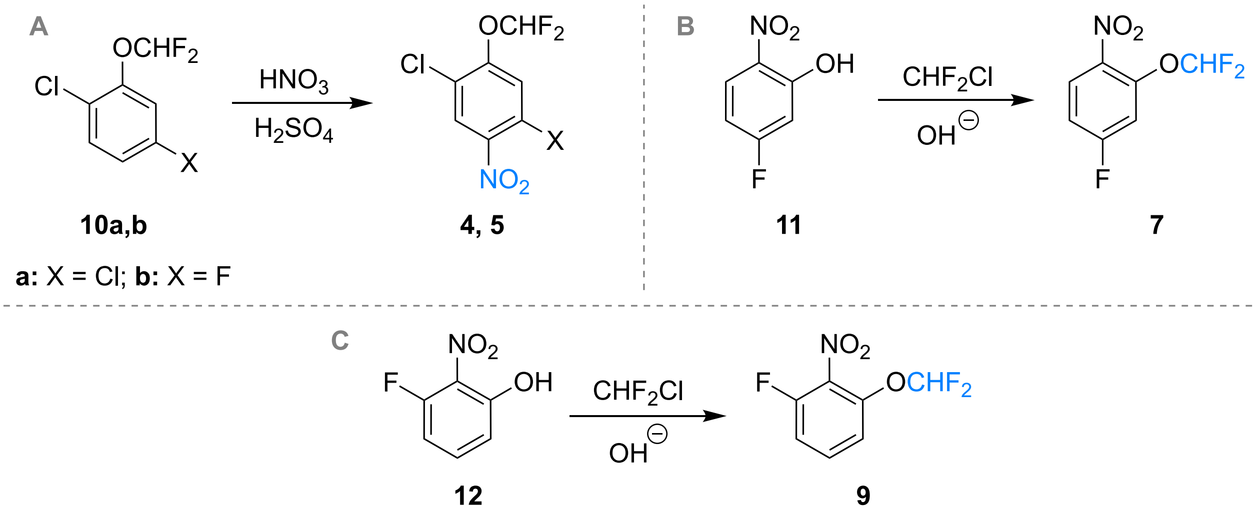


Figure 2. Starting compounds



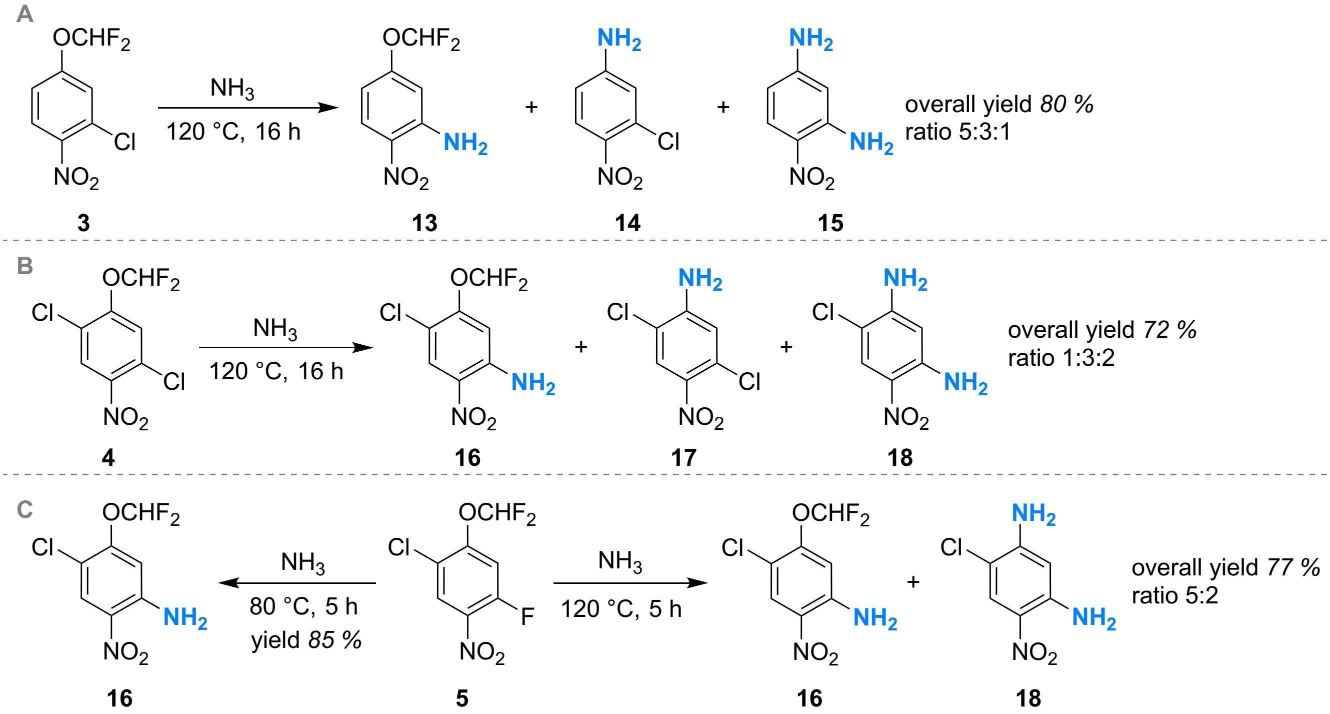
Scheme 2. The synthesis of starting compounds

alkaline medium in the presence of a phase-transfer catalyst.

In the case of compounds **3**–**5**, the halogen atom was in the *ortho*-position to the nitro group and was therefore more activated towards the nucleophilic substitution (due to both inductive and mesomeric effects) compared to the *para*-difluoromethoxy group. The interaction of **3** and **4** with aqueous ammonia in a high-pressure reaction vessel occurred at 120°C and led to product mixtures (**Scheme 3**). In each case, the formation of three products – difluoromethoxy nitroanilines **13** or **16** (the chlorine atom substitution), chloronitroanilines **14** or **17** (the difluoromethoxy group substitution), and *meta*-phenylenediamines **15** or **18** (the simultaneous substitution of both the chlorine atom and the difluoromethoxy group) were observed.

The presence of a chlorine atom in position 5 promoted the substitution of the difluoromethoxy group. Thus, when compound **3** was reacted with aqueous ammonia under the conditions studied, product **13** was obtained in a higher yield than product **14** (**Scheme 3**, *A*). In contrast, for the starting compound **4**, the major product was compound **17**. When the reaction was carried out at 160°C in both cases, the complete double substitution occurred, giving products **15** and **18**, respectively, in the yield approximately 65–70% (**Scheme 3**, *A* and *B*).

As expected, the substitution of the fluorine atom in compound **5** proceeded more readily.



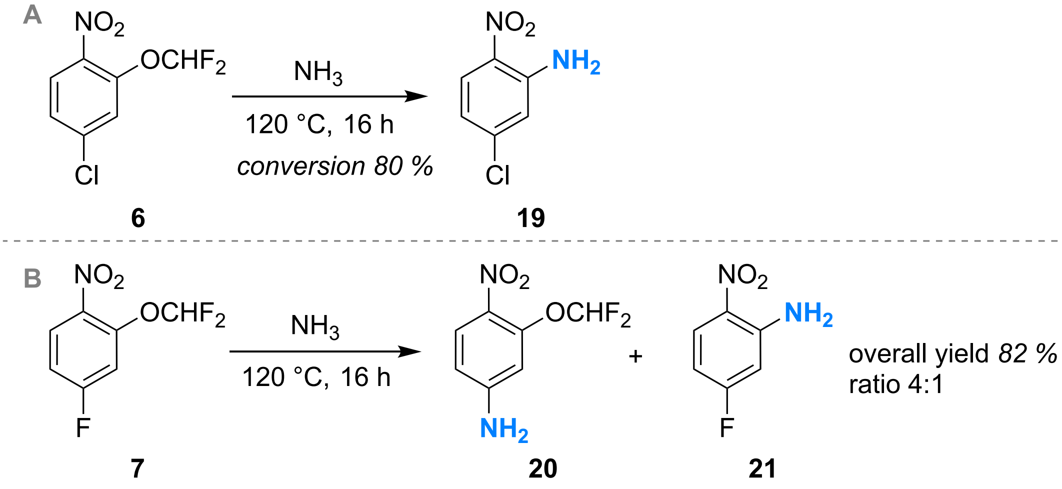
Scheme 3. The aminodehalogenation of nitrobenzenes with the difluoromethoxy group in the *para*-position

The reaction reached the complete conversion within 6 h at 80°C without affecting the difluoromethoxy group. However, performing the reaction at 120°C over the same time period resulted in a mixture of monosubstituted and double substituted products in a ratio of 5:2 (**Scheme 3**, *C*).

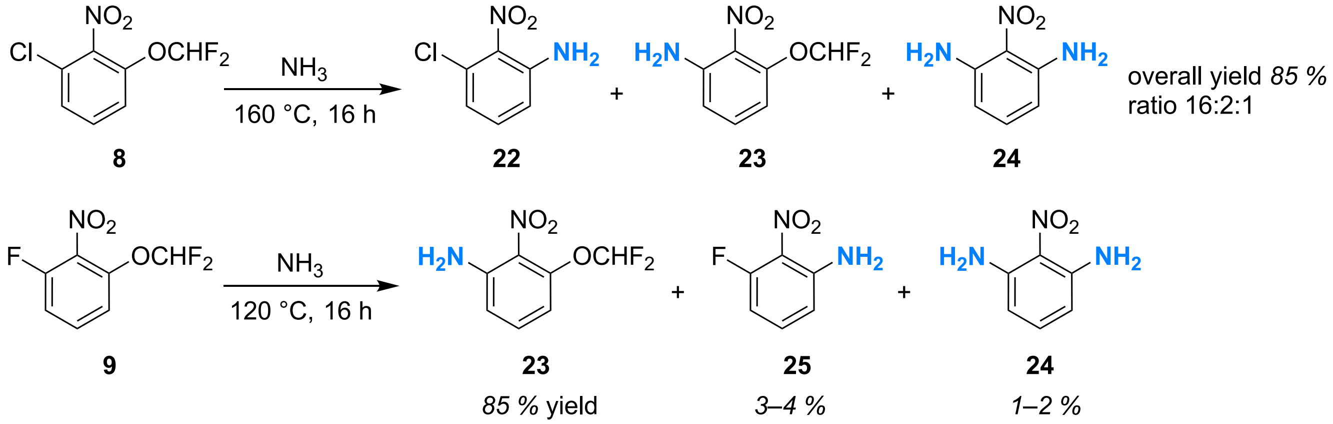
In the case of compounds **6** and **7**, the halogen atom was in the *para*-position to the nitro group and was therefore less activated towards the nucleophilic substitution compared to the difluoromethoxy group, which was in the *ortho*-position.

The reaction of compound **6** at 120°C did not lead to the substitution of the chlorine atom, but instead resulted exclusively in the substitution of the difluoromethoxy group, yielding compound **19** as the sole product (**Scheme 4**, *A*). In 16 h, the conversion reached approximately 80%. Under the same conditions, the reaction of compound **7** containing a fluorine atom proceeded to the complete conversion within this time frame and produced a mixture of fluorine-substituted product **20** and difluoromethoxy-substituted product **21** in a ratio of 4:1 (**Scheme 4**, *B*).

To reliably assess the relative reactivity of the halogen atom and the difluoromethoxy group, substrates, in which both substituents occupied the same (*ortho*) positions, were most suitable. Therefore, we studied compounds **8** and **9** with these groups in the *ortho*-position. The reaction of compound **8** with aqueous ammonia proceeded very slowly at 120°C; after 6 h of heating in a high-pressure vessel, NMR spectra showed virtually no signals corresponding to substitution products. However, conducting the reaction at 160°C led to a mixture, in which product **22** (resulting from the substitution of the difluoromethoxy group) was approximately 8 times more abundant than product **23** (resulting from the chlorine substitution). Additionally, the NMR analysis revealed the presence of a minor amount of double-substitution product **24**. These results clearly indicated that the difluoromethoxy group was substituted much more readily than the chlorine atom when both were located at an equivalent position. As expected, the reaction of fluoronitrobenzene **9** proceeded almost exclusively to give compound **23**



Scheme 4. The aminodehalogenation of nitrobenzenes with a halogen atom in the *para*-position and the difluoromethoxy group in the *ortho*-position



Scheme 5. The aminodehalogenation of nitrobenzenes with a halogen atom and the difluoromethoxy group in the *ortho*-position

in the yield of approximately 85%. According to NMR data, minor impurities of the fluorine-substituted product **25** and the double-substituted product **24** did not exceed 5–6% and were not isolated (**Scheme 5**).

■ Conclusions

Thus, we have studied the dehaloamination of various nitrobenzenes containing activated halogen atoms (fluorine and chlorine) and the difluoromethoxy group with aqueous ammonia in an autoclave at 80–160°C. The dependencies of the ratio of substitution products on the position of leaving groups (halogen or difluoromethoxy group) have been found. It has been shown that in the presence of the difluoromethoxy group in nitrobenzene, the nucleophilic substitution of halogen occurs unambiguously only in the case of an activated fluorine atom, whereas the chlorine atom is replaced significantly more slowly than the difluoromethoxy group.

■ Experimental part

Melting points were measured in an open capillary and were given uncorrected. ^{1}H NMR (300 MHz, $CDCl_3$) spectra, and ^{19}F NMR (282 MHz, $CDCl_3$) spectra were recorded on a Varian Mercury 300 spectrometer using TMS and CCl_3F as internal standards. The reaction progress was controlled by TLC on Silufol UV-254 plates. Chromatographic separation of the products was carried out on a "Puriflash XS 520 Plus" chromatograph using "Kieselgel MN 40-60" silica gel. The eluent was hexane-ethyl acetate (0–20% ethyl acetate) with a gradient increase in polarity.

The general procedure for the synthesis of 1,4-dichloro-2-(difluoromethoxy)-5-nitrobenzene (4) and 1-chloro-2-(difluoromethoxy)-4-fluoro-5-nitrobenzene (5)

Haloaryldifluoromethyl ether **10a** or **10b** (0.1 mol) was added dropwise or in portions to a mixture of 96% sulfuric acid (50 mL) and 100% nitric acid (25 mL), keeping the temperature within the range of 20–30°C. The mixture was stirred at this temperature for 30 min, after which the reaction was quenched by pouring it onto ice. The resulting mixture was extracted with MTBE (2×200 mL), and the combined organic layers were washed with 5% aqueous sodium bicarbonate solution (3×300 mL), followed by water until the washes became colorless. The organic phase was dried over $MgSO_4$, the solvent was evaporated, and the residue was crystallized from hexane by freezing at –18 °C, giving the target products as almost colorless, slightly yellow-tinted, low-melting crystals.

1,4-Dichloro-2-(difluoromethoxy)-5-nitrobenzene (**4**)

A white solid. Yield – 22.4 g (87%). M. p. 41–42 °C. Anal. Calcd for $C_7H_3Cl_2F_2NO_3$, %: C 32.59, H 1.17, N 5.43. Found, %: C 32.48, H 1.11, N 5.57. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.65 (1H, t, $^1J_{HF}$ = 72 Hz, O-CHF_2), 7.22 (1H, s, ArH), 8.21 (1H, s, ArH). ^{19}F NMR (282 MHz, $CDCl_3$), δ, ppm: -84.7 (d, J = 72 Hz, O-CHF_2).

1-Chloro-2-(difluoromethoxy)-4-fluoro-5-nitrobenzene (**5**)

A white solid. Yield – 21.5 g (89%). M. p. 38–39 °C. Anal. Calcd for $C_7H_3ClF_3NO_3$, %: C 34.81, H 1.25, N 5.80. Found, %: C 34.78, H 1.28, N 5.90. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.66 (1H, t, $^1J_{HF}$ = 72 Hz, O-CHF_2), 7.24 (1H, d, J = 9 Hz, ArH), 8.21 (7.24 (1H, d, J = 3 Hz ArH). ^{19}F NMR (282 MHz, $CDCl_3$), δ, ppm: -115.2 (1F, d, $^3J_{HF}$ = 9 Hz, ArF), -84.4 (2F, d, $^1J_{HF}$ = 72 Hz, O-CHF_2).

The general procedure for the synthesis of 2-(difluoromethoxy)-4-fluoro-1-nitrobenzene (7) and 1-(difluoromethoxy)-3-fluoro-2-nitrobenzene (9)

A solution of the corresponding nitrophenols **11** or **12** (47.1 g, 0.3 mol) and Bu_4NBr (4 g) in THF (500 mL) was stirred and cooled, followed by the dropwise addition of a solution of KOH (90 g, 1.6 mol) in H_2O (180 mL). Freon-22 was then bubbled through the vigorously stirred mixture at 30–35 °C (with water cooling bath) until the gas absorption stops, accompanied by a noticeable exothermic effect. If TLC monitoring indicated the incomplete conversion of the starting nitrophenol, an additional portion of KOH (30 g) was added, and bubbling of Freon-22 continued until the gas uptake stopped, and the reaction mixture changed color from cherry-red to lemon-yellow. The total reaction time was approximately 4–5 h. After completion, water (300 mL) and hexane (300 mL) were added, and the mixture was extracted by shaking. The organic layer was separated, washed with 10% aqueous NaCl solution (300 mL), dried over anhydrous K_2CO_3, and concentrated under reduced pressure. The crude products were purified by vacuum distillation.

2-(Difluoromethoxy)-4-fluoro-1-nitrobenzene (**7**)

A yellow liquid. Yield – 56.4 g (91%). B. p. 88–90°C at 0.5 Torr. Anal. Calcd for $C_7H_4F_3NO_3$, %: C 40.60, H 1.95, N 6.76. Found, %: C 40.55, H 2.01, N 6.72. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm:

6.57 (1H, t, $^1J_{HF}$ = 72 Hz, O-CHF_2), 6.90–7.10 (2H, m, ArH), 7.95–8.05 (1H, m, ArH). ^{19}F NMR (282 MHz, $CDCl_3$), δ, ppm: -82.3 (2F, d, $^1J_{HF}$ = 72 Hz, O-CHF_2), -102.6 (1F, d, J = 9 Hz, ArF).

1-(Difluoromethoxy)-3-fluoro-2-nitrobenzene (**9**)

A yellow liquid. Yield – 58.8 g (95%). B. p. 85–87 °C at 0.5 Torr. Anal. Calcd for $C_7H_4F_3NO_3$, %: C 40.60, H 1.95, N 6.76. Found, %: C 40.42, H 2.10, N 6.53. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.56 (1H, t, $^1J_{HF}$ = 72 Hz, O-CHF_2), 7.12–7.26 (2H, m, ArH), 7.45–7.55 (1H, m, ArH). ^{19}F NMR (282 MHz, $CDCl_3$), δ, ppm: -120.6 (m, 1F, ArF), -82.2 (d, $^1J_{HF}$ = 72 Hz, O-CHF_2).

The general procedure for the aminodehalogenation of halonitrobenzenes 3–9

Compounds **3**–**9** (0.1 mol) and 25% aqueous ammonia (100 mL) were placed in a Teflon vessel within an autoclave and stirred at the selected temperature for 5 to 16 h, depending on the compound under study. After completion, the reaction mixture was extracted with MTBE (500 mL), washed with water (3×300 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography.

Halonitroanilines **14** (CAS 825-41-2), **17** (CAS 6627-34-5), **19** (CAS 1635-61-6), **21** (CAS 2369-11-1), **22** (CAS 59483-54-4), as well as *meta*-phenylenediamines **15** (CAS 5131-58-8), **18** (CAS 89487-54-7) and **24** (CAS 567-63-5) were commercially available products, and their characteristics corresponded to the known ones. Nitroaniline **13** was described recently [4]; the product we received complied with the described compound.

4-Chloro-5-(difluoromethoxy)-2-nitroaniline (**16**)

Yellow crystals. Yield – 20.2 g (83%). M. p. 112–114 °C. Anal. Calcd for $C_7H_5ClF_2N_2O_3$, %: C 35.24, H 2.11, N 11.74. Found, %: C 35.42, H 2.18, N 11.81. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.15 (2H, br.s. NH_2), 6.47 (1H, t, $^1J_{HF}$ = 72 Hz, O-CHF_2), 6.95 (1H, s, ArH), 8.02 (1H, s, ArH). ^{19}F NMR (282 MHz, $CDCl_3$), δ, ppm: -81.1 (d, $^1J_{HF}$ = 72 Hz, O-CHF_2).

3-(Difluoromethoxy)-4-nitroaniline (**20**)

Yellow crystals. Yield – 14.0 g (65%). M. p. 122–124 °C. Anal. Calcd for $C_7H_6F_2N_2O_3$, %: C 41.19, H 2.96, N 13.72. Found, %: C 41.23, H 2.78, N 13.88. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 5.49 (2H, br.s. NH_2), 6.30–6.33 (2H, m, ArH), 6.47 (1H, t, $^1J_{HF}$ = 72 Hz, O-CHF_2), 7.73 (1H, d, J = 8 Hz, ArH). ^{19}F NMR (282 MHz, $CDCl_3$), δ, ppm: -81.9 (d, $^1J_{HF}$ = 72 Hz, O-CHF_2).

3-(Difluoromethoxy)-2-nitroaniline (**23**)

Yellow crystals. Yield – 17.5 g (85%). M. p. 52–53 °C. Anal. Calcd for $C_7H_6F_2N_2O_3$, %: C 41.19, H 2.96, N 13.72. Found, %: C 41.21, H 2.82, N 13.69. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 5.21 (2H, br.s. NH_2), 6.54 (1H, t, $^1J_{HF}$ = 72 Hz, O-CHF_2), 6.56 (1H, d, J = 7 Hz, ArH), 6.70 (1H, d, J = 7 Hz, ArH), 7.22 (1H, t, J = 7 Hz, ArH). ^{19}F NMR (282 MHz, $CDCl_3$), δ, ppm: -81.4 (d, $^1J_{HF}$ = 72 Hz, O-CHF_2).

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Development of a Multistage Technology for the Industrial Synthesis of the Levosimendan API and Enantiomeric Separation of Intermediates

Abstract

A method for obtaining Levosimendan suitable for industrial application has been developed. Two literature routes for the synthesis have been evaluated. It has been found that the use of enantiopure (*R*)-2-chloropropionyl chloride in the initial step is ineffective due to racemization at the stage of the synthesis based on the malonic ester. Instead, a reported method based on the synthesis of the Levosimendan precursor, 6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**1**), from racemic 2-bromopropionyl bromide has been modified to allow for scale-up and adaptation to industrial processes. A practical resolution method has been developed to isolate the (*R*)-enantiomer of amine **1** from the racemic mixture with a high enantiomeric purity (the content of (*R*)-enantiomer is up to 99 %). It has been shown that (*R*)-**1** can be converted to Levosimendan in a high yield without the stereochemical purity loss at the chiral center.

***Keywords**:* Levosimendan; 4,5-dihydropyridazine-3(2*H*)-one; enantiomers separation; diastereomeric salts; *S*,*S*-2,3-*bis*-(4-methoxybenzoiloxy)butanedioic acid

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Розробка багатостадійної технології промислового синтезу АФІ левосимендану та енантіомерного розділення проміжних продуктів

Анотація

Розроблено метод одержання левосимендану, придатний для промислового використання. Перевірено два літературних методи синтезу левосимендану та з’ясовано, що використання (*R*)-2-хлоропропіонілхлориду на першій стадії не ефективне через рацемізацію на стадії синтезу на основі малонового естеру. Літературний метод синтезу попередника левосимендану, 6-(4-амінофеніл)-5-метил-4,5-дигідропіридазин-3(2*H*)-ону (**1**), було модифіковано з використанням рацемічного 2-бромопропіонілброміду з метою зробити його придатним для масштабування та перетворення на промислову технологію. Розроблено метод виділення (*R*)-енантіомеру аміну **1** з рацемату з високою енантіомерною чистотою (вміст (*R*)-енантіомеру до 99 %). Показано, що амін (*R*)-**1** може бути перетворено на левосимендан зі збереженням конфігурації хірального центру та високим виходом.

***Ключові слова**:* левосимендан; 4,5-дигідропіридазин-3(2*H*)-он; розділення енантіомерів; діастереомерні солі; *S*,*S*-2,3-*біс*-(4-метоксибензоїлокси)бутандіова кислота

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■ Introduction

Levosimendan (**Figure 1**) represents a new class of cardiotonic agents reported as Ca^{2+} sensitizers without cardiovascular side effects. It increases the sensitivity of contractile proteins to calcium by binding to cardiotroponin C. Levosimendan increases the strength of contractions but does not depend on the ventricular relaxation. In addition, Levosimendan opens ATP-sensitive potassium channels in the vascular smooth muscle, stimulating the vasodilation of systemic arteries, coronary arteries, and systemic veins. It is a selective phosphodiesterase III inhibitor *in vitro*. In patients with heart failure, the positive inotropic and vasodilator effects of Levosimendan lead to an increase in the contractile force of the myocardium and a decrease in the preload and postload without the adverse impact on the diastolic function. Levosimendan activates the “ischemic” myocardium in patients after coronary angioplasty or thrombolysis [1–3]. Levosimendan is used for the short-term treatment of acute, severe decompensated chronic heart failure [2]. This drug is registered in Ukraine, and at least one domestic manufacturer, JSC Farmak, is present in the pharmaceutical market of Ukraine.

Due to the complicated logistics, the development of a domestic industrial method for the synthesis of Levosimendan is an urgent task. The commercial production of Levosimendan requires a cheap, convenient, and efficient synthetic approach, which can be converted into technology.

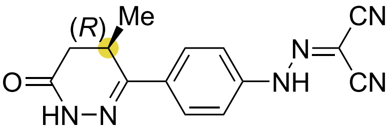


Figure 1. The structure of Levosimendan

In all methods of the synthesis of Levosimendan described, the last stage is common, namely the conversion of the *R*-enantiomer of amine **1** ((*R*)**-1**) into a diazo compound, followed by the interaction with malononitrile, as it has been presented in the patent [4] (**Scheme 1**). This makes amine **1** the key compound in the synthesis of Levosimendan.

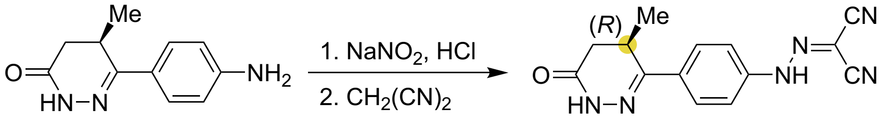
The scientific literature describes the four main approaches to 6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one **1** [5–9] (Routes 1–4, **Schemes 2–5**).

Scheme 2 (Route 1) shows the method based on utilizing the chiral starting materials from the first stage [5]. The authors reported that this route led to a crude amine (*R*)**-1** with 84% *ee* in the total yield of 30%, and further recrystallization of the crude product from ethyl acetate increased *ee* up to 98%.

Similar methods of the preparation of amine **1** starting from racemic 2-bromopropionyl bromide [6] or propionyl chloride [7] were described with the total yields of racemic compound **1** of 58% and 22%, respectively (Route 2, **Scheme 3**). In the work by *Wang et al.* [7], the separation of pyridazine-3(2*H*)-one **1** enantiomers *via* the crystallization of diastereomeric salts with *L*-(+)-tartaric acid was reported with the yield of 8%.

If a racemic 2-chloropropionyl chloride was used in such a route, racemic amine **1** was obtained with the total yield of 23% [8].

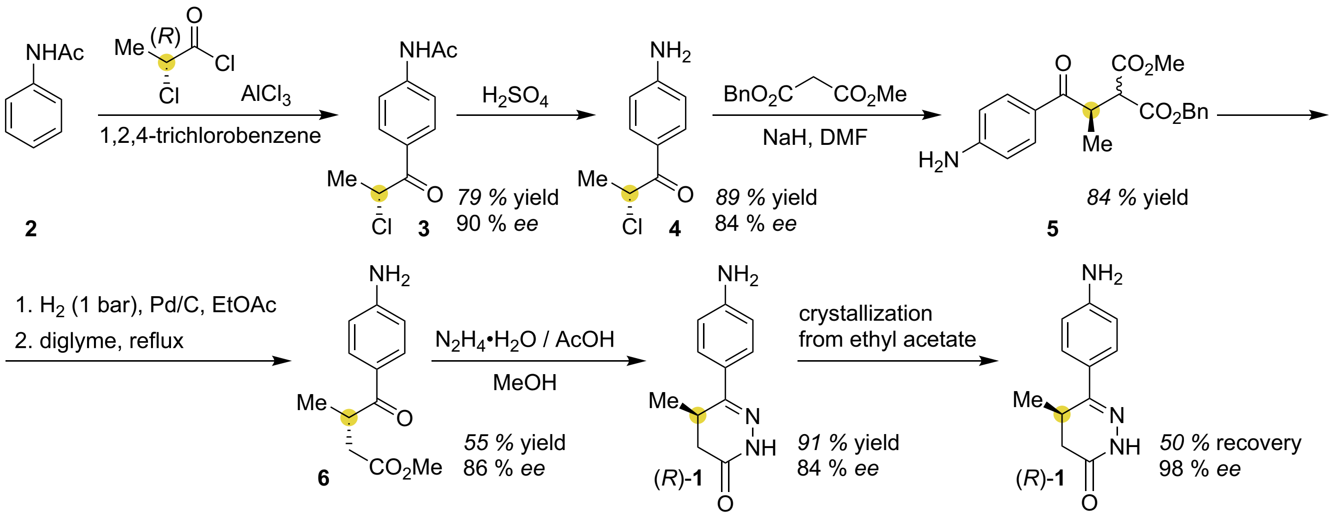
The preparation of the enantiomerically pure amine (*R*)**-1** starting from acetanilide **2** and citraconic anhydride (Route 3, **Scheme 4**) was described in [9]. This method includes a double bond reduction stage by hydrogen in the presence of a chiral Ru-catalyst (*S*)-BINAP-Ru. The total yield of the product (*R*)**-1** was ~14%.



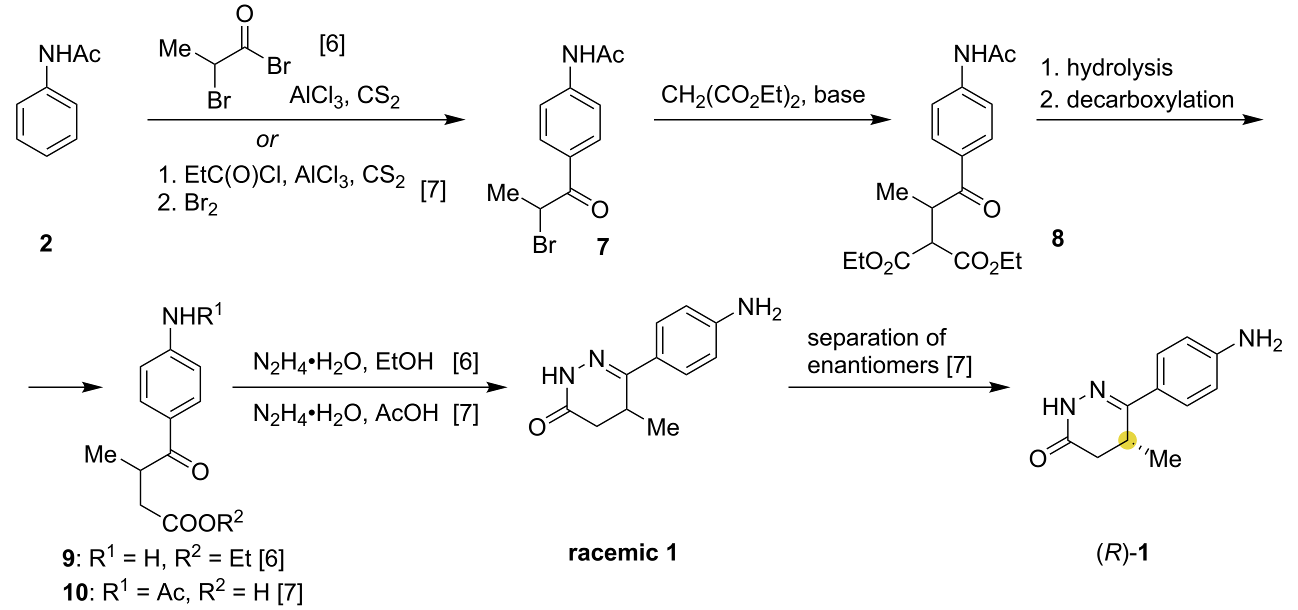
(*R*)**-1**

Levosimendan, *80 %*

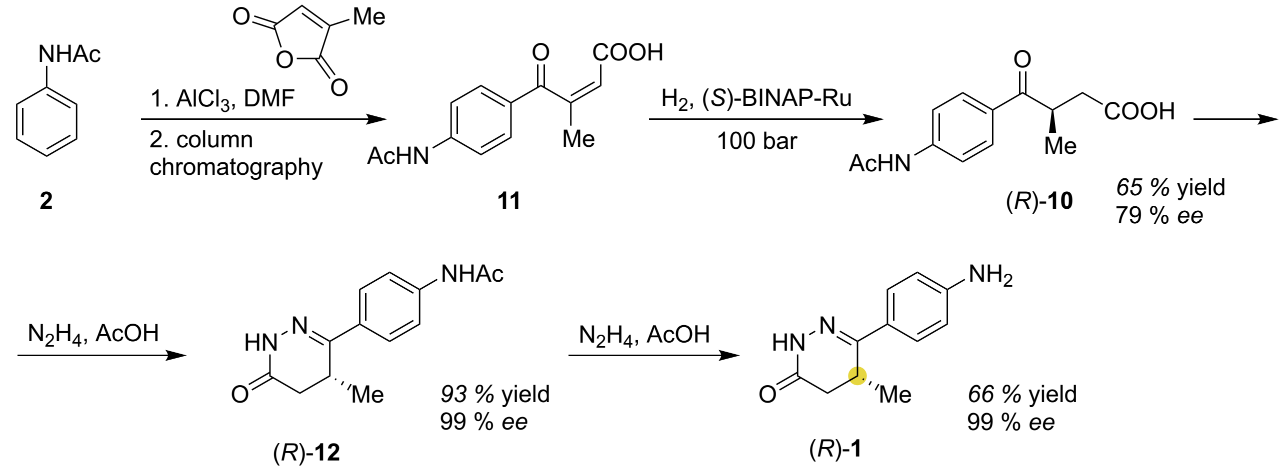
Scheme 1. The last stage of the Levosimendan synthesis [4]



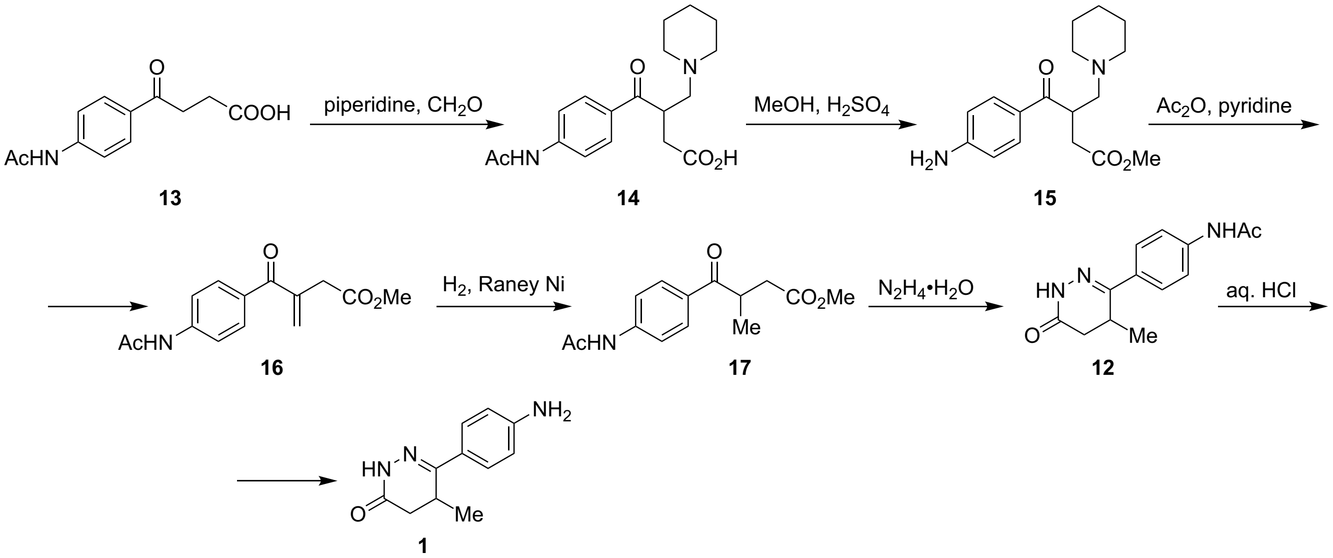
Scheme 2. The synthesis of 6-(4-Aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one starting from (*R*)-2-chloropropionyl chloride [5]



Scheme 3. The preparation of 6-(4-Aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one starting from racemic 2-bromopropionyl bromide or propionyl chloride [6, 7]



Scheme 4. The preparation of the enantiomerically pure (*R*)-6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one starting from citraconic anhydride *via* the double bond reduction stage [9]



Scheme 5. The preparation of racemic 6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one using 4-(4-acetamidophenyl)-4-oxobutanoic acid [8]

Another method for the preparation of racemic amine **1** using keto-acid **13** with the total yield of 28% was reported in [8] (Route 4, **Scheme 5**). This method, like the previous one, includes a double bond reduction with hydrogen on a Raney Ni catalyst.

As can be seen from the literature data, the enantiomerically pure amine (*R*)**-1** was obtained either by using chiral substances from the first stage [5], or by creating the desired configuration of the chiral center during the synthesis process [9], or by separating the racemate of amine **1** [4, 7]. The comparison of the aforementioned synthetic pathways is shown in **Table 1**.

The aim of this study was to evaluate the known methods of synthesis of Levosimendan and develop an optimal synthetic route suitable for converting into the technology and production of Levosimendan on the industrial scale.

Results and discussion

The synthesis pathways to 6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**1**), including the stage of reduction with gaseous hydrogen (Routes 3, 4; **Schemes 4**, **5**), are unsuitable for industrial use at JSC "Farmak" due to the lack of specific conditions for working with gaseous hydrogen under high pressure.

Therefore, for our research, we chose two methods shown in **Scheme 2** [5] and **Scheme 3** [6] (Routes 1, 2), starting from (*R*)-2-chloropropionyl chloride or 2-bromopropionyl bromide, respectively.

Table 1. The comparison of the literature synthetic pathways of 6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one

Route 1 (**Scheme 2** [5])	**Route 2** (**Scheme 3** [6, 7])	**Route 3** (**Scheme 4** [9])	**Route 4** (**Scheme 5** [8])
• total yield – 30 % • *ee* – 84 %	• total yield – 22-58 %[a] • racemate	• total yield – 14 % • *ee* – 99 %	• total yield – 28 % • racemate
+ high *ee*[b] + without the enantiomer separation	+ cheap and available starting materials	+ creation of a chiral center with high *ee* in the synthesis process + without the enantiomer separation	+ cheap and available starting materials
– the use of a non-commercial unsymmetrical malonic ester[c] – the additional stage of the benzyl methyl malonate synthesis	– the low total yield starting from 2-propionyl chloride [7] – the low yield (8 %) at the enantiomer separation stage [7]	– the mixture of products at the first stage requires the column chromatography for separation – the low yield (34 %) of desired product at the first stage – the use of **gaseous hydrogen** – expensive Ru-catalysts – the low total yield	– the use of **gaseous hydrogen** – expensive catalysts

Notes: [a] 22 % yield starting from propionyl chloride [7]; 58 % yield starting from 2-bromopropionyl bromide [6]; [b] "+" indicates advantages of the method; [c] "–" indicates disadvantages of the method

The authors in [5] (**Scheme 2**) noted that the use of unsymmetrical benzyl methyl malonate allowed obtaining compound **6** under mild conditions while preserving the configuration of the chiral center. In addition, it was stated that the use of aniline **4** (rather than acyl-protected aniline **3**) in the reaction with malonic ester allowed them to analyze the enantiomeric purity of the product by the HPLC method using chromatographic columns with a chiral stationary phase.

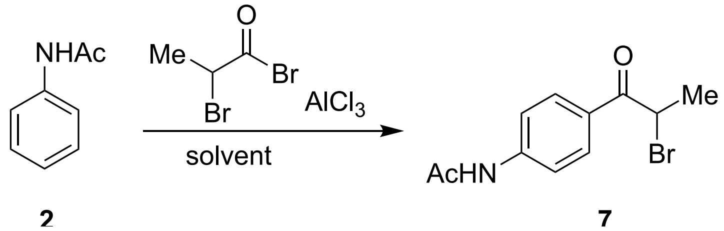
While reproducing this scheme (**Scheme 2**), we faced some difficulties. Compound **4** was obtained as described in [5] with the same yield and *ee*. However, the following stages gave unexpected and disappointing results. The interaction of chloride **4** with unsymmetrical malonic ester using the conditions described proceeded very slowly. To achieve a conversion of 90%, it was necessary to carry out the reaction for 6 days, contrary to 24 h in [5]. Moreover, the analysis of the enantiomeric purity of product **5** showed that during the interaction of compound **4** with benzyl methyl malonate, the racemization of the initial chiral center occurred. In addition, unreacted amine **4** with the initial *ee* of 92% was recovered from the reaction mixture as a racemate. This indicates that the racemization occurred in starting amine **4** due to the enolization of the keto function under the action of the base. Attempts to use a symmetrical dimethyl malonate in the reaction with either amine **4** or acylated amine **3** resulted in the racemization of the initial chiral center as well.

This failure showed that the utilization of a chiral starting material, namely (*R*)-2-chloropropionyl chloride, was ineffective. Therefore, we evaluated the second selected route starting from 2-bromopropionyl bromide [6] (**Scheme 3**) with the following separation of the enantiomers of amine **1** *via* the crystallization of diastereomeric salts.

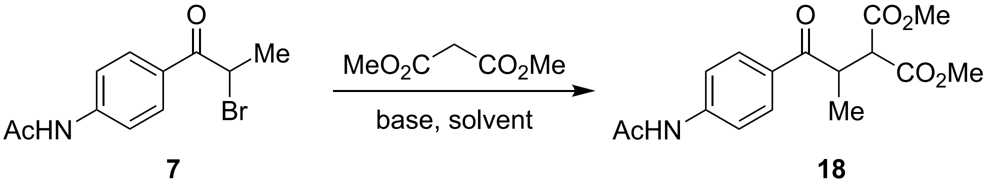
The first stage of the synthesis, namely the Friedel-Crafts reaction, was described in [6] using carbon disulfide as a solvent. This compound is very toxic and flammable; therefore, it is unsuitable for application in modern pharmaceutical manufacturing. We tested other organic solvents in this reaction to find the optimal conditions that would give high yields of product **7** (**Scheme 6**). Thus, heating the reaction mixture in dichloroethane at 80°C for 1.5 h led to the significant tar formation, and as a result, the product isolation failed. If the reaction mixture was refluxed in dichloromethane for 4 or 6 h, the conversion of acetanilide **2** was about 90%. An isolated yield of product **7** was 80% after column chromatography. The best results were achieved in 1,2,4-trichlorobenzene at 80°C after heating for 3 h, as described for (*R*)-2-chloropropionyl chloride in [5]. Product **7** was isolated in the yield of 99%.

The malonic synthesis was described using diethyl malonate, sodium hydride as a base and THF as a solvent [6]. We used dimethylmalonate instead of diethylmalonate in our research (**Scheme 7**). This choice is made as at the next step of hydrolysis/decarboxylation, an alcoholic solution of HCl is used, and the solution of HCl in methanol is a commercial reagent. In addition, it is difficult to obtain such a solution from ethanol in the laboratory or industry since absolute alcohol is required to prepare the solution.

Sodium hydride or potassium *tert*-butoxide was used as a base, and DMF or THF as a solvent. **Table 2** summarizes the results of the experiments.



Scheme 6. The Friedel-Crafts reaction of acetanilide and 2-bromopropionyl bromide



Scheme 7. The synthesis of dimethyl 2-(1-(4-acetamidophenyl)-1-oxopropan-2-yl)malonate via the malonic ester synthesis

Table 2. The malonic ester synthesis – optimization of reaction conditions

Entry	Base	Equiv. of the base and dimethyl malonate	Solvent	Isolated yield of **18**, %	LC-MS purity of **18**, %
1	NaH	2	DMF	30	78
2	*t*BuOK	2	DMF	67	83
3	*t*BuOK	2	THF	97	100
4	*t*BuOK	1	THF	94	93
5	*t*BuOK	1.25	THF	96	93

It is evident from **Table 2** that *t*BuOK gave better results if compared with sodium hydride, and THF was a better solvent than DMF for this reaction. It should be noted that when using 1.0 equiv. *t*BuOK and dimethyl malonate in THF the starting bromide in the amount of up to 1% was identified in the ^{1}H NMR spectrum. The use of 1.25 equiv. *t*BuOK and dimethyl malonate in THF was shown to be optimal (see *entry 5*).

It is noteworthy to mention that attempts to purify product **18** by the recrystallization were unsuccessful. However, it was found that all the impurities present in the product after the malonic synthesis disappeared after the next stage of the hydrolysis/decarboxylation sequence. Therefore, we believe that it is impractical to purify compound **18** before the next step.

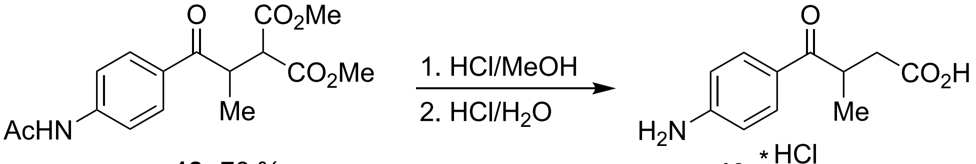
The stages of hydrolysis and decarboxylation (**Scheme 8**) were carried out similarly to the transformations described in [6]. As we used dimethyl ester instead of diethyl, we also used the methanol solution rather than the ethanol solution of HCl.

The cyclization reaction (**Scheme 9**) was performed according to [6]. We only slightly modified amine **1** isolation since the procedure described was not reproducible. If the precipitate product was isolated by filtration from the ethanolic reaction mixture as described in [6], the yield of amine **1** was up to 50%. Therefore, we first removed the solvent (EtOH) from the reaction mixture to dryness and then treated the residue with water. The precipitate formed was filtered and purified as described in the article [6], yielding pure amine **1** with a high yield.

Thus, the overall optimized scheme for the synthesis of racemic amine **1** is as follows (**Scheme 10**) with the total isolated yield of 67%. All stages can be easily scaled up in the laboratory and amount of each substance obtained per loading is shown in **Scheme 10**.

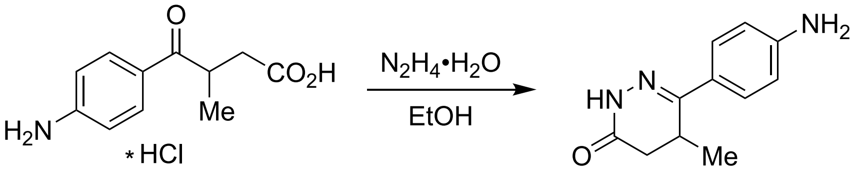
The separation of racemic amine **1** was described in [7] and included the following stages: **(1)** the synthesis of the salt with *L*-(+)-tartaric acid; **(2)** the crystallization of the resulting mixture of diastereomeric salts using 2-propanol; **(3)** the conversion of the salt to amine **1**. It was mentioned in the article that one crystallization was required for the complete separation of enantiomers.

We have found that amine **1** with (*R*)-enantiomer content >98% can be reached by 20–32 crystallizations of diastereomeric salts, depending on the amount of the starting mixture of diastereomeric salts. If 4.5 g of the mixture was used for the separation, the (*R*)-enantiomer content of 98.4% was reached after 20 crystallizations. At the same time, 45 g of the mixture of diastereomeric salts needed 32 crystallizations



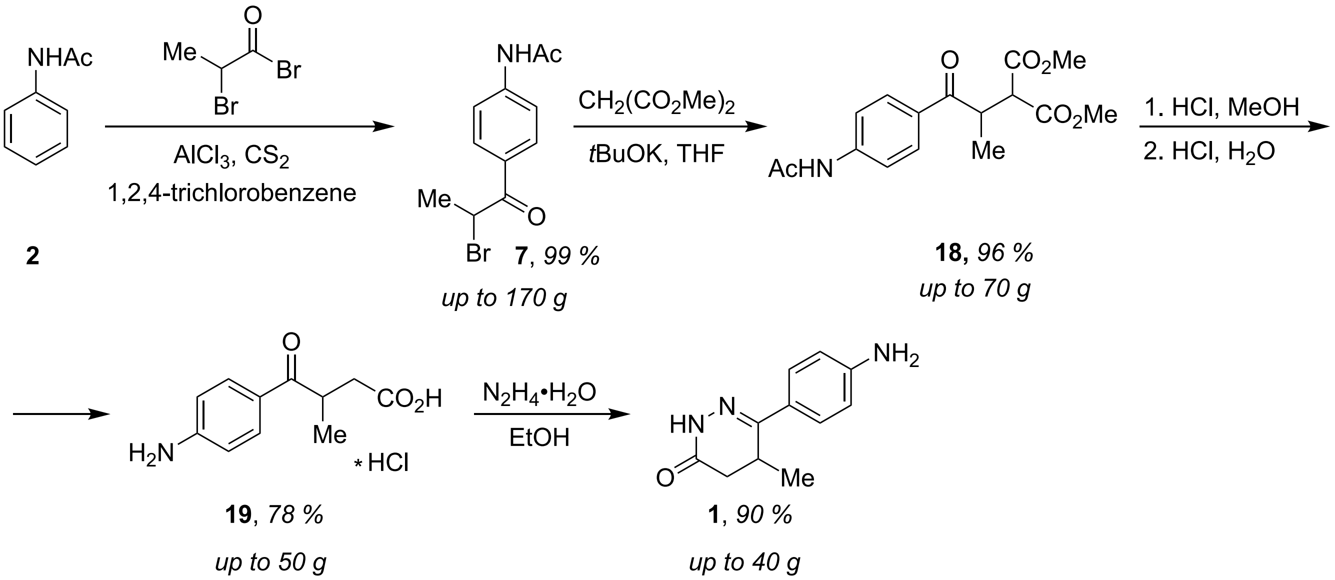
18, *78 %*   **19**

Scheme 8. The preparation of 4-(4-Aminophenyl)-3-methyl-4-oxobutanoic acid hydrochloride *via* the hydrolysis and decarboxylation of dimethyl 2-(1-(4-acetamidophenyl)-1-oxopropan-2-yl)malonate



19   **1**, *90 %*

Scheme 9. The cyclization reaction of 4-(4-aminophenyl)-3-methyl-4-oxobutanoic acid hydrochloride with hydrazine hydrate



Scheme 10. The optimized scheme for the synthesis of racemic 6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one

for the isolation of the *R*-enantiomer with its content of 98.6%.

The application of tartaric acid derivatives **20**,**21** for the separation of enantiomers of 6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**1**) for the further use of the desired *R*-enantiomer in the synthesis of Levosimendan was described in the patent [4]. The patent stated that any derivative **20**,**21** with any configuration of chiral centers can be used for the separation (**Figure 2**). The separation of enantiomers using acids **20**,**21** included the following stages as in the case of *L*-(+)-tartaric acid: **(1)** the synthesis of the salt with tartaric acid derivative **20**,**21**; **(2)** the crystallization of the resulting mixture of diastereomeric salts using the ethanol/H_2O 1:1 mixture; **(3)** the conversion of the salt to amine **1**. Authors of [4] stated that one crystallization was sufficient to separate diastereomeric salts. Depending on the configuration of acids **20**,**21** used, the desired (*R*)-**1** either precipitated or remained in the solution.

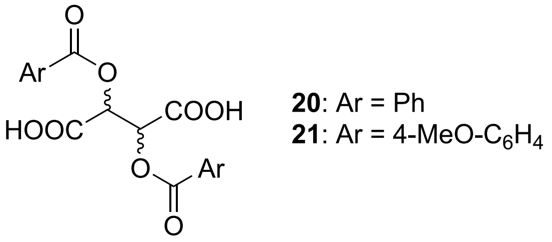
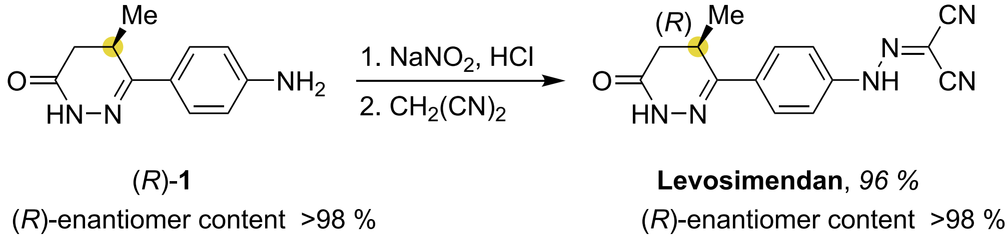


Figure 2. Tartaric acid derivatives used for the separation of enantiomers of amines [4]

When we used acid **20** for the enantiomer separation as it was described in patent [4], after two crystallizations of diastereomeric salts we obtained racemic amine **1** without any enrichment with a desired (*R*)-enantiomer. We showed that the best results were achieved when using a small excess of *S*,*S*-2,3-*bis*-(4-methoxybenzoyloxy)butanedioic acid (**21**). One crystallization of the mixture of diastereomeric salts of racemic amine **1**, as it was described in [4], did not lead to the full enantiomer separation. The *R*-enantiomer of amine **1** with the (*R*)-enantiomer content of up to 99% was isolated after five crystallizations of the mixture of diastereomeric salts.

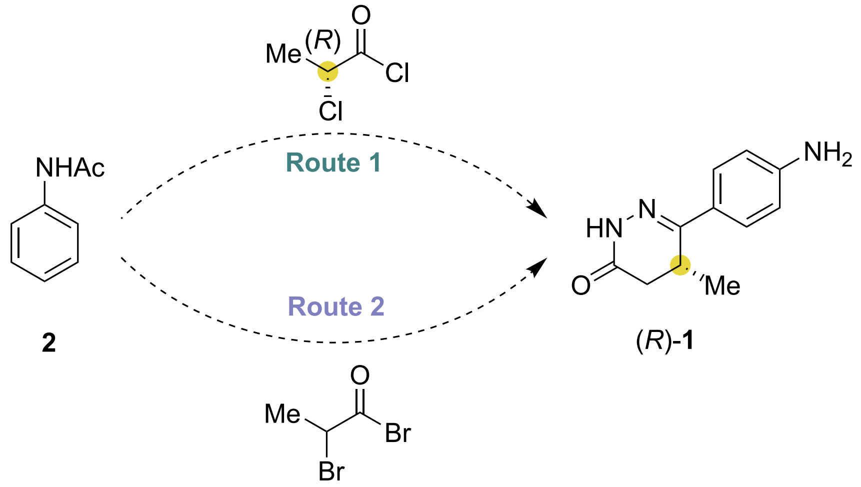
Table 3 summarizes our results of both methods selected for obtaining (*R*)-6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**1**).

(*R*)-**1** was easily converted into Levosimendan as it was described in [4] with preserving the configuration of the chiral center and the yield of 96% (**Scheme 11**).



Scheme 11. The last step for the preparation of Levosimendan

Table 3. A brief summary of our results for obtaining (*R*)-6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**1**)



Route 1	Route 2
– the expensive chiral starting compound^a – racemization on the malonic synthesis stage	+ high yields at all stages^b + 67 % total yield of the racemate + 24 % yield at the enantiomer separation stage + the separation of enantiomers up to 99 % of the (*R*)-enantiomer content + scalable

Notes: ^{a} "–" indicates disadvantages of the method; ^{b}"+" indicates advantages of the method

The (*R*)-Enantiomer content was the main quality indicator that was focused on in the process of the synthetic route optimization.

Since Levosimendan is the active pharmaceutical ingredient (API), it is important to check certain quality parameters specific to such substances. The quality tests were performed according to the following general chapters of the European Pharmacopoeia (EP): identification by NMR (2.2.33), loss on drying (2.2.32), sulfated ash (2.4.14), and HPLC assay, related substances, and (*R*)-enantiomer content tests (2.2.29, 2.2.46) [12]. The results of the final sample quality of the Levosimendan obtained are shown in **Table 4**.

Table 4. The results of quality testing of the final sample of Levosimendan

Parameter	Eur. Ph. General Chapter	Results
Appearance		A dark-yellow crystalline powder
Solubility		Very slightly soluble in ethanol (96 %)
Identification	2.2.33	Conform to the structure
pH	2.2.3	6.00
Loss on drying	2.2.32	1.26 %
Sulfated ash	2.4.14	3.13 %
Impurities: • individual impurity • total impurities	2.2.29, 2.2.46	 0.30 % 1.21 %
(*R*)-Enantiomer content		up to 99 %
Assay		93.1 %

Conclusions

We have evaluated two literature methods for obtaining 6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**1**). It has been found that the use of (*R*)-2-chloropropionyl chloride in the initial step is ineffective due to racemization at the stage of the synthesis based on the malonic ester. The method of the synthesis of 6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**1**) starting from racemic 2-bromopropionyl bromide has been modified to be suitable for scaling up and used for converting it into the industrial technology. The separation of racemic 6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one yielding *R*-enantiomer with the high enantiomeric purity ((*R*)-enantiomer content of up to 99%) has been developed. It has been shown that amine (*R*)**-1** can be converted into Levosimendan with the configuration retention of the chiral center and a high yield.

■ Experimental part

^{1}H NMR spectra were recorded using a Varian VXR-300 instrument at 300 MHz, or a Varian UNITY-Plus 400 instrument at 400 MHz. ^{13}C NMR spectra (proton decoupled) were recorded on a Bruker AVANCE DRX 500 instrument at 125 MHz. The chemical shifts are given in ppm relative to TMS as an internal or external standard.

Thin-layer chromatography (TLC) was carried out on aluminium-backed plates coated with silica gel (Merck Kieselgel 60 F254). LC-MS spectra were registered on an "Agilent 1100 Series" instrument with a diode-matrix and an "Agilent 1100 LS/MSD SL" mass-selective detector (the ionization method – chemical ionization at atmospheric pressure; the ionization chamber operation conditions – simultaneous scanning of positive and negative ions in the range of 80–1000 m/z).

Melting points were determined in open capillaries using a SMP3 instrument (Stuart Scientific Bibby Sterlin Ltd, Stone, Staffordshire, UK).

Unless otherwise stated, commercially available reagents were used without purification after being purchased. The solvents were purified according to standard procedures.

***N*-(4-(2-Bromopropanoyl)phenyl)acetamide (7)**

Acetanilide **2** (30 g, 0.222 mol) in 1,2,4-trichlorobenzene (500 mL) was placed into a three-necked flask equipped with a thermometer, a mechanical stirrer, and an addition funnel. Anhydrous aluminum chloride (90 g, 0.667 mol) was added to the solution. The reaction mixture was heated to 70°C, and 2-bromopropionyl bromide (60 g, 0.25 mol) was added dropwise for ~30 min at such a rate that the temperature did not rise higher than 80°C. After the addition was completed, the reaction mixture was heated at 80°C for 3 h. The heating source was removed, and dichloromethane (500 mL) was added to the reaction mixture at 80°C. The temperature of the reaction mixture decreased to (50±5)°C. The warm reaction mixture was slowly poured into the ice/water mixture (1 L). The organic layer was separated, and the product was extracted from water with dichloromethane (5×100 mL). Dichloromethane solutions were combined, washed with water (5×70 mL), and dried over $MgSO_4$. The solvent was evaporated in vacuum. The residue containing product **7** and 1,2,4-trichlorobenzene was washed with hexane (5×200 mL) to remove 1,2,4-trichlorobenzene. After removing 1,2,4-trichlorobenzene, the residue was placed into the flask and dried in vacuum (0.5–1 mm Hg) at 50°C for 4–5 h.

A yellow solid. Yield – 59 g (99%). M. p. 118–120°C (Lit. 128–131°C [6]). ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 1.88 (3H, d, $^3J_{HH}$ = 6.6 Hz, CH_3), 2.21 (3H, s, $COCH_3$), 5.26 (1H, q, $^3J_{HH}$ = 6.6 Hz, CH), 7.65 (2H, d, $^3J_{HH}$ = 8.7 Hz, ArH), 7.98 (2H, d, $^3J_{HH}$ = 8.7 Hz, ArH). (Lit. [10])

Dimethyl 2-(1-(4-acetamidophenyl)-1-oxopropan-2-yl)malonate (18)

Dimethyl malonate (37 g, 0.28 mol) was added dropwise to the solution of *t*BuOK (31 g, 0.28 mol) in THF (350 mL). The reaction mixture was stirred at room temperature (15–20°C) for 1 h, and bromide **7** (60 g, 0.22 mol) in THF (300 mL) was slowly added at the same temperature. The reaction mixture was stirred at room temperature (15–20°C) for 48 h (until the disappearance of the starting bromide **7** by TLC, eluent hexane/MTBE 1:5, R_f (**7**) = 0.3, R_f (**18**) = 0.2), and then poured into water (700 mL). The pH of the solution was adjusted to 5.5–6 using 10% HCl solution. The product was extracted with MTBE (4×300 mL), and the organic layer was washed with water (3×250 mL) and dried over $MgSO_4$. The solvent was distilled off in vacuum (10 mm Hg), then the residual solvent and the excess of dimethyl malonate were removed in vacuum (1 mm Hg, 60°C, 6 h), yielding **18** as a yellow solid (68 g, 96%).

^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 1.18 (3H, d, $^3J_{HH}$ = 7.2 Hz, CH_3), 2.20 (3H, s, $COCH_3$), 3.66 (3H, s, $COOCH_3$), 3.80 (3H, s, $COOCH_3$), 4.00 (1H, d, $^3J_{HH}$ = 10.9 Hz, CH), 4.12–4.14 (1H, m, CH), 7.60 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 7.95 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH). LC-MS, m/z: 320 $[M–H]^-$ (negative ionization); 322 $[M+H]^+$ (positive ionization).

4-(4-Aminophenyl)-3-methyl-4-oxobutanoic acid hydrochloride (19)

To compound **18** (74 g, 0.23 mol), the solution of HCl in methanol (1.4 L, c = 3 mol L^{-1}) was added, and the reaction mixture was refluxed for 8 h. The solvent was removed to dryness in vacuum, and an aqueous solution of HCl (1.4 L, c = 6 mol L^{-1}) was added to the residue. The resulting solution was refluxed for 5 h. The solvent was evaporated to dryness in vacuum, and 50 mL of conc. HCl was added to the residue. The precipitate was filtered off and washed with conc. HCl (10 mL) and 2-propanol (40 mL), and dried in vacuum (1 mm Hg, 60°C, 4 h).

A brownish solid. Yield – 43.5 g (78%). M. p. 186–188°C (dec.) (Lit. 187–188°C (dec.) [6]). ^{1}H NMR (300 MHz, D_2O), δ, ppm: 1.16 (3H, d, $^3J_{HH}$ = 7.2 Hz,

CH_3), 2.62 (1H, dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 4.8 Hz, CH_2), 2.85 (1H, dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 9.3 Hz, CH_2), 3.91-3.99 (1H, m, CH), 7.44 (2H, d, $^3J_{HH}$ = 8.7 Hz, ArH), 8.07 (2H, d, $^3J_{HH}$ = 8.7 Hz, ArH).

6-(4-Aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (1)

The hydrazine hydrate solution (90 mL, 90% aqueous solution) was added to the solution of compound **19** (44 g, 0.18 mol) in ethanol (500 mL). The reaction mixture was refluxed for 5 h and then cooled to room temperature. The solvent was removed in vacuum to dryness. Water (50 mL) was added to the residue. The precipitate was filtered off, washed with water and 2-propanol, and dried in vacuum (1 mm Hg, 50 °C, 4 h).

A brownish solid. Yield – 33 g (90%). M. p. 193–195°C (Lit. 211–212°C [9], 195–197°C [6]). ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 1.03 (3H, d, $^3J_{HH}$ = 7.2 Hz, CH_3), 2.17 (1H, d, $^2J_{HH}$ = 16.7 Hz, CH_2), 2.59 (1H, dd, $^2J_{HH}$ = 16.7 Hz, $^3J_{HH}$ = 6.6 Hz, CH_2), 3.23–3.29 (1H, m, CH), 5.49 (2H, s, NH_2), 6.57 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.48 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 10.67 (1H, s, NH). (Lit. [5])

(*R*)-6-(4-Aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one ((*R*)-1). The enantiomer separation using *L*-(+)-tartaric acid

The racemate of amine **1** (23 g, 0.11 mol), *L*-(+)-tartaric acid (34 g, 0.23 mol), and 2-propanol (450 mL) were placed into a flask and heated under reflux for 30 min. The reaction mixture was allowed to cool to room temperature overnight. The precipitate was filtered off and dried in vacuum (1 mm Hg, 40°C, 5 h), yielding 45 g (100%) of a mixture of diastereomeric salts as a solvate with one molecule of 2-propanol.

The mixture of diastereomeric salts was crystallized from 2-propanol 32 times (until the (*R*)-enantiomer content in the sample reached 98.6%). The first crystallization was carried out using activated carbon. As the amount of the precipitate used for the crystallization decreased, the amount of the solvent decreased proportionally (for example, 450 mL of the solvent was used for 45 g of the precipitate, and 300 mL of the solvent was used for 30 g of the precipitate).

When required the (*R*)-enantiomer content in the sample was reached, (*R*)-6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one *L*-(+)-tartrate was converted to (*R*)-6-(4-Aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one ((*R*)-**1**) as follows.

An aqueous solution of potassium carbonate was added to the suspension of (*R*)-6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one *L*-(+)-tartrate (7 g, 21 mmol) in water (50 mL) to pH 8. The precipitate was filtered off, washed with the aqueous solution of potassium carbonate (15 mL) and water (2×35 mL), and dried in vacuum (1 mm Hg, 40°C, 5 hours), yielding 3 g (86%) of amine (*R*)-**1** with the (*R*)-enantiomer content of 98.6%.

(*R*)-6-(4-Aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one ((*R*)-1). Enantiomers separation using *S*,*S*-2,3-*bis*-(4-methoxybenzoyloxy)butanedioic acid (21)

The racemate of amine **1** (23 g, 0.11 mol) was placed into a 1-L flask, ethanol (200 mL) was added, and the suspension formed was heated at 65°C for 30 min, followed by the addition of *S*,*S*-2,3-*bis*-(4-methoxybenzoyloxy)butanedioic acid (**21**) (57 g, 0.136 mol) and water (200 mL) at the same temperature. The resulting solution was heated at 65°C for 1 h, and then refluxed for 5 min. The reaction mixture was allowed to cool to room temperature. In 24 h, the precipitate was filtered off and used for further crystallization.

After obtaining the salt or after the preliminary crystallization, the crude precipitate was placed into a flask, the solvent (ethanol/water 1:1) was added, and the resulting solution was refluxed for 5–10 min and allowed to slowly cool to room temperature. In 24 h, the precipitate was filtered and used for the subsequent crystallization. For the first crystallization, approximately the same amount of the solvent was used as for the preparation of the salt. During the subsequent crystallizations, the amount of the solvent was gradually reduced (1/3 of the previous volume of the solvent was added, the suspension was heated to boiling, and more solvent was added in portions until a clear solution was formed). The first crystallization was carried out using activated carbon. After the fifth crystallization, the precipitate was dried in vacuum (1 mm Hg, 65°C, 1 h) from alcohol residues and used for conversion to the amine.

A 25% aqueous solution of ammonia was added to the suspension of the salt of amine ((*R*)-**1**) with acid (**21**) in water (~4 mL of water per 1 g of the salt) to pH 8. The suspension was stirred for 15–20 min, and the pH was again controlled. If the medium became neutral, the solution of ammonia was added to pH 8. The addition of the ammonia solution was repeated until the pH of the medium (pH 8) did not change while stirring for 30–40 min. The precipitate was filtered off, washed with water, and dried in vacuum (1 mm Hg, 60°C, 2 h), yielding 2.8 g (12% based on the racemate, 24% based on the content of the *R*-enantiomer in the racemate) of amine ((*R*)-**1**) with the (*R*)-enantiomer content of up to 99%.

(*R*)-N-(4-(4-Methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl)-carbono-hydrazonoyl dicyanide (Levosimendan)

The solution of sodium nitrite (1.16 g, 17 mmol) in water (20 mL) was added dropwise to the solution of amine (*R*)-**1** (3.4 g, 17 mmol, the (*R*)-enantiomer content >98%) in a diluted HCl (prepared from 10 mL of conc. HCl and 135 mL of water) at 10–12°C. The reaction mixture was stirred at this temperature for 10 min, and the solution of malononitrile (1.11 g, 17 mmol) in water (20 mL) was added dropwise at the same temperature. The reaction mixture was stirred at room temperature (20°C) for 1 h and then neutralized with an aqueous solution of sodium acetate to pH 7. The suspension formed was stirred for 30 min at room temperature. The precipitate was filtered off, washed with water (4×50 mL), and dried in vacuum (1 mm Hg, 65°C, 4 h).

A yellow solid. Yield – 4.5 g (96%). M. p. >210°C (dec) (Lit. 210–214°C [13]). (*R*)-enantiomer content >98%. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 1.07 (3H, d, $^3J_{HH} = 6.4$ Hz, CH$_3$), 2.24 (1H, d, $^2J_{HH} = 16.4$ Hz, CH$_2$), 2.65 (1H, dd, $^2J_{HH} = 16.4$ Hz, $^3J_{HH} = 6.0$ Hz, CH$_2$), 3.33–3.37 (1H, m, CH), 7.48 (2H, d, $^3J_{HH} = 8.0$ Hz, ArH), 7.81 (2H, d, $^3J_{HH} = 8.0$ Hz, ArH), 10.96 (1H, s, NH), 12.77–13.32 (1H, br.s, NH). ^{13}C NMR (125.6 MHz, DMSO-d$_6$), δ, ppm: 16.8, 28.0, 34.4, 86.2, 110.7, 115.1, 117.4, 127.9, 133.0, 142.8, 152.7, 167.3. (Lit. [11]).

The (*R*)-enantiomer content analysis

The (*R*)-enantiomer content was determined by the HPLC method on an Agilent 1260 Infinity II instrument. The separation was performed on a Lux Cellulose-3 column (250 mm × 4.6 mm and 5 µm particle size) at a flow rate of 1.0 mL min^{-1} and the UV detection at 311 nm. The column temperature was set at 25°C. The isocratic elution was carried out using a mobile phase composed of water, acetonitrile, and acetic acid (60:40:0.1 *v*/*v*/*v*, respectively).

In a typical analysis system, the suitability solution containing Levosimendan and Dextrosimendan (0.25 mg mL^{-1}, Clearsynth) was used. It was previously dissolved in DMSO and then diluted with the mobile phase. The test solution was prepared in the same way at a concentration of about 1 mg mL^{-1}. The volume of the injected solutions was 10 µL.

Typical chromatograms of blank, system suitability, and test solutions are shown in **Figure 3**. The chromatographic system was considered suitable if the resolution between Levosimendan and Dextrosimendan peaks calculated from the system suitability solution chromatogram was not less than 2.0.

The Levosimendan assay in the final sample was carried out by the HPLC method on an Agilent 1260 Infinity II instrument. A Hypersil BDS C18 column (250 mm × 4.6 mm and 5 µm particle size) was used as the stationary phase. The column temperature was set at 40°C. A mobile phase mixture of acetonitrile, water, and 0.1% trifluoroacetic acid solution adjusted to pH 3.0 with triethylamine (40:10:50 *v*/*v*/*v*, respectively) was used. The isocratic elution was performed at a flow rate of 1.0 mL min^{-1} with the UV detection at 375 nm.

As a reference solution, 0.1 mg mL^{-1} Levosimendan solution, previously dissolved in DMSO and then diluted with mobile phase, was used. The test solution was prepared in the same way in the same concentration. The volume of the injected solutions was 10 µL.

Typical chromatograms of blank, reference, and test solutions are shown in **Figure 4**. The chromatographic system was considered suitable if the relative standard deviation calculated for

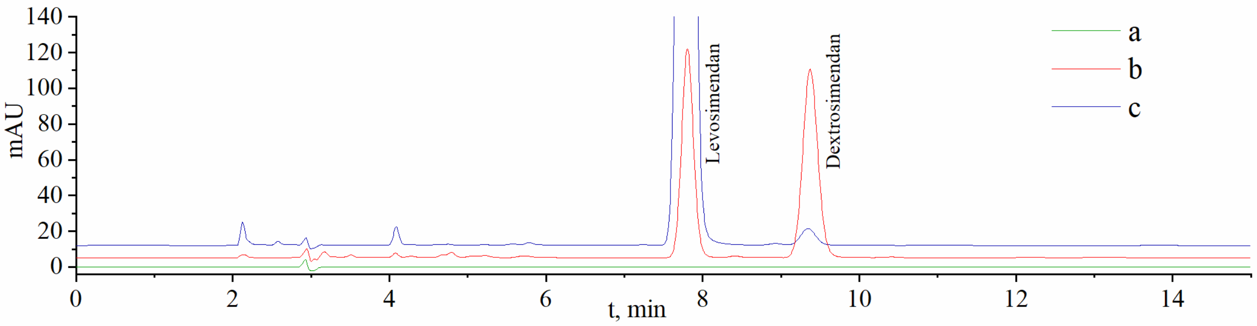


Figure 3. The (*R*)-enantiomer content test of the Levosimendan final sample, typical chromatograms: **a** – blank solution, **b** – system suitability solution, **c** – test solution

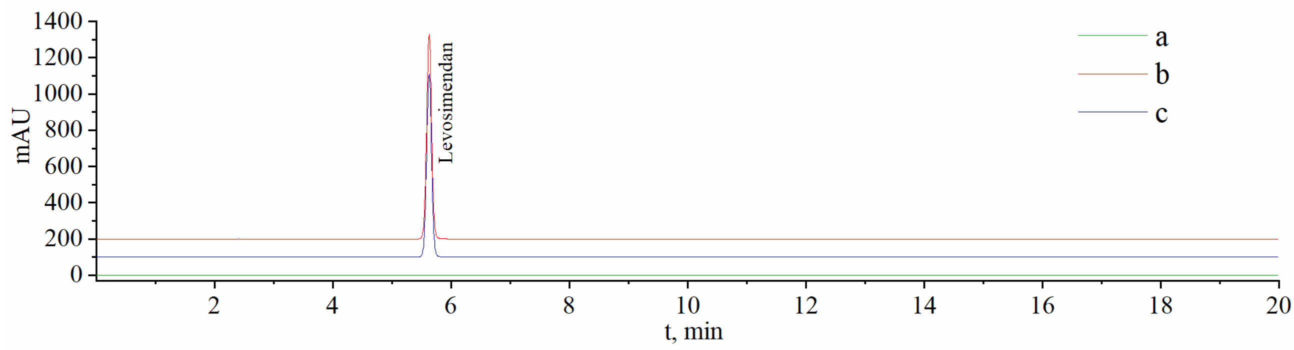


Figure 4. The assay test of the Levosimendan final sample typical chromatograms: **a** – reference solution, **b** – test solution, **c** – blank solution

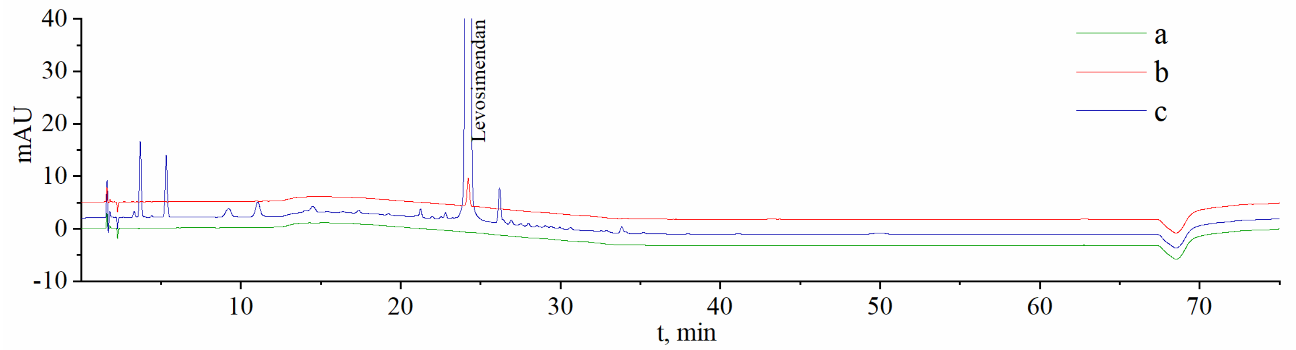


Figure 5. The assay test of the Levosimendan final sample typical chromatograms: **a** – reference solution, **b** – test solution, **c** – blank solution

6 injections of the reference solution chromatograms was not more than 2.0%, and the peak symmetry was not more than 2.0.

The test of related substances in the final sample was performed by the HPLC method on an Agilent Infinity II instrument and a Hypersil BDS C18 column (150 mm × 4.6 mm and 5 µm particle size) with the UV detection at 285 nm. The column temperature was set at 30°C. *Mobile phase A* was 0.2% triethylamine solution with pH 4.0 adjusted with trifluoroacetic acid, and *mobile phase B* was methanol. The gradient elution was carried out with a gradient program (0–10 min: 70% *A* – 30% *B*; 10–30 min: 40% *A* – 60% *B*, 30–65 min: 40% *A* – 60% *B*, 65–66 min: 70% *A* – 30% *B*, 66–75 min: 70% *A* – 30% *B*) and the flow rate at 1.0 mL min^{-1}.

The Levosimendan solution (0.003 mg mL^{-1}) was used as a reference solution. It was previously dissolved in DMSO, and then diluted with the solvent (0.05% trifluoroacetic acid solution in 50% methanol water solution). The solution of the final sample (2 mg mL^{-1}) was prepared for the test in the same way as the reference solution. All solutions were prepared in amber volumetric flasks, and the volumes of the injected solutions were 10 µL.

Typical chromatograms of blank, reference, and test solutions are shown in **Figure 5**. The chromatographic system was considered suitable if the relative standard deviation calculated for 6 injections of the reference solution chromatograms was not more than 5%, and the retention time was approximately 23 min.

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Review Article

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The Synthesis of Pyrroles from Nitroolefins

Abstract

The synthesis of pyrroles occupies a key place in synthetic organic chemistry due to the numerous biological properties of pyrrole derivatives, in particular antimicrobial, antibacterial, antifungal, antimalarial, anticancer activities, etc. Therefore, pyrroles serve as building blocks in the creation of potential pharmaceuticals and also serve as the basis for the synthesis of boradipyrromethene dyes. One of the most well-known approaches to the synthesis of pyrroles is the reaction between nitroolefins, 1,3-dicarbonyl compounds, and amines, also known as the Grob-Camenisch reaction. This review is devoted to the historical chronology from the discovery of this transformation dating back to 1950s to the present, and covers the development of various modifications of the above reaction in the synthesis of pyrroles.

Keywords: pyrrole; Grob–Camenisch reaction; nitroolefines

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Синтез піролів з нітроолефінів

Анотація

Синтез піролів займає ключове місце в синтетичній органічній хімії завдяки численним біологічним властивостям похідних піролу, зокрема антимікробній, антибактеріальній, протигрибковій, антималярійній, протираковій тощо. Саме тому піроли слугують будівельними блоками у створенні потенційних фармацевтичних препаратів, а також є основою для синтезу барвників бордипірометенового ряду. Одним із найвідоміших підходів до синтезу піролів є реакція між нітроолефінами, 1,3-дикарбонільними сполуками та амінами, відома як реакція Гроба-Каменіша. Цей огляд висвітлює історичну хронологію від відкриття цього перетворення, датованого 1950-ми роками, до сьогодення та охоплює розробку різноманітних модифікацій вищезгаданої реакції в синтезі піролів.

Ключові слова: пірол; реакція Гроба-Каменіша; нітроолефіни

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■ Introduction

Heterocyclic compounds are very important in the field of organic chemistry as they are widely spread in nature and commonly used as building blocks in pharmacology. Among heterocycles, pyrrole is of great interest due to its presence in a variety of medicines, such as atorvastatin [1], tolmetin [2], ketorolac [3] etc., and its application in the dye synthesis, for example, BODIPY [4]. Therefore, the pyrrole core synthesis methods play a key role in contemporary organic chemistry.

There are some well-known synthetic routes for the pyrrole synthesis. The first one is the Hantzsch reaction, including the transformation between β-ketoesters, ammonia source, and haloketones [5]. Alternatively, the Knorr synthesis (the reaction between α-amino-ketones and 1,3-dicarbonyl compounds) [6] or the Paal-Knorr synthesis (the reaction between 1,4-diketones and different ammonia sources) [7] can be employed. Due to increased interest, other methods of the pyrrole synthesis were developed. One of them is based on the *aza*-Wittig reaction, involving the interaction between l-aza-l,3-*bis*(triphenylphosphoranylidene)propane and 1,2-diketo-compounds [8], and another one includes the reaction between 3-formylchromones and amines under TMSCl-mediated conditions [9].

Nitroolefins are an efficient initial material for the synthesis of organic compounds. Their synthetic attractiveness refers to the simplicity of their preparation *via* the condensation between nitroalkanes and aldehydes, known as the Henry reaction [10]. In ß-nitrostyrene, the conjugation of the double bond with the nitro group enables it to participate in the Michael addition [11], a reaction that plays a crucial role in the synthesis of heterocycles. For example, nitroolefins are widely used in the synthesis of aziridines, pyrrolidines, oxazoles, indoles, etc. [12].

Taking the aforementioned information into account, the aim of this review is to discuss the historical development and progress in the pyrrole synthesis methods from nitroolefin derivatives.

Discovery of the Grob-Camenisch reaction

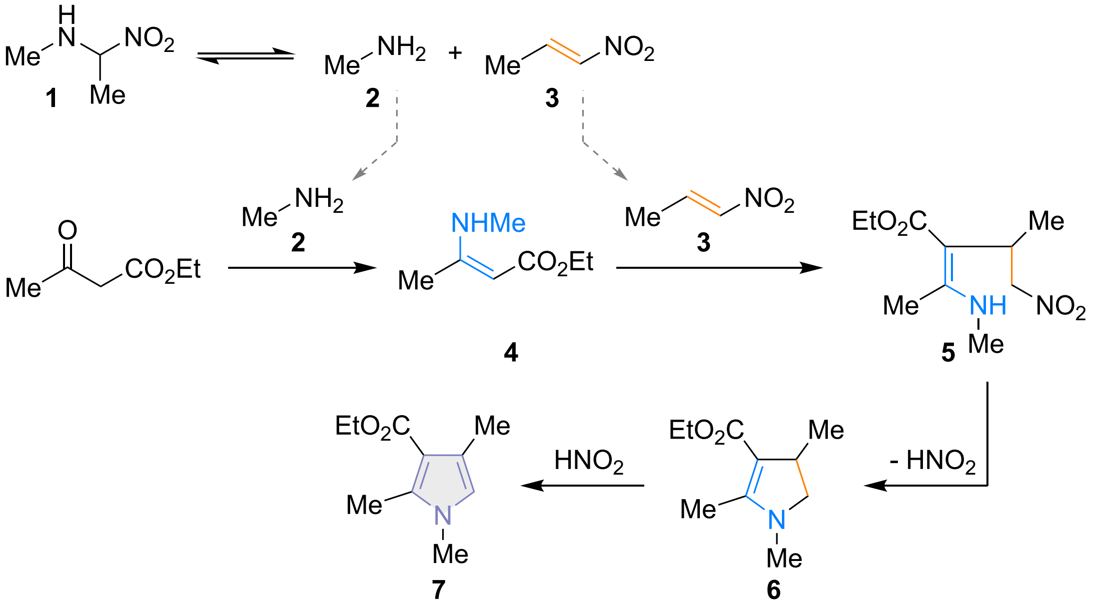
The first literary mention of the pyrroles synthesis from nitro compounds refers to the work of Grob and Kamenisch, dating back to 1953 [13]. Using 1-nitro-2-methylaminopropane and acetoacetic ester, the authors synthesized ethyl 1,2,4-trimethyl-2-pyrrolecarboxylate with a yield of 31%. They suggested the following mechanism (**Scheme 1**). In the solution, 1-nitro-2-methylaminopropane (**1**) exists in equilibrium with methylamine (**2**) and 1-nitropropene (**3**). After the addition of acetoacetic ester, the latter undergoes the condensation to form the corresponding enamine **4**, which further reacts with 1-nitropropene, resulting in Michael's product **5**. This product **5** cyclizes into dihydropyrrole **6**, eliminating a molecule of nitrous acid, which, in turn, oxidizes intermediate **6**, forming pyrrole **7**.

The further development of the reaction involving nitroolefins, 1,3-dicarbonyl compounds, and amines focused on identifying alternative synthetic approaches to increase pyrrole yields and expand the range of substrates that could be used. Currently, several variants of this reaction are known, including two-, three-, and four-component Grob-Camenisch-type reactions.

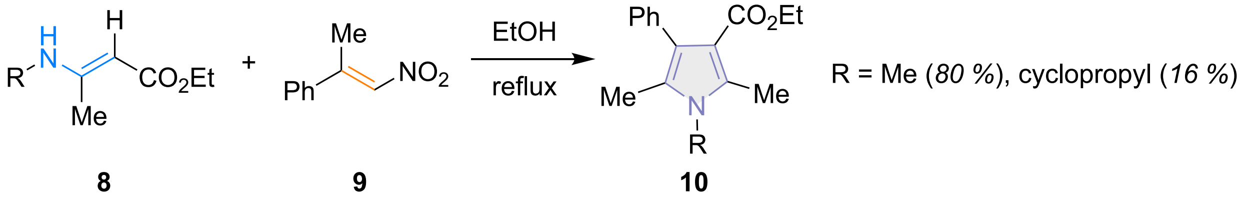
A two-component Grob-Camenisch-type reaction

The two-component Grob-Camenisch-type synthesis of pyrroles involves the reaction of ß-enaminoesters or ketones with nitrostyrenes. First reported in 1981, this method utilized enamines **8**, derived from acetoacetic ester and (*E*)-(2-nitroprop-1-en-1-yl)benzene (**9**) [14]. Refluxing the reaction mixture in ethanol for four to six hours allows the pyrroles **10** to be obtained with yields ranging from 16% to 80% (**Scheme 2**).

The authors also found that using *N*-unsubstituted enamine **11** in the reaction with nitro



Scheme 1. The synthesis of pyrrole by Grob–Camenisch



Scheme 2. The synthesis of pyrroles from methyl- and cyclopropyl-derived enaminoesters

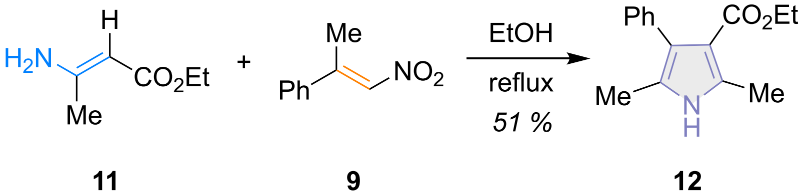
compound **9** by refluxing in ethanol for 14 hours could produce pyrrole **12** with a yield of 51% (**Scheme 3**).

Enaminoketones can also be used in a Grob-Camenisch-type reaction. However, harsher conditions are required, delivering the products with lower yields compared to standard substrates. Specifically, the reaction of enamine **13** with nitrostyrene **10** in a melt at 150°C produces pyrrole **14** with a yield of only 26% (**Scheme 4**) [14].

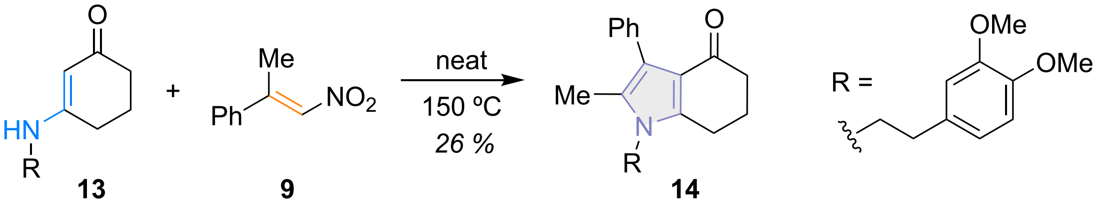
Further studies of the pyrrole synthesis from nitrostyrenes and β-enaminoesters or β-enaminoketones showed that enaminones **15** reacted with nitrostyrene or *p*-tolylnitrostyrene (**16**) under solvent-free conditions, yielding pyrroles in 70–90% yield (**Scheme 5**) [15]. The mechanism proposed involves the Michael-type addition of β-enaminones to nitroolefins, forming intermediate **17**, which cyclizes to pyrroline **18** with the elimination of nitrous acid. The subsequent oxidation results in the production of the final pyrrole **19**.

The scope and diversity of pyrroles synthesized from β-enaminones or esters and nitroolefins can be enhanced by using solvents or catalysts. For instance, the reaction of *N*-phenyl-substituted enamine **20** with substituted nitropropene **21** in methanol at 120°C yields pentasubstituted pyrroles **22** (**Scheme 6**) [16].

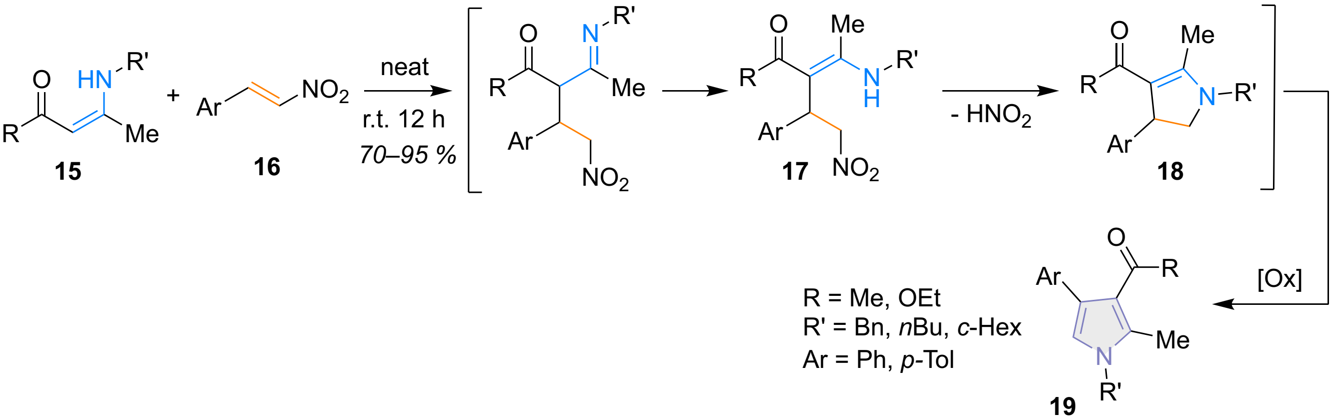
The authors observed that catalytic amounts of bases (e.g., sodium acetate or piperidine) and polar aprotic solvents (e.g., DMSO or acetonitrile)



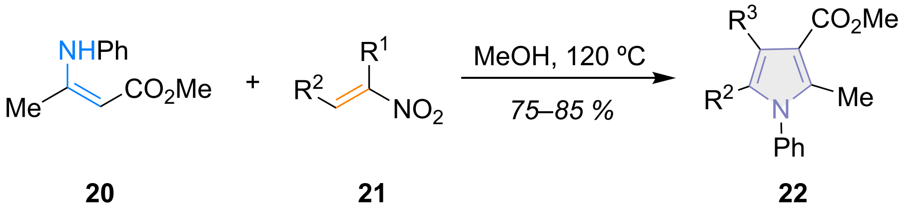
Scheme 3. The synthesis of pyrrole from *N*-unsubstituted enaminoester



Scheme 4. The synthesis of pyrrole from enaminone based on dimedone



Scheme 5. The reaction mechanism of the pyrrole formation in the reaction between enamines and nitrostyrenes



R^1 = H, Me

R^2 = Ph, 4-Me-C_6H_4, 3-Me-C_6H_4, 4-OMe-C_6H_4, 4-Me-C_6H_4, 4-NMe$_2$-C_6H_4, 4-F-C_6H_4, 2-furfuryl

Scheme 6. The synthesis of *N*-substituted pyrroles **22**

significantly decreased pyrrole yields. Electron-donating substituents on the aryl groups of nitrostyrenes and β-enaminoesters substantially improve yields compared to electron-withdrawing ones. It is noteworthy that the use of [2-nitroprop-1-en-1-yl]furan made it possible to synthesize pyrrole with a furyl group in position 3, yielding 79% of the product. Additionally, the application of nitrostyrene as a reagent facilitates the production of α-CH pyrrole with good yields.

Catalytic reactions provide an effective preparative method for synthesizing pyrroles from β-enaminoesters and nitroolefins. For instance, using iodine as a catalyst allows the formation of *N*-substituted pyrroles from nitrostyrene and β-enaminoesters derived from the acetoacetic ester. It is noteworthy that nitrostyrenes bearing electron-donating substituents result in pyrroles with significantly higher efficiency, whereas *N*-alkyl-substituted 3-aminobut-2-enoates lead to slightly lower yields due to competing side reactions [17].

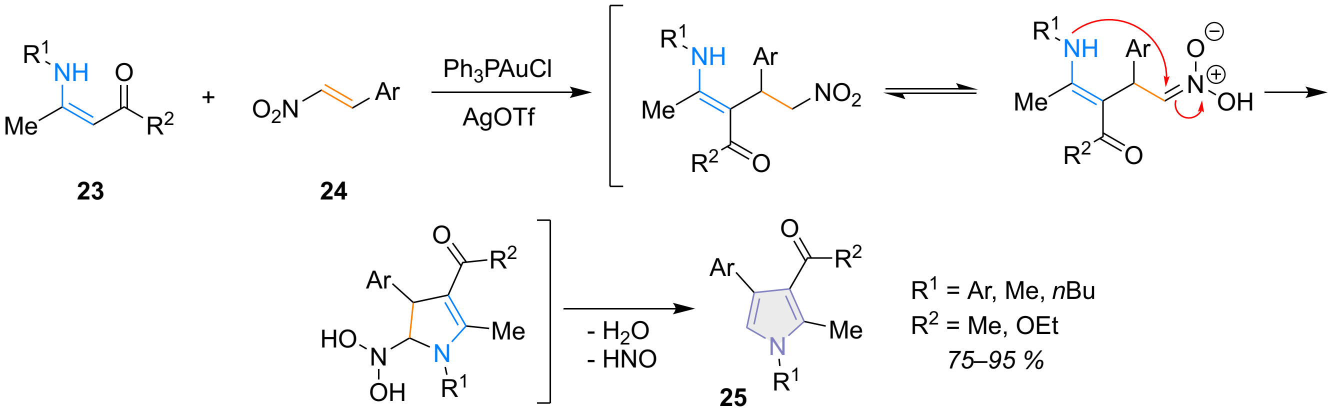
The Ph_3PAuCl catalyst combined with AgOTf significantly enhances the pyrrole synthesis *via* a two-component reaction. Reactions of *N*-substituted enamines **23** obtained from acetoacetic ester or acetylacetone with substituted nitrostyrenes **24** lead to pyrroles **25** with yields exceeding 80% (**Scheme 7**) [18]. It is noteworthy that the nature of substituents in aryl groups has minimal impact on pyrrole yields, and *N*-alkyl-substituted enamines react without side reactions, also giving pyrroles in high yields.

The PEG-400 catalyst demonstrated a high effectiveness for synthesizing isoxazole derivatives bearing a pyrrole moiety in position 4 [19]. The reaction of ethyl 3-((3-methyl-5-((*E*)-styryl)-isoxazol-4-yl)amino)but-2-enoate derivatives (**26**) with nitrostyrenes **27** gave the corresponding pyrroles **28** with yields from 70 to 90% (**Scheme 8**).

A solid-phase method for the pyrrole synthesis was also developed [20]. Initially, Rink Amide resin (**29**) is acetoacetylated with diketene to form amide **30**, which is subsequently converted to polymer-bound enaminone **31** upon the treatment with primary amines. Further reaction of polymer-bound **31** with nitroolefins in a DMF/EtOH solvent mixture at 60°C yielded pyrroles **32**, which upon the treatment with trifluoroacetic acid produced final amides **33**. In this method, the pyrrole yield exceeds 80% when using both aliphatic and aromatic amines, as well as aliphatic nitroolefins (**Scheme 9**).

A three-component Grob-Camenisch-type reaction

The three-component Grob-Camenisch synthesis of pyrroles involves the reaction of amines, 1,3-dicarbonyl compounds, and nitrostyrenes,

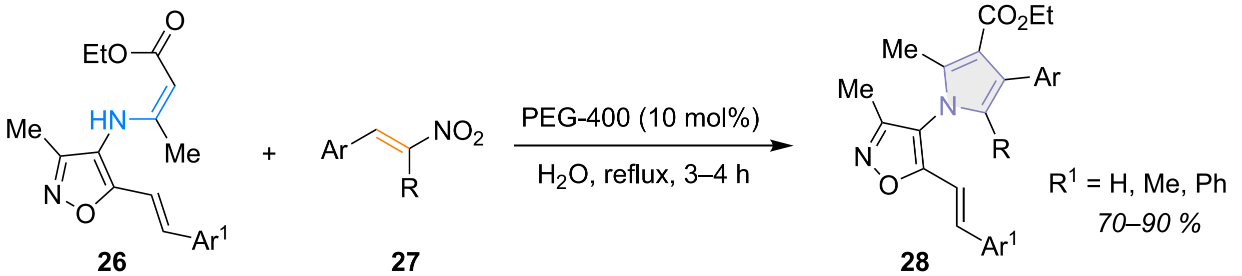


R^1 = Ar, Me, *n*Bu

R^2 = Me, OEt

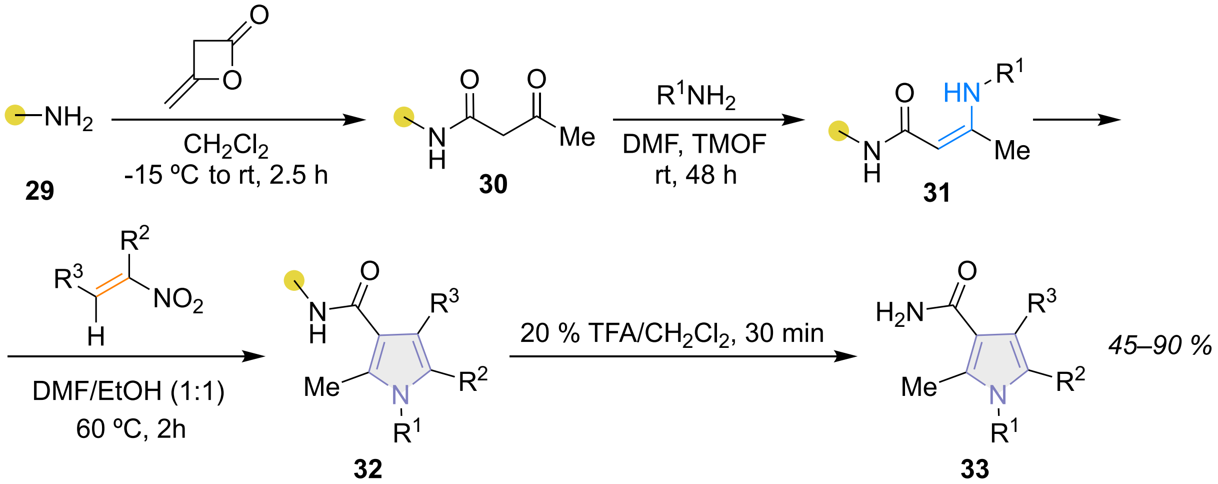
75–95 %

Scheme 7. The reaction mechanism of the pyrrole formation in the reaction between enamines and nitrostyrenes catalyzed with Ph_3PAuCl



26 **27** **28**

Scheme 8. The synthesis of pyrroles **28**



29 **30** **31** **32** **33**

R^1 = 2-phenylethyl, pyperonyl, cyclopropyl, 2-furfuryl, thiophene-2-ethyl,
R^2 = H, Me
R^3 = H, Ph, *p*-Cl-C_6H_4, 4-OMe-C_6H_4, 3-OMe-C_6H_4, 4-bromothienyl, cyclohexyl

Scheme 9. The solid-phase synthesis of pyrroles from nitroolefins

which make it possible to prepare pyrroles with catalytic activity. For instance, research [21] demonstrates that lactic acid serves as an effective medium for synthesizing tetrasubstituted pyrroles from acetylacetone and substituted anilines, achieving yields of approximately 70–90%. The study indicates that neither electron-withdrawing nor electron-donating substituents on the aniline significantly influence pyrrole yields.

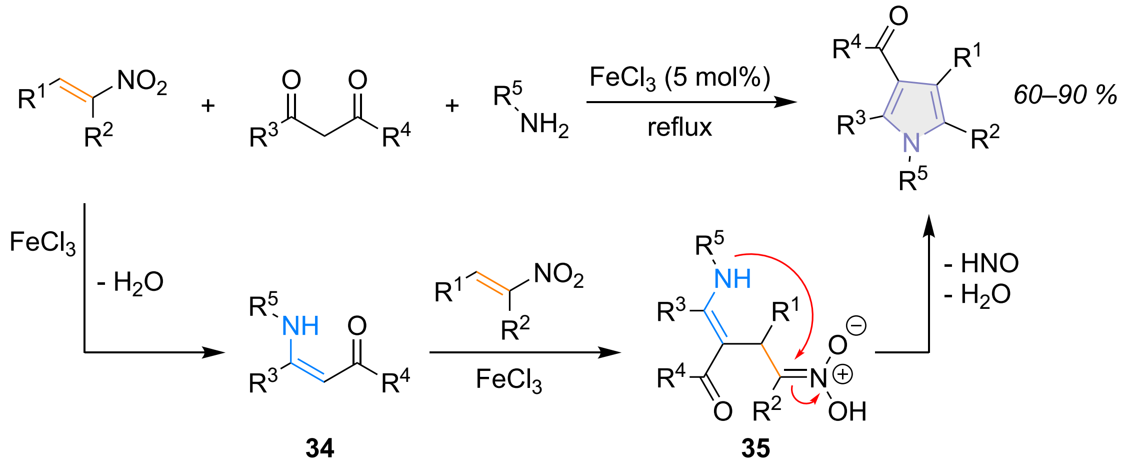
Iron-based catalysts, such as $FeCl_3$, are widely employed in the catalytic synthesis of pyrroles from nitroolefins and 1,3-dicarbonyl compounds. For instance, $FeCl_3$ facilitates a three-component reaction, yielding pyrroles at 70–80% using 1,3-dicarbonyl compounds like acetoacetic ester, acetylacetone, or ethylbenzyl acetate [22]. As a Lewis acid, $FeCl_3$ promotes the formation of β-enaminoester **34**, which undergoes the Michael-type addition to nitrostyrene, followed by the cyclization of the resulting adduct **35** into pyrrole *via* the nitro group conversion to its aci-nitro form (**Scheme 10**).

Interestingly, iron(III) chloride makes it possible to synthesize pyrroles from nitrostyrene bearing ethynyl substituents in the *ortho*-position, obtaining the target products with a yield of about 50% [23]. Additionally, the catalyst facilitates the pyrrole synthesis from peptides with a free amino group [24].

An alternative to $FeCl_3$ is the use of Fe_3O_4 nanoparticles, in particular Fe_3O_4@SiO_2-CPTMS-guanidine-SO_3H, which contain a terminal sulfo group [24]. This catalyst allows the synthesis of tetrasubstituted pyrroles from acetoacetic ester, acetylacetone, and *para*-chloro- or *para*-bromoanilines with yields of approximately 90% (**Scheme 11**). The sulfo group is supposed to catalyze the reaction similarly to $FeCl_3$.

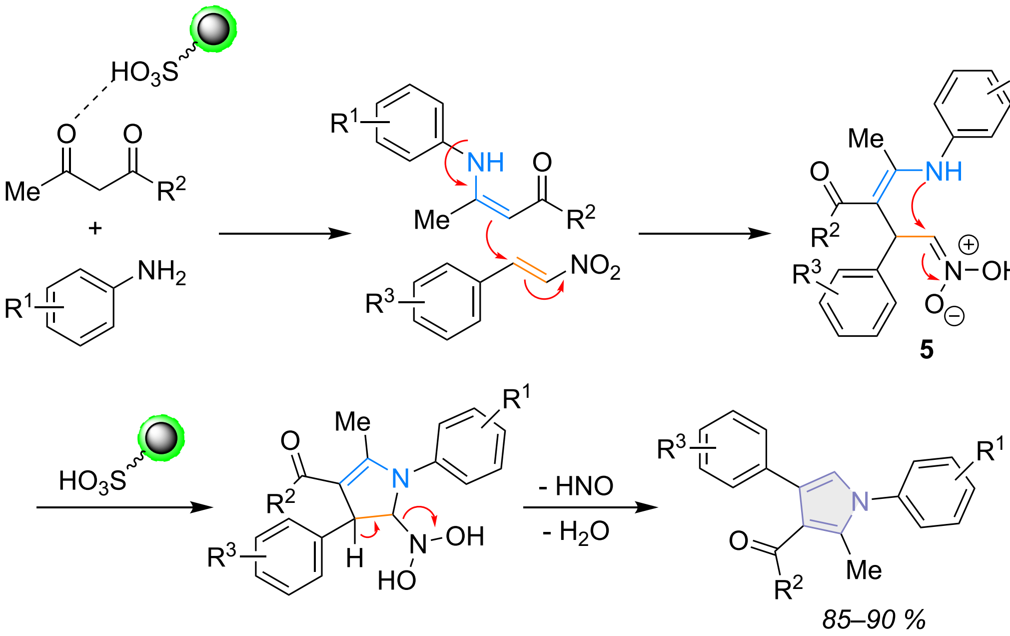
Cerium(III) chloride serves as an alternative catalyst to $FeCl_3$, effective in the microwave-assisted synthesis using nitromethane as a solvent [26]. This method allows the synthesis of tetrasubstituted pyrroles from acetoacetic ester or acetylacetone, nitrostyrenes, and anilines, with yields of about 80%. However, when *para*-chloronitrostyrene is used, the yield decreases to about 50%.

An alternative to $CeCl_3$ is cerium(IV) ammonium nitrate (CAN), which catalyzes the reaction of nitrostyrene **38**, acetoacetic ester (**36**),



R^1 = Ph, 4-Me-C_6H_4, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-Cl-C_6H_4, Br-C_6H_4, 2-thiophenyl, 2-naphtyl
R^2 = H, Me
R^3 = Me, Ph
R^4 = Me, OEt
R^5 = 4-Me-C_6H_4, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, Br-C_6H_4, 2-naphtyl

Scheme 10. The reaction mechanism of the three-component synthesis of pyrroles from nitroolefins catalyzed with $FeCl_3$



R^1 = Ph, 4-Cl, 4-Br
R^2 = Me, OEt
R^3 = H, 4-Me, 4-Cl, 4-OMe

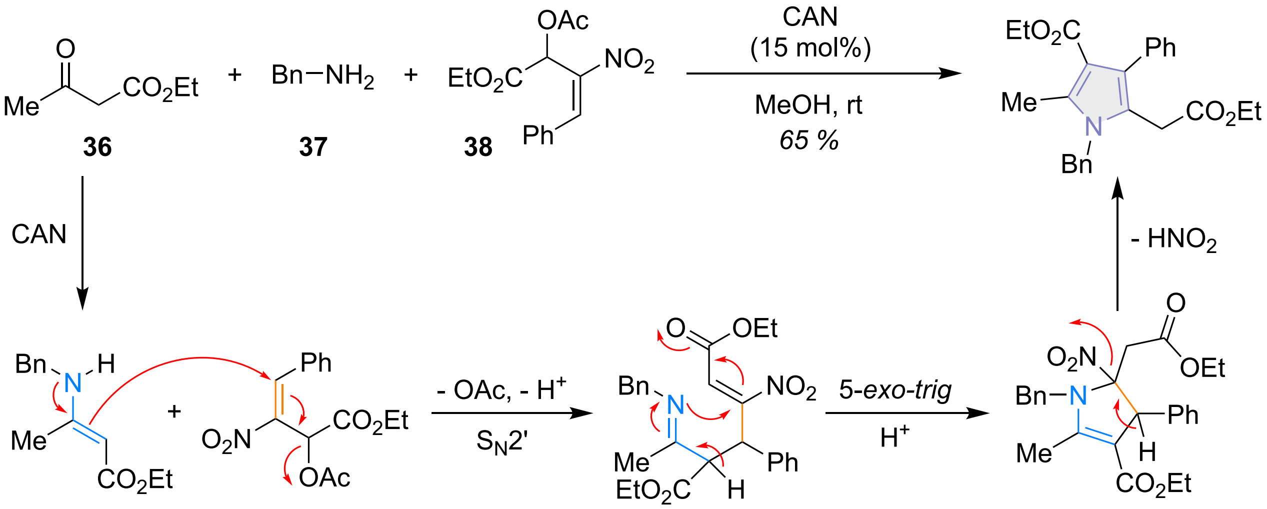
Scheme 11. The reaction mechanism of the three-component synthesis of pyrroles from nitroolefins catalyzed with Fe_3O_4@SiO_2-CPTMS-guanidine-SO_3H

and benzylamine (**37**) at room temperature in methanol [27]. This method produces pyrroles with yields ranging from 50 to 75% (**Scheme 12**).

In addition to other metal-containing catalysts, Ph_3PAuCl combined with AgOTf [28] and zirconyl dichloride complexes [29] makes it possible to use acetoacetic ester and various ß-diketoamides as 1,3-dicarbonyl compounds, yielding pyrroles at approximately 70%.

Furthermore, diacetoxyiodobenzene serves as an effective non-metal catalyst for the pyrrole synthesis, producing pyrroles from acetoacetic ester and acetylacetone with yields of about 70%, unaffected by substituents on nitrostyrene or aniline [30, 31].

The combination of oxone and iodobenzene makes it possible to synthesize pyrroles from nitrostyrenes, acetylacetone, or acetoacetic ester, and anilines, yielding 80–90% of the desired product. Notably, neither electron-donating nor electron-withdrawing substituents on nitrostyrene or aniline impact the pyrrole yield [31].



Scheme 12. The reaction mechanism of the three-component synthesis of pyrroles from nitroolefin **38**

Ionic liquids, such as *N*-methyl-2-pyrrolidonium methyl sulfonate, serve as effective catalysts for the three-component synthesis of pyrrole involving nitroolefins, amines, and 1,3-dicarbonyl compounds. Notably, the yields of pyrroles from substituted nitrostyrenes and anilines, ranging from 70 to 90%, show no correlation with the substituent effects. However, using aliphatic nitroolefins and amines decreases yields to 30% [32].

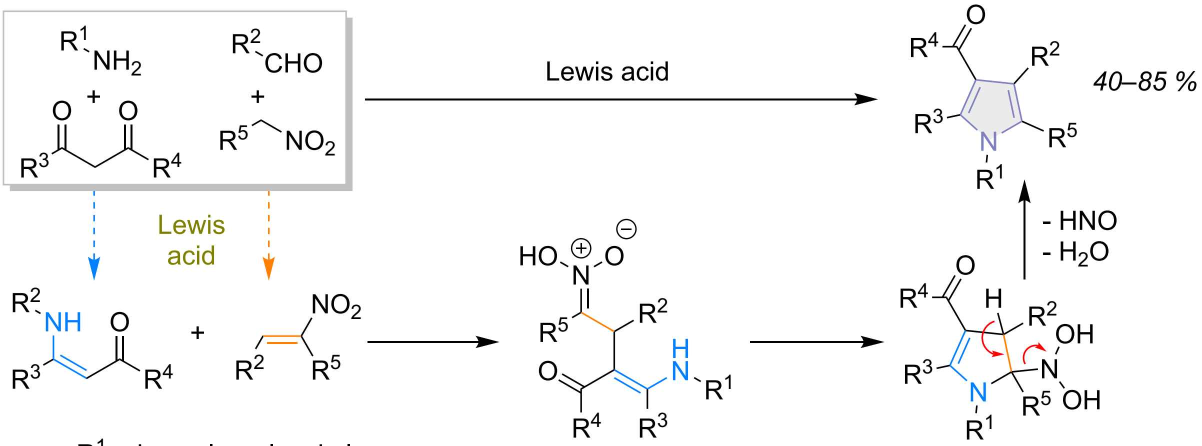
A four-component Grob-Camenisch-type reaction

Another convenient option for the synthesis of pyrroles is a four-component reaction involving aldehydes, nitroalkanes, 1,3-dicarbonyl compounds, and amines. Currently, only catalytic variants of this transformation have been developed using $FeCl_3$ [32], palladium [34], and tungsten-based complexes [35], CuO nanoparticles [36], ionic liquids [37, 38], iodine [39], clay [40], $NiCl_2 \cdot 6H_2O$ [41], as well as organic acids – lactic and gluconic [42] (**Scheme 13**).

The reaction mechanism includes the catalyzed formation of a β-enaminone from a nitroolefin, followed by the Michael addition to form an intermediate. This intermediate undergoes elimination of a hyponitrous acid molecule, resulting in the formation of pyrrole.

The synthesis of *N*-unsubstituted α-CH pyrroles

The synthesis of N-H α-CH pyrroles is of significant interest in the Grob cyclization, as these compounds serve as precursors for luminescent BODIPY borofluoride complexes and porphyrins. The earliest reported attempt to synthesize such



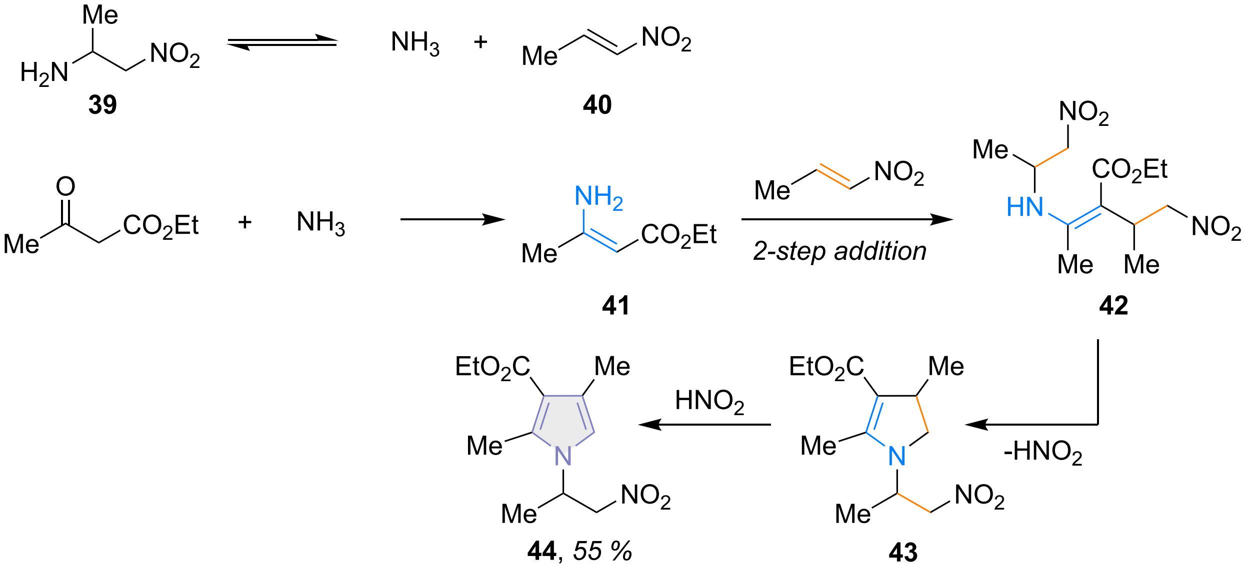
R^1 = benzyl, cycloxehyl
R^2 = Ph, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CN-C_6H_4, 4-NO_2-C_6H_4, 2-thiophenyl, 2- furfuryl, 2-naphtyl
R^3 =Ph, Me
R^4 = OMe, OEt
R^5 = H, Me

Scheme 13. The reaction mechanism of the four-component synthesis of pyrroles from nitroolefins catalyzed by Lewis acids pyrroles was by Grob [13] where 1-nitropropan-2-amine **39** and acetoacetic ester were used. However, instead of the expected N-H pyrrole, an *N*-substituted derivative **44** was obtained. This outcome was attributed to intermediate **41** possessing two nucleophilic centers: a carbon atom and a nitrogen one. Hence, two Michael additions occur, leading to intermediate **42**, which undergoes further cyclization, thus yielding *N*-isopropyl derivative **44** instead of the expected N-H one (**Scheme 14**).

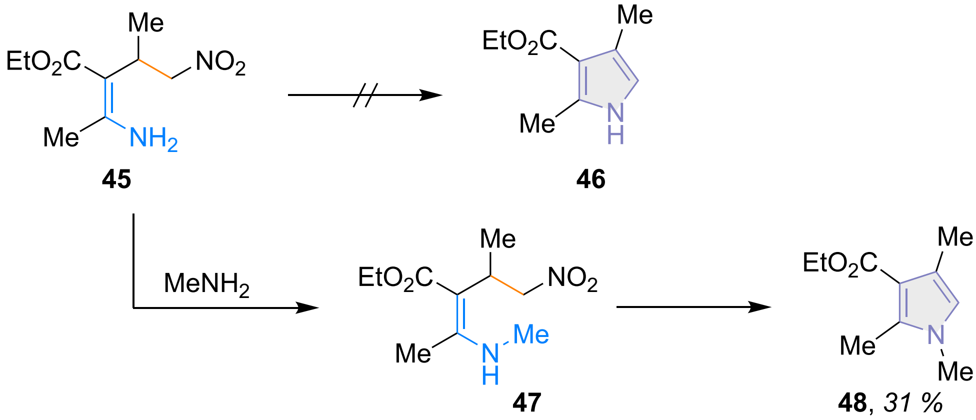
In order to synthesize the corresponding N-H α-CH pyrrole, Grob first isolated intermediate **45**, which failed to transform into pyrrole **46** under different conditions (**Scheme 15**). The author attributed this to the conjugation of the nitrogen atom lone pair in intermediate **45** with the ethoxycarbonyl group reducing its nucleophilicity. However, interestingly, upon the treatment of **45** with methylamine, pyrrole **48** could be isolated, assuming that the transamination occurred with the formation of **47**, which then cyclized to **48**. From this observation, it could be suspected that the presence of even weak electron-donating groups favors the pyrrole synthesis by the Grob cyclization.

In the subsequent study, Gómez-Sánchez [43] investigated the synthesis of N-H α-CH pyrroles using nitro compounds, with a focus on the formation of anomalous Michael products from nitrostyrene and acetylacetone. By employing non-catalytic amounts of sodium methoxide with acetylacetone and nitrostyrene **49**, the authors obtained anomalous Michael products **50** (**Scheme 16**). The latter product, upon the treatment with saturated methanolic ammonia solution at 0°C, gives rise to pyrrole **51** (**Scheme 16**).

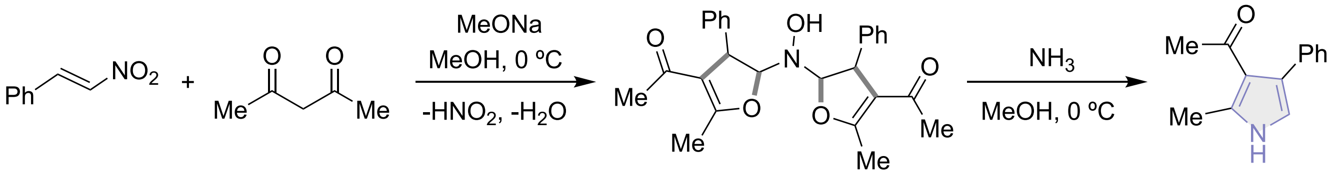
Based on this observation, the authors developed a one-pot procedure of the pyrrole synthesis, including the treatment of nitrostyrene **49** with acetylacetone, acetoacetic ester, or methyl acetoacetate in methanol with a non-catalytic



Scheme 14. The synthesis of pyrrole by Grob-Camenisch

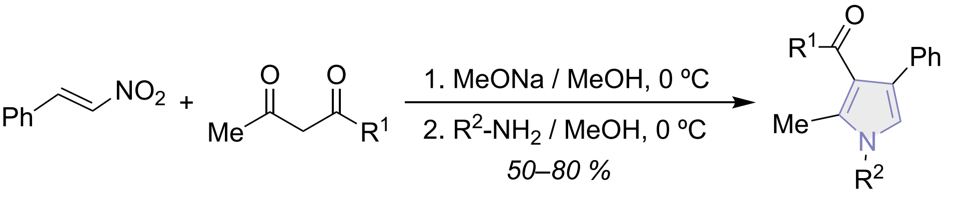


Scheme 15. Transformations of intermediate **45**



49 **50**, *92 %* **51**, *93 %*

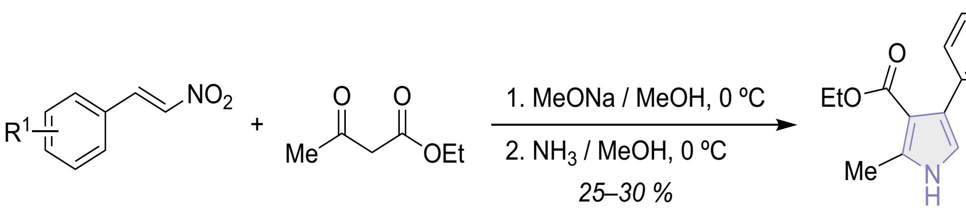
Scheme 16. The synthesis of anomalous Michael's product **50** and pyrrole **51**



49 **52**

a: R^1 = OMe, R^2 = H
b: R^1 = OEt, R^2 = H
c: R^1 = Me, R^2 = H
d: R^1 = OMe, R^2 = CH_2Ph
e: R^1 = OMe, R^2 = Ph
f: R^1 = O*t*Bu, R^2 = H

Scheme 17. The one-pot pyrrole synthesis by Gómez-Sánchez



R^1 = 4-NC-C_6H_4, 2-O_2N-C_6H_4

49 **52**

Scheme 18. The synthesis of other pyrrole derivatives by the Gómez-Sánchez-like procedure

amount of sodium methoxide at 0°C for 1 hour with further addition of an ammonia source, such as aniline, benzylamine or saturated methanolic ammonia solution. This synthetic procedure allowed obtaining pyrroles **52** with yields of up to 80% (**Scheme 17**).

Two additional literature references describe similar methods for synthesizing N-H α-CH pyrroles, involving the initial formation of the Michael addition product between nitrostyrenes **53** and acetoacetic ester, followed by the treatment with ammonia (**Scheme 18**). Using this approach, pyrroles **54** were obtained, though in low yields, from 25 to 30% [44, 45].

Conclusions

The Grob-Camenisch synthesis of pyrroles is highly valued for its straightforward methods and procedures, as evidenced by numerous publications. The main advantage of this reaction is the possibility of obtaining tetra- and three-substituted pyrrole derivatives. This reaction also allows the synthesis of pyrroles in multi-gram amounts. It is noteworthy that for this method, it is possible to use catalysts of different types (Lewis and Brønsted acids, nanoparticles, etc.), which broadens the synthetic possibilities of the pyrrole synthesis.

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