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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 non-racemic 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].

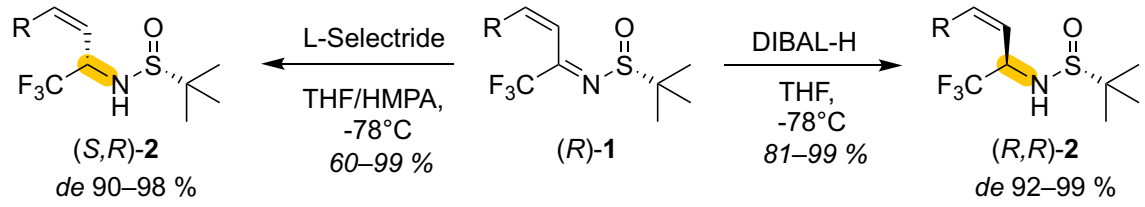
The screening of the spectrum of sodium or lithium borohydrides and aluminum hydrides ($NaBH_4$, $LiBH_4$, $NaBH_3CN$, CatBH, $LiAlH_4$, Red-Al, $LiBHEt_3$, L-Selectride) showed that the highest diastereoselectivity (90–99%) could be achieved when using DIBAL-H in THF and L-Selectride in a mixture of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

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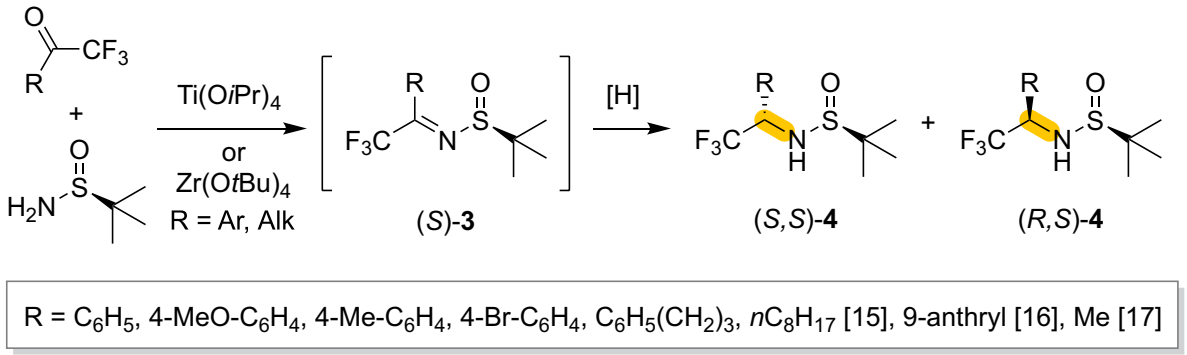
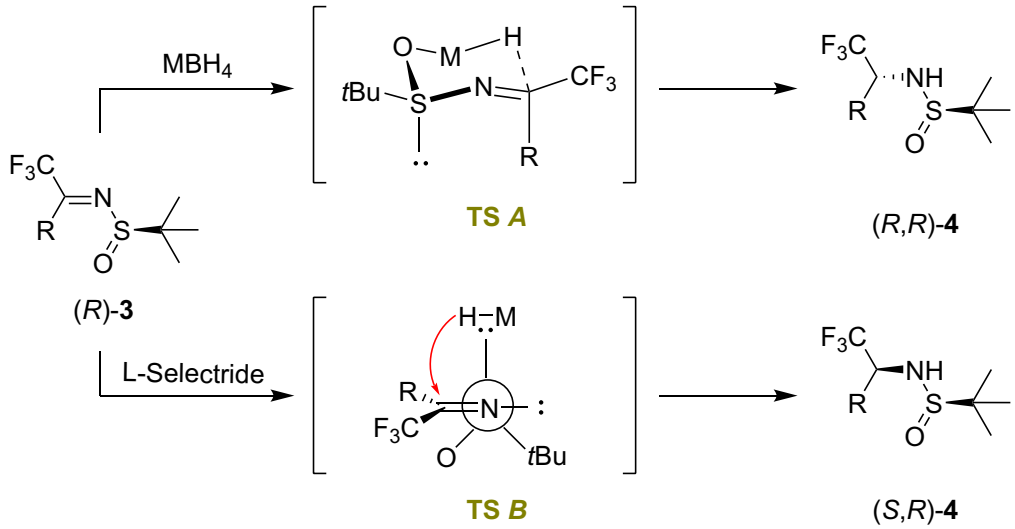


Scheme 2. The reduction of aryl- and alkyl trifluoromethyl ketimines

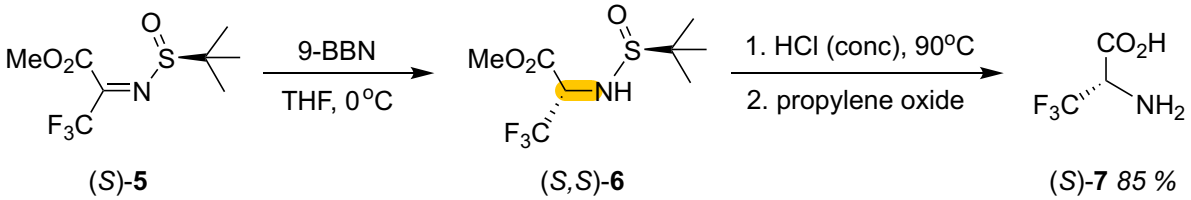


Scheme 3. Possible mechanisms of the reduction of the C=N bond of *N-tert*-butylsulfinyl trifluoromethyl ketimines

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

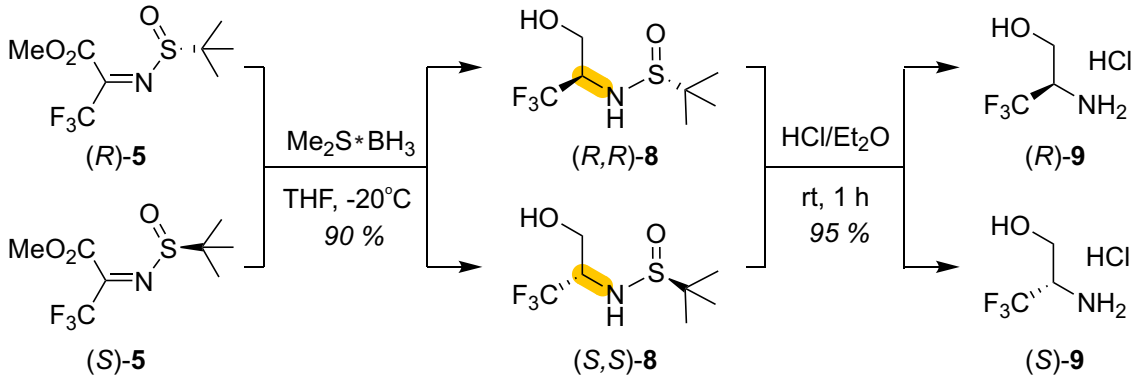


Scheme 4. A stereoselective reduction of the C=N bond of *N-tert*-butylsulfinyl trifluoromethyl iminopyruvates

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 ^1H and ^{19}F NMR data



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

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

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

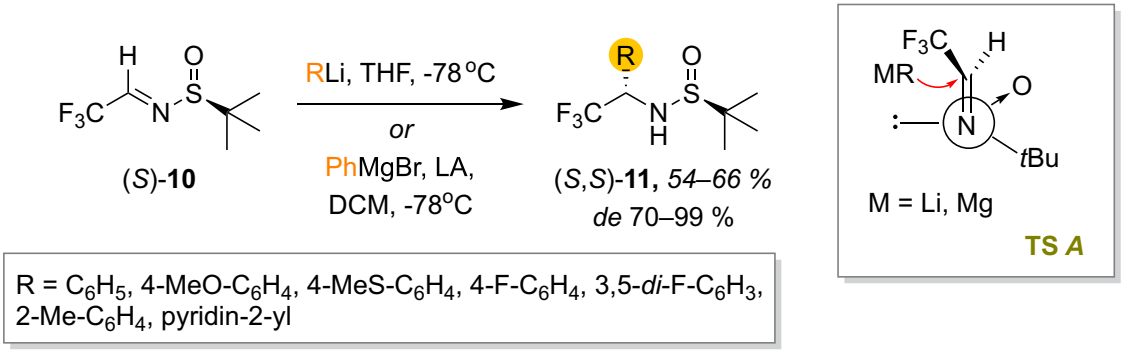
The addition of Li- and Mg-organic compounds to the azomethine bond of imines, including *N*-(*tert*-butylsulfinyl)imines, is a convenient method for forming a new C-C bond with the concurrent generation of a new stereogenic carbon atom. The interaction of imine of fluoral (*S*)-**10** (generated *in 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,ß-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



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

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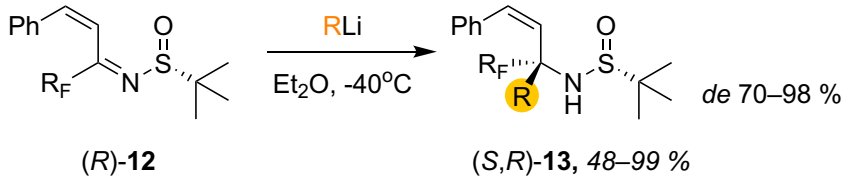
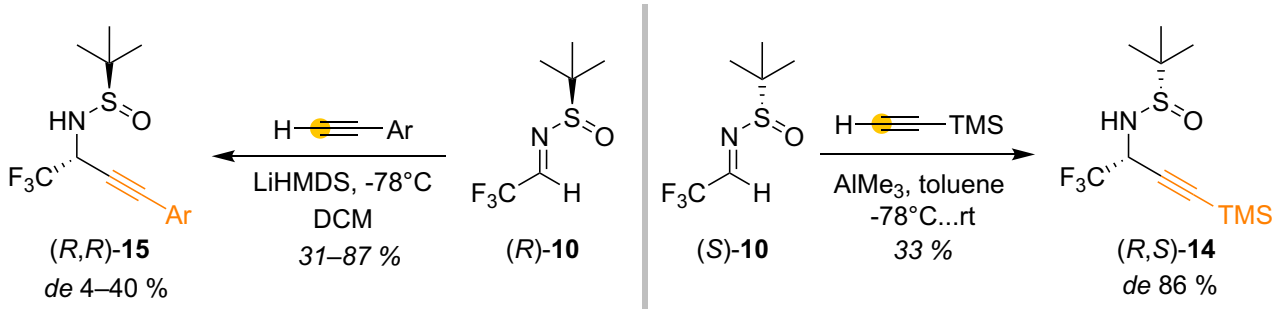


(*R*)-**12** (*S*,*R*)-**13,** *48–99 %*

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



(*R*,*R*)-**15** *de* 4–40 % (*R*)-**10** (*S*)-**10** (*R*,*S*)-**14** *de* 86 %

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

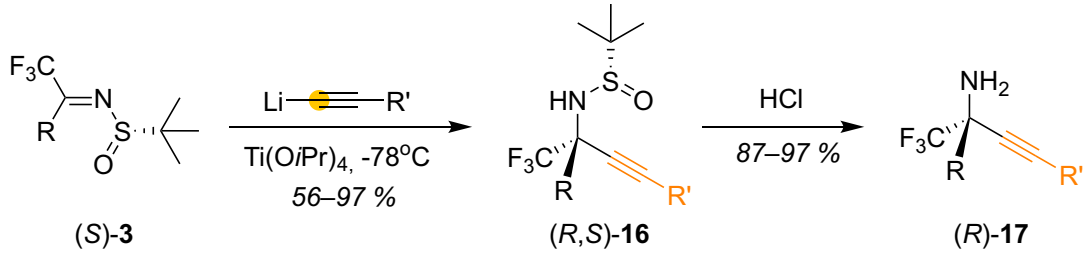
Scheme 8. *N*-(*tert*-butylsulfinyl)imine of fluoral in the reactions with Li-acetylides

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.

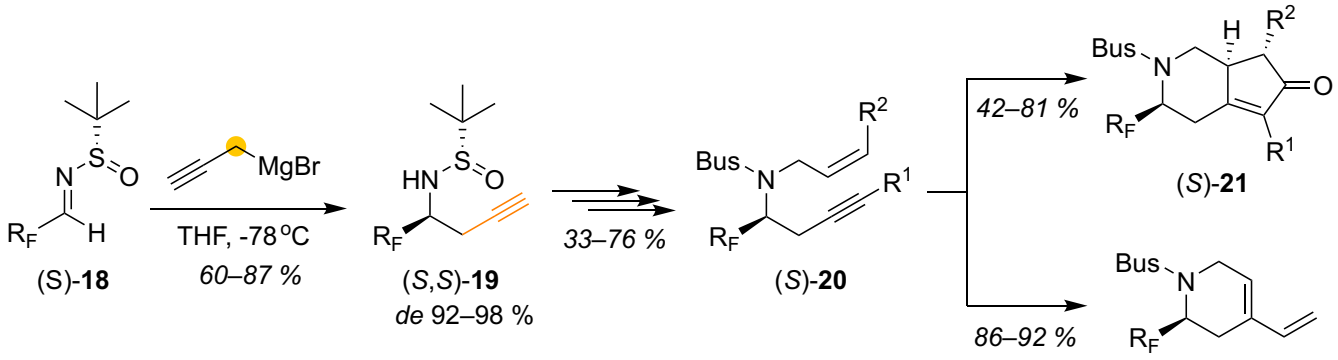
The interaction of α,β-unsaturated *N*-(*tert*-butylsulfinyl)ketimines (*R*)-**26** with ethyl bromoacetate in the presence of zinc occurred with a high regio- and chemoselectivity (**Scheme 13**) [31].



(*S*)-**3** (*R*,*S*)-**16** *de* 98 % (*R*)-**17**

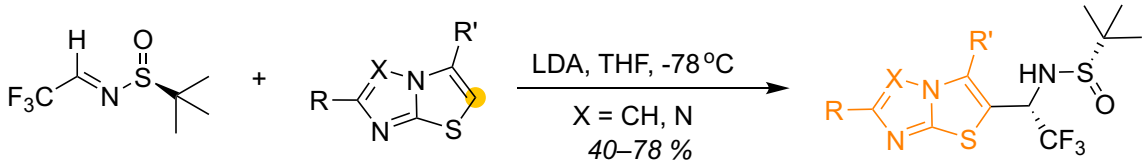
R = C_6H_5, 4-MeO-C_6H_4, 4-Cl-C_6H_4, nC_6H_{11}; R' = *n*Bu, *n*Hex, cyclopropyl, TMS, C_6H_5, CF_3

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

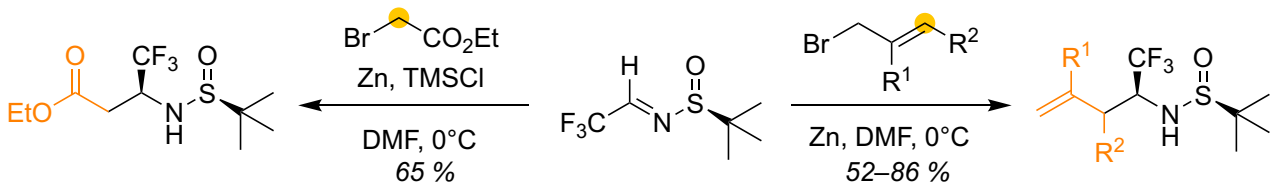
Scheme 10. The addition of propargyl magnesium bromide to *N*-(*tert*-butylsulfinyl)imine of fluoral



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

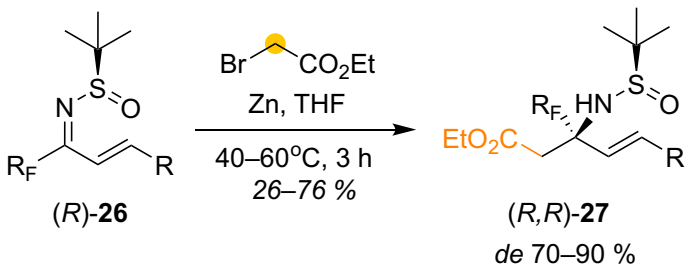


R^1 = R^2 = H, R^1 = R^2 =

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

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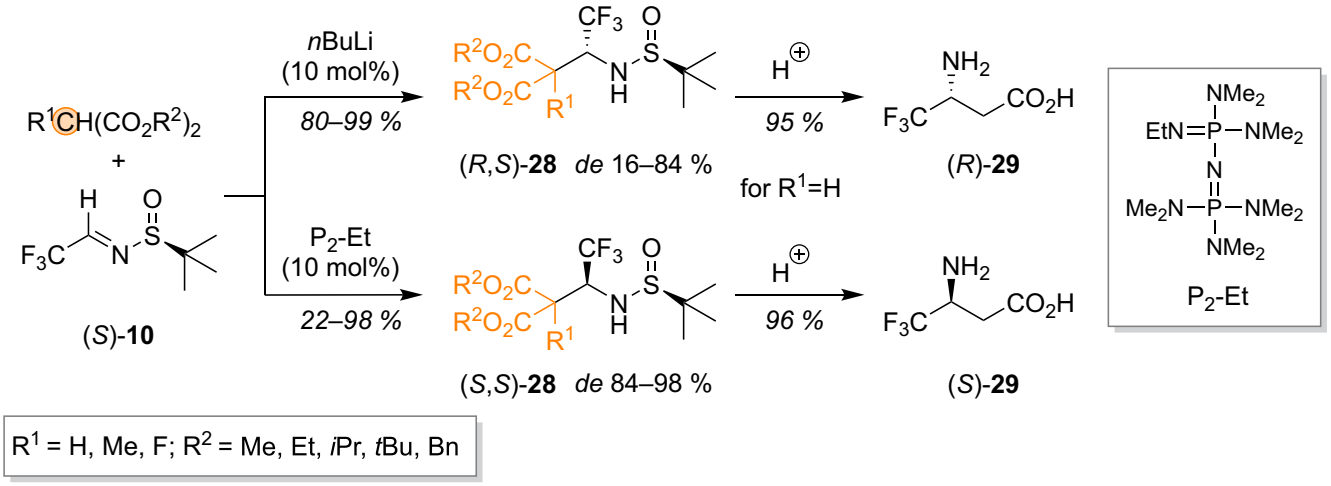
3. Reaction of *N*-(*tert*-butylsulfinyl)polyfluoroalkyl imines with CH-acids

The reaction of polyfluoroalkyl imines with esters of carboxylic acids is a convenient method for the synthesis of fluorine-containing compounds with a ß-aminocarboxylic acid fragment. Thus, ß-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 ß-trifluoromethyl-ß-alanine enantiomers (*R*)- and (*S*)-**29** [32, 33].

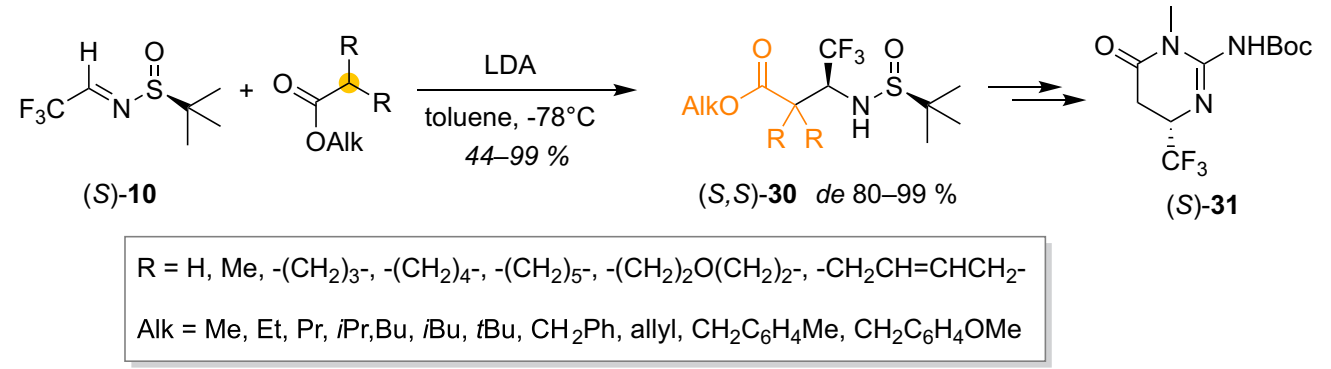
Esters of ß-trifluoromethyl-ß-amino acids can be obtained directly, without an additional decarboxylation step, by the reaction of imines with alkyl acetates in the presence of LDA. (*S*,*S*)-diastereomer **30** was formed stereospecifically (*de*>99%). The removal of the sulfinyl group and the subsequent cyclization with a substituted thiourea yielded tetrahydro-6-oxo-pyrimidine (*S*)-**31**, a potential ß-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].

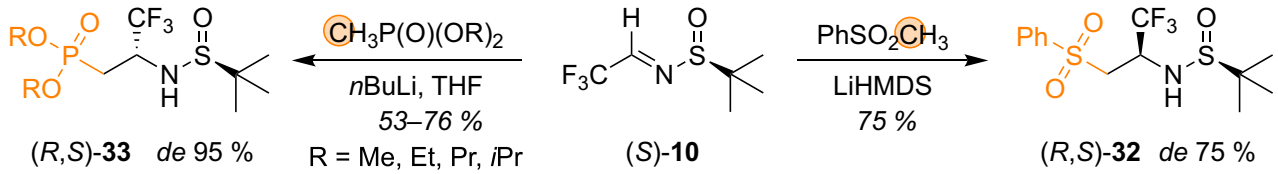
N-*tert*-butylsulfinyl polyfluoroalkyl aldimines **18** were successfully involved in the *aza*-Henry reaction with nitromethane under mild conditions. The study of various factors, such as the nature of the base, solvent, temperature and the



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



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].

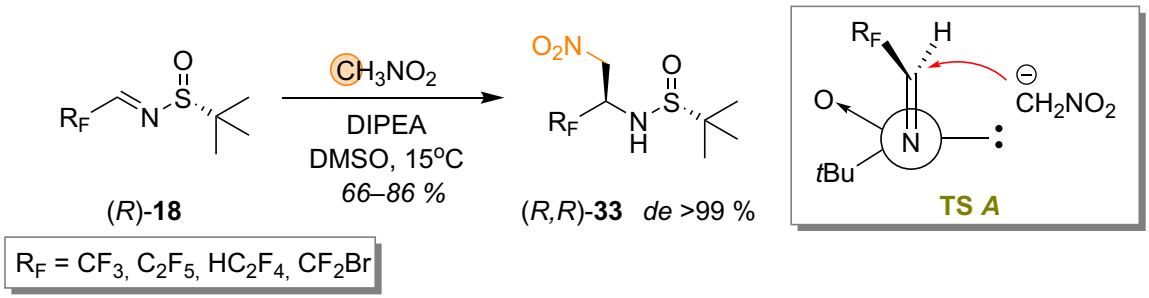
The reaction of *N*-(*tert*-butylsulfinyl)imines of trifluoropyruvate **5** with nitromethane in the presence of quinine allowed for obtaining enantiomerically pure α-trifluoromethyl substituted α-amino-ß-nitrocarboxylates **34** (**Scheme 18**) [19].

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**).

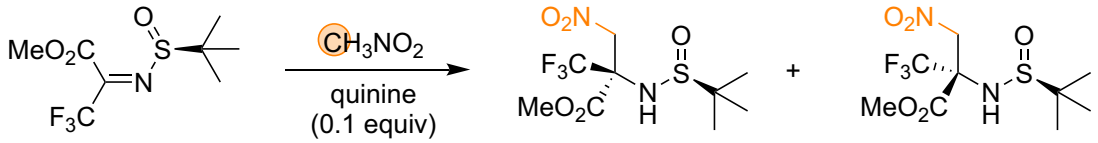
The addition of ketones to fluorinated *N*-(*tert*-butylsulfinyl)imines provides access to another class of optically active compounds – ß-amino-ketones **35** – precursors of nitrogen-containing heterocycles, 1,3-diamines, γ-aminoalcohols, and other polyfunctional compounds. However, the yields and 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].

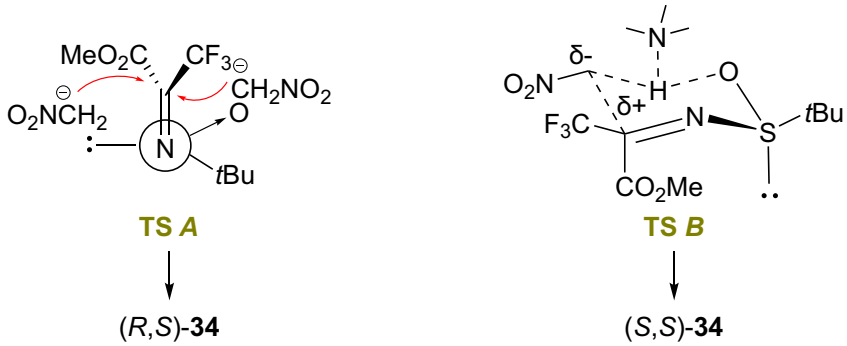
However, it turned out that the addition of *tert*-butyl acetate and *tert*-butyl acetoacetate to *N*-(sulfinyl)-α-fluoromethylaryl imines (*R*)-**38** led to the opposite stereochemical result, and in the case of the reaction with (*R*)-imine **38**, the newly created stereocenter has (*S*)-configuration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

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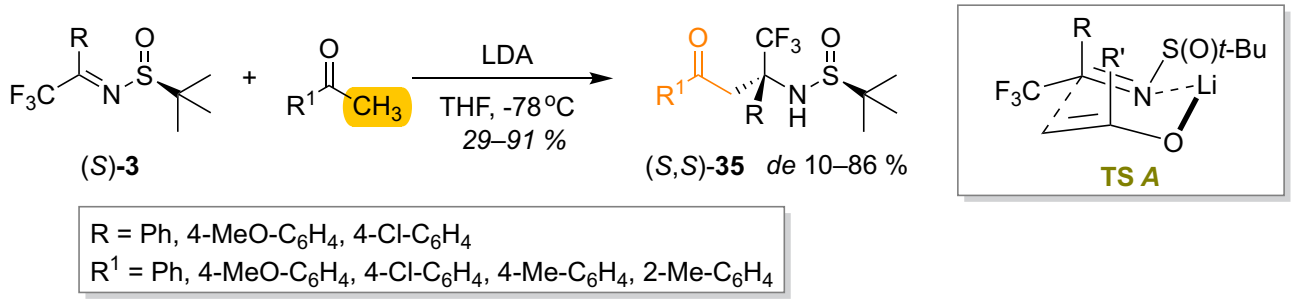
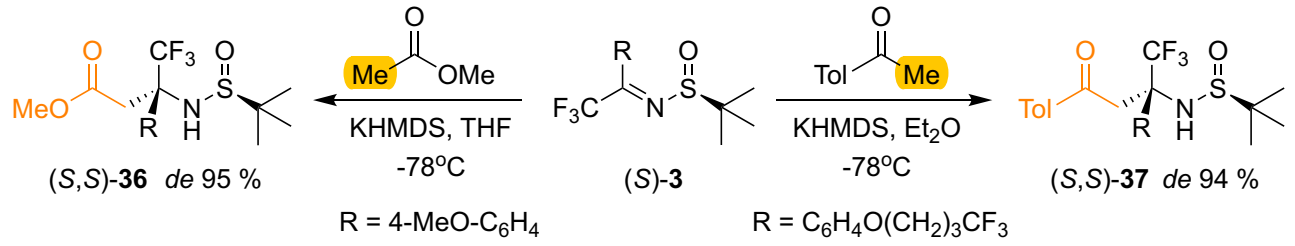
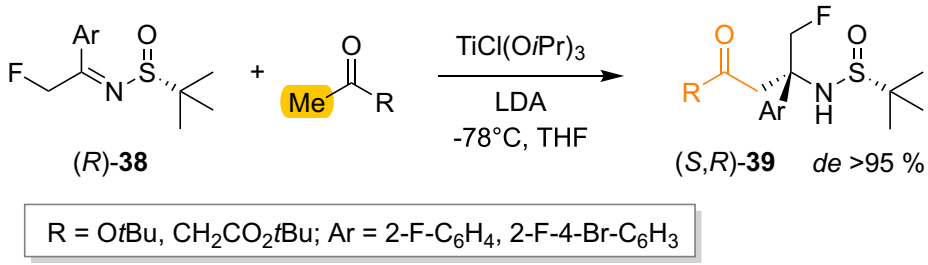


Scheme 20. The reaction of *N-tert*-butylsulfinyl trifluoromethyl ketimines with ketones



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



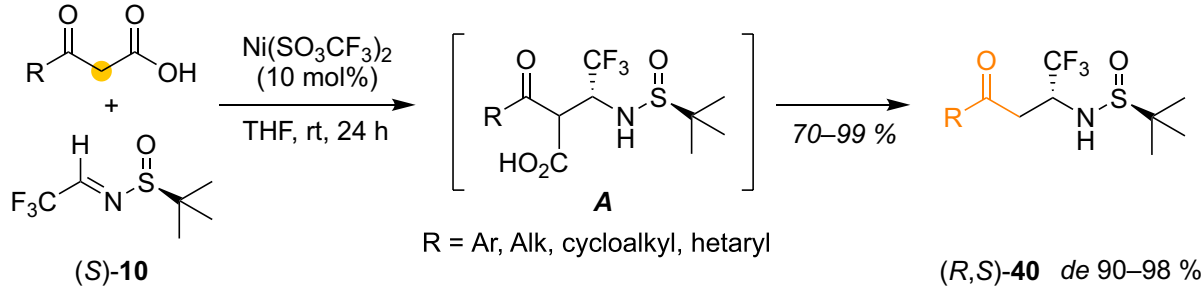
Scheme 22. The reaction of *N-tert*-butylsulfinyl fluoromethyl ketimines with ketones and alkyl acetates

The reaction of imine **10** with ß-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].

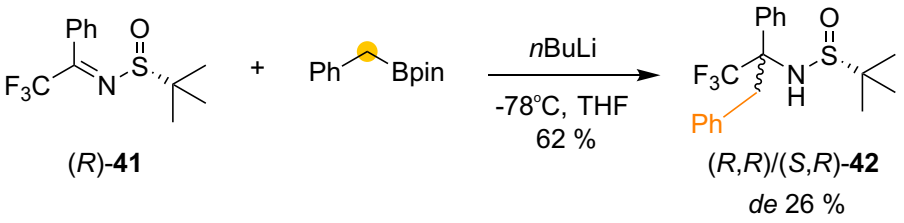
In 2019, the addition of a derivative of boronic acids – benzylboropinacolate – to the C=N bond of *N*-(*tert*-butylsulfinyl)imine of trifluoroacetophenone (*R*)-**41** (**Scheme 24**) was reported for the first time [44, 45]. Similarly to other classes of esters, anion was generated in the presence 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].

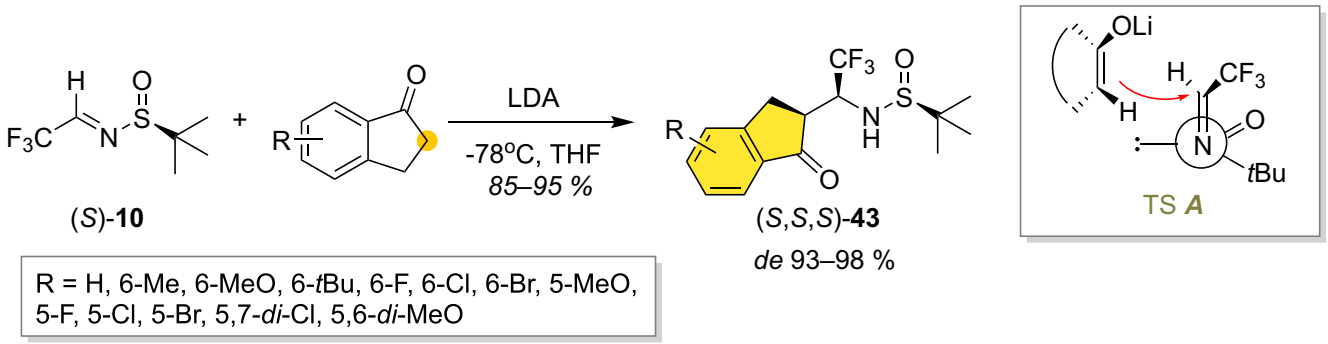
The reaction of aldimine **10** with indanone containing a thiocyanate group led to the formation of both the product of the conventional Mannich nucleophilic addition **44** and the spirocyclic



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

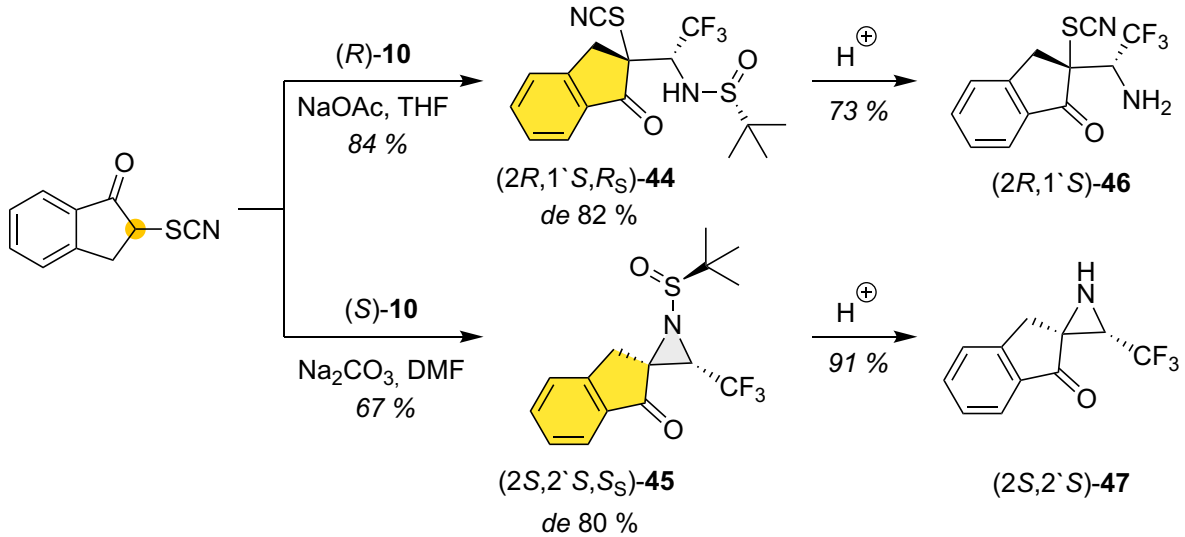
aziridine **45**, which was the result of nucleophilic substitution of the thiocyanate group. The screening of various bases showed that the percentage of aziridine **45** increased with the increase in basicity of the inorganic salt. Replacing the solvent with a more polar DMF facilitating the intramolecular 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 ß-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-ß-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-ß-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

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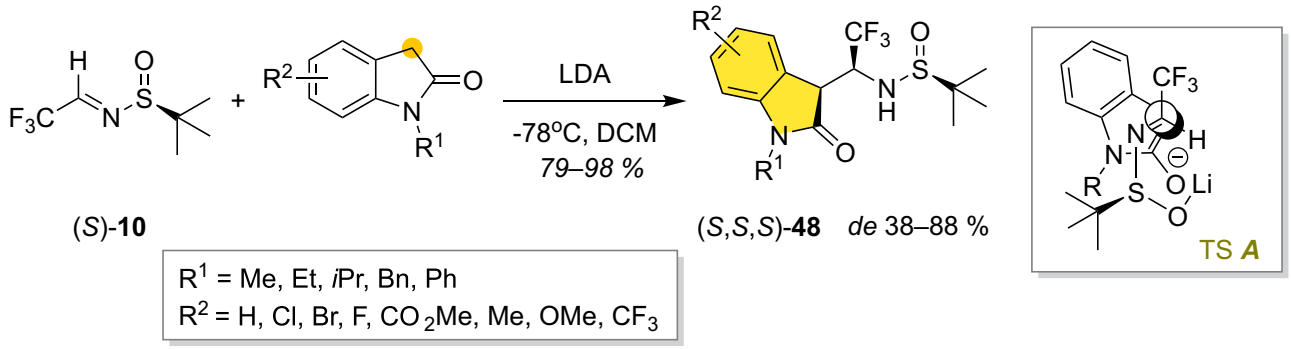
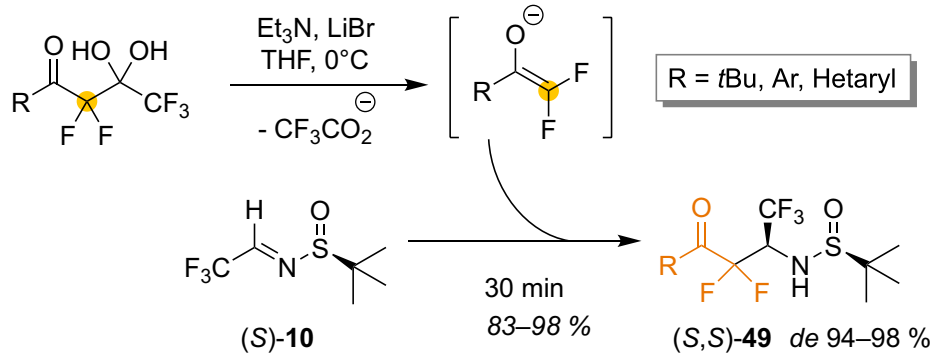
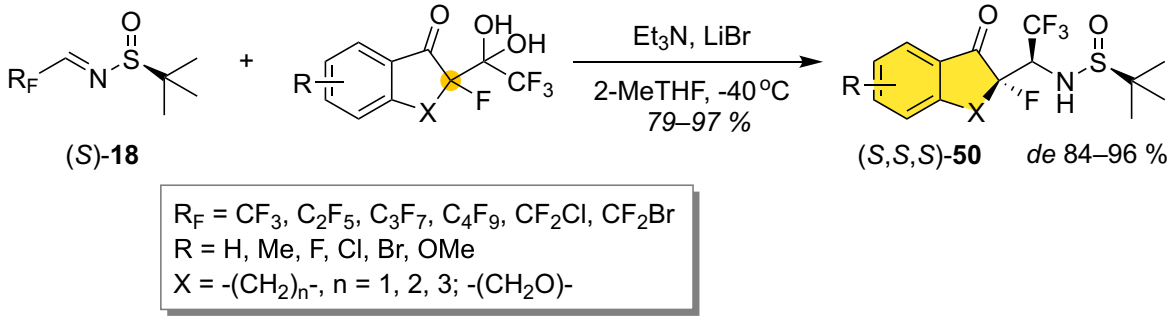


Scheme 27. The addition of indol-2-ones to *N*-*tert*-butylsulfinyl imine of fluoral



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

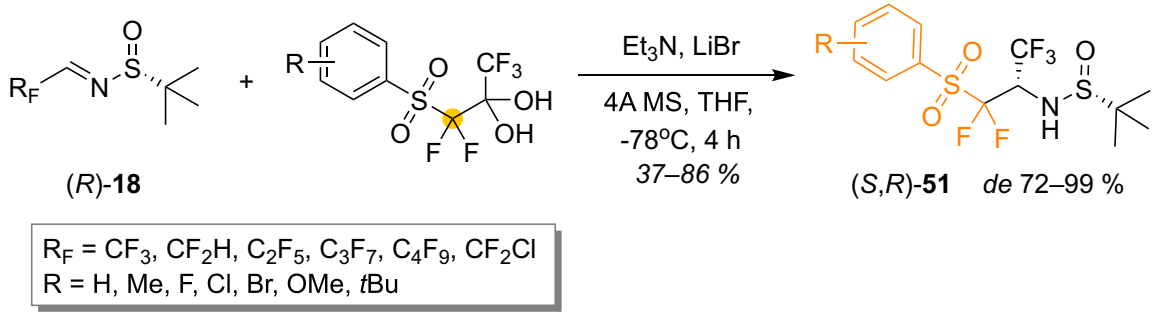


Scheme 29. The detrifluoroacetylative Mannich reaction in the synthesis of quaternary α-fluoro-β-ketoamines

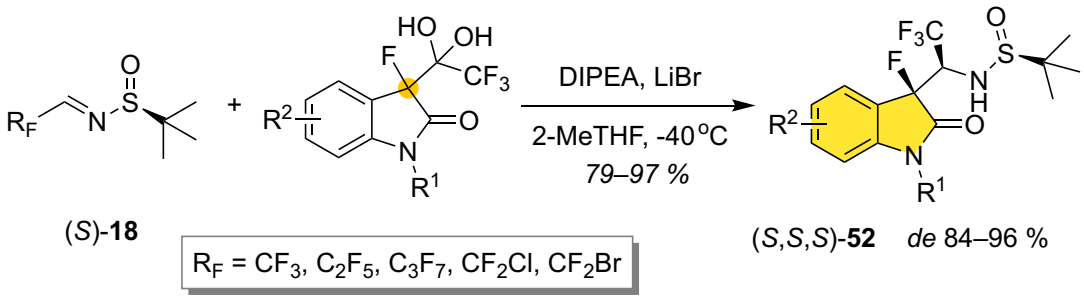
that the optimal values of yields and diastereomeric excess were achieved only when the reaction time was extended to 4 hours (**Scheme 30**) [53].

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].

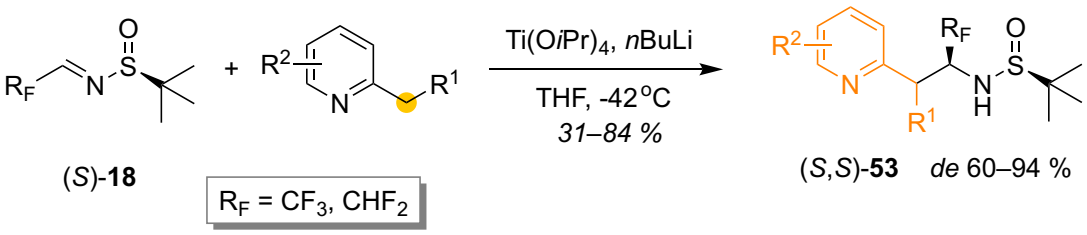
It is known that 2-alkylpyridines can be used as CH-acids in functionalizations with carbonyl compounds and imines under catalysis by Brønsted or Lewis acids [55–57]. The use of optically active *N*-(*tert*-butylsulfinyl)polyfluoroalkyl imines (*S*)-**18** allowed for the preparation of enantiomerically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



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

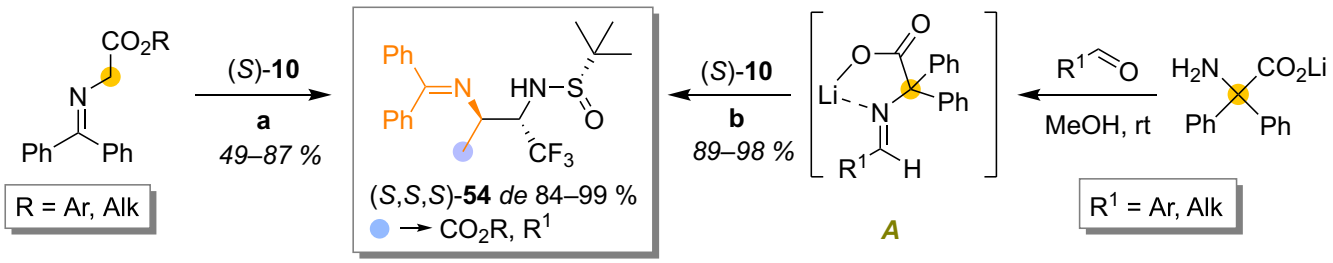


Scheme 32. 2-Alkylpyridines as CH-acids in the addition reaction with *N-tert*-butylsulfinyl polyfluoroalkyl aldimines

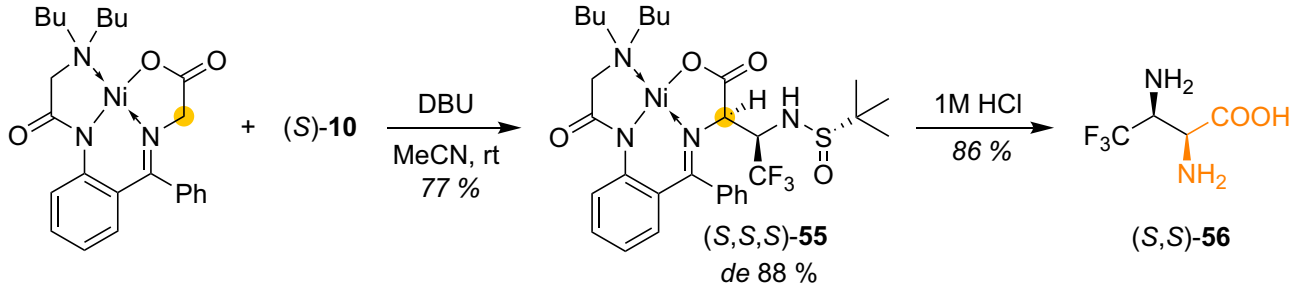
N-(*tert*-Butylsulfinyl)imine of fluoral **10** successfully reacted with enolates of glycine esters in the presence of organic (Et_3N, DMAP, DBU, LiHMDS, *t*BuOLi) and inorganic (K_2CO_3 and Cs_2CO_3, NaOH) bases. The best yields (*49–87%*) and diastereoselectivity (84–98%) were achieved when using 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].

ß-Trifluoromethyl-α,ß-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 ß-amino-ß-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-substituted vicinal diamines



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

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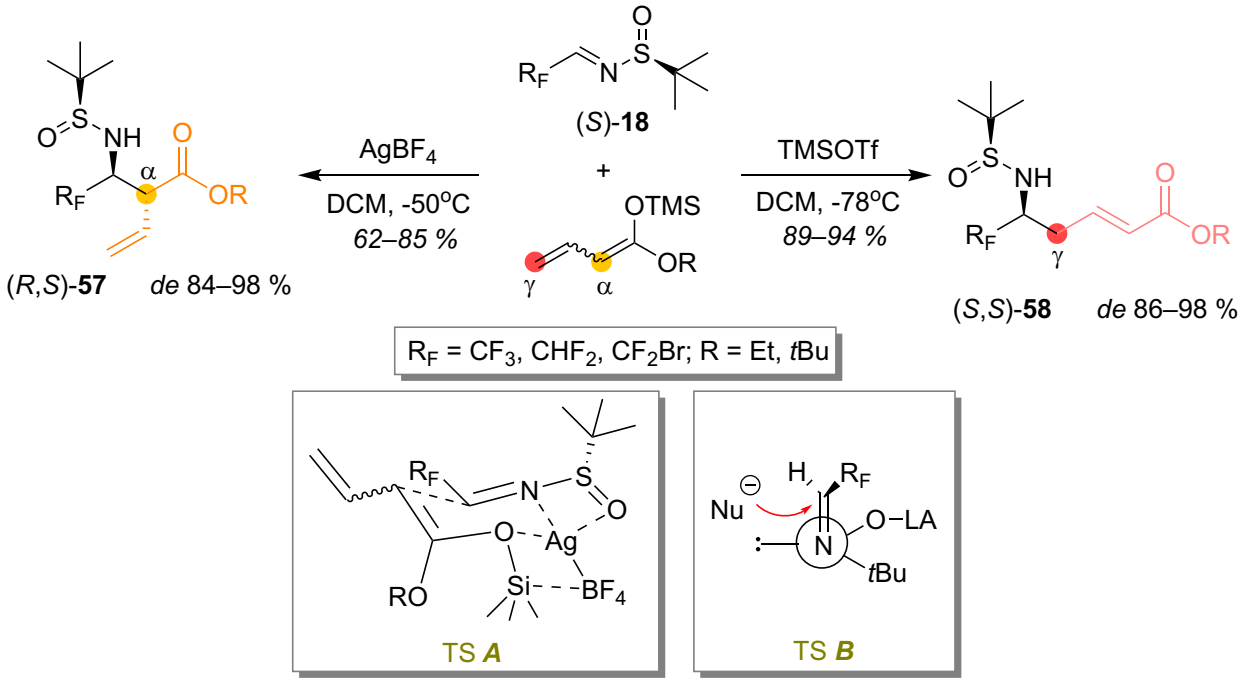
related to the formation of chelated TS ***A***, in which the metal atom is coordinated with two oxygen atoms (of enolate and sulfinyl groups) and a nitrogen atom, and as a result, an "α-product" with the (*R*,*S*)-configuration is formed. In the case of the catalysis by TMSOTf, the γ-addition takes 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].

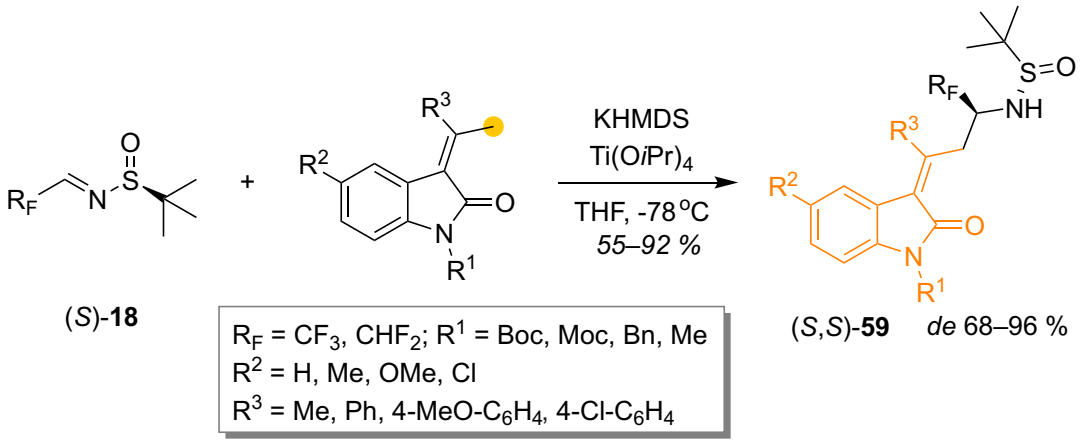
In contrast to reactions with silyldienolates and oxoindoles, the interaction of imines (*S*)-**18** with α,α-dicyanoalkenes led to (*R*,*S*)-isomers of γ-products **60**. This is explained by the formation of TS ***A***, in which the metal atom of the enolate chelates with the nitrogen atom of the aldimine,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

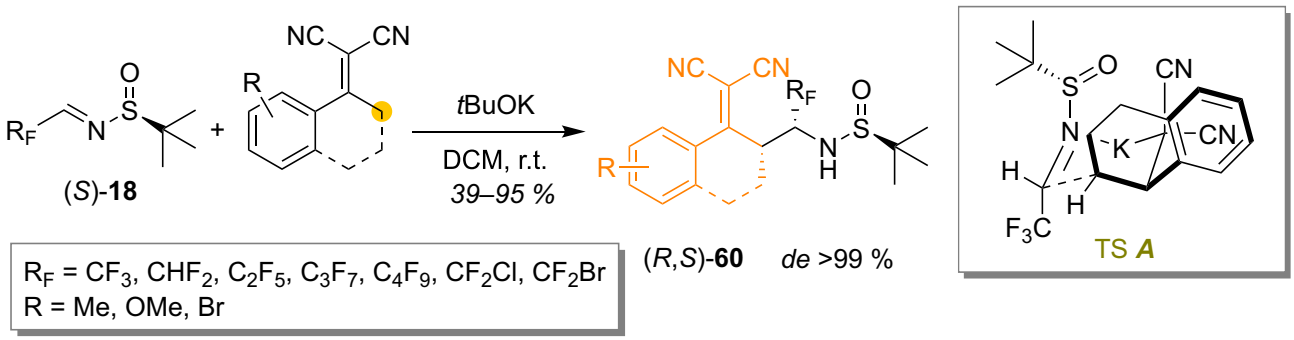
The reaction of aldimines (*S*)-**18** with indoles occurred chemo- and stereoselectively in the presence of $BF_3 \cdot Et_2O$ (in DCM) or LDA (in THF) and led to compounds **63** bearing an indole nucleus and the pharmacophoric 2,2,2-trifluoro-1-aminoethyl function (**Scheme 39**) [67–69].



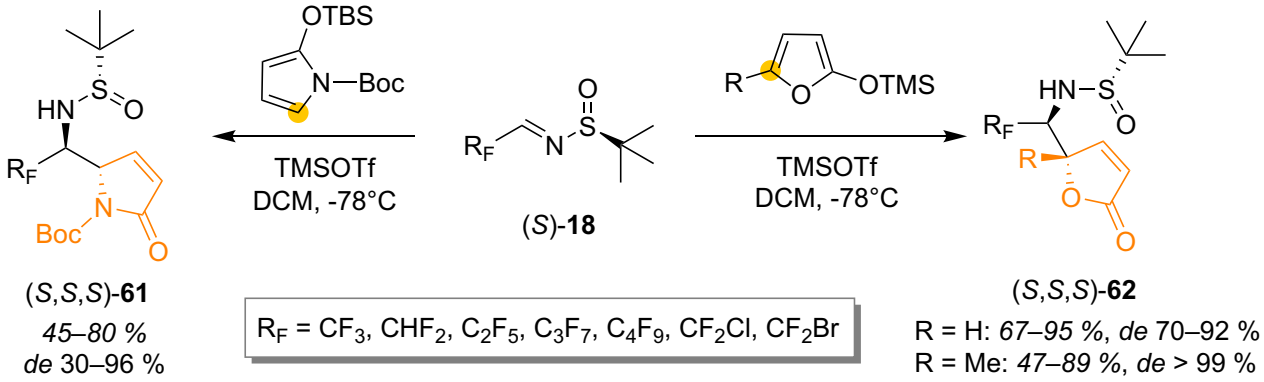
Scheme 35. Different pathways of the silylated dienolates addition to *N-tert*-butylsulfinyl polyfluoroalkyl aldimines



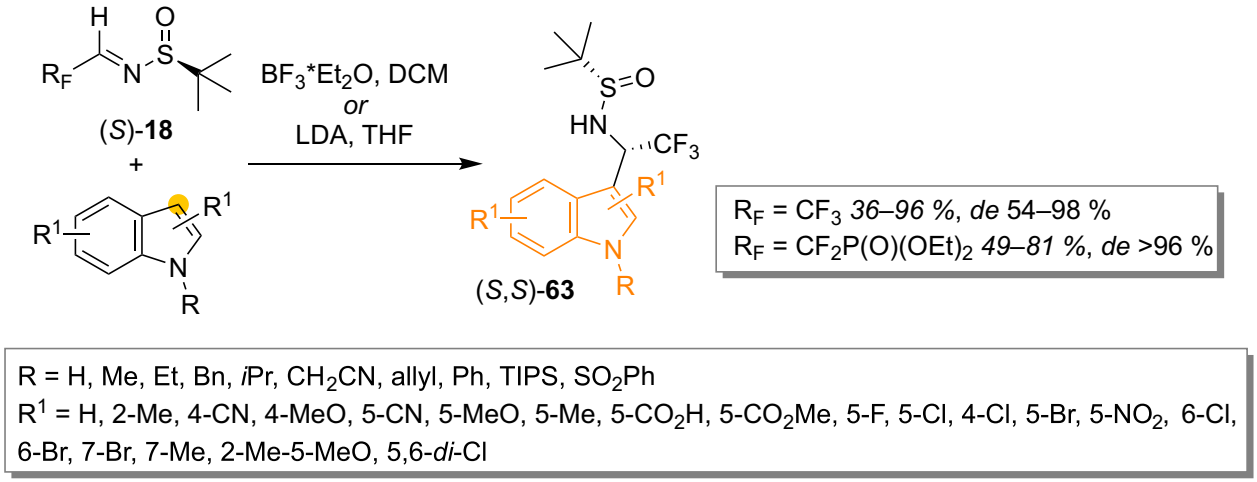
Scheme 36. The vinylogous Mannich reaction of 3-alkenyl-2-oxoindoles with *N-tert*-butylsulfinyl polyfluoroalkyl aldimines



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-ß-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

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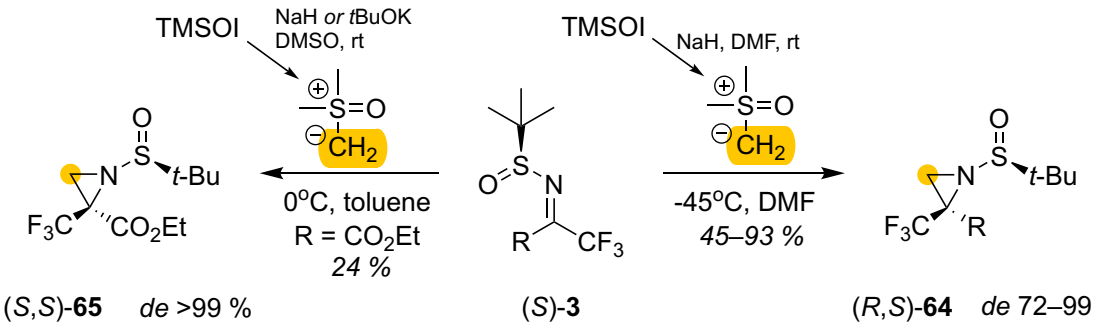
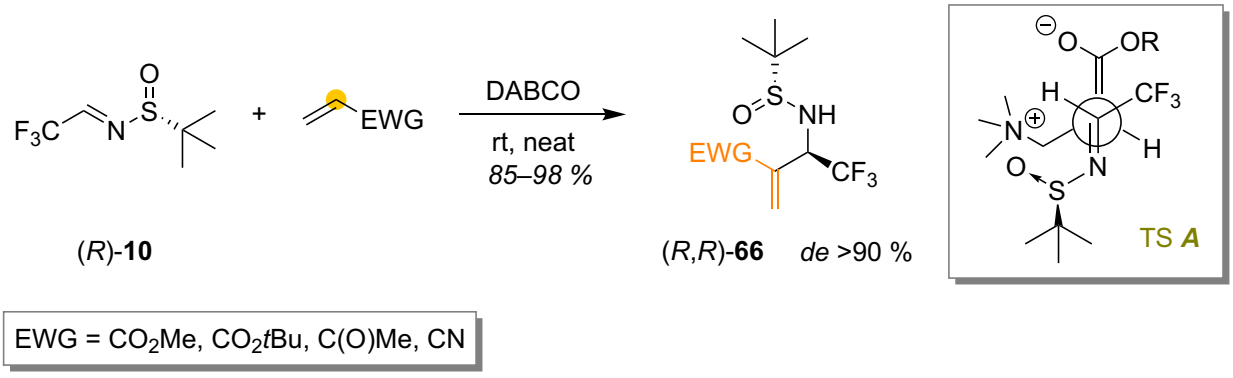


Scheme 40. The *aza*-Corey-Chaykovsky reaction of *N*-*tert*-butylsulfinyl trifluoromethyl ketimines in the synthesis of 2-trifluoromethylaziridines



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

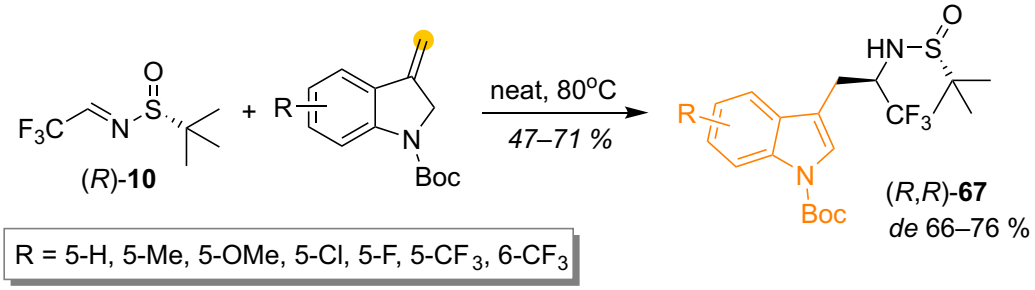
analogs [73, 74], which supports the conclusion that the process proceeds as an attack in the open TS ***A*** as in most reactions with polyfluoroalkyl aldimines.

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].

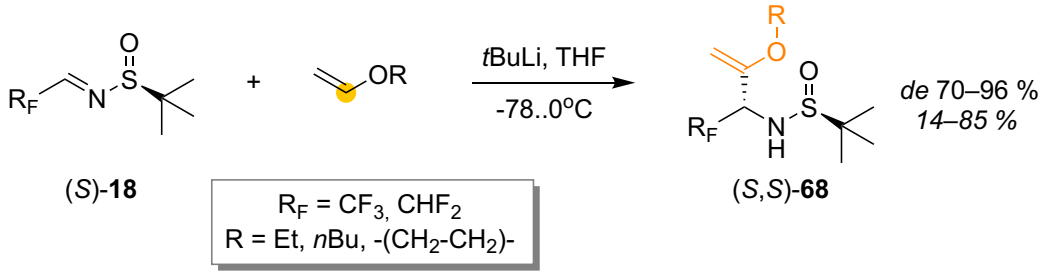
Lithiated ethyl and butyl vinyl ethers successfully reacted with polyfluoroalkyl aldimines (*S*)-**18** giving optically enriched amines **68** with a high diastereoselectivity (**Scheme 43**). The configuration of the product was assumed to be (*S*,*S*) based on previous observations for these types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

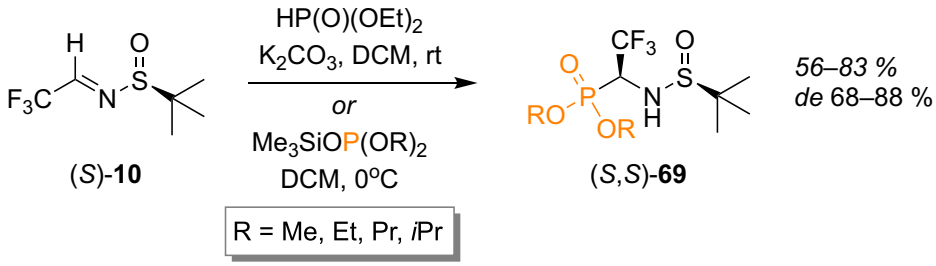
Trifluoromethylketimines (*R*)-**70** also enter the reaction with phosphites under catalysis by $Ti(OiPr)_4$ [78]. The reaction is effective for both



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

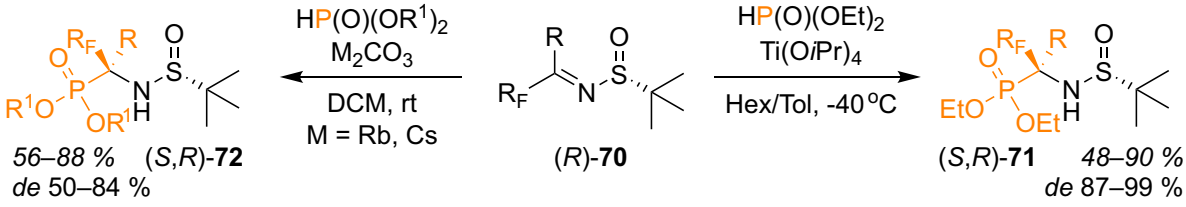


Scheme 44. *N*-(*tert*-butylsulfinyl)imines of fluoral in the asymmetric synthesis of α-trifluoromethyl α-aminophosphonic acids

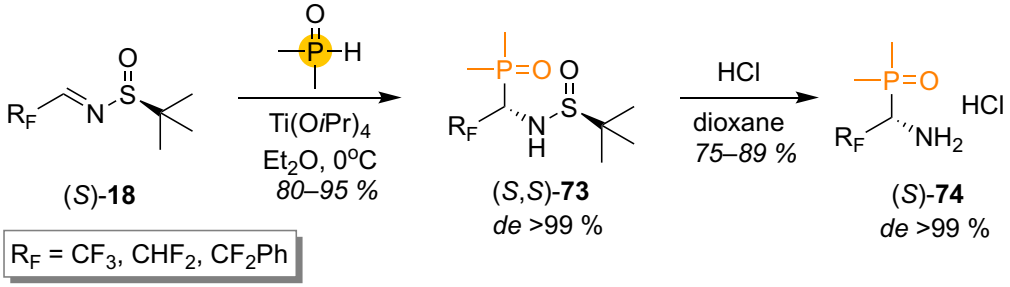
alkyl and aryl ketimines and leads to the formation of α-trifluoromethylaminophosphonates (*S*,*R*)-**71** with a stereoselectivity from 87 to 99%. Although, in contrast to the reaction with imine of fluoral, the use of K_2CO_3 in the reaction with polyfluoroalkyl ketimines did not lead to the desired 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 $Ti(OiPr)_4$, 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

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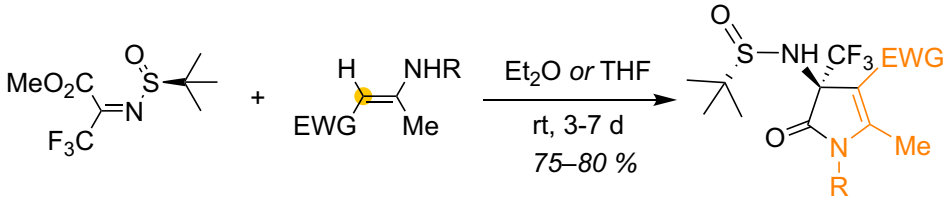
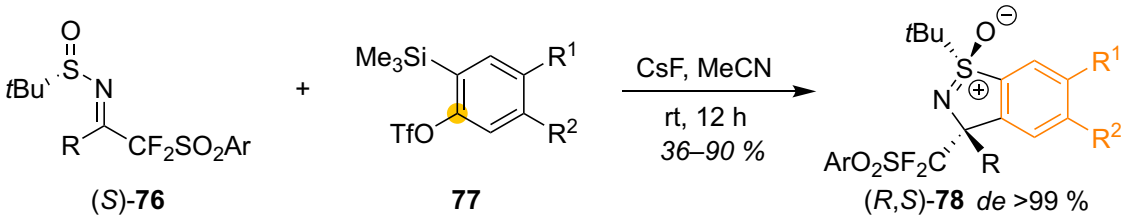


(*S*)-**5**

(*S*,*S*)-**75a–c**
de 70–90 %

a: EWG = CO_2Et, R = H; **b**: EWG = CO_2Me, 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_6H_4, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-MeO-C_6H_4, 4-MeO-C_6H_4, 4-CF_3-C_6H_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_6H_4, 4-Me-C_6H_4, 3-MeO-C_6H_4, 4-MeO-C_6H_4, 4-CF_3-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-Ph-C_6H_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 $ArSO_2CF_2$-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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