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RIGA TECHNICAL UNIVERSITY
Faculty of Materials Science and Applied Chemistry
Institute of Technology of Organic Chemistry

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JAUNU METOŽU IZVEIDE AMINOSPIRTU SINTĒZEI UN C–H FUNKCIONALIZĒŠANAI

Promocijas darba kopsavilkums

NEW METHODS FOR THE SYNTHESIS AND C–H FUNCTIONALIZATION OF AMINO ALCOHOLS

Summary of the Doctoral Thesis

Zinātniskais vadītājs
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DOCTORAL THESIS PROPOSED TO RIGA TECHNICAL UNIVERSITY FOR THE PROMOTION TO THE SCIENTIFIC DEGREE OF DOCTOR OF SCIENCE

To be granted the scientific degree of Doctor of Science (Ph. D.), the present Doctoral Thesis has been submitted for the defence at the open meeting of RTU Promotion Council on 10 September 2020 at the Faculty of Materials Science and Applied Chemistry of Riga Technical University, 3/7 Paula Valdena Street , Room 272.

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DECLARATION OF ACADEMIC INTEGRITY

I hereby declare that the Doctoral Thesis submitted for the review to Riga Technical University for the promotion to the scientific degree of Doctor of Science (Ph. D.) is my own. I confirm that this Doctoral Thesis had not been submitted to any other university for the promotion to a scientific degree.

Jekaterina Boļšakova ……. (signature)

Date…….

The Doctoral Thesis has been prepared as thematically united collection of scientific publications. It consists of a five scientific publications and a summary. Publications are written in English. The total number of pages is 407, including electronical data.

CONTENTS

GENERAL OVERVIEW OF THE THESIS

Introduction

Alkynylglycinols **A** have found application as important multifunctional building blocks for the construction of complex molecules.[1] Triple bond in compounds **A** provides broad modification possibilities (Fig. 1): a) cycloaddition reactions of triple bond to produce different heterocycles **C**; b) reduction of triple bond to form (*Z*)- and (*E*)-**D** double bond isomers; c) alkylation, arylation and alkynylation of terminal triple bond; and d) triple bond reactions with different O-, N- and S-nucleophiles to give derivatives **F**,**G**. Moreover, oxidation of hydroxyl group in compound **A** is straightforward approach to α-ethynylglycine **B** derivatives the simplest member of which, 2-aminobut-3-ynoic acid, was shown to exhibit antimicrobial activity against *Streptomyces aureus*.

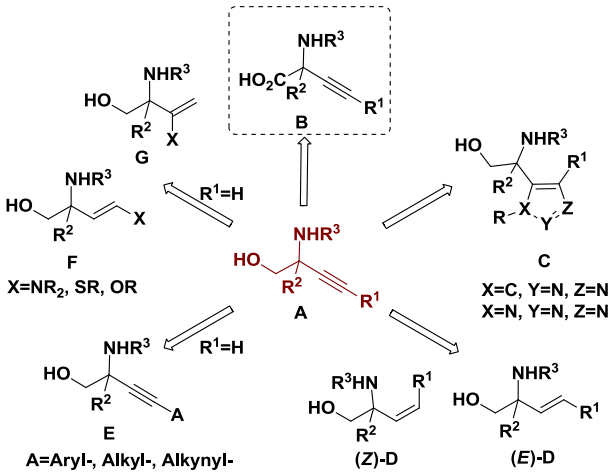


Fig. 1. Modification potential of alkynylglycinols **A**.

The literature review revealed that there is limited number of methods for the synthesis of ethynylglycinols **A** and ethynylglycines **B**. Synthetic routes typically rely on derivatization of Garner's aldehyde[3] and Ellman-type addition reactions of terminal alkynes to *N*-sulfinyl imines.[4] Furthermore the direct access to C-quaternary alkynyl glycinols **A** is limited to few alternatives beyond the reduction of carboxyl group in glycine **B**. The literature search revealed that methods known for the construction of C-quaternary alkynyl glycinols **A** are the Seyferth–Gilbert homologation of a serinal derivative[5], aminolysis of alkynyl epoxides[6], and the insertion of a nitrene into a propargylic C–H bond[7]. Thus, we focused our research to development of new methods for the synthesis of ethynylglycinol derivatives **A**, which involve propargylic amination of *bis*-imidates **H** and the Ritter reaction of ethynylglycol cobalt complexes **I** (Fig. 2).

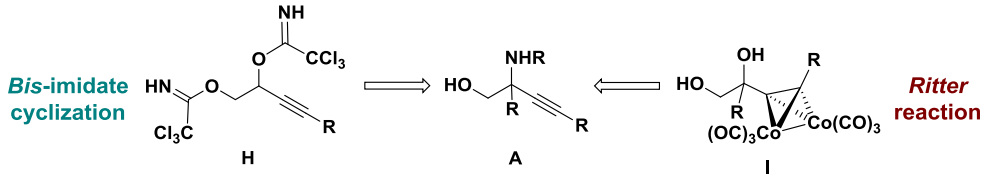


Fig. 2. New methods for the synthesis of ethynylglycinols **A**.

Amino alcohol is a substructure of many pharmaceutically relevant compounds, therefore functionalization of amino alcohols is of high importance. C–H functionalization is a very attractive approach as it does not require pre-functionalized starting materials and stoichiometric amount of transition metal catalyst in contrast to traditionally used methods. C–H functionalization of benzylamides containing picolinamide directing group using cobalt catalysts has been shown, nevertheless, the known methods lack diversity of substitution at benzylic position[8]. Research was focused on picolinamide directed C–H functionalization of phenylglycinol derivatives **J** with internal and terminal alkynes using cobalt catalyst for intermediate cobaltocycle **K** formation, which provides dihydroisoquinoline derivatives **L** (Fig. 3).

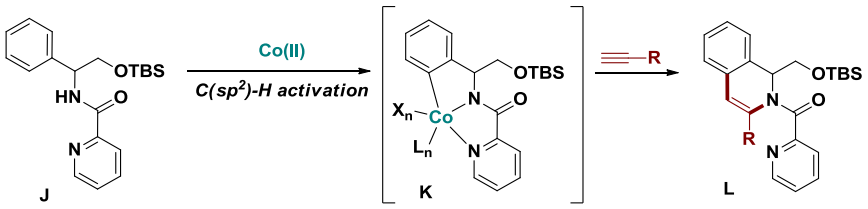


Fig. 3. New method for C–H functionalization of phenylglycinols **J**.

Aims and Objectives

The aim of the Thesis is to develop new synthetic methods for the synthesis of ethynylglycinols and investigate C–H functionalization of phenylglycinols using cobalt catalysis.

The following tasks were set:

1) to investigate intramolecular propargylic amination of *bis*-imidates for the synthesis of enantioenriched ethynylglycinols;
2) to investigate the Ritter reaction of ethynylglycols cobalt complexes for the synthesis of quaternary alkynylglycinols;
3) to develop efficient method for C–H functionalization of phenylglycinols using cobalt catalyst.

Scientific Novelty and Main Results

As the result of Thesis, several new methods for the synthesis of ethynylglycinol derivatives were developed: 1) propargylic substitution of *bis*-imidates was successfully applied for the synthesis of racemic and enantioenriched ethynylglycinols; 2) Ritter reaction of ethynylglycol cobalt complexes was applied for the synthesis of quaternary ethynylglycinols; 3) new conditions for the decomplexation of alkyne-cobalt complexes were established using DDQ as an oxidant; 4) a new method for cobalt catalyzed C–H functionalization of phenylglycinol derivatives with terminal and internal alkynes directed by picolinamide auxiliary was demonstrated. This constitutes efficient and regioselective synthesis method of enantioenriched dihydroisoquinoline derivatives.

Structure of the Thesis

The Thesis is a thematically linked collection of scientific publications focused on the development of new synthesis methods of racemic and enantioenriched glycinols involving: a) intramolecular propargylic substitution of *bis*-amides; b) Ritter reaction of ethynylglycinol cobalt complexes; and c) cobalt catalyzed C–H functionalization of phenylglycinols.

Publications and Approbation of the Thesis

Main results of the Thesis were summarized in five scientific publications. Results of the research were presented at six conferences.

Scientific publications

1. **Sirotkina**, **J**., Grigorjeva, L., Jirgensons, A. Synthesis of Alkynyl Glycinols *via* Lewis Acid Catalyzed Propargylic Substitution of bis-Imidates. *Eur. J. Org. Chem*. **2015**, *31*, 6900–6908.
2. **Bolsakova**, **J**., Jirgensons, A. Synthesis of α-Ethynyl Glycines. *Eur. J. Org. Chem*. **2016**, *27*, 4591–4602.
3. Grammatoglou, K., **Bolsakova**, **J**., Jirgensons, A. C-Quaternary alkynyl glycinols *via* the Ritter reaction of cobalt complexed alkynyl glycols. *RSC Adv*. **2017**, *7*, 27530–27537.
4. **Bolsakova**, **J**., Jirgensons, A. The Ritter reaction for the synthesis of heterocycles. *Chem*. *Heterocyc. Compd*. **2017**, *53*, 1167–1177.
5. **Bolsakova**, **J**., Lukasevics, L., Grigorjeva, L. Cobalt-catalyzed, directed C–H functionalization/annulation of phenylglycinol derivatives with alkynes. *J. Org. Chem*. **2020**, *85*, 4482–4499.

Results of the Thesis were presented at the following conferences

1. **Sirotkina**, **J**., Jirgensons, A. Synthesis of enantioenriched ethynyl glycinols *via* acids catalyzed cyclization of *bis*-trichloroacetimidates. *Balticum Organicum Syntheticum (BOS 2014).* Vilnius, Lithuania, 6−9 July **2014**.

2. **Sirotkina**, **J**. The Ritter reaction of cobalt carbonyl complexed propargylic alcohols. *9th Paul Walden Symposium on Organic Chemistry*. Riga, Latvia, 21–22 May **2015**.
3. **Sirotkina**, **J**., Jirgensons, A. 4-Substituted-4-alkynyl 2-oxaolines *via* the Ritter reaction. *19th European Symposium of Organic Chemistry*. Lisbon, Portugal, 12−16 July **2015**.
4. Grammatoglou, K., **Bolsakova**, **J**., Jirgensons, A. Synthesis of 4-alkynyl 2-oxazolines *via* the Ritter reaction. *Balticum Organicum Syntheticum (BOS 2016).* Riga, Latvia, 3−6 July **2016**.
5. **Bolsakova**, **J**., Grigorjeva, L. Cobalt catalyzed sp^2 C–H alkenylation of phenylglycine and phenylalanine. *International Symposium on Synthesis and Catalysis.* Evora, Portugal, 3−6 September **2019**.
6. **Bolsakova, J**., Grigorjeva, L. Cobalt catalyzed sp^2 C–H alkenylation of phenylglycine and phenylalanine. *11th Paul Walden Symposium on Organic Chemistry.* Riga, Latvia, 19−20 September **2019**.

MAIN RESULTS OF THE THESIS

Synthesis of Alkynylglycinols by Propargylic Substitution of *bis*-imidates

A new approach was developed for the synthesis of racemic and enantioenriched alkynylglycinols based on Lewis acid catalyzed intramolecular propargylic substitution of *bis*-imidates **1a-m**. In this transformation, one imidate group serves as an internal N-nucleophile while the other is activated by Lewis acid catalyst and acts as a leaving group to form oxazolines **2a-m**. Cyclization of *bis*-imidates **1a-m** was achieved in good yields with a wide range of Lewis acid catalysts: TMSOTf, $BF_3 \cdot Et_2O$, $AlCl_3$, $FeCl_3$ (Table 1). Cyclization proceeded highly regioselectively to give 4-alkynyl-oxazolines **2a-m** as propargylic substitution products (Fig. 4, pathway **a**) while isomeric 5-alkynyl-oxazolines **2'a-m** were formed as minor products in less than 8 %. In the case when trimethylsilyl substituted *bis*-imidate **1b**, the desired selectivity for propargylic substitution product **2b** was improved by replacing TMSOTf with $AlCl_3$ (Table 1, entries 2 and 3). Structure of the major regioisomer **2b** was confirmed by X-ray diffraction analysis.

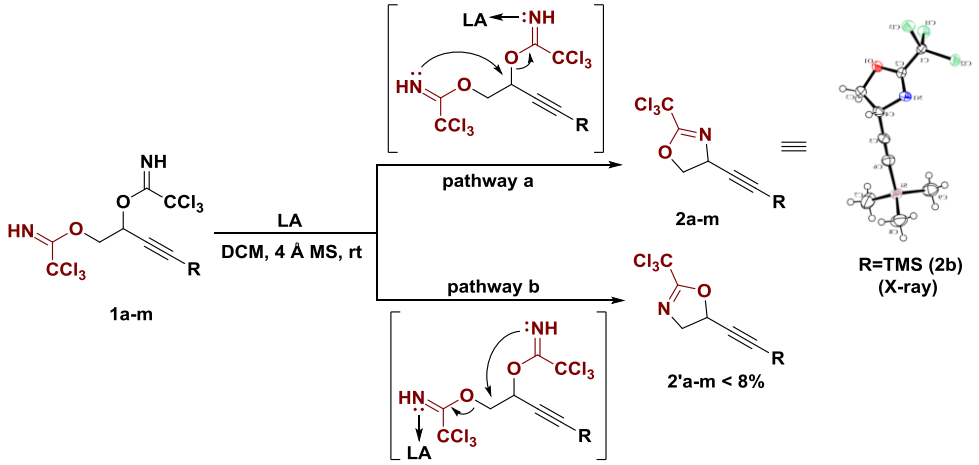


Fig. 4. Oxazolines by intramolecular amination of *bis*-imidates **1a-m**.

Table 1

Yields and Lewis Acids for Amination Reaction

Entry	R	LA[a]	Ratio of **2/2'**[b]	**2**, Yield, %
1	Me	TMSOTf	> 50 : 1	**2a**, 71
2	TMS	TMSOTf	9 : 1	**2b**, 82
3	TMS	$AlCl_3$	35 : 1	**2b**, 91

[a] Reaction conditions: Lewis acid catalyst (10 mol %), DCM (0.1 M), molecular sieves (4 Å), r. t. , 1–10 min. [b] Ratio of **2/2'** regioisomers was determined using GC-MS.

Table 1(continued)

Yields and Lewis Acids for Propargylic Amination Reaction

Entry	R	LA[a]	Ratio of **2/2'**[b]	**2**, Yield, %
4	$BnOCH_2$	$AlCl_3$	8 : 1	**2c**, 75
5	$BnOCH_2CH_2$	$AlCl_3$	41 : 1	**2d**, 80
6	*t*Bu	$AlCl_3$	> 50 : 1	**2e**, 84
7	Pent	TMSOTf	> 50 : 1	**2f**, 82
8	TIPS	$AlCl_3$	23 : 1	**2g**, 73
9	Ph	TMSOTf	25 : 1	**2h**, 79
10	2-ClC_6H_4	TMSOTf	> 50 : 1	**2i**, 70
11	3,5-ClC_6H_3	$AlCl_3$	32 : 1	**2j**, 95
12	PentC≡C	$AlCl_3$	11 : 1	**2k**, 86
13	TIPSC≡C	$AlCl_3$	> 50 : 1	**2l**, 69
14	CH_2=CH	$AlCl_3$	> 50 : 1	**2m**, 80

[a] Reaction conditions: Lewis acid catalyst (10 mol %), DCM (0.1 M), molecular sieves (4 Å), r. t. , 1–10 min. [b] Ratio of **2/2'** regioisomers was determined using GC-MS.

The chirality transfer was explored in cyclization of enantioenriched (*R*)-*bis*-imidates **1a-j** containing alkyl, trimethylsilyl and aryl substituents at acetylene terminal position. Under the standard reaction conditions, enantioenriched (*R*)-*bis*-imidates **1a-e** containing alkyl and trimethylsilyl substituents gave internal amination products (*S*)-**2a-e** with complete inversion of configuration at the chiral center and enantiomeric excess up to 96 % (Table 2, entries 1−5). These results indicate that cyclization of alkyl and trimethylsilyl substituted (*R*)-*bis*-imidates **1a-e** proceeds by S_N2 type mechanism (Fig. 5). In turn, cyclization of enantioenriched (*R*)-*bis*-imidate **1h** (entry 6) with phenyl substituent at acethylene terminal position proceeded with considerable degree of racemization indicating mixed S_N1 and S_N2 type mechanisms (Fig. 5). Introduction of electron-withdrawing chlorine substituent at the benzene ring of substrate (*R*)-**1i** partially suppressed the racemization (entries 7−9). Moreover, incorporation of two chlorines at the benzene ring of substrate (*R*)-**1j** minimized racemization and oxazoline product (*R*)-**2j** was obtained in 89 % *ee* (entry 11).

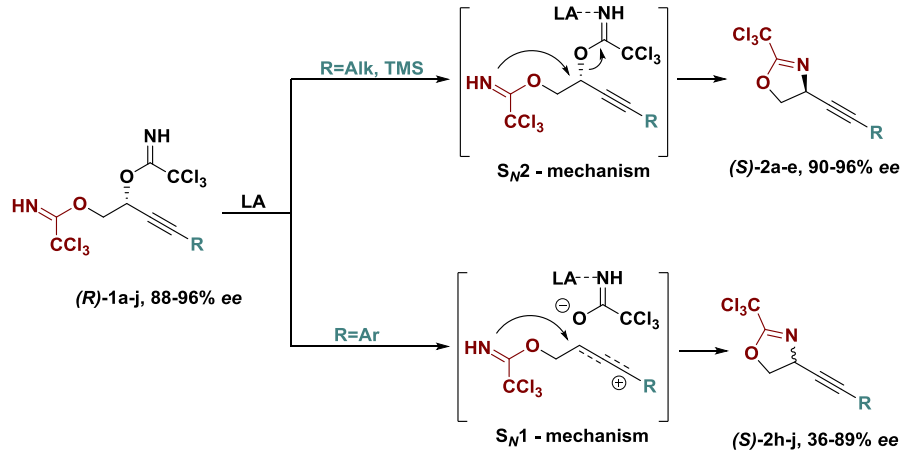


Fig. 5. Intramolecular amination of enantioenriched (*R*)-*bis*-imidates **1a-j**.

Table 2

Yields and *ee* of Amination Reaction of Enantioenriched (*R*)-*bis*-imidates **1a-j**[a]

Entry	R	(*R*)-**1,** (*ee* %)[b]	LA	(*S*)-**2**, Yield, % (*ee* %)[b]
1	Me	(*R*)-**1a,** (90)	$AlCl_3$	(*S*)-**2a**, 80 (90)
2	TMS	(*R*)-**1b,** (96)		(*S*)-**2b**, 90 (96)
3	$BnOCH_2$	(*R*)-**1c,** (92)		(*S*)-**2c**, 70 (92)
4	$BnOCH_2CH_2$	(*R*)-**1d,** (93)		(*S*)-**2d**, 75 (92)
5	*t*Bu	(*R*)-**1e,** (93)	TMSOTf	(*S*)-**2e**, 84 (93)
6	Ph	(*R*)-**1h,** (88)	$BF_3{\cdot}Et_2O$	(*S*)-**2h**, 80 (36)
7	$2\text{-}ClC_6H_4$	(*R*)-**1i,** (90)	$BF_3{\cdot}Et_2O$	(*S*)-**2i**, 90 (52)
8			TMSOTf	(*S*)-**2i**, 75 (57)
9			$AlCl_3$	(*S*)-**2i**, 89 (52)
10	$3,5\text{-}ClC_6H_3$	(*R*)-**1j,** (93)	$BF_3{\cdot}Et_2O$	(*S*)-**2j**, 56 (86)
11			TMSOTf	(*S*)-**2j**, 50 (89)
12			$AlCl_3$	(*S*)-**2j**, 79 (76)

[a] Reaction conditions: Lewis acid catalyst (10 mol %), DCM (0.1 M), molecular sieves (4 Å), r. t. , 1–10 min. [b] *ee* was determined by HPLC using chiral column Chiralpak IB.

Oxazolines **2** prepared by *bis*-imidate **1** cyclization reaction were successfully transformed to ethynylglycinol derivatives **3b-e,j** and **4,5** (Fig. 6). (*S*)-Alkynylglycinols **3b-e** and **3j** were prepared from (*S*)-oxazolines **2b-e** and **2j** using strong acidic hydrolysis (Table 3). The hydrolysis of oxazoline **2h** was followed by *tert*-butoxycarbonyl protection without isolation of an intermediate to give protected alkynylglycinol **4**. Mild acidic hydrolysis of oxazoline **2b** with trimethylsilyl substituent at acethylene terminal position provided N-trichloroacetyl alkynylglycinol **5**.

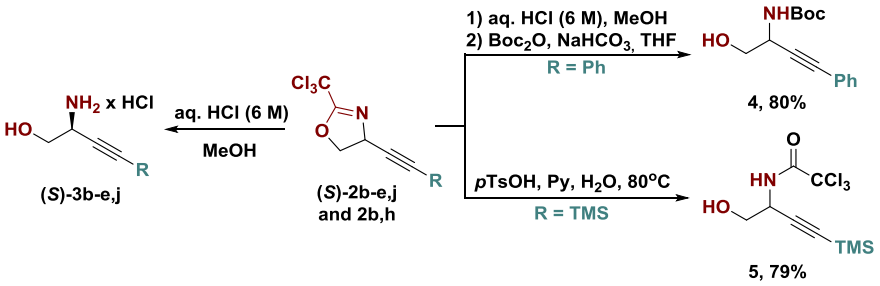


Fig. 6. Synthesis of ethynylglycinol derivatives **3b-e,j** and **4,5**.

Table 3

Yields of (*S*)-Ethynylglycinol Derivatives **3b-e,j**

Entry	R	(*S*)-**3**, Yield, %
1	H	(*S*)-**3b**, 90
2	CH_2OBn	(*S*)-**3c**, 75
3	$(CH_2)_2OBn$	(*S*)-**3d**, 89
4	*t*Bu	(*S*)-**3e**, 74
5	$3,5\text{-}Cl_2OC_6H_3$	(*S*)-**3j**, 74

The absolute configuration of the representive ethynylglycinols (*S*)-**3b,j** was determined by analysis of ^{1}H-NMR spectra of the diastereomers (*S,S*)-**6b,j** and (*R,S*)-**6b,j** resulting from derivatization with (*R*)- and (*S*)-1-fluoro-2,4-dinitrophenyl-5-phenylethylamines (Fig. 7). The conformation of FDPEA derivatives (*S,S*)-**6b,j** and (*R,S*)-**6b,j** is fixed by the hydrogen bonding. Due to the anisotropic effect of benzene ring, HOC**H**$_2$- group proton signals in derivatives (*R,S*)-**6b,j** are shifted to stronger fields compared to diastereomer (*S,S*)-**6b,j**. Additionally, acetylenic C**H** group proton signal in derivative (*S,S*)-**6b** is shifted to stronger fields compared to the diastereomer (*R,S*)-**6b**.

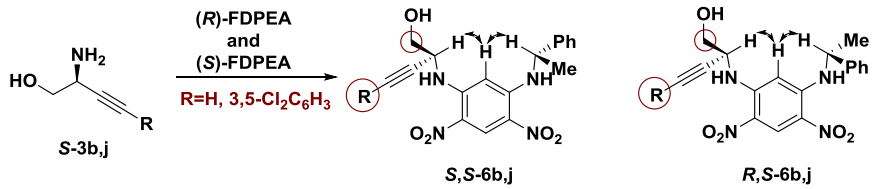


Fig. 7. FDPEA derived diastereomers (*S,S*)-**6b,j** and (*R,S*)-**6b,j**.

Synthesis of *Q*-Ethynylglycinols by the Ritter Reaction of Ethynylglycols

Next attention was focused on the synthesis of quaternary ethynylglycinols due to their broad utility in the construction of complex molecules. First, an attempt to extend previously developed method was applied for the synthesis of C-quaternary ethynylglycinols using Lewis acids catalysed cyclization of *bis*-imidates. Unfortunatelly, this turned out not to be applicable because C-quaternary ethynylglycol **7** reacted with trichloroacetonitrile to produce monoimidate **8**, followed by *in situ* cyclization to 1,3-dioxolane derivative **9** (Fig. 8).

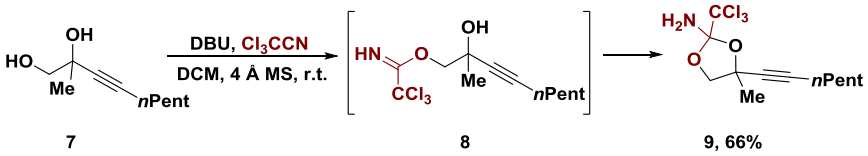


Fig. 8. Reaction of quaternary ethynylglycol **7** with trichloroacetonitrile.

As an alternative approach, the Ritter reaction of 1,2-diols with acetonitrile was explored, which is known in literature for the synthesis of oxazolines and imidazolines. The prerequisite for the successfull Ritter reaction is formation of stable carbocation intermediate. However, when ethynylglycol **7** was directly subjected to the Ritter reaction conditions (MeCN, AcOH, H_2SO_4), the expected oxazoline **10** was obtained in very low yield (<10 %) (Fig. 9). Such an outcome can be explained by the formation of relatively unstable propargylic cation **I** in which the positive charge is delocalysed on sp^2 and sp hybridized carbon atoms (**I-1** and **I-2**). Moreover, the carbocation **I** can undergo various side reactions (e.g. *Meyer-Schuster* or *Rupe* rearrangements) competing with the formation of nitrilium ion **II**.

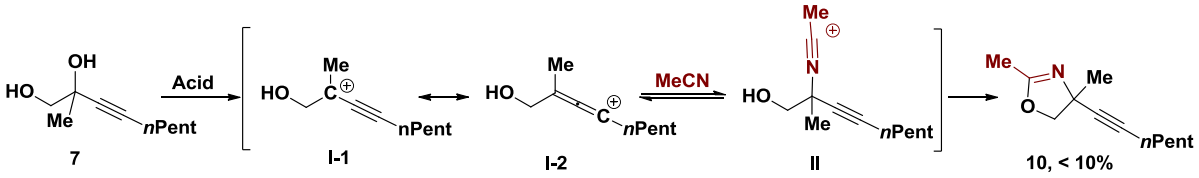


Fig. 9. Ritter reaction of quaternary ethynylglycol **7**.

Next, Ritter reaction of cobalt complexed ethynylglycol **11** was investigated. Ethynylglycol **11** has higher ability to stabilize carbenium ion intermediate through the resonance structures **III** and **IV** (Fig. 10). Subsequently, carbenium ion **III** or **IV** could react with acetonitrile to produce nitrilium ion **V** intermediate, which is traped by intramolecular attack of hydroxyl group to form oxazoline **12**. In the presence of acid such as H_2SO_4 or $BF_3{\cdot}Et_2O$, cobalt complexed ethynylglycol **11** reacted with acetonitrile to give expected oxazolines **12a-h**,**k-m** in moderate to good yields. Wide range of substituents at the terminal alkyne position in substrate **11** were tolerated under reaction conditions (Table 4). Substrates **11l,m** with hydroxymethyl substituent at the reaction center gave Ritter products **12l,m** in 46 % and 81 % yields, respectively (Table 4, entries 16 and 17). Moreover, secondary alcohol **11k** could be successfully subjected to the Ritter reaction conditions to provide oxazoline **12k** in good yield (Table 4, entry 15). Some limitations of reaction were observed: diols **11i,j** containing phenyl group at the reaction center found as poor substrates for Ritter reaction giving no expected oxazolines **12i,j** (Table 4, entries 13 and 14).

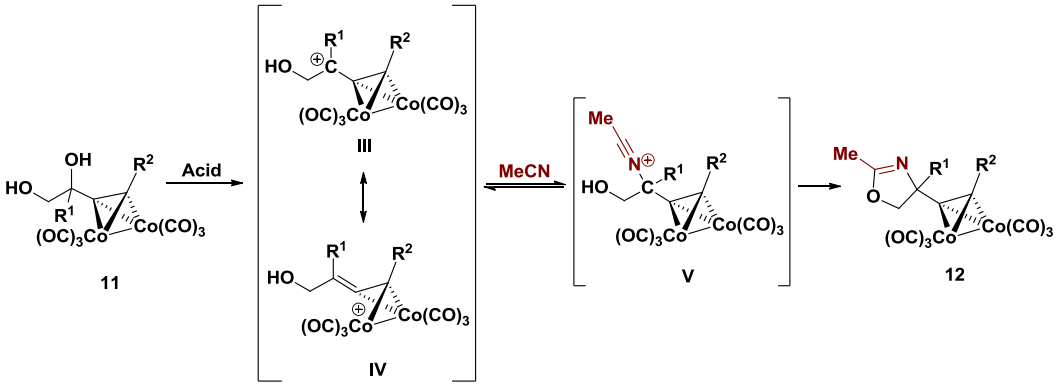


Fig. 10. The Ritter reaction of cobalt complexed ethynylglycols **11**.

Table 4

Yields and Acids Promoters of the Ritter Reaction

Entry	R^1	R^2	Acid	**12**, Yield, %
1	Me	*n*Pent	H_2SO_4[a]	**12a**, 58
2			$BF_3{\cdot}Et_2O$[b]	**12a**, 78
3	Me	*t*Bu	H_2SO_4[a]	**12b**, 75
4			$BF_3{\cdot}Et_2O$[b]	**12b**, 82
5	Me	TMS	H_2SO_4[a]	**12c**, 89
6			$BF_3{\cdot}Et_2O$[b]	**12c**, 84
7	Me	Ph	H_2SO_4[a]	**12d**, 57
8			$BF_3{\cdot}Et_2O$[b]	**12d**, 86
9	Me	2-ClPh		**12e**, 61
10	Me	4-MeOPh		**12f**, 63
11	Me	CH_2OBn		**12g**, 78
12	Me	Me		**12h**, 74
13	Ph	*n*Pent	$BF_3{\cdot}Et_2O$[b]	**12i**, 0
14	Ph	Ph		**12j**, 0
15	H	*n*Pent		**12k**, 77
16	CH_2OH	*n*Pent		**12l,** 46
17	CH_2OH	Ph		**12m**, 81

[a] Reagents and conditions: MeCN (54 equiv), H_2SO_4 (9 equiv), AcOH (8 equiv), 0 °C – r. t., 1–10 min. [b] Reagents and conditions: $BF_3{\cdot}Et_2O$ (10 equiv), MeCN (0.1 M),0 °C – r. t., 5–10 min.

Next several reaction conditions for the cleavage of cobalt complex **12a** to obtain uncomplexed oxazoline **13a** were investigated (Fig. 11). It is described in the literature that primary amines react with alkyne-$Co_2(CO)_6$ complexes to liberate alkynes. These results led to investigation of cleavage reaction of cobalt complex **12a** with ethylenediamine. Unfortunatly uncomplexed oxazoline **13a** was obtained in low 28 % yield. Next, oxidative conditions using DDQ, NMO and CAN as reagents were explored. The best yield of oxazoline **13a** was obtained using DDQ as oxidant (Table 5), which constitutes a new method for the decomplexation of

alkyne-cobalt complexes. NMO was better suited as oxidant for the cleavage of cobalt complexes **12l,m** containing hydroxymethyl group at the quaternary carbon center to provide oxazoline products **13l,m** (entries 12 and 14).

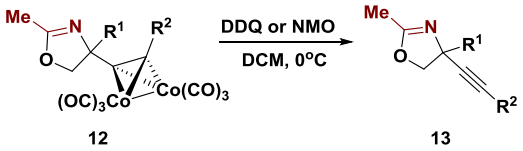


Fig. 11. Cleavage of cobalt complexes **12**.

Table 5

Yields and Conditions for Cleavage of Cobalt Complexes **12**

Entry	R^1	R^2	Oxidant	**13**, Yield, %
1	Me	*n*Pent	DDQ[a]	**13a**, 84
2			NMO[b]	**13a**, 42
3	Me	*t*Bu	DDQ[a]	**13b**, 64
4	Me	TMS		**13c**, 88
5	Me	Ph		**13d**, 83
6	Me	2-ClPh		**13e**, 92
7	Me	4-MeOPh		**13f**, 85
8	Me	CH_2OBn		**13g**, 82
9	Me	Me		**13h**, 46
10	H	*n*Pent		**13k**, 78
11	CH_2OH	*n*Pent	DDQ[a]	**13l,** 61
12			NMO[b]	**13l,** 65
13	CH_2OH	Ph	DDQ[a]	**13m,** 26
14			NMO[b]	**13m,** 65

[a] Reagents and conditions: DDQ (3 equiv), DCM (0.1 M), 0 °C, 30 min to 2 h. [b] Reagents and conditions: NMO (10 equiv), DCM (0.1 M), 0 °C, 30 min.

In order to demonstrate the utility of oxazolines **13**, selected oxazolines **13d,g,h,l,m** were transformed to amino alcohols **14** by using acidic hydrolysis (Fig. 12). The hydrolysis reaction proceeded in good yields to produce C-quaternary ethynylglycinols **14d,g,h,l,m** (Table 6).

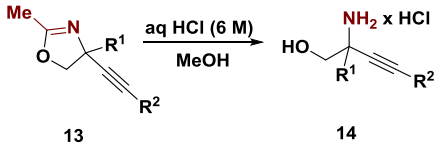


Fig. 12. Synthesis of C-quaternary ethynylglycinols **14**.

Table 6

Yields of Quaternary Ethynylglycinols **14d,g,h,l,m**

Entry	R^1	R^2	**14**, Yield, %
1		Ph	**14d,** 96
2	Me	CH_2OBn	**14g,** 64
3		Me	**14h,** 62
4	CH_2OH	*n*Pent	**14l,** 82
5	CH_2OH	Ph	**14m,** 77

C–H Functionalization of Phenylglycinols Using Cobalt Catalyst

Second part of research was devoted to picolinamide directed C–H functionalization of phenylglycinols **15** with alkynes under cobalt catalysis (Fig. 13). During the optimization studies, a range of cobalt catalysts, oxidants, base additives and reaction solvents were investigated (Table 7). Initial screening revealed that the reaction between phenylglycinol derivative **15a** and 3,3-dimethyl-1-butyne in the presence of $Co(OAc)_2$ catalyst, NaOPiv base and AgOAc oxidant in MeOH at 80 °C leads to the regioselective formation of 1-hydroxymethyl-1,2-dihydroisoquinoline derivative **16aa** in 5 % yield (entry 1). Regiochemistry of product **16aa** was confirmed by 2D-NOESY spectra. Alternative oxidant screening showed that product **16aa** yield could be slightly improved by using of $Mn(OAc)_3{\cdot}2\ H_2O$ in combination with oxygen (entries 2−5). Reducing the amount of NaOPiv enhanced the product **16aa** yield to 28 % (entry 6). Screening of different solvents revealed that MeOH is the solvent of choice. Alternative Co(II) and Co(III) catalysts also were examined, these revealded that $Co(dpm)_2$ catalyst is crucial for successful reaction, yielding the product **16aa** in 82 % yield as single regioisomer (entries 7−9). The prolonged reaction time 24 h only slightly improved yield of product **16aa** to 84 % (entry 10). Control experiments excluding catalyst or oxidant showed no product **16aa** formation.

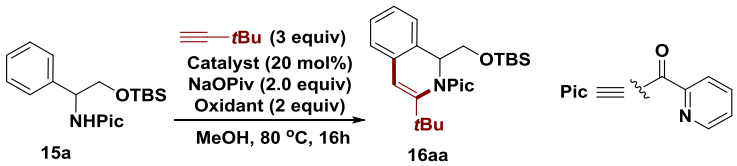


Fig. 13. Phenylglycinol **15a** reaction with *terc*-butylacethylene.

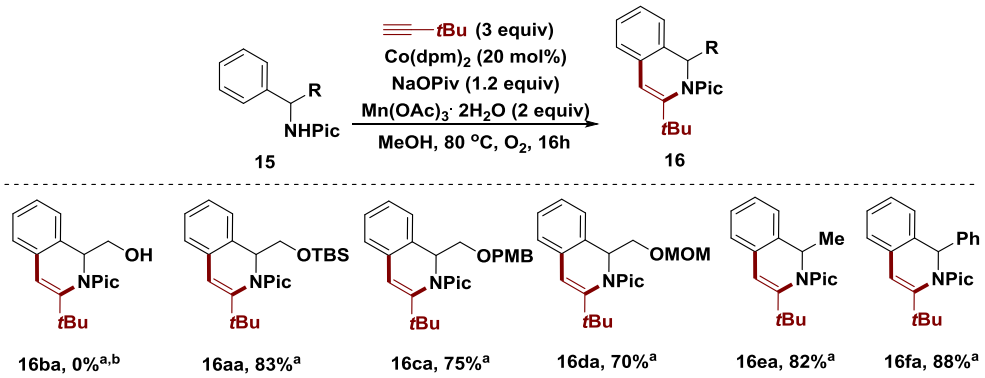
Table 7

Optimization of Reaction Conditions

Entry	Catalyst	Oxidant	**15a/16aa**	Yield, %[a]
1	$Co(OAc)_2$	AgOAc	17 : 1	5
2	$Co(OAc)_2$	MnO_2	11 : 1	4
3	$Co(OAc)_2$	$Mn(OAc)_2{\cdot}4H_2O$	19 : 1	5
4	$Co(OAc)_2$	$Mn(OAc)_3{\cdot}2H_2O$	7 : 1	12
5	$Co(OAc)_2$	$Mn(OAc)_3{\cdot}2H_2O/O_2$	5.3 : 1	16
6[b]	$Co(OAc)_2$	$Mn(OAc)_3{\cdot}2H_2O/O_2$	2.5 : 1	28
7[b]	$CoCl_2$	$Mn(OAc)_3{\cdot}2H_2O/O_2$	> 10 : 1	–
8[b]	$Co(acac)_2$	$Mn(OAc)_3{\cdot}2H_2O/O_2$	2.3 : 1	30
9[b,c]	**$Co(dpm)_2$**	**$Mn(OAc)_3{\cdot}2H_2O/O_2$**	**1 : 13.7**	**82**
10[b,c,d]	**$Co(dpm)_2$**	**$Mn(OAc)_3{\cdot}2H_2O/O_2$**	**1 : 16.8**	**84**

[a] NMR yield using triphenylmethane as an internal standard. [b] NaOPiv (0.12 mmol, 1.2 equiv). [c] $Co(dpm)_2$ – bis(2,2,6,6-tetramethyl-3,5-heptanedionato)-cobalt(II), CAS: 13986-53-3. [d] Time: 24h.

Next, picolinamides **15** with different substituents at the benzylic position were examined (Fig. 14). It was found that picolinamide **15b** with unprotected alcohol function decomposed under the reaction conditions. On the oher hand, TBS-, PMB- and MOM- protected phenylglycinol derivatives **15a,c,d** gave corresponding products **16aa,ca,da** as single regioisomers in very good yields (70–83 %). Moreover, benzylamide derivatives **15e-f** also gave products **16ea-fa** in excellent yields.

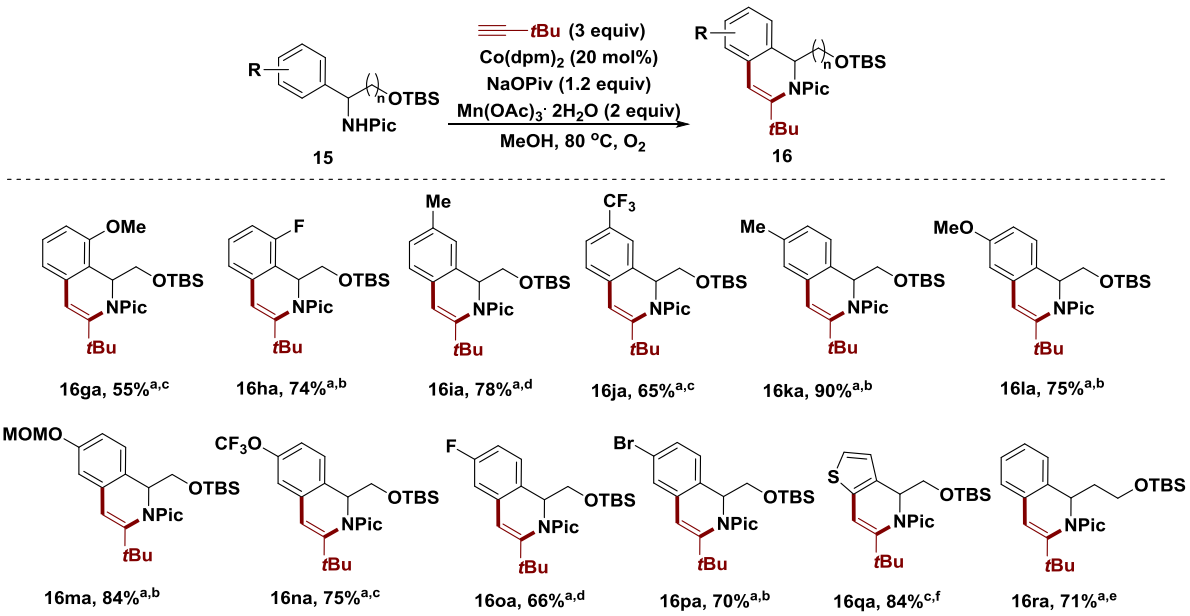


[a] Isolated yields are given. [b] Decomposition of substrate.

Fig. 14. Reaction scope with respect to picolinamides **15**.

Subsequently, the scope of phenylglycinol derivatives **15** with diverse functional groups at benzene ring was examined (Fig. 15). The annulation reactions were successful with phenylglycinol derivatives **15** bearing *para*-, *meta*- and *ortho*-substituents at benzene ring. In the case of *meta*-substituted substrates **15i** and **15j**, the less hindered C–H bonds were

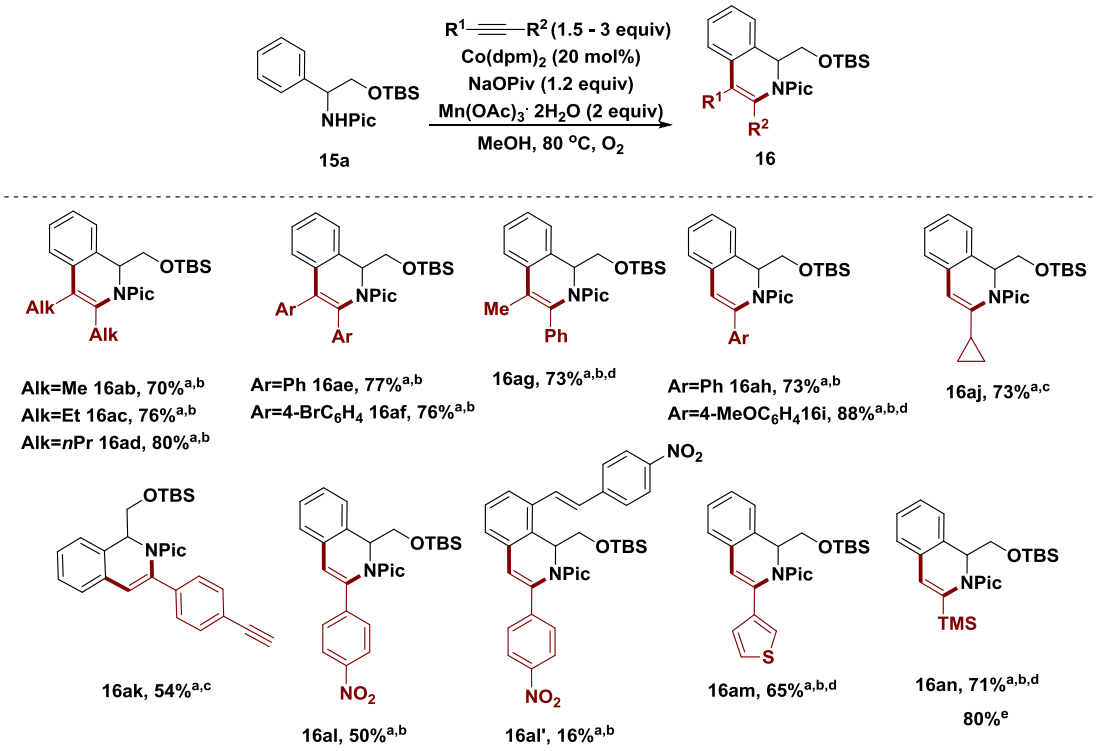
activiated to produce single regioisomers **16ia,ja,** which is consistent with literature examples. Furthermore, different electron-donating groups, such as alkyl (**15i, 15k**), methoxy (**15g, 15l**), methoxymethyl ether (**15m**), as well as electron-withdrawing groups, such as trifluoromethyl (**15j**), trifluoromethoxy (**15n**) and halogen substituents (**15h, 15o, 15p**) at benzene ring of substrates **15** were tolerated. β-Phenylalaninol derivative **15r** was also competent substrate and gave corresponding product **16ra** in very good yield – 71 %. Moreover, glycinol **15q** containing thiophene heterocycle gave product **16qa** as the main regioisomer in ratio 2.5/1 to isomer functionalized at the 4th position of thiophene ring.



[a] Isolated yields are given; All products were isolated as single regioisomers. [b] Time: 16–17 h. [c] Time: 20 h. [d] Time: 24 h. [e] Time: 40 h. [f] Isolated as 2.5 : 1 mixture of thiophene regioisomers, major product shown.

Fig. 15. Reaction scope with respect to phenylglycinols derivatives **15**.

The reaction scope with respect to alkynes (Fig. 16) was also investigated. Aliphatic and aromatic internal alkynes reacted smoothly to give corresponding products **16ab-af** in good yields 70−80 %. Unsymmetrically substituted internal alkynes are known as challenging reaction partners for the annulation reactions due to difficulty to achieve high regioselectivity. Succesfully was found that 1-phenyl-1-propyne reacted smoothly to afford the corresponding product **16ag** as a single regioisomer in 73 % yield. Also terminal alkynes with alkyl, aryl and heteroaryl substituents reacted smoothly under reaction conditions, affording products **16ah-j**,**m,n** in good yields as single regioisomers. Reaction of trimethylsilylacetylene with phenylglycinol **15a** was performed on 1 g scale, giving product **16an** in a very good 80 % yield. Interestingly, 4-nitrophenylacetylene afforded mono C–H alkenylation/cyclization product **2al** (50 %) together with *bis*-functionalized product **2al'** (16 %).



[a] Isolated yields are given. [b] Time: 16–17 h. [c] Time: 20 h. [d] Isolated as single regioisomer. [e] Gram-scale synthesis, starting from 1 g of picolinamide **15a**.

Fig. 16. Reaction scope with respect to alkynes.

The reaction of enantiopure (*S*)-phenylglycinol derivative **15a** with terminal and internal alkynes under the optimized reaction conditions was investigated (Fig. 17). Conservation of chirality was confirmed by high enantiopurity of products (**16aa**, **16ab**, **16ae**, **16ah**).

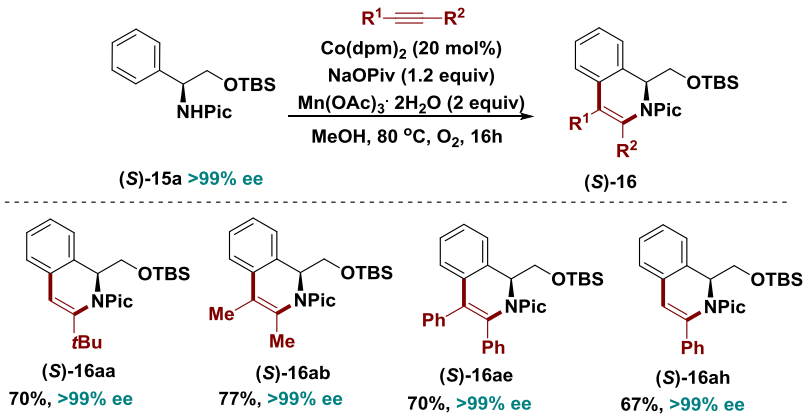


Fig. 17. Conservation of chirality.

The application of the developed methodology was shown by accessing valuable tetrahydroisoquinoline derivative **(*S*,*S*)-18an** (Fig. 18). Reduction of enantiopure **(*S*)-16an** with Na in NH_3 proceeded in highly diastereoselective manner (>20/1) to give tetrahydroisoquinoline **(*S*,*S*)-17an**.

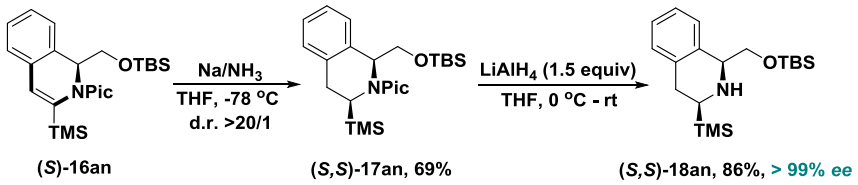
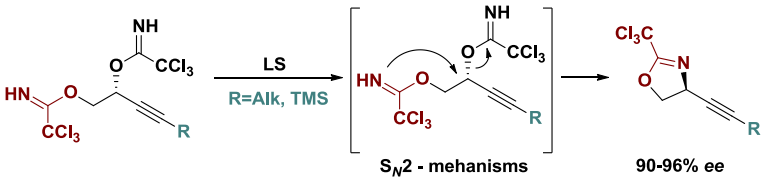


Fig. 18. Synthesis of tetrahydroisoquinoline **(*S*,*S*)-18an**.

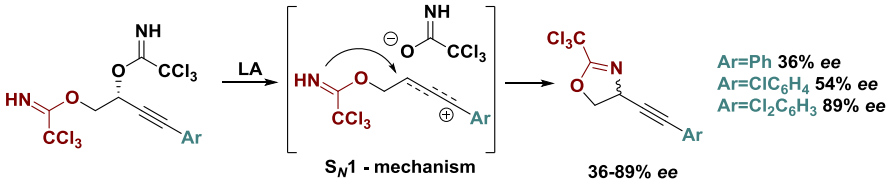
Subsequent directing group removal using $LiAlH_4$ gave the corresponding tetrahydroisoquinoline **(*S*,*S*)-18an** in good yield without the loss of stereochemical purity.

CONCLUSIONS

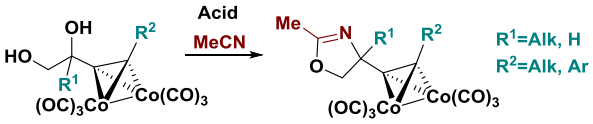
1. *Bis*-imidates derived from ethynylglycols with alkyl and trimethylsilyl terminal substituents undergo Lewis acid catalysed propargylic amination leading to regioselective oxazoline formation. Complete inversion of absolute stereochemistry at chiral center was obserserved starting from enantioenriched substrates indicating S_N2 type mechanism.



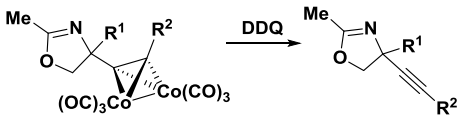
2. Cyclization of *bis*-imidates derived from ethynylglycols with terminal phenyl substituent also proceed regioselectively affording propargylic substitution products. However, enatioenriched substrates gave products with partial racemization of a chiral center, indicating mixed S_N1 and S_N2 type mechanisms. Incorporation of electron-withdrawing chlorine groups at the benzene ring of a substrate significantly suppressed the racemization as a result of destabilized intermediate carbenium ion.



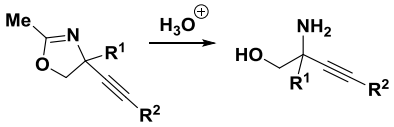
3. Etnynylglycol cobalt complexes are suitable substrates for the Ritter reaction with acetonitrile to produce C-quaternary oxazolines. Reaction conditions tolerates broad substrate scope, while the limitation are substrates bearing phenyl substituent at the quaternary carbon.



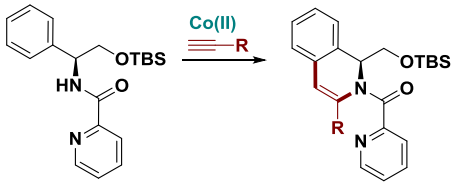
4. Alkyne-$Co_2(CO)_6$ complexes can be successfully cleaved using DDQ oxidant to obtain the desired oxazolines in good yield.



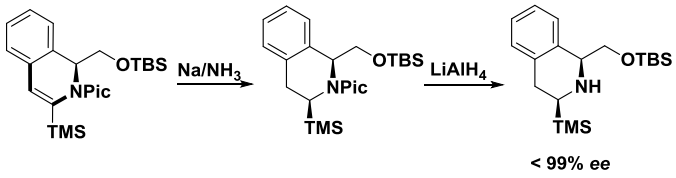
5. Oxazolines obtained by *bis*-imidate cyclization and Ritter reaction can be efficiently transformed into corresponding ethynylglycinols under acidic hydrolysis conditions.



6. Picolinamide directed C–H functionalization of O-protected phenylglycinols with alkynes using cobalt catalyst leads to 1-hydroxymethyl-1,2-dihydroisoquinoline derivatives. Optimized reaction conditions are with $Co(dpm)_2$ as catalyst, $Mn(OAc)_3$ as an oxidant, molecular oxygen as a co-oxidant, NaOPiv as a base, and MeOH as a solvent 80 °C. Both terminal and internal alkynes are suitable reagents for this transformation. In the case of monosubstituted and unsymmetrically substituted internal alkynes, the annulation reaction is highly regioselective. The complete conservation of stereochemistry for dihydroisoquinoline formation was confirmed by transformation of enantioenriched phenylglycinol derivatives.



7. (*S*,*S*)-Tetrahydroisoquinolines can be obtained in good yield from 1,2-dihydroisoquinoline derivatives without the loss of stereochemical purity in two steps, which involves diastereoselective reduction with Na/NH_3 followed by the cleavage of picolinamide with $LiAlH_4$.



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