RĪGAS TEHNISKĀ UNIVERSITĀTE
Materiālzinātnes un lietišķās ķīmijas fakultāte
Organiskās ķīmijas tehnoloģijas institūts

RIGA TECHNICAL UNIVERSITY
Faculty of Materials Science and Applied Chemistry
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JAUNU METOŽU IZVEIDE AMINOSPIRTU SINTĒZEI UN C–H FUNKCIONALIZĒŠANAI

Promocijas darbs

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

Doctoral Thesis

Zinātniskais vadītājs
Profesors *Dr. chem.*
AIGARS JIRGENSONS

Scientific supervisor
Professor Dr. chem.
AIGARS JIRGENSONS

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APSTIPRINĀJUMS

Apstiprinu, ka esmu izstrādājusi šo promocijas darbu, kas iesniegts izskatīšanai Rīgas Tehniskajā universitātē zinātnes doktora (*Ph. D.*) grāda iegūšanai. Promocijas darbs zinātniskā grāda iegūšanai nav iesniegts nevienā citā universitātē.

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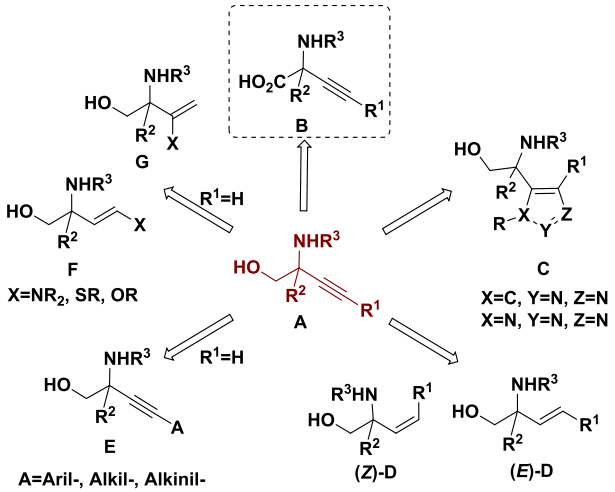
SATURS

PROMOCIJAS DARBA VISPĀRĒJS RAKSTUROJUMS

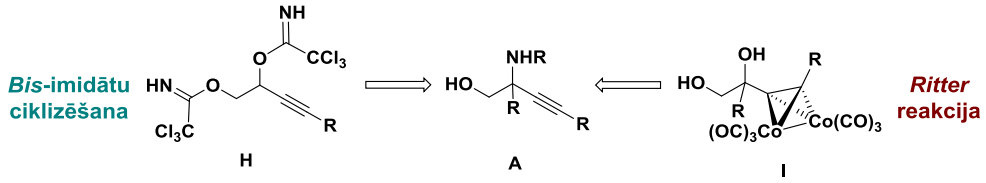
Tēmas aktualitāte

Etīnilglicinola atvasinājumi **A** ir vērtīgi būvbloki farmaceitiski nozīmīgu savienojumu un dabasvielu totālajā sintēzē.[1] Trīskāršā saite šajos savienojumos nodrošina plašas modificēšanas iespējas (1. att.): trīskāršās saites ciklopievienošanās reakcijās veidojas dažādi heterocikli **C**, reducējot trīskāršo saiti, var iegūt (*Z*)- un (*E*)-**D** dubultsaites izomērus, iespējamas terminālās trīskāršās saites alkilēšanas, arilēšanas un alkinilēšanas reakcijas, veidojot produktus **E**, kā arī reakcijās ar dažādiem O-, N- un S-nukleofīliem iespējams izolēt savienojumus **F** un **G**. Oksidējot hidroksilgrupu savienojumā **A**, var vienā stadijā iegūt *α*-etīnilglicīnu **B** (R^1 = H) – 2-aminobut-3-īnskābes atvasinājumu, kam piemīt antibakteriālas īpašības pret *Streptomyces aureus*.[2]



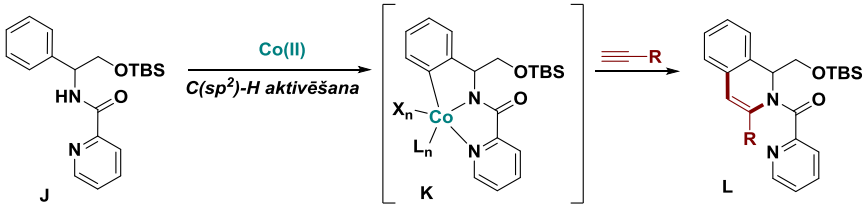
1. att. Alkīnilglicīnola **A** modificēšanas iespējas.

Neskatoties uz etīnilglicīnolu **A** augsto izmantošanas potenciālu, literatūrā ir zināms ļoti ierobežots metožu skaits etīnilglicīnola **A** un etīnilglicīna **B** atvasinājumu iegūšanai. Zināmās metodes pamatā balstās uz *Garner* aldehīda atvasināšanu[3] un terminālu alkīnu pievienošanās reakcijām pie *Ellman*-tipa *N*-sulfīnilimīniem,[4] turklāt vienkāršota pieeja C-kvaternāro etīnilglicīnolu **A** atvasinājumu sintēzei ir karboksilgrupas reducēšana etīnilglicīnā **2**. Literatūrā ir zināmas tikai dažas alternatīvas metodes C-kvaternārā etīnilglicīnola **A** fragmenta konstruēšanai: serināla atvasinājumu *Seyferth–Gilbert* homologēšana,[5] alkīnilepoksīdu aminolīze[6] un nitrēnu iespiešanās propargiliskā C–H saitē.[7] Balstoties uz iegūto informāciju, tika iesākti pētījumi jaunu metožu izveidei etīnilglicīnola **A** atvasinājumu sintēzei, kas ietver *bis*-imidātu **H** propargiliskās aminēšanas reakciju vai etīnilglikola kobalta kompleksa **I** *Ritter* reakciju (2. att.).



2. att. Jaunas metodes etīnilglicīnolu **A** sintēzei.

Aminospirti ir daudzu farmaceitiski nozīmīgu savienojumu un dabas vielu struktūrelementi, tāpēc metodes aminospirtu modificēšanai ir ļoti pieprasītas. Īpaši pievilcīga ir aminospirtu transformēšana, izmantojot C–H saites funkcionalizēšanu, jo tā ļauj iegūt kompleksus atvasinājumus salīdzinoši īsā sintēzē, izmantojot katalītisku pārejas metāla katalizatora daudzumu. Pikolīnamīda virzīta benzilamīdu C–H funkcionalizēšana ar alkīniem, izmantojot kobalta katalizatoru, ir literatūrā zināma,[8] tomēr zināmā metode ir ierobežota līdz metil- un fenil- aizvietotājiem benziliskajā pozīcijā, kā arī metodē ir ierobežots izmantojamais alkīnu klāsts. Mūsu pētījumi vērsti uz fenilglicīnola atvasinājumu **J** C(sp^2)–H saites aktivēšanu, izmantojot lētu un komerciāli pieejamu kobalta katalizatoru, veidojot starpproduktu **K**, un tam sekojošu funkcionalizēšanu ar termināliem un diaizvietotiem alkīniem, veidojot 1,2-dihidroizohinolīna atvasinājumu **L** (3. att.).



3. att. Jauna metode fenilglicīnola **J** C–H funkcionalizēšanai.

Pētījuma mērķis un uzdevumi

Promocijas darba mērķis ir jaunu sintēzes metožu izveide etīnilglicīnolu sintēzei un fenilglicīnolu C–H funkcionalizēšanai, izmantojot kobalta katalizatoru.

Darba mērķa īstenošanai tika definēti šādi uzdevumi:

1) izpētīt *bis*-imidātu iekšmolekulāru propargilisku aminēšanas reakciju enantiobagātinātu etīnilglicīnolu sintēzei;
2) demonstrēt etīnilglikolu kobalta kompleksu izmantošanu *Ritter* reakcijā C-kvaternāro etīnilglicīnolu sintēzei;
3) izstrādāt efektīvu metodi fenilglicīnolu C–H funkcionalizēšanai ar diaizvietotiem un terminālajiem alkīniem, izmantojot kobalta katalizatoru.

Zinātniskā novitāte un galvenie rezultāti

Pētījumu rezultātā izstrādātas jaunas metodes etīnilglicīnola atvasinājumu sintēzei: 1) *bis*-imidātu iekšmolekulāra propargiliskā aizvietošanās reakcija demonstrēta racēmisku un enantiobagātinātu etīnilglicīnolu iegūšanai; 2) etīnilglikolu kobalta kompleksu *Ritter* reakcija

izmantota C-kvaternāro etīnilglicīnolu iegūšanai; 3) demonstrēti jauni apstākļi alkīna-kobalta kompleksa nošķelšanai, izmantojot DDQ oksidētāju; 4) izstrādāta jauna un efektīva metode pikolīnamīda virzītai, kobalta katalizētai fenilglicīnolu C–H funkcionalizēšanai ar diaizvietotiem un terminālajiem alkīniem. Metode piemērota reģioselektīvai enantiobagātinātu dihidroizohinolīna atvasinājumu sintēzei.

Darba struktūra un apjoms

Promocijas darbs sagatavots kā tematiski vienota zinātnisko publikāciju kopa par: a) *bis*-imidātu iekšmolekulāru propargilisku aizvietošanās reakciju; b) etīnilglikolu kobalta kompleksu *Ritter* reakciju; c) kobalta katalizētu fenilglicīnolu C–H funkcionalizēšanu.

Darba aprobācija un publikācijas

Promocijas darba galvenie rezultāti apkopoti piecās zinātniskajās oriģinālpublikācijās. Pētījuma rezultāti prezentēti sešās konferencēs.

Zinātniskās publikācijas

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.

Darba rezultāti prezentēti zinātniskajās konferencēs

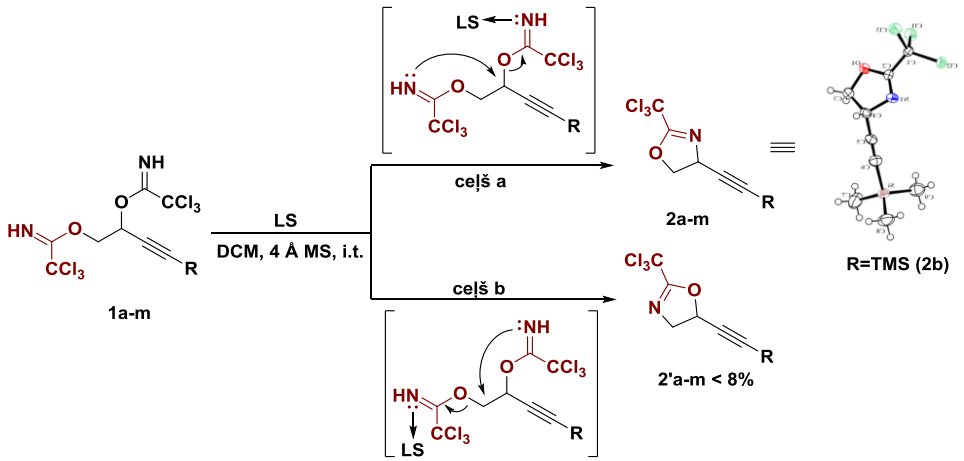
1. **Sirotkina**, **J**., Jirgensons, A. Synthesis of enantioenriched ethynyl glycinols *via* acid catalyzed cyclization of *bis*-trichloroacetimidates. *Balticum Organicum Syntheticum (BOS 2014).* Vilnius, Lithuania, 6–9 July **2014**.
2. **Sirotkina**, **J**. The Ritter reaction of cobalt carbonyl 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**.

PROMOCIJAS DARBA GALVENIE REZULTĀTI

Etīnilglicīnolu iegūšana *bis*-imidātu ciklizēšanas reakcijā

Promocijas darbā izstrādāta jauna metode racēmisku un enantiobagātinātu etīnilglicīnola atvasinājumu iegūšanai, kas balstīta uz Luisa skābes katalizētu *bis*-imidātu **1a-m** ciklizēšanas reakciju (4. att.). Ciklizēšanas reakcijā vienas *bis*-imidāta grupas slāpekļa atoms kalpo kā iekšmolekulārs N-nukleofīls, savukārt otra *bis*-imidāta grupa tiek aktivēta ar Luisa skābi un tādējādi kalpo kā laba aizejošā grupa. Imidātu **1a-m** aktivēšanai kā katalizatori izmantotas Luisa skābes: TMSOTf, $AlCl_3$, $BF_3{\cdot}Et_2O$, $FeCl_3$, kā rezultātā iegūti oksazolīni **2a-m** ar ļoti labiem iznākumiem (1. tabula). Novērots, ka ciklizēšanas reakcija notiek reģioselektīvi, pamatā veidojot propargiliskās aizvietošanās produktus **2a-m** (4. att., ceļš **a**), savukārt minorie reģioizomēri **2'a-m** veidojās mazāk par 8 %. Trimetilsililaizvietota *bis*-imidāta **1b** gadījumā reģioselektivitāti izdevās ievērojami uzlabot, aizstājot TMSOTf ar $AlCl_3$ (1. tabula, 2. un 3. ailes). Pamatreģioizomēra **2b** struktūra tika pierādīta ar rentgenstruktūranalīzes palīdzību.



4. att. Oksazolīnu **2** un **2'** veidošanās no *bis*-imidātiem.

1. tabula

Produktu **2** iznākumi un reakcijā izmantotās Luisa skābes[a]

Nr. p. k.	R	LS[a]	Produkti **2/2'**[b]	**2**, Iznākums, %
1	Me	TMSOTf	> 50 : 1	**2a**, 71
2	TMS	TMSOTf	9 : 1	**2b**, 82
3	TMS	$AlCl_3$	35 : 1	**2b**, 91
4	$BnOCH_2$	$AlCl_3$	8 : 1	**2c**, 75

[a] Reakcijas apstākļi: Luisa skābe (10 mol %), DCM (0,1 M), molekulārie sieti (4 Å), i. t., 1–10 min. [b] Reakcijas maisījuma produktu **2/2'** attiecība noteikta, izmantojot GH-MS.

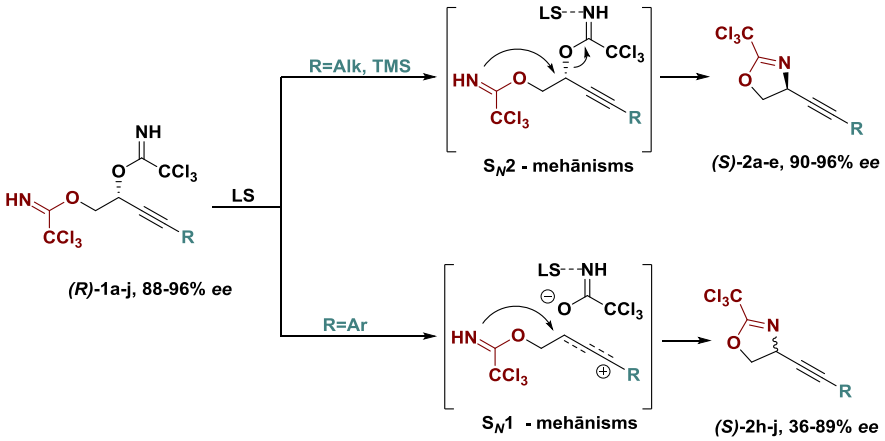
1. tabulas turpinājums

Produktu **2** iznākumi un reakcijā izmantotās Luisa skābes[a]

Nr. p. k.	R	LS	Produkti **2/2'**[b]	**2**, Iznākums, %
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] Reakcijas apstākļi: Luisa skābe (10 mol %), DCM (0,1 M), molekulārie sieti (4 Å), i. t., 1–10 min. [b] Reakcijas maisījuma produktu **2/2'** attiecība noteikta, izmantojot GH-MS.

Lai pārbaudītu hiralitātes pārnesi *bis*-imidātu ciklizēšanas reakcijā, kā substrāti tika izmantoti enantiobagātināti (*R*)-*bis*-imidāti **1a-j** ar alkil-, trimetilsilil- un aril- aizvietotājiem pie trīskāršās saites. Standartapstākļos alkil-, trimetilsililaizvietotu (*R*)-*bis*-imidātu **1a-e** ciklizēšanās notika ar praktiski pilnīgu absolūtās konfigurācijas apgriešanu pie hirālā centra. Produkti (*S*)-**2a-e** tika iegūti ar enantiomēro pārākumu virs 90 % (2. tabula, 1.−5. aile). Pilnīga hiralitātes pārnese un konfigurācijas apgriešana pie hirālā centra ļāva secināt, ka (*R*)-*bis*-imidātu **1a-e** ciklizēšana par oksazolīniem (*S*)-**2a-e** notiek pēc S_N2 tipa mehānisma (5. att.). Fenilaizvietota (*R*)-*bis*-imidāta **1h** (6. aile) gadījumā tika novērota racemizēšana, veidojot produktu **2h** ar enantiomēro pārākumu 36 %. Šo rezultātu var skaidrot ar konkurējošu S_N1 mehānismu, ko nodrošina fenilgrupas karbkatjonu stabilizējošais efekts. Tika novērots, ka hlora atoma ievadīšana (*R*)-*bis*-imidāta **2h** benzola gredzenā nedaudz samazināja racemizēšanās procesu (2. tabula, 7. −9. aile). Savukārt divu hlora atomu ievadīšana benzola gredzenā ļāva būtiski samazināt racemizēšanos un iegūt (*S*)-oksazolīnu **2j** ar 89 % *ee* (2. tabula, 11. aile). Šos rezultātus var skaidrot ar to, ka hlora aizvietotāju ievadīšana benzola gredzenā samazina karbkatjona starpprodukta stabilitāti un tādējādi sekmē reakcijas norisi pēc S_N2 mehānisma ar konfigurācijas apgriešanu.



5. att. Enantiobagātinātu (*R*)-*bis*-imidātu **1a-j** iekšmolekulārā aminēšana.

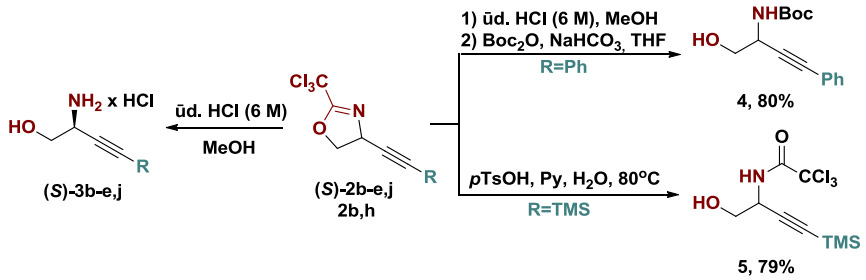
2. tabula

Produktu (*S*)-**2** iznākumi un enantiomērais parākums[a]

Nr. p. k.	R	**1,** (*ee*, %)[b]	LS	(*S*)-**2**, Iznākums, % (*ee*, %)[a]
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-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-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] Reakcijas apstākļi: Luisa skābe (10 mol %), DCM (0.1 M), molekulārie sieti (4 Å), i. t., 1–10 min. [b] Produktu enantiomērais pārākums noteikts, izmantojot AEŠH (kolonna: *Chiralpak IB*).

Lai demonstrētu metodes izmantošanu etīnilglicīnolu iegūšanai, oksazolīni **2** tika transformēti par attiecīgajiem etīnilglicīnola atvasinājumiem **3**–**5** (6. att.). Hidrolizējot (*S*)-oksazolīnus **2b-e,j** 6 M ūd. HCl un MeOH maisījumā, ar labiem iznākumiem tika iegūti (*S*)-enantiobagātināti etīnilglicīnoli **3b-e,j** (3. tabula). Tika izmantota arī metode, kurā oksazolīnu **2h** hidrolizē līdz aminospirtam un, neizdalot starpproduktu, aminofunkciju aizsargā ar Boc-grupu, veidojot produktu **4**. Trimetilsililaizvietota oksazolīna **2b** gadījumā cikla uzšķelšanai tika izmantoti vāji skābi apstākļi (*p*-TsOH, Py:H_2O, 4 : 1) un iegūts trihloracetamīds **5** ar 79 % iznākumu.



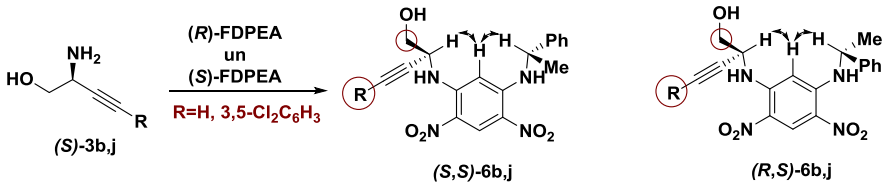
6. att. (*S*)-Etīnilglicīnolu atvasinājumu **3, 4** un **5** iegūšana no oksazolīniem **2**.

3. tabula

Enantiobagātinātu etīnilglicīnolu (*S*)-**3** iznākumi

Nr. p. k.	R	(*S*)-**3**, Iznākums, %
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-$Cl_2C_6H_3$	(*S*)-**3j**, 74

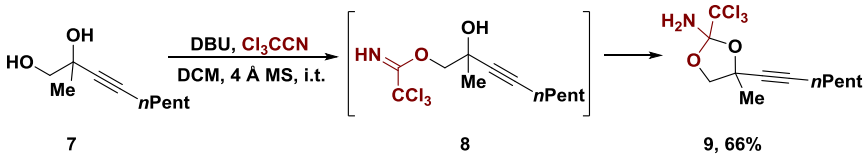
Iegūto etīnilglicīnolu absolūtā konfigurācija tika noteikta, atvasinot (*S*)-aminospirtus **3b,j** ar (*S*)- un (*R*)-1-fluoro-2,4-dinitrofenil-5-feniletilamīnu (7. att.). Pateicoties iekšmolekulārai ūdeņraža saitei, diastereomēri (*S,S*)-**6b,j** un (*R,S*)-**6b,j** atrodas stabilā konformācijā. Benzola gredzena anizotropijas efekta dēļ ^{1}H KMR spektrā tika novērots, ka diastereomērā (*R,S*)-**6b,j** HOC**H**$_2$- grupas protonu signāli ir novirzīti stiprākā laukā, salīdzinot ar diastereomēru (*S,S*)-**6b,j** protonu signāliem, turklāt diastereomērā (*S,S*)-**6b** propargilpozīcijas protons ir novirzīts stiprākā laukā, salīdzinot ar diastereomēru (*R,S*)-**6b**.



7. att. FDPEA diastereomēri (*S,S*)-**6b,j** un (*R,S*)-**6b,j**.

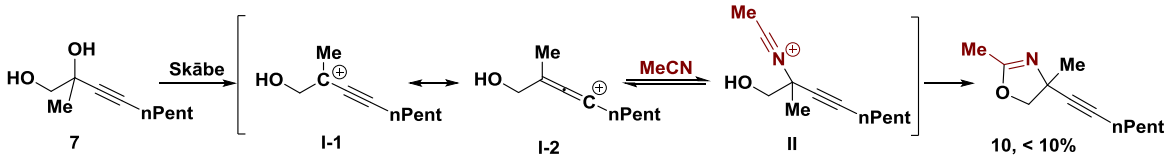
C-kvaternāro etīnilglicīnolu sintēze no kobalta kompleksiem *Ritter* reakcijā

Ņemot vērā C-kvaternāro etīnilglicīnolu plašās izmantošanas iespējas kompleksu savienojumu sintēzē, tika veikts pētījums par jaunu metožu izveidi šo aminospirtu konstruēšanai. Sākotnēji tika izmēģināta iepriekš izstrādāta metode etīnilglicīnola atvasinājumu iegūšanai Luisa skābes katalizētā *bis*-imidātu ciklizēšanas reakcijā (8. att.), tomēr šī metode izrādījās nepiemērota, jo C-kvaternāro etīnilglikolu **7** reakcijā ar trihloracetonitrilu veidojās *mono*-imidāts **8**, kas reakcijas maisījumā *in situ* ciklizējās par 1,3-diooksolāna atvasinājumu **9**.



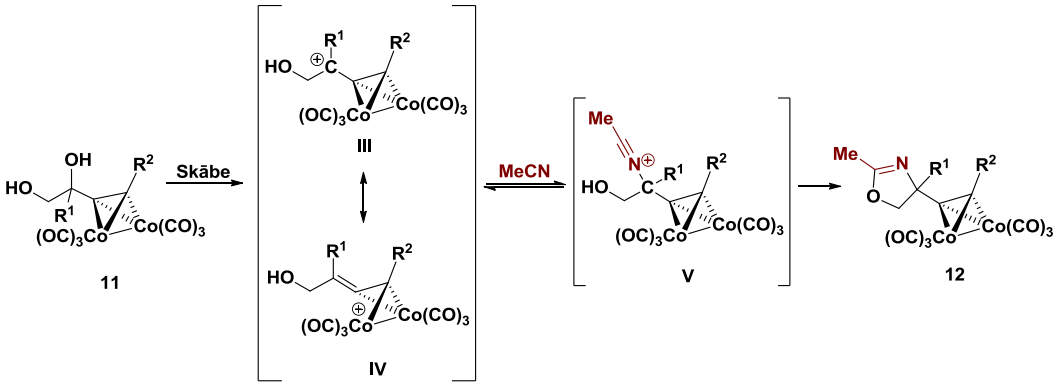
8. att. C-kvaternārā etīnilglikola **7** reakcija ar trihloracetonitrilu.

Kā alternatīva pieeja C-kvaternāro etīnilglicīnolu sintēzei tika pētīta 1,2-diolu *Ritter* reakcija ar acetonitrilu, ko izmanto dažādu heterociklu, piemēram, oksazolīnu un imidazolīnu sintēzei. Galvenais nosacījums reakcijas veiksmīgai realizēšanai ir stabilizēta karbkatjona starpprodukta veidošanās, tomēr, etīnilglikolu **7** pakļaujot *Ritter* reakcijas apstākļiem (MeCN, AcOH, H_2SO_4), sagaidāmais oksazolīns **10** veidojās ar ļoti zemu iznākumu (<10 %) (9. att.). Šādu reakcijas rezultātu var skaidrot ar relatīvi nestabila propargilkatjona veidošanos, kurā pozitīvais lādiņš ir delokalizēts uz sp^2 un sp hibridizētiem oglekļa atomiem (**I-1** un **I-2**), turklāt karbkatjoni **I-1,2** var stāties dažādās blakusreakcijās (piemēram, *Meyer-Schuster* vai *Rupe* pārgrupēšanās reakcijās), neveidojot vēlamo nitrīlija starpproduktu **II**.



9. att. C-kvaternārā etīnilglikola **7** *Ritter* reakcija.

Turpinot pētījumus, uzmanība tika pievērsta *Ritter* reakcijai, izmantojot etīnilglikola kobalta kompleksus **11**, no kuriem atvasinātais karbkatjona starpprodukts **III** ir stabilizēts ar pozitīva lādiņa delokalizāciju starp rezonanses struktūrām **III** un **IV** (10. att.). Stabilizētais karbkatjons **III** var reaģēt ar acetonitrilu, veidojot nitrīlija jona starpproduktu **V**, kas iekšmolekulārā reakcijā ar hidroksilgrupu veido oksazolīna kobalta kompleksu **12**. Izmantojot tādas skābes kā H_2SO_4 un $BF_3{\cdot}Et_2O$, etīnilglikola kobalta kompleksi **11** reaģēja ar acetonitrilu, veidojot oksazolīnus **12a-h, k-e** ar vidējiem un labiem iznākumiem. Ar reakcijas apstākļiem bija savietojams plašs substrātu klāsts ar aizvietotājiem (R^2 = alkil-, aril-) pie terminālā trīskāršās saites oglekļa (4. tabula). Substrāti **11l,m** ar hidroksimetilaizvietotāju pie kvaternārā oglekļa atoma veidoja *Ritter* reakcijas produktus **12l,m** ar 46 % un 81 % iznākumu (4. tabula, 16. un 17. ailes). Arī otrējais spirts **11k** stājās *Ritter* reakcijā, veidojot oksazolīnu **12k** ar labu iznākumu (4. tabula, 15. aile). Tika novērot ka jaunizveidotajai metodei ir arī ierobežojumi. Substrāti **11i,j**, kas saturēja fenilaizvietotāju pie kvaternārā oglekļa atoma, neveidoja attiecīgos oksazolīnus **12i,j**, ko var skaidrot ar pārāk lielu karbkatjona **III** stabilitāti (4. tabula, 13. un 14. aile).



10. att. C-kvaternārā etīnilglikola kobalta kompleksa **11** *Ritter* reakcija.

4. tabula

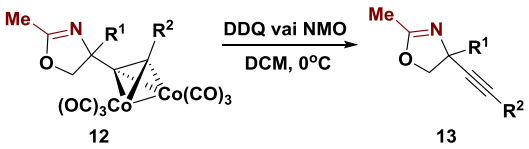
Produkta **12** iznākums un reakcijā izmantotā skābe

Nr. p. k.	R^1	R^2	Skābe	**12**, Iznākums, %
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		Ph		**12m**, 81

[a] Reakcijas apstākļi: MeCN (54 ekviv), H_2SO_4 (9 ekviv), AcOH (8 ekviv), no 0 °C līdz i. t., 1–10 min. [b] Reakcijas apstākļi: $BF_3{\cdot}Et_2O$ (10 ekviv), MeCN (0,1 M),0 °C – i. t., 5–10 min.

Lai iegūtu oksazolīnu **13a**, tika apskatīti vairāki reakcijas apstākļi kobalta kompleksa **12a** šķelšanai (11. att.). Literatūrā ir zināms, ka pirmējie amīni, reaģējot ar alkīna-$Co_2(CO)_6$ kompleksiem, atbrīvo alkīnu. Balstoties uz šiem rezultātiem, tika izpētītaalkīna-$Co_2(CO)_6$ kompleksa **12a** šķelšanas reakcija, izmantojot helatējošu diamīna ligandu – etilēndiamīnu. Diemžēl, izmantojot šo metodi, oksazolīna **13a** iznākums bija tikai 28 %. Tālāk tika pārbaudīti oksidējoši šķelšanas apstākļi, izmantojot DDQ, NMO un CAN. Pētījuma rezultātā tika atklāta selektīva un efektīva metode alkīna-$Co_2(CO)_6$ kompleksa **12a** šķelšanai, kā oksidētāju

izmantojot DDQ (5. tabula). Hidroksimetilgrupu saturošu kobalta kompleksu **12l,m** šķelšanai DDQ vietā tika izmantots NMO. Tas ļāva iegūt oksazolīnus **13l,m** ar vidējiem iznākumiem (5. tabula, 12. un 14. aile).



12 13

11. att. Alkīna-$Co_2(CO)_6$ kompleksa **12** šķelšana.

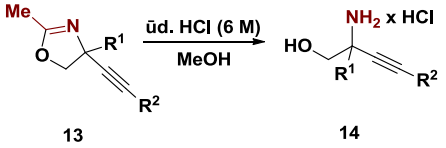
5. tabula

Iznākumi un apstākļi kobalta kompleksa **12** šķelšanai

Nr. p. k.	R^1	R^2	Metode	**13**, Iznākums, %
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] Reakcijas apstākļi: DDQ (3 ekviv), DCM (0,1 M), 0 °C, no 30 min līdz 2 h. [b] Reakcijas apstākļi: NMO (10 ekviv), DCM (0,1 M), 0 °C, 30 min.

Tika demonstrēts, ka iegūtos oksazolīnus **13** var veiksmīgi pārvērst par attiecīgajiem C-kvaternārajiem alkīnilglicīnoliem **14d,g,h,l,m**, izmantojot skābes hidrolīzi (12. att., 6. tabula).



13 14

12. att. C-kvaternāro alkīnilglicīnolu **14d,g,h,l,m** sintēze.

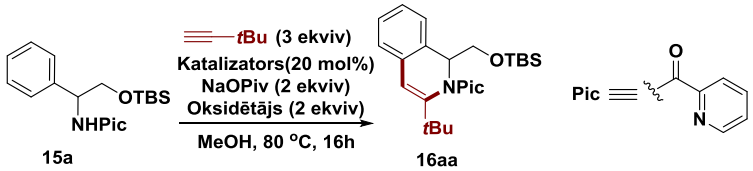
6. tabula

C-kvaternāro alkīnilglicīnolu **14d,g,h,l,m** iznākumi

Nr. p. k.	R^1	R^2	**14**, Iznākums, %
1	Me	Ph	**14d,** 96
2		CH_2OBn	**14g,** 64
3		Me	**14h,** 62
4	CH_2OH	*n*Pent	**14l,** 82
5		Ph	**14m,** 77

Kobalta katalizēta fenilglicīnola C–H funkcionalizēšana ar alkīniem

Otrs pētījuma virziens bija pikolīnamīda virzīta fenilglicīnola atvasinājuma **15a** C–H saites funkcionalizēšana ar alkīniem benzola gredzena *orto*-pozīcijā, izmantojot kobalta katalizatoru (13. att.). Reakcijas apstākļu optimizēšanas posmā tika pārbaudīti dažādi kobalta katalizatori, oksidētāji, bāzes un reakcijas šķīdinātāji (7. tabula). Sākotnējos pētījumos tika atklāts, ka fenilglicīnola **15a** reakcijā ar *terc*-butilacetilēnu, izmantojot $Co(OAc)_2$ katalizatoru, NaOPiv kā bāzi, AgOAc kā oksidētāju metanolā, 80 °C temperatūrā, reģioselektīvi veidojās 1,2-dihidroizohinolīna atvasinājums **16aa** ar 5 % iznākumu (7. tabula, 1. aile). Iegūtā reģioizomēra **16aa** struktūra tika pieradīta ar 2D-NOESY eksperimentu. Pētījuma gaitā noskaidrots, ka, izmantojot $Mn(OAc)_3$ kā oksidētāju un molekulāro skābekli kā līdzoksidētāju, produkta **16aa** iznākumu iespējams uzlabot līdz 16 % (2.–5. aile). Reakcijas veiksmīgai īstenošanai svarīgs bija arī bāzes daudzums. Noskaidrots, ka optimālais bāzes daudzums ir 1,2 ekvivalenti, un tas ļāva uzlabot produkta **16aa** iznākumu līdz 28 % (6. aile). Turpinot reakcijas apstākļu optimizēšanu, tika pārbaudīta reakcijas šķīdinātāja ietekme uz produkta **16aa** iznākumu un konstatēts, ka labākais šķīdinātājs ir MeOH. Optimizēšanas gaitā tika pierādīts, ka produkta **16aa** iegūšanai izšķirošā loma ir kobalta katalizatoram. Pārbaudot vairākus Co(II) un Co(III) katalizatorus, tika atklāts, ka efektīvākais katalizators fenilglicīnola atvasinājuma **15a** anelēšanai ar alkīniem ir $Co(dpm)_2$. Izmantojot piemeklēto katalītisko sistēmu $Co(dpm)_2/Mn(OAc)_3$/NaOPiv, produktu **16aa** izdevās iegūt ar 82 % iznākumu. Palielinot reakcijas laiku, produkta **16aa** iznākums nedaudz uzlabojās līdz 84 %. Kontroleksperimenti parādīja, ka bez oksidētāja vai katalizatora anelēšanas produkts **16aa** neveidojas.



13. att. Kobalta katalizēta fenilglicīnola **15a** reakcija ar *terc*-butilacetilēnu.

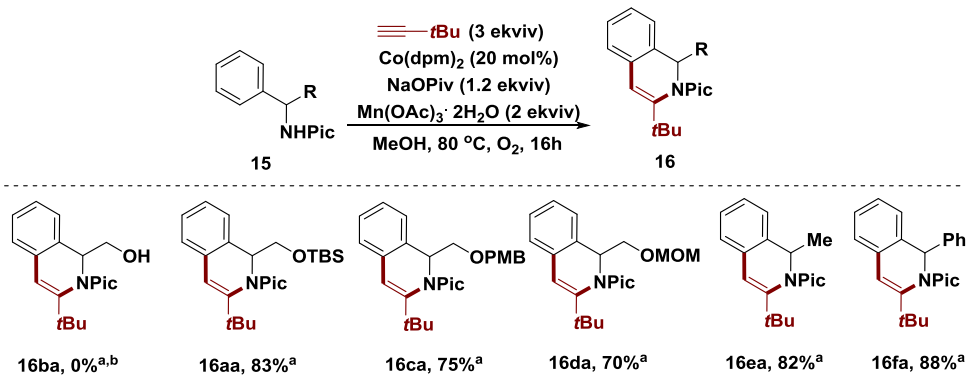
7. tabula

Reakcijas apstākļu optimizēšana[a]

Nr. p. k.	Katalizators	Oksidētājs	**15a**/**16aa**	**16aa**, Iznākums, %[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 iznākums ir noteikts, izmantojot trifenilmetānu kā iekšējo standartu. [b] NaOPiv (0,12 mmol, 1,2 ekviv). [c] $Co(dpm)_2$ – bis(2,2,6,6-tetrametil-3,5-heptanedionato)kobalts (II), CAS: 13986-53-3. [d] Laiks: 24 h.

Turpinot pētījumus, kobalta katalizētā fenilglicīnola **15a** reakcijā ar *terc*-butilacetilēnu tika pārbaudīti pikolīnamīda atvasinājumi **15** ar dažādiem aizvietotājiem benzilpozīcijā (14. att.). Šie pētījumi parādīja, ka pikolīnamīds **15b** ar brīvu spirta funkciju optimizētos reakcijas apstākļos neveido produktu **16ba**. Savukārt TBS-, PMB- un MOM- aizsargātu fenilglicīnolu atvasinājumu **15a,c,d** gadījumā produkti **16aa,ca,da** veidojās reģioselektīvi un ar ļoti labiem iznākumiem (70–83 %), turklāt benzilamīda atvasinājumi **15e**,**f** arī veido produktus **16ea**,**fa** ar ļoti labiem iznākumiem, kas palielina metodes izmantošanas iespējas.

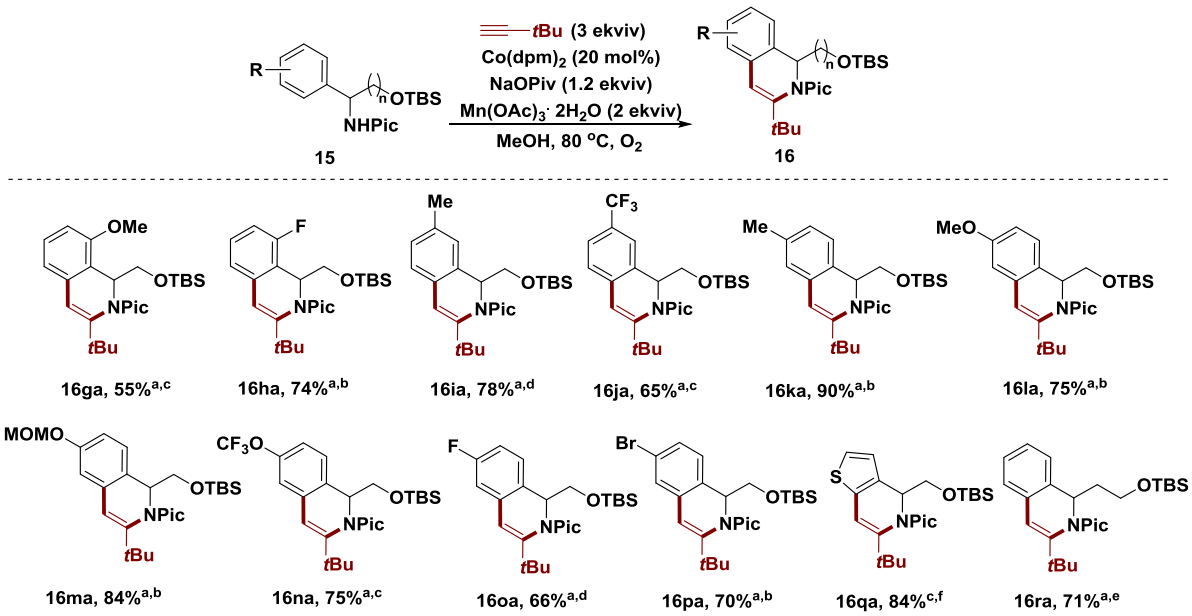


[a] Izolētais iznākums. [b] Izejviela reakcijas apstākļos degradējas.

14. att. Kobalta katalizēta pikolīnamīdu **15** anelēšanas reakcija.

Substrāta klāsta pētījumos tika noskaidrots, ka benzola gredzenā *para*-, *meta*- un *orto*-aizvietoti fenilglicīnola atvasinājumi ir piemēroti anelēšanas reakcijai (15. att.). Jāpiemin, ka *meta*- aizvietotu substrātu **15i** un **15j** gadījumā veidojās tikai viens reģioizomērs **16ia**,**ja**, ko

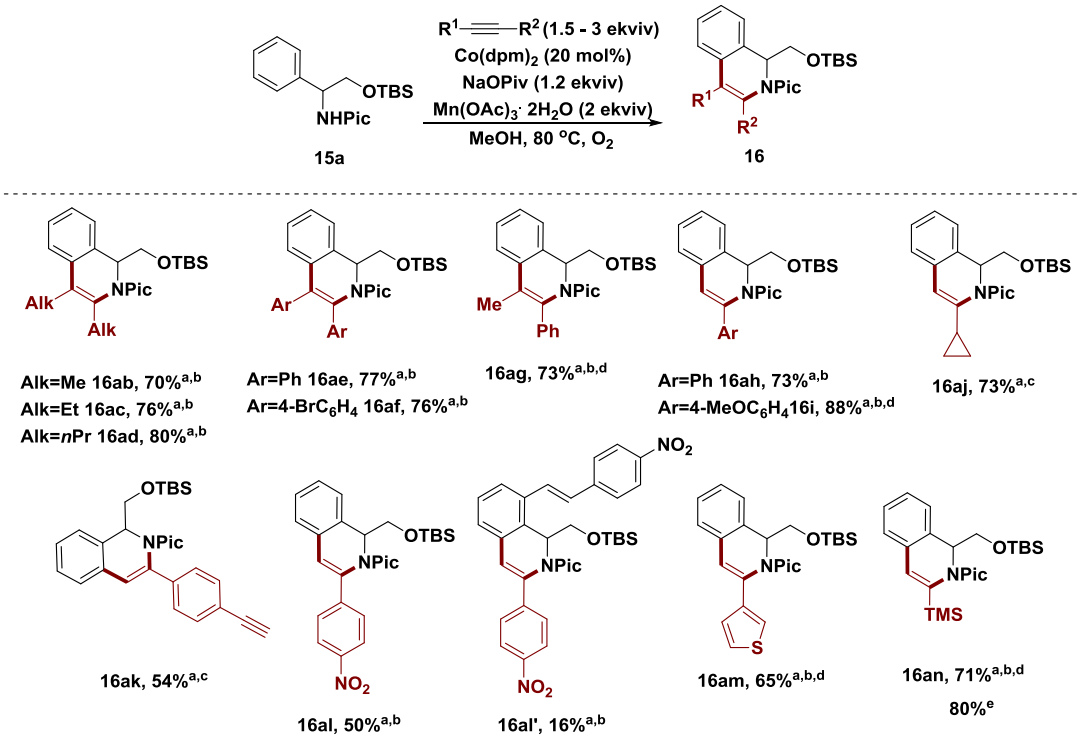
var skaidrot ar kobalta iespiešanos telpiski mazāk traucētā C–H saitē. Tomēr tiofēnu saturoša glicīnola **15q** gadījumā pamatreģioizomērs **16qa** veidojās maisījumā ar otru izomēru attiecībā 2,5/1 (C–H funkcionalizēšana tiofēna gredzenā noris arī 4. pozīcijā). Tika parādīts, ka fenilglicīnola atvasinājumi **15** ar dažādiem aizvietotājiem benzola gredzenā, kā alkil- (**15i, 15k**), metoksi- (**15g, 15l**), metoksimetil- (**15m**), trifluormetil- (**15j**), trifluormetoksi- (**15n**) un halogēni (**15h, 15o, 15p**), veido atbilstošos produktus **16** ar labiem iznākumiem. *β*-Fenilalaninola atvasinājuma **15r** gadījumā attiecīgais produkts **16ra** veidojās ar labu iznākumu 71 %.



[a] Izolēti iznākumi pamtareģioizomēram. [b] Laiks: 16–17 h. [c] Laiks: 20 h. [d] Laiks: 24 h. [e] Laiks: 40 h. [f] Izolēts tiofēna reģioizomēru maisījums ar attiecību 2,5 : 1, norādīta pamatreģioizomēra struktūra.

15. att. Fenilglicīnola **15** atvasinājumu klāsta pētījumi.

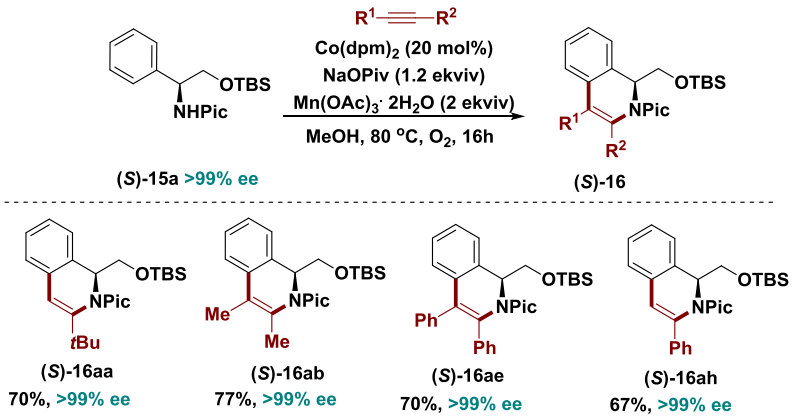
Fenilglicīnolu **15a** anelēšanai tika pārbaudīta arī virkne strukturāli atšķirīgu alkīnu (16. att.). Alifātiskas un aromātiskas grupas saturoši diaizvietoti alkīni reaģēja, veidojot attiecīgos produktus **16ab-af** ar ļoti labiem iznākumiem (70–80 %). Jāuzsver, ka anelēšana ar asimetriskiem alkīniem ir liels izaicinājums metālu katalizētās reakcijās, jo ir grūti panākt vērā ņemamu reģioselektivitāti. Izmantotajos reakcijas apstākļos 1-fenil-1-propīns reaģēja ar fenilglicīnola atvasinājumu **15a**, veidojot tikai vienu reģioizomēru **16ag** ar 73 % iznākumu. Arī terminālie alkīni ar alkil-, aril- un heteroaril aizvietotājiem bija piemēroti reaģenti, veidojot produktus **16ah**,**j**,**k**,**m**,**n** ar augstu reģioselektivitāti. Trimetilsililacetilēna reakcija ar fenilglicīnola atvasinājumu **15a** tika realizēta 1 g mērogā, veidojot produktu **16an** ar 80 % iznākumu. Interesanti, ka 4-nitrofenilacetilēna gadījumā kā blakusprodukts mono C–H alkēnilēšanas/ciklizēšanas produktam **16al** (50 %) veidojās arī dialkenilēšanas produkts **2al'** ar 16 % iznākumu.



[a] Izolēti iznākumi pamtareģioizomēram. [b] Laiks: 16–17 h. [c] Laiks: 20 h. [d] Izdalīts tikai viens pamatreģioizomērs; [e] *Gram-scale* sintēze no 1 g pikolīnamīda **15a**.

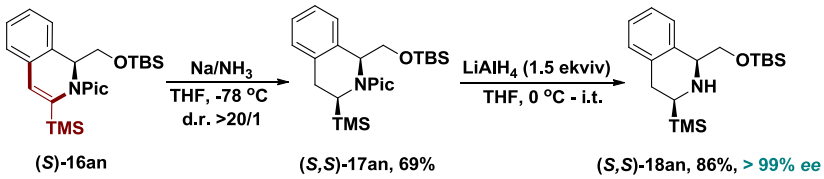
16. att. Alkīnu klāsta pētījumi.

Lai parbaudītu, vai kobalta katalizēta anelēšana notiek ar hirālā centra stereoķīmijas saglabāšanu, reakcijā ar terminäliem un diaizvietotiem alkīniem tika izmantots enantiobagātināts (*S*)-fenilglicīnola atvasinājums (*S*)-**15a** (17. att.). Produktu (*S*)-**16aa-ah** analīze liecināja, ka optimizētajos reakcijas apstākļos C–H funkcionalizēšana ar alkīniem notiek ar pilnīgu stereoķīmijas saglabāšanu.



17. att. Anelēšanas reakcijas hirālitātes saglabāšanas pētījumi.

Lai demonstrētu metodes izmantošanas iespējas, tika parādīts ka 1,2-dihidroizohinolīna atvasinājumā **16an** dubultsaiti iespējams reducēt ar nātriju šķidrā amonjakā, iegūstot 1,2,3,4-tetrahidroizohinolīna atvasinājuma **17an** (*S*,*S*)-stereoizomēru ar labu iznākumu un augstu diastereoselektivitāti (18. att.).

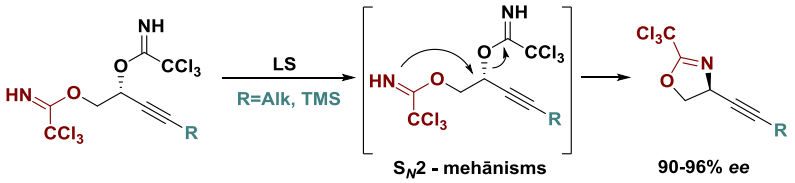


18. att. 1,2,3,4-tetrahidroizohinolīna atvasinājuma (*S*,*S*)-**18an** sintēze.

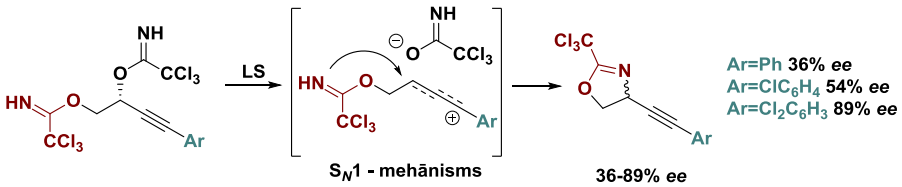
Tika atrasta arī piemērota metode pikolīnamīda vīrzošās grupas noškelšanai savienojumā **17an**, izmantojot $LiAlH_4$. Jāpiemin, ka produkts **18an** veidojās ar ļoti labu iznākumu 86 %, saglabājot sākotnējo stereoķīmiju (>99 % *ee*).

SECINĀJUMI

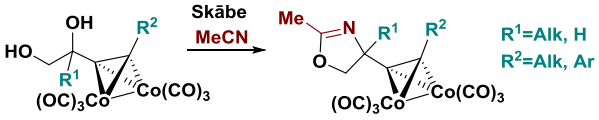
1. Alkil- un trimetilsilil- aizvietotu etīnil-*bis*-imidātu Luisa skābes katalizētā propargiliskās aminēšanas reakcijā selektīvi veidojas 4-etīniloksazolīna reģioizomērs. Enantiobagātinātu substrātu ciklizēšana notiek ar absolūtās konfigurācijas apgriešanu pie hirālā centra un ar pilnīgu hiralitātes pārnesi, kas liecina par S_N2 tipa reakcijas mehānismu.



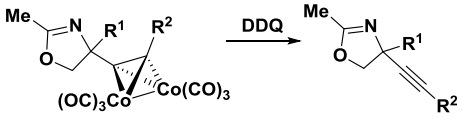
2. Fenilaizvietotu etīnil-*bis*-imidātu Luisa skābes katalizētā ciklizēšanas reakcijā selektīvi veidojas 4-etīniloksazolīna reģioizomērs. Tomēr fenilaizvietotu enantiobagātinātu substrātu ciklizēšana notiek ar hirālā centra daļēju racemizāciju, kas liecina par jauktu S_N1 un S_N2 tipa reakcijas mehānismu. Elektronakceptoru hlora atomu ievietošana *bis*-imidāta benzola gredzenā būtiski novērš racemizēšanās procesu, ko var skaidrot ar karbkatjona starpprodukta stabilitātes samazināšanos, kas sekmē reakcijas norisi pēc S_N2 mehānisma ar konfigurācijas apgriešanu.



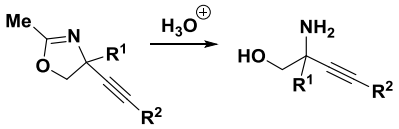
3. Etīnilglikola kobalta kompleksi stājas *Ritter* reakcijā ar acetonitrilu, veidojot C-kvaternārus oksazolīnus. Reakcijas apstākļi ir piemēroti plašam substrātu klāstam, ierobežojums ir substrāti ar fenil- aizvietotāju pie kvaternārā oglekļa atoma (R^1).



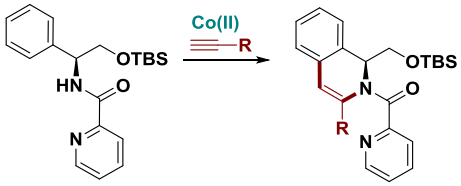
4. Alkīna-$Co_2(CO)_6$ kompleksu var viegli šķelt ar DDQ, veidojot vēlamos oksazolīnus ar labiem iznākumiem.



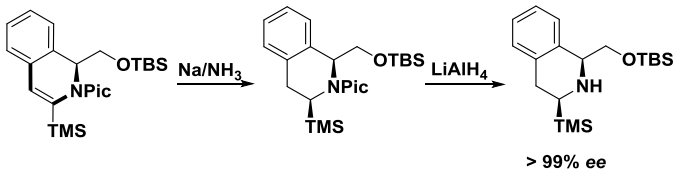
5. Oksazolīni, kas iegūti *bis*-imidātu ciklizēšanas un *Ritter* reakcijās, skābes hidrolīzes apstākļos veido etīnilglicīnola atvasinājumus.



6. Pikolīnamīda virzīta C–H saites O-aizsargātu fenilglicīnolu funkcionalizēšanā ar alkīniem, izmantojot kobalta katalizatoru, veidojas 1-hidroksimetil-1,2-dihidroizohinolīna atvasinājumi. Optimizētā katalītiskā sistēma un reakcijas apstākļi – $Co(dpm)_2$, $Mn(OAc)_3$, molekulārais skābeklis kā līdzoksidētājs, NaOPiv metanolā, 80 °C. Reakcijas apstākļos termināli un diaizvietoti alkīni ir piemēroti substrāti, turklāt monoaizvietoti un asimetriski diaizvietoti alkīni veido attiecīgus produktus ar izcilu reģioselektivitāti. Dihidroizohinolīna veidošanās notiek ar absolūtās stereoķīmijas saglabāšanos pie hirālā centra, izmantojot enantiobagātinātus (*S*)-fenilglicīnola atvasinājumus.



7. (*S*,*S*)-Tetrahidroizohinolīnu var iegūt no 1,2-dihidroizohinolīna atvasinājuma, saglabājot hirālā centra absolūto konfigurāciju, divās stadijās – diastereoselektīvā reducēšanas reakcijā ar Na/NH_3 un tai sekojošā pikolīnamīda virzošās grupas nošķelšanas reakcijā ar $LiAlH_4$.



LITERATŪRAS SARAKSTS

1. a) Fukumoto, H., Takahashi, K., Ishihara, J., Hatakeyama, S. *Angew. Chem*., **2006**, *118*, 2797–2800. b) Goswami, K., Duttagupta, I., Sinha, S. *J. Org. Chem.*, **2012**, *77*, 7081−7085.
2. Kuroda, Y., Okuhara, M., Goto, T., Iguchi, E., Kohsaka, M., Aoki, H, Imanaka, H. J. Antibiot., **1980**, *33*, 125−131.
3. a) Reginato, G., Meffre, P., Gaggini, F. *Amino Acids*, **2005**, *29*, 81–87. b) Benfodda, Z., Bénimélis, D., Reginato, G., Meffre, P. Amino Acids, **2015**, *47*, 271–279.
4. a) Tang, T. P., Volkman, S. K., Ellman, J. A. *J. Org. Chem.*, **2001,** *66*, 8772-8778. b) Chen, B.-L., Wang, B., Lin, G.-Q. *J. Org. Chem.*, **2010**, *75*, 941–944.
5. Benfodda, Z., Benimelis, D., Jean, M., Naubron, J.-V., Rolland, V., Meffre, P. *Amino Acids*, **2015**, *47*, 899−907.
6. a) Brennan, C. J., Pattenden, G., Rescourio, G. *Tetrahedron Lett.*, **2003**, *44*, 8757–8760. b) Pattenden, G., Rescourio, G. *Org. Biomol. Chem.*, **2008**, *6*, 3428–3438. c) Hattori, G., Yoshida, A., Miyake, Y., Nishibayashi, Y. *J. Org. Chem.*, **2009**, *74*, 7603–7607.
7. Grigg, R. D., Rigoli, J. W., Pearce, S. D., Schomaker, J. M. *Org. Lett.*, **2012**, *14*, 280−283.
8. a) Grigorjeva, L., Dauglis, O. *Angew. Chem. Int. Ed.*, **2014**, *53*, 10209−10212. b) Martinez, M., Rodriguez, N., Gomez-Arrayas, R., Carretero, J. C. *Chem. Eur. J.*, **2017**, *23*, 11669−11676. c) Kuai, C., Wang, L., Li, B., Yang, Z., Cui, X. *Org. Lett.*, **2017**, *19*, 2102−2105.

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.

OFFICIAL REVIEWERS

Professor Dr. chem. Māris Turks
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Professor Dr. chem. Valdis Kokars
Riga Technical University, Latvia

Professor Ph. D. Antimo Gioiello
University of Perugia, Italy

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*.

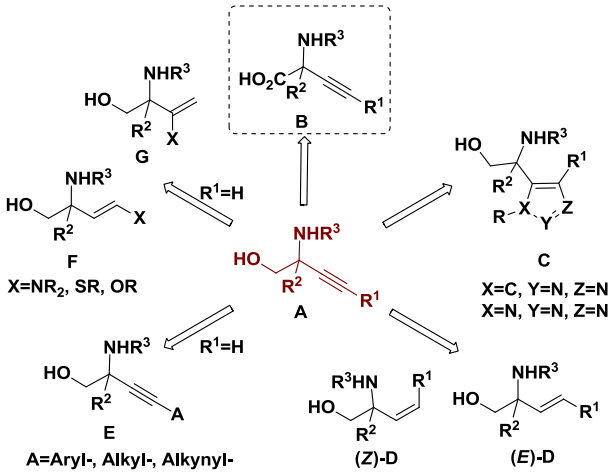


Fig. 1. Modification potential of alkynylglycinols **A**.

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).

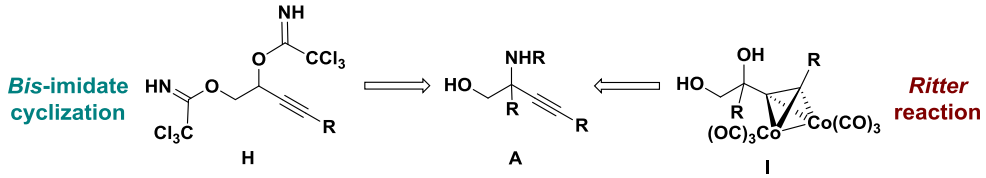


Fig. 2. New methods for the synthesis of ethynylglycinols **A**.

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).

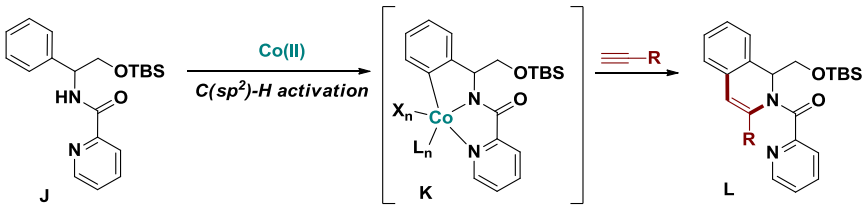


Fig. 3. New method for C–H functionalization of phenylglycinols **J**.

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.

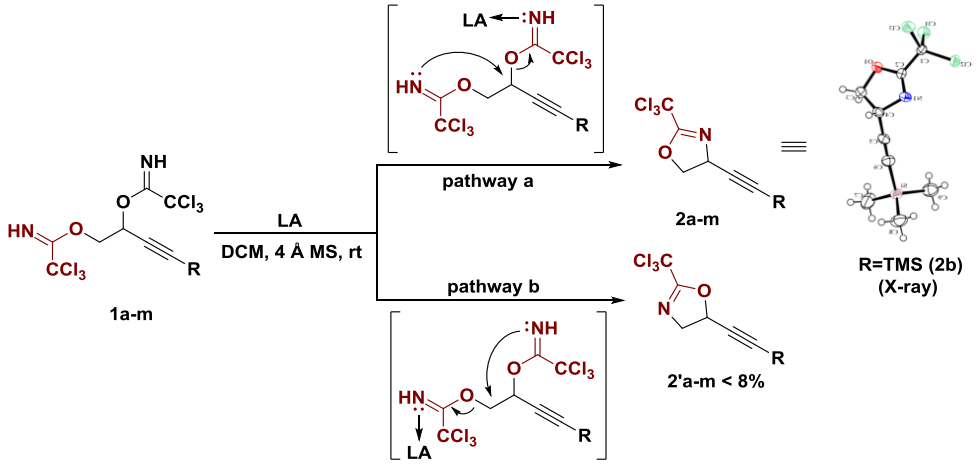


Fig. 4. Oxazolines by intramolecular amination of *bis*-imidates **1a-m**.

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).

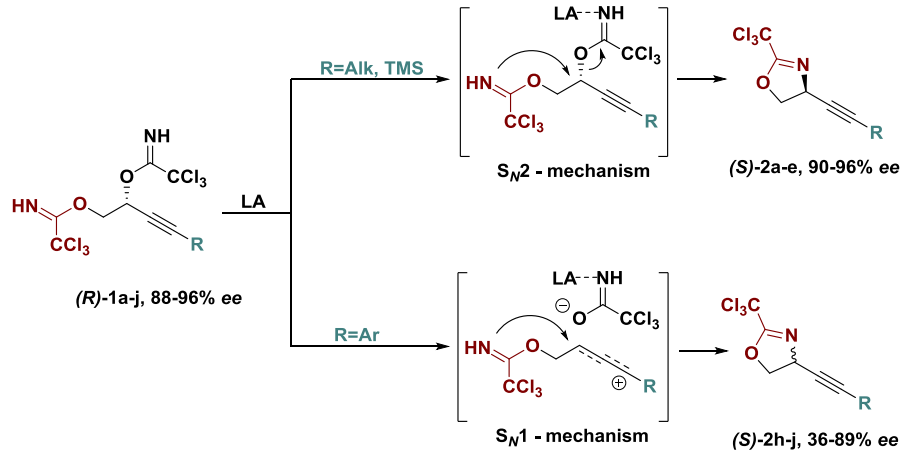


Fig. 5. Intramolecular amination of enantioenriched (*R*)-*bis*-imidates **1a-j**.

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**.

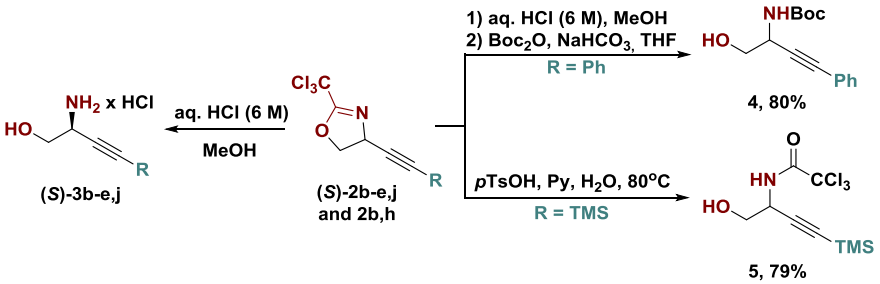


Fig. 6. Synthesis of ethynylglycinol derivatives **3b-e,j** and **4,5**.

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-$Cl_2OC_6H_3$	(*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**.

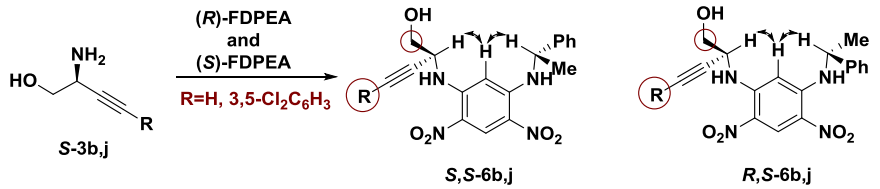


Fig. 7. FDPEA derived diastereomers (*S,S*)-**6b,j** and (*R,S*)-**6b,j**.

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).

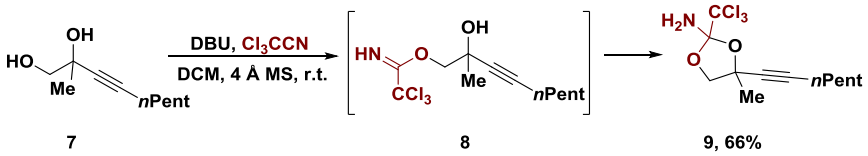


Fig. 8. Reaction of quaternary ethynylglycol **7** with trichloroacetonitrile.

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**.

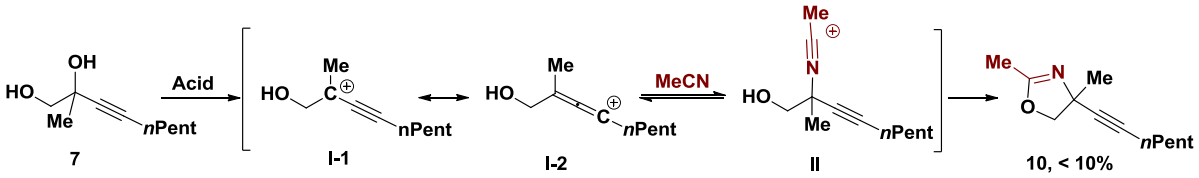


Fig. 9. Ritter reaction of quaternary ethynylglycol **7**.

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).

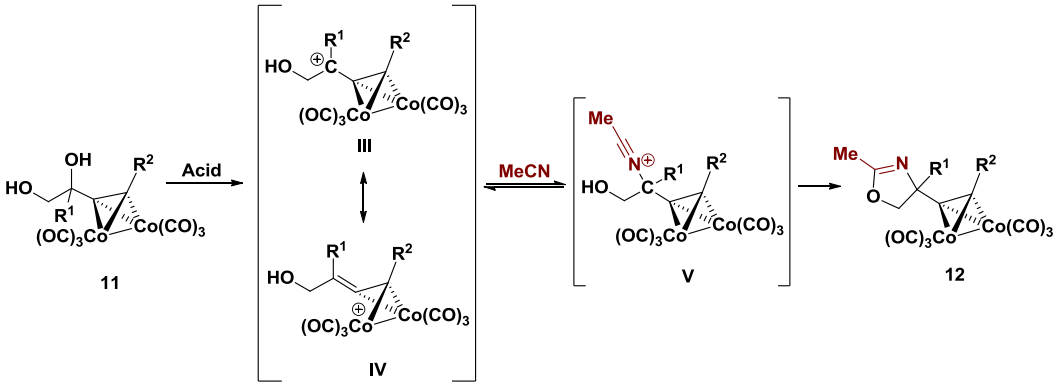


Fig. 10. The Ritter reaction of cobalt complexed ethynylglycols **11**.

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).

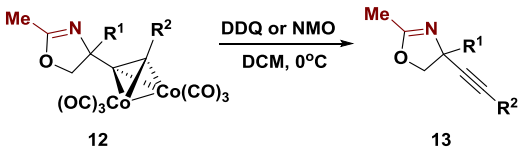


Fig. 11. Cleavage of cobalt complexes **12**.

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).

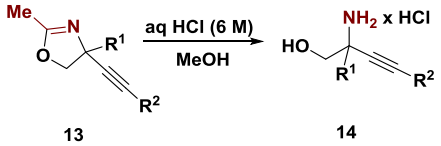


Fig. 12. Synthesis of C-quaternary ethynylglycinols **14**.

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.

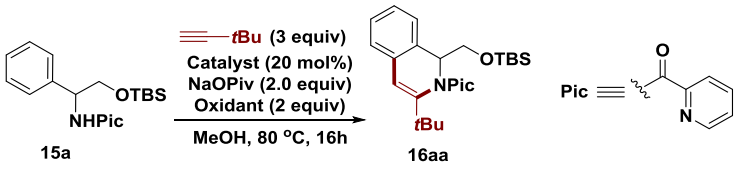


Fig. 13. Phenylglycinol **15a** reaction with *terc*-butylacethylene.

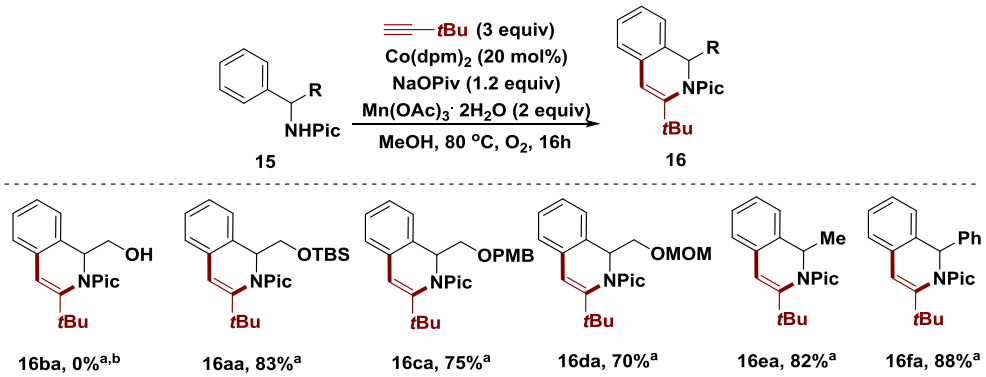
Table 7

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.

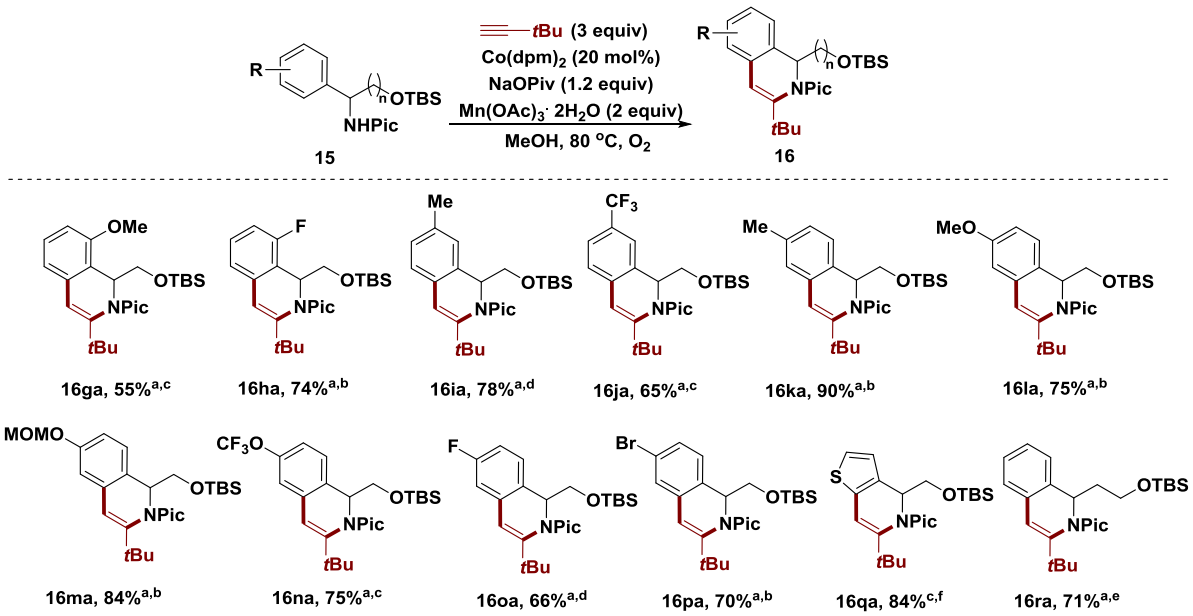


[a] Isolated yields are given. [b] Decomposition of substrate.

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

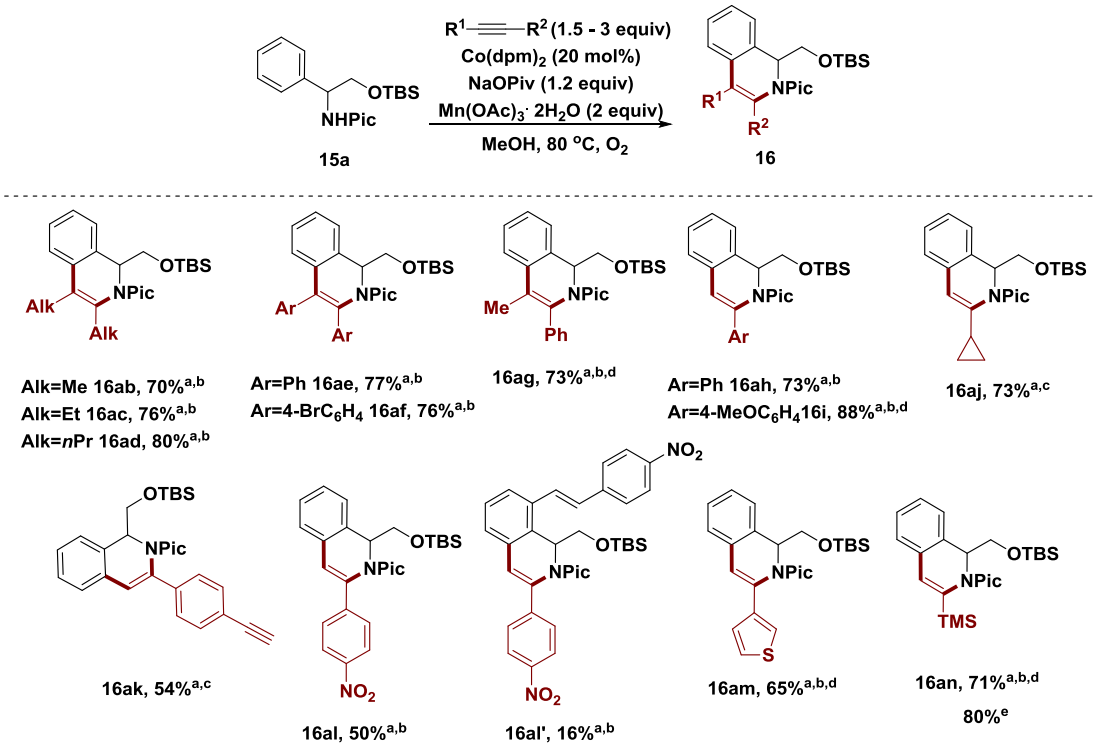
activiated to produce single regioisomers **16ia,ja,** which is consistent with literature examples. Furthermore, different electron-donating groups, such as alkyl (**15i, 15k**), methoxy (**15g, 15l**), methoxymethyl ether (**15m**), as well as electron-withdrawing groups, such as trifluoromethyl (**15j**), 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**).

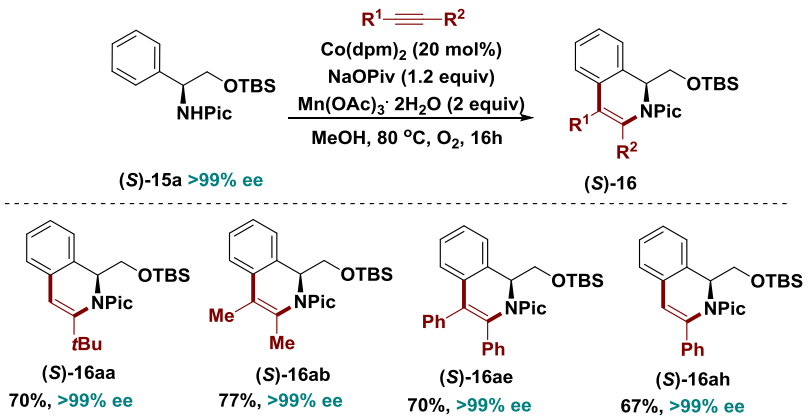


Fig. 17. Conservation of chirality.

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**.

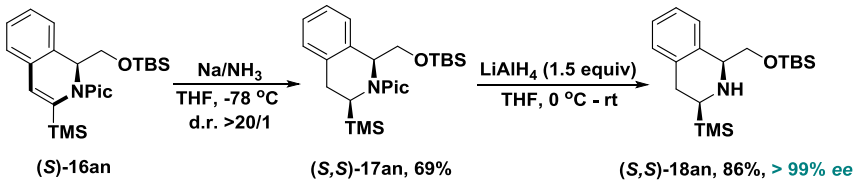
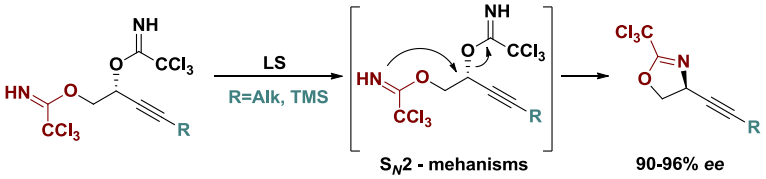


Fig. 18. Synthesis of tetrahydroisoquinoline **(*S*,*S*)-18an**.

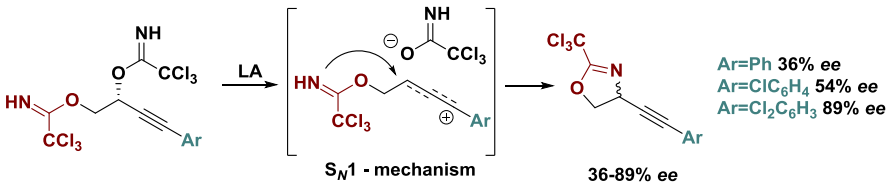
Subsequent directing group removal using $LiAlH_4$ gave the corresponding tetrahydroisoquinoline **(*S*,*S*)-18an** in good yield without the loss of stereochemical purity.

CONCLUSIONS

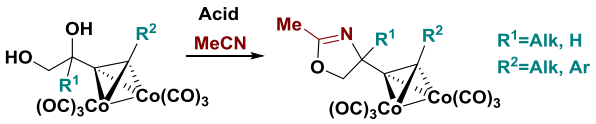
1. *Bis*-imidates derived from ethynylglycols with alkyl and trimethylsilyl terminal substituents undergo Lewis acid catalysed propargylic amination leading to regioselective oxazoline formation. Complete inversion of absolute stereochemistry at chiral center was obserserved starting from enantioenriched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



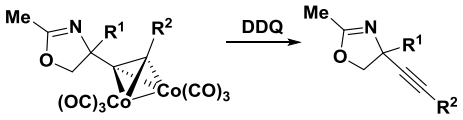
2. Cyclization of *bis*-imidates derived from ethynylglycols with terminal phenyl substituent also proceed regioselectively affording propargylic substitution products. However, enatioenriched substrates gave products with partial racemization of a chiral center, indicating mixed S_N1 and S_N2 type mechanisms. 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.



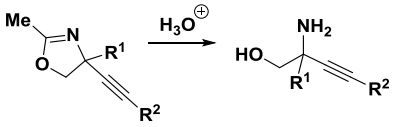
3. Etnynylglycol cobalt complexes are suitable substrates for the Ritter reaction with acetonitrile to produce C-quaternary oxazolines. Reaction conditions tolerates broad substrate scope, while the limitation are substrates bearing phenyl substituent at the quaternary carbon.



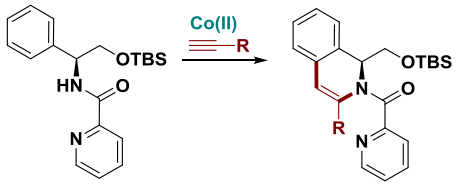
4. Alkyne-$Co_2(CO)_6$ complexes can be successfully cleaved using DDQ oxidant to obtain the desired oxazolines in good yield.



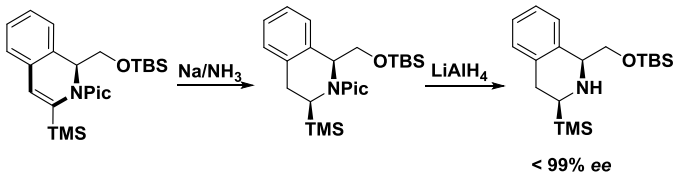
5. Oxazolines obtained by *bis*-imidate cyclization and Ritter reaction can be efficiently transformed into corresponding ethynylglycinols under acidic hydrolysis conditions.



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 $LiAlH_4$.



REFERENCES

1. a) Fukumoto, H., Takahashi, K., Ishihara, J., Hatakeyama, S. *Angew. Chem*., **2006**, *118*, 2797–2800. b) Goswami, K., Duttagupta, I., Sinha, S. *J. Org. Chem.*, **2012**, *77*, 7081−7085.
2. Kuroda, Y., Okuhara, M., Goto, T., Iguchi, E., Kohsaka, M., Aoki, H, Imanaka, H. J. Antibiot., **1980**, *33*, 125−131.
3. a) Reginato, G., Meffre, P., Gaggini, F. *Amino Acids*, **2005**, *29*, 81–87. b) Benfodda, Z., Bénimélis, D., Reginato, G., Meffre, P. Amino Acids, **2015**, *47*, 271–279.
4. a) Tang, T. P., Volkman, S. K., Ellman, J. A. *J. Org. Chem.*, **2001,** *66*, 8772-8778. b) Chen, B.-L., Wang, B., Lin, G.-Q. *J. Org. Chem.*, **2010**, *75*, 941–944.
5. Benfodda, Z., Benimelis, D., Jean, M., Naubron, J.-V., Rolland, V., Meffre, P. *Amino Acids*, **2015**, *47*, 899−907.
6. a) Brennan, C. J., Pattenden, G., Rescourio, G. *Tetrahedron Lett.*, **2003**, *44*, 8757–8760. b) Pattenden, G., Rescourio, G. *Org. Biomol. Chem.*, **2008**, *6*, 3428–3438. c) Hattori, G., Yoshida, A., Miyake, Y., Nishibayashi, Y. *J. Org. Chem.*, **2009**, *74*, 7603–7607.
7. Grigg, R. D., Rigoli, J. W., Pearce, S. D., Schomaker, J. M. *Org. Lett.*, **2012**, *14*, 280−283.
8. a) Grigorjeva, L., Dauglis, O. *Angew. Chem. Int. Ed.*, **2014**, *53*, 10209−10212. b) Martinez, M., Rodriguez, N., Gomez-Arrayas, R., Carretero, J. C. *Chem. Eur. J.*, **2017**, *23*, 11669−11676. c) Kuai, C., Wang, L., Li, B., Yang, Z., Cui, X. *Org. Lett.*, **2017**, *19*, 2102−2105.

PIELIKUMI/PUBLICATIONS

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Synthesis of Alkynyl-Glycinols by Lewis Acid Catalyzed Propargylic Substitution of Bis-Imidates

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Keywords: Synthetic methods / Nucleophilic substitution / Alkynes / Cyclization / Lewis acids

Racemic and enantioenriched alkynyl-glycinols can be synthesized by Lewis acid catalyzed cyclization reaction of bis-trichloracetimidates derived from alkynyl-glycols. The cyclization proceeds selectively to give 4-alkynyl-oxazolines as the propargylic substitution products. Enantioenriched bis-imidates that contain an alkyl or trimethylsilyl substituent at the acetylene gave oxazolines with complete inversion of configuration. In turn, considerable racemization was observed in the cyclization of bis-imidates that contain a phenyl substituent. The racemization for these substrates can be suppressed by introduction of the electronegative substituent at the phenyl ring. Oxazolines prepared by bis-imidate cyclization reaction can be readily transformed to protected alkynyl-glycol derivatives.

Introduction

Alkynyl-glycinols **3** (Figure 1) have found application as important multifunctional building blocks for the construction of complex molecules.[1–10] Nevertheless, the literature review revealed that there is a limited number of methods for the synthesis of such compound types.[11–19] Of particular interest is the access to enantioenriched alkynyl-glycinols that typically relies on derivatization of Garner's aldehyde[5,11,12,20,21] and Ellman-type addition reactions of terminal alkynes to *N*-sulfinyl imines.[14,17]

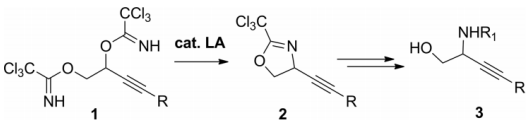

Figure 1. Alkynyl-glycinols **3** by propargylic substitution of bis-imidates **1**.

Previously we developed the synthesis of unsaturated amino alcohols based on allylic substitution in bis-imidates.[22–27] In these systems, one of the imidates serves as an *N*-nucleophile and the other as a leaving group when activated by the acid catalyst. Here we report investigation of the propargylic substitution reaction of bis-imidates **1** derived from alkynyl-glycols (Figure 1). Both regioselectivity and chirality transfer of the cyclization were explored with an aim to prepare alkynyl-oxazolines **2**, which are precursors of alkynyl-glycinols **3**.

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Results and Discussion

Racemic alkynyl-glycols **6a–6j** required for the synthesis of bis-imidate **1** were prepared by addition of magnesium or lithium acetylenides to protected acetaldehydes **4a** and **4b** followed by deprotection of intermediates **5a–5j**.

For the synthesis of diinyl-glycols **6k** and **6l**, intermediate **5b** was first de-silylated and then subjected to Glaser coupling with bromoalkynes (Table 1). For the synthesis of vinylacetylenyl-glycol **6m**, de-silylation of intermediate **5b** was followed by Sonogashira coupling with vinyl bromide (Table 1).[28]

Enantioenriched ethynyl-glycols *R*-**6a–6e** were prepared by using Noyori asymmetric hydrogenation reaction of protected hydroxyl ketones **7a–7f** as a key step (Table 2).[29] Ketones **7a–7e** were prepared by oxidation of protected diols **5a–5e**.

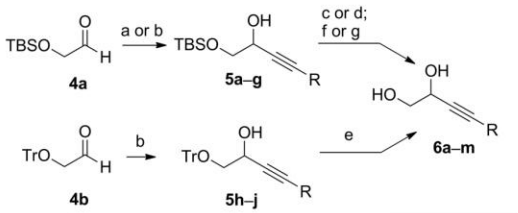
Carreira's asymmetric addition of alkynes to protected hydroxy ketone **4b**[30] was found to be the method of choice for the synthesis of enantioenriched aryl-substituted ethynyl-glycols *R*-**6h–6j** (Table 3).

The absolute configuration for representative diols *R*-**6b** and *R*-**6j** was determined by analysis of the ^{1}H NMR spectroscopic data of the diastereoisomeric diesters that resulted from derivatization with *R*- and *S*-α-metoxyphenylacetic acids (see Supporting Information).[31]

Diols **6a–6m** were converted into bis-imidates **1a–1m** in good yields by the reaction with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; Table 4).

Cyclization of bis-imidates **1a–1m** was achieved in good yields with a wide range of Lewis acid catalysts: trimethylsilyl (TMS)OTf, $BF_3{\cdot}Et_2O$, $AlCl_3$, $FeCl_3$ (Table 5). In this reaction, 4-alkynyloxazolines **2a–2m** typically were obtained with high selectivity over regioisomers **7a–7m**. In the

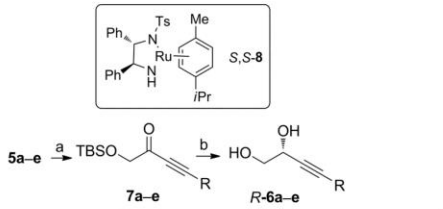
Table 1. Preparation of racemic alkynyl-glycols **6**.[a]



Entry	R	**5**, yield [%]	**6**, yield [%]
1	Me	**5a**, 87	**6a**, 81
2	TMS	**5b**, 81	**6b**, 94
3	$BnOCH_2$	**5c**, 27	**6c**, 93
4	$BnOCH_2CH_2$	**5d**, 45	**6d**, > 99
5	*t*Bu	**5e**, 78	**6e**, 88
6	Pent	**5f**, 76	**6f**, 90
7	TIPS	**5g**, 60	**6g**, 97
8	Ph	**5h**, 70	**6h**, 91
9	2-ClC_6H_4	**5i**, 70	**6i**, 95
10	3,5-ClC_6H_3	**5j**, 56	**6j**, 82
11	PentC≡C	–	**6k**, 88[b]
12	TIPSC≡C	–	**6l**, 79[b]
13	CH_2=CH	–	**6m**, 88[b]

[a] Reagents and conditions: (a) **4a**, MeC≡CMgBr, Et_2O, 0 °C for **5a**; (b) **4a** or **4b**, RC≡CH, *n*BuLi, THF, –78 °C for **5b**–**5j**; (c) **5a** and **5c**–**5f**, TBAF, AcOH, THF room temp. for **6a** and **6c**–**6f**; (d) **5b**, **g**, 1% HCl, MeOH, room temp. for **6b**, **g**; (e) **5h**–**5j**, 15 mol-% *p*TsOH·H_2O, MeOH, CH_2Cl_2, room temp. for **6h**–**6j**; (f) **5b**, KF, MeOH 50 °C then PentC≡CBr or triisopropylsilyl (TIPS)C≡CBr, NH_2OH·HCl, 20 mol-% CuCl, $BuNH_2$, room temp. for **6k** and **6l**; (g) **5b**, KF, MeOH 50 °C then 10 mol-% CuI, 2 mol-% $Pd(PPh_3)_4$, diethanolamine, vinyl bromide, THF, room temp. for **6m**. [b] Diols **6k**–**6m** were prepared from intermediate **5b**.

Table 2. Preparation of enantioenriched alkynyl-glycols **6** by using Noyori asymmetric reduction reaction.[a]

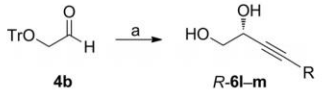


Entry	R	**7**, yield [%]	**6**, yield [%] (*ee* [%])[b]
1	Me	**7a**, 70	*R*-**6a**, 72 (90)
2	TMS	**7b**, 70	*R*-**6b**, 68 (96)
3	$BnOCH_2$	**7c**, 83	*R*-**6c**, 61 (92)
4	$BnOCHCH_2$	**7d**, 70	*R*-**6d**, 43 (93)
5	*t*Bu	**7e**, 50	*R*-**6e**, 63 (93)

[a] Reagents and conditions: (a) Dess–Martin periodinane, CH_2Cl_2, room temp. (b) Cat. **8** (6 mol-%), *i*PrOH room temp., then TBAF, AcOH, THF room temp. [b] *ee* was determined by chiral GC for **6a**, **6b**, and **6e**, or by HPLC by using chiral column Chiralpak IB for **6c** and **6d**.

case of TMS-substituted substrate **1b**, the desired selectivity for oxazoline **2b** formation was improved by replacing the TMSOTf catalyst with $AlCl_3$ (Table 5, Entries 2 and 3).

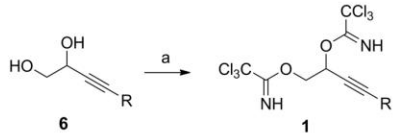
Table 3. Preparation of enantioenriched alkynyl-glycols by using Carreira's asymmetric alkynylation.[a]



Entry	R	**6**, yield [%] (*ee* [%])[b]
1	Ph	*R*-**6h**, 79 (88)
2	2-ClC_6H_4	*R*-**6i**, 88 (90)
3	3,5-ClC_6H_3	*R*-**6j**, 60 (93)

[a] Reagents and conditions: (a) RC≡CH (2.5 equiv.), (–)-*N*-methylephedrine (2.2 equiv.), $Zn(OTf)_2$ (2.0 equiv.), TEA (2.2 equiv.), toluene room temp. then *p*TsOH·H_2O (15 mol-%), MeOH, CH_2Cl_2, room temp. [b] *ee* was determined by HPLC by chiral column Chiralpak IB.

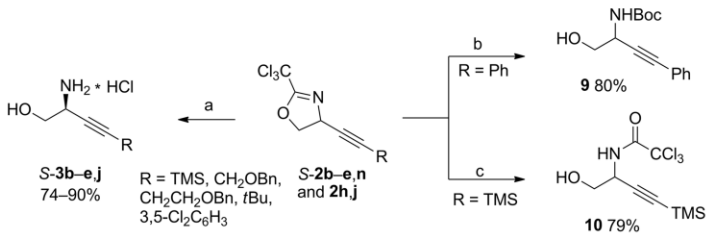
Table 4. Preparation of bis-imidates **1** from alkynyl-glycols **6**.[a]



Entry	R	**1**, yield [%][b]
1	Me	**1a**, 73
2	TMS	**1b**, 85
3	$BnOCH_2$	**1c**, 92
4	$BnOCH_2CH_2$	**1d**, 97
5	*t*Bu	**1e**, 90
6	Pent	**1f**, 88
7	TIPS	**1g**, 99
8	Ph	**1h**, 80
9	2-ClC_6H_4	**1i**, 85
10	3,5-ClC_6H_3	**1j**, 88
11	Pent–C≡C	**1k**, 83
12	TIPS–C≡C	**1l**, 50
13	CH_2=CH	**1m**, 85

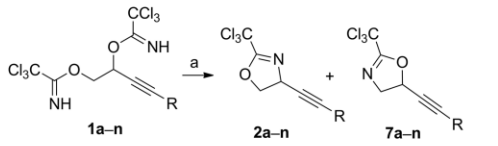
[a] Reagents and conditions: (a) CCl_3CN, 20 mol-% DBU, molecular sieves (4 Å), CH_2Cl_2, 0 °C. [b] Enantioenriched bis-imidates *R*-**1** were prepared by the same procedure as the racemic compound in similar yields.

Chirality transfer in the cyclization reaction of enantioenriched bis-imidates *R*-**1** was investigated. Substrates *R*-**1a**–**1e** that contained an alkyl or TMS substituent gave oxazolines *S*-**2a**–**2e** with complete inversion of configuration at the stereocenter (Table 6, Entries 1–5). This stereochemical outcome indicates that the S_N2 type substitution of the Lewis acid complexed propargylic imidate with the uncomplexed imidate (Figure 2). Notably, this is different from allylic substitution reaction with bis-imidates, which proceed by an S_N1 type reaction mechanism.[22,24,26] In turn, phenyl-substituted bis-imidate *R*-**1h** formed oxazoline **2h** with a considerable degree of racemization (Table 6, Entry 6). One chlorine substituent in the phenyl ring in substrate *R*-**1i** slightly suppressed the racemization in the cyclization to oxazoline **2i** (Table 6, Entries 7–9). With two chlorines in the phenyl ring in substrate *R*-**1j** the racemization was minimal with all the catalysts explored and oxazoline *S*-**2j** was



Scheme 1. Transformation of oxazolines **2** into amino alcohol derivatives **3**, **9**, and **10**. Reagents and conditions: (a) Aqueous HCl (6 M), MeOH, room temp.; (b) Aqueous HCl (6 M), MeOH room temp. then Boc_2O, $NaHCO_3$, THF room temp.; (c) *p*TsOH, pyridine, H_2O 80 °C.

Table 5. Substrate scope in the cyclization reaction of bis-imidates **1** to oxazolines **2**.[a]



1a–n **2a–n** **7a–n**

Entry	R	Cat.[b]	**2**/**7**	**2**, yield [%]
1	Me	TMSOTf	> 50:1	**2a**, 71
2	TMS	TMSOTf	9:1	**2b**, 82
3	TMS	$AlCl_3$	35:1	**2b**, 91
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] Reagents and conditions: (a) Lewis acid, CH_2Cl_2, room temp. [b] From the range of catalysts screened (TMSOTf, $BF_3{\cdot}Et_2O$, $AlCl_3$, $FeCl_3$) only the result for the best performing catalyst is shown.

Table 6. Chirality transfer in the cyclization reaction of enantioenriched bis-imidates **1** to oxazolines **2**.

Entry	R	**1**, (*ee* [%])	Cat.	**2**, yield [%] (*ee* [%])
1	Me	*R*-**1a**, (90)	$AlCl_3$	*S*-**2a**, 80 (90)
2	TMS	*R*-**1b**, (96)	$AlCl_3$	*S*-**2b**, 90[a] (96)
3	$BnOCH_2$	*R*-**1c**, (92)	$AlCl_3$	*S*-**2c**, 70 (92)
4	$BnOCHCH_2$	*R*-**1d**, (93)	$AlCl_3$	*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-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-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] ^{1}H NMR yield. 1,4-bis(trichloromethyl)benzene was used as an internal standard.

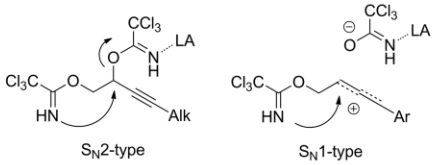


Figure 2. Proposed mechanisms for bis-imidate **1** cyclization reaction in the case of alkyl and aryl substitution.

observed in high enantiopurity (Table 6, Entries 10–12). These results indicate a mixed S_N1/S_N2 type mechanism in the case of substrates that bear a phenyl group in acetylenic position (Figure 2). The S_N1 pathway is obviously diminished by decreasing the carbenium ion stabilizing effect of the phenyl group in substrates *R*-**1i** and *R*-**1j**.

The synthetic utility of oxazolines **2** was demonstrated by transforming them into alkynyl-glycinol derivatives (Scheme 1). Strong acidic hydrolysis of oxazolines *S*-**2b**–**2e** and *S*-**2j** led to alkynyl-glycinols *S*-**3b**–**3e** and *S*-**3j**. The absolute configuration for the representative amino alcohols *S*-**3b** and *S*-**3j** was determined by analysis of the ^{1}H NMR spectra of the diastereoisomeric arylamines resulting from derivatization with *R*- and *S*-1-fluoro-2,4-dinitrophenyl-5-phenylethylamines (see Supporting Information).[32]

The hydrolysis of oxazoline **2h** was followed by *tert*-butoxycarbonyl (Boc)-protection without isolation of an intermediate to give protected amino alcohol **9**. Mild acidic hydrolysis of oxazoline **2b** provided *N*-trichloroacetyl amino alcohol **10**.

Conclusions

In summary, we have developed a new approach to enantioenriched alkynyl-glycinols based on cyclization reaction of bis-trichloroacetimidates derived from alkynyl-glycols. The cyclization reaction of bis-imidates proceeds selectively to give 4-alkynyl-oxazolines as propargylic substitution products. Enantioenriched bis-imidates that contain an alkyl or TMS substituent at acetylene give oxazolines with complete inversion of configuration. In turn, considerable racemization was observed in the cyclization reaction of bis-imidates that contain a phenyl substituent. The race-

mization for these substrates can be suppressed by introduction of electronegative substituents in the phenyl ring. The oxazolines prepared by bis-imidate cyclization can be readily transformed into alkynyl-glycinol derivatives.

Experimental Section

General Information: Commercially available reagents were used without further purification. Ru(p-cymene)[(*S*,*S*)-TsDPEN] catalyst *S*,S-**8**[33] and protected aldehydes **4a**[34] and **4b**[35] were prepared in accordance with the procedures described in the literature. *i*PrOH was distilled from CaH_2. All air- or moisture-sensitive reactions were carried out under an argon atmosphere with oven-dried glassware. Flash chromatography was carried out with Merck Kieselgel 60 (230–400 mesh). Thin-layer chromatography was performed on silica gel and was visualized by staining with $KMnO_4$. NMR spectra were recorded with a Varian Mercury spectrometer (400 MHz) and a Bruker Fourier spectrometer (300 MHz) with chemical shift values reported relative to tetramethylsilane by using the residual chloroform signal as an internal standard. Elemental analyses were performed with a Carlo-Erba EA1108 Elemental Analyzer. HRMS were obtained with a Q-TOF micro high-resolution mass spectrometer with ESI (ESI+/ESI–). Chiral HPLC was carried out with a Chiralpak IB column. Chiral GC was carried out with 6-TBDMS-2,3-Me-β-CD 50%, 25 m as the chiral stationary phase.

General Procedure for the Synthesis of Protected Diols 5a–5j: *n*BuLi solution in hexanes (2.5 M, 0.44 mL, 1.2 mmol) was added dropwise to a solution of alkyne (1.1 mmol) in tetrahydrofuran (THF; 8 mL) at –78 °C. The resulting reaction mixture was stirred at –78 °C for 30 min, then a solution of aldehyde **4a** (174 mg, 1.0 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 2 h (TLC control) then saturated aqueous NH_4Cl (5 mL) and Et_2O (10 mL) were added. The organic phase was separated and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and the solvents evaporated. The crude residue was purified by chromatography on silica gel (ethyl acetate/hexanes, 1:10–1:6) to afford alcohols **rac-5**.

Compounds **5a**,[36] **5b**,[37] and **5e**[38] are known.

5-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)pent-3-yn-2-ol (5c): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5 H, -C_6H_5), 4.59 (s, 2 H, -OCH_2Ph), 4.49–4.43 (m, 1 H, -CHO-), 4.21 (d, J = 1.7 Hz, 2 H, -CH_2OBn), 3.79 (dd, J = 10.0, 3.8 Hz, 1 H, -CH_2O-), 3.67 (dd, J = 10.0, 7.1 Hz, 1 H, -CH_2O-), 2.74–2.62 (m, 1 H, -O*H*), 0.91 [s, 9 H, -SiC(CH_3)$_3$], 0.11 [s, 6 H, -Si(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 128.5, 128.2, 128.0, 84.6, 81.5, 71.7, 67.0, 63.3, 57.5, 25.8, 18.5, –5.2 ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{18}H_{29}O_3Si$ [M + H]$^+$ 321.1880; found 321.1889.

6-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)hex-3-yn-2-ol (5d): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H, -C_6H_5), 4.54 (s, 2 H, -OCH_2Ph), 4.41–4.34 (m, 1 H, -C*H*O-), 3.74 (dd, J = 10.0, 3.7 Hz, 1 H, -CH_2OTBS), 3.63–3.55 (m, 3 H, two signals overlapping, -CH_2OTBS, -CH_2CH_2OBn), 2.53 (td, J = 7.1, 2.0 Hz, 2 H, -CH_2CH_2OBn), 0.91 [s, 9 H, -SiC(CH_3)$_3$], 0.09 [s, 6 H, -Si(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2, 128.6, 128.2, 128.0, 83.0, 79.1, 73.1, 68.4, 67.4, 63.4, 26.0, 20.3, 18.5, –5.2 ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{19}H_{31}O_3Si$ [M + H]$^+$ 335.2037; found 335.2034.

1-(*tert*-Butyldimethylsilyloxy)non-3-yn-2-ol (5f): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.41–4.34 (m, 1 H, -C*H*O-), 3.74 (dd, J = 10.0, 3.7 Hz, 1 H, -CH_2O-), 3.60 (dd, J = 10.0, 7.5 Hz, 1 H, -CH_2O-), 2.54 (d, J = 4.2 Hz, 1 H, -OH), 2.20 [td, J = 7.2, 2.0 Hz, 2 H, -$CH_2(CH_2)_3CH_3$], 1.54–1.46 [m, 2 H, -CH_2CH_2-$(CH_2)_2CH_3$], 1.40–1.25 [m, 4 H, -$CH_2CH_2(CH_2)_2CH_3$], 0.93–0.87 [two signals overlapping, 12 H, -SiC(CH_3)$_3$, -$(CH_2)_4CH_3$], 0.09 [s, 6 H, -Si(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 86.5, 77.9, 67.5, 63.5, 31.2, 28.4, 26.0, 22.3, 18.8, 18.5, 14.1, –5.2 ppm. GC–MS (EI): *m*/*z* = 270 [M]$^+$. No ionization under HRMS conditions.

1-[(*tert*-Butyldimethylsilyl)oxy]-4-(triisopropylsilyl)but-3-yn-2-ol (5g): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.46–4.38 (m, 1 H, -C*H*O-), 3.77 (dd, J = 9.9, 3.9 Hz, 1 H, -CH_2O-), 3.65 (dd, J = 9.9, 6.5 Hz, 1 H, -CH_2O-), 2.53 (d, J = 5.4 Hz, 1 H, -OH), 1.11–1.02 {m, 23 H, -Si[$CH(CH_3)_2]_3$} 0.91 [s, 9 H, -SiC(CH_3)$_3$], 0.10 [s, 6 H, -Si(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 105.78, 86.29, 67.21, 63.75, 25.99, 18.72, 18.45, 11.26, –5.23 ppm. GC–MS (EI): *m*/*z* = 299.1[M – *t*Bu]$^+$.

4-Phenyl-1-(trityloxy)but-3-yn-2-ol (5h): Viscous colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.21 [m, 20 H, C_6H_5-, -C(C_6H_5)$_3$], 4,78–4.69 (br., 1 H, -C*H*O-), 3.50–3.36 (m, 2 H, -CH_2O-), 2.68–2.56 (br., 1 H, -O*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 131.8, 128.7, 128.5, 128.3, 128.0, 127.2, 122.4, 87.4, 86.9, 85.5, 67.3, 62.6 ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{29}H_{25}O_2$ 405.1849; found 405.1846 [M + H]$^+$.

4-(2-Chlorophenyl)-1-(trityloxy)but-3-yn-2-ol (5i): Viscous colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 [m, 19 H, 2-ClC_6H_4-, -C(C_6H_5)$_3$], 4.77 (m, 1 H, -C*H*O-), 3.50 (dd, J = 9.3, 6.1 Hz, 1 H, -CH_2O-), 3.43 (dd, J = 9.3, 4.1 Hz, 1 H, -CH_2O-), 2.68 (d, J = 5.5 Hz, 1 H, -O*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 136.1, 133.7, 129.6, 129.3, 128.8, 128.0, 127.3, 126.5, 122.5, 93.0, 87.0, 82.2, 67.2, 62.7 ppm. No ionization under HRMS conditions.

4-(3,5-Dichlorophenyl)-1-(trityloxy)but-3-yn-2-ol (5j): Viscous colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.43 [m, 6 H, 3,5-ClC_6H_3-, -C(C_6H_5)$_3$], 7.34–7.22 [m, 12 H, -C(C_6H_5)$_3$], 4.66 (td, J = 6.0, 4.3 Hz, 1 H, -C*H*O-), 3.43–3.35 (m, 2 H, -CH_2O-), 2.57 (d, J = 5.7 Hz, 1 H, -O*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 135.0, 130.1, 129.1, 128.8, 128.1, 127.4, 125.4, 90.0, 87.2, 83.0, 67.1, 62.6 ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{29}H_{22}Cl_2O_2Na$ [M + Na]$^+$ 495.0889; found 495.0891.

General Procedure for the Synthesis of Diols 6a, 6c–6f: To a solution of substrate **5a**, or **5c**–**5f** (1.00 mmol) in THF (12 mL), AcOH (0.17 mL, 3.00 mmol) and tetra-*n*-butylammonium fluoride (TBAF; 0.95 g, 3.00 mmol) were added. The reaction mixture was stirred until complete conversion (TLC control). Then triethylamine (TEA; 0.40 mL) and silica gel were added and the solvent was evaporated. The residue was purified by chromatography on a short silica gel column (light petroleum ether/ethyl acetate, 2:1) to afford the product.

Compound ***R*-6a**[39] is known. NMR spectroscopic data for racemic compound **6a** matched these reported for enantioenriched compound ***R*-6a**.

5-(Benzyloxy)pent-3-yne-1,2-diol (6c): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H, -$CH_2C_6H_5$), 4.57 (s, 2 H, -OCH_2Ph), 4.51–4.44 (m, 1 H, -C*H*OH), 4.19 (d, J = 1.7 Hz, 2 H, -CH_2OBn), 3.76–3.60 (m, 2 H, -CH_2OH), 3.45–3.33 (br., 1 H, -O*H*), 3.12–3.00 (br., 1 H, -O*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.2, 128.6, 128.2, 128.1, 84.6, 82.0, 72.1, 66.5, 63.3, 57.5 ppm. (*R*-**6c**): $[\alpha]_D^{20}$ = –13.1 (c = 1, CH_2Cl_2).

6-(Benzyloxy)hex-3-yne-1,2-diol (6d): Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.33 (m, 5 H, -$CH_2C_6H_5$), 4.57 (s, 2

H, -OCH_2Ph), 4.50–4.40 (m, 1 H, -C*H*OH), 3.77–3.64 (m, 2 H, -CH_2OH), 3.60 (t, *J* = 6.9 Hz, 2 H, -CH_2CH_2OBn), 2.56 (td, *J* = 6.9, 1.9 Hz, 2 H, -CH_2CH_2OBn), 2.16 (br., 1 H, -O*H*), 2.06–1.97 (br., 1 H, -O*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 128.5, 127.9, 127.8, 83.4, 79.4, 73.0, 68.2, 66.7, 63.3, 20.1 ppm. (*R*-**6d**): $[\alpha]_D^{20}$ = –9.3 (*c* = 0.8, CH_2Cl_2).

5,5-Dimethylhex-3-yne-1,2-diol (6e): White powder, m.p. 74–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.37 (dd, *J* = 7.5, 3.6 Hz, 1 H, -C*H*OH), 3.62 (dd, *J* = 11.4, 3.6 Hz, 1 H, -CH_2OH), 3.53 (dd, *J* = 11.4, 7.5 Hz, 1 H, -CH_2OH), 3.47–3.19 (br., 2 H, two signals overlapping, -O*H*), 1.15 [s, 9 H, -C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 95.5, 76.2, 67.0, 63.5, 31.0, 27.5 ppm. No ionization under HRMS conditions. (*R*-**6e**): $[\alpha]_D^{20}$ = –18.6 (*c* = 1, CH_2Cl_2). $C_8H_{14}O_2$: C 67.57, H 9.92; found C 67.16, H 9.96.

Non-3-yne-1,2-diol (6f): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.47–4.40 (br., 1 H, HOC*H*-), 3.75–3.67 (br., 1 H, HOCH_2-), 3.63 (dd, 1 H, HOCH_2-), 2.39–2.28 (m, 1 H, *H*O-), 2.20 [td, *J* = 7.2, 2.0 Hz, 3 H, two signals overlapping: *H*O- un -CH_2-(CH_2)$_3$CH_3], 1.56–1.45 [m, 2 H, -CH_2CH_2(CH_2)$_2$CH_3], 1.40–1.25 [m, 4 H, -(CH_2)$_2$(CH_2)$_2$CH_3], 0.89 [t, *J* = 7.1 Hz, 3 H, -(CH_2)$_4$-CH_3] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 87.6, 77.9, 67.1, 63.7, 31.3, 28.4, 22.4, 18.9, 14.2 ppm. No ionization under HRMS conditions.

General Procedure for the Synthesis of Diols 6b, and 6g: Substrate **5b**, or **5g** (1.00 mmol) was dissolved in a methanolic HCl solution (1%, 10 mL). The reaction mixture was stirred until complete conversion (TLC control). Then TEA (0.40 mL) and silica gel were added and the solvent was evaporated. The residue was purified by chromatography on a short silica-gel column (light petroleum ether/ethyl acetate, 1:1) to afford the product.

Compound **6g**[40] is known.

4-(Trimethylsilyl)but-3-yne-1,2-diol (6b): White powder, m.p. 53–54 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.52–4.39 (br., 1 H, -C*H*OH), 3.81–3.59 (m, 2 H, -CH_2OH), 2.36–2.22 (br., 1 H, -O*H*), 2.15–1.98 (br., 1 H, -O*H*), 0.18 [s, 9 H, -Si(CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 103.1, 91.7, 66.6, 63.9, –0.1 ppm. No ionization under HRMS conditions. (*R*-**6b**): $[\alpha]_D^{20}$ = –24.3 (*c* = 1, CH_2Cl_2). $C_7H_{14}O_2Si$: C 53.12, H 8.92; found C 53.00, H 8.91.

General Procedure for the Synthesis of Diols 6h–6j: To a solution of substrate **5h–5j** (1 mmol) in a mixture of CH_2Cl_2 and MeOH (2.5 mL/1.35 mL), *p*TsOH·H_2O (0.15 mmol) was added. The reaction mixture was stirred until complete conversion (TLC control), typically overnight. Then TEA (20 μL) and silica gel were added and the solvent evaporated. The residue was purified by chromatography on a short silica-gel column (light petroleum ether/ethyl acetate, 1:1) to afford the product.

Racemic compound **6h**[41] is known.

4-(Phenyl)but-3-yne-1,2-diol (*R*-6h): NMR spectroscopic data corresponded to these reported in the literature for the racemic compound. White powder, m.p. 60–62 °C. $[\alpha]_D^{20}$ = –26.8 (*c* = 1.0, CH_2Cl_2). No ionization under HRMS conditions. $C_{10}H_{10}O_2$·1/6H_2O: C 72.71, H 6.31; found C 72.94, H 6.24.

4-(2-Chlorophenyl)but-3-yne-1,2-diol (6i): White powder, m.p. 110–112 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.51 (dd, *J* = 7.4, 2.0 Hz, 1 H, -C$_6H_4$), 7.43 (dd, *J* = 7.7, 1.5 Hz, 1 H, -C$_6H_4$), 7.32 (td, *J* = 7.7, 2.0 Hz, 1 H, -C$_6H_4$), 7.26 (td, *J* = 7.4, 1.5 Hz, 1 H, -C$_6H_4$), 4.59 (dd, *J* = 7.2, 4.7 Hz, 1 H, -C*H*OH), 3.73 (dd, *J* = 11.2, 4.7 Hz, 1 H, -CH_2OH), 3.67 (dd, *J* = 11.2, 7.2 Hz, 1 H, -CH_2OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.8, 134.6, 130.8, 130.3, 127.8, 123.9, 94.6, 82.4, 67.3, 64.7 ppm. (*R*-**6i**): $[\alpha]_D^{20}$ = –13.3 (*c* = 0.7, CH_2Cl_2). No ionization under HRMS conditions.

4-(3,5-Dichlorophenyl)but-3-yne-1,2-diol (6j): White powder, m.p. 115–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 3 H, -C$_6H_3$), 4.67 (dd, *J* = 6.4, 3.7 Hz, 1 H, -C*H*OH), 3.84 (dd, *J* = 11.4, 3.7 Hz, 1 H, -CH_2OH), 3.77 (dd, *J* = 11.4, 6.4 Hz, 1 H, -CH_2OH), 2.46–2.33 (br., 1 H, -O*H*), 2.16–1.96 (br., 1 H, -O*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.1, 130.131, 129.3, 125.0, 89.2, 83.7, 66.4, 63.7 ppm. No ionization under HRMS conditions. (*R*-**6j**): $[\alpha]_D^{20}$ = –5.4 (*c* = 0.7, MeOH).

Undeca-3,5-diyne-1,2-diol (6k): To a solution of substrate **5b** (0.20 g, 0.73 mmol) in MeOH (8 mL) KF (0.11 g, 1.83 mmol) was added. The reaction mixture was heated at 50 °C for 7 h. After the desilylation reaction was complete (TLC control), the reaction mixture was cooled to room temp. and CuCl (14 mg, 0.15 mmol), NH_2OH·HCl (76 mg, 1.1 mmol), and $PentNH_2$ (0.85 mL) were added. The reaction mixture was stirred at room temp. for 10 min. A solution of 1-bromoalkyne (0.19 g, 1.1 mmol) in MeOH (3 mL) was added and stirring was continued for an additional 40 min until TLC showed complete conversion. The reaction mixture was poured into water (15 mL) and extracted with Et_2O (3× 15 mL). The combined organic phase was washed with saturated aqueous $KHSO_4$ (10 mL), saturated aqueous NaCl (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 1:1) to give diol **6k** (115 mg, 88%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.52–4.47 (m, 1 H, HOC*H*-), 3.70–3.57 (m, 2 H, HOCH_2-), 2.47–2.37 (br., 1 H, *H*O-), 2.28 [td, *J* = 7.0, 0.9 Hz, 2 H, -CH_2(CH_2)$_3$CH_3], 2.21–2.09 (m, 1 H, *H*O-), 1.53 [m, 2 H, -CH_2CH_2(CH_2)$_2$CH_3], 1.42–1.27 [m, 4 H, -(CH_2)$_2$-(CH_2)$_2$CH_3], 0.90 [t, *J* = 7.1 Hz, 3 H, -(CH_2)$_4$CH_3] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.3, 72.9, 71.3, 66.3, 64.1, 63.6, 30.9, 27.7, 22.1, 19.2, 13.9 ppm.

6-(Triisopropylsilyl)hexa-3,5-diyne-1,2-diol (6l): Prepared similar to compound **6k** from but-3-yne-1,2-diol (41 mg), yield 101 mg (79%), slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.50–4.41 (m, 1 H, HOC*H*-), 3.76–3.61 (m, 2 H, HOCH_2-), 2.45–2.33 (br., 1 H, *H*O-), 2.14–2.02 (br., 1 H, *H*O-), 1.02 (s, 21 H, 3 *i*Pr) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 90.5, 87.3, 76.0, 73.2, 68.1, 65.5, 20.5, 13.2 ppm. No ionization under HRMS conditions.

Hex-5-en-3-yne-1,2-diol (6m): Following the reported procedure,[28] CuI (12.8 mg, 0.067 mmol, 10 mol-%) and $Pd(PPh_3)_4$ (15.6 mg, 0.013 mmol, 2 mol-%) were dissolved in diethylamine (0.6 mL) at room temp. under an argon atmosphere. To this reaction mixture, a solution of but-3-yne-1,2-diol (58 mg, 0.67 mmol, 1.0 equiv.) in THF and vinyl bromide in THF (1 M, 1.0 mL, 1.01 mmol, 1.5 equiv.) were sequentially added dropwise and the resulting suspension was stirred at room temp. for 4 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 1:1) as an eluent to give diol **6m** (66 mg, 88%) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD): δ = 5.84 (ddd, *J* = 17.6, 11.1, 1.8 Hz, 1 H, -C*H*=CH$_2$), 5.59 (dd, *J* = 17.6, 2.2 Hz, 1 H, -CH=CH_2), 5.46 (dd, *J* = 11.1, 2.2 Hz, 1 H, -CH=CH_2), 4.40 (ddd, *J* = 6.9, 4.9, 1.8 Hz, 1 H, -C*H*O-), 3.58 (dd, *J* = 11.2, 4.9 Hz, 1 H, -CH_2O-), 3.53 (dd, *J* = 11.2, 6.9 Hz, 1 H, -CH_2O-) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 127.6, 118.0, 89.7, 84.5, 67.3, 64.5 ppm. No ionization under HRMS conditions.

General Procedure for the Synthesis of Ketones 7a–7e: To a solution of alcohol **5a–5e** (0.28 g, 1.31 mmol) in CH_2Cl_2 (7 mL) Dess–Martin periodinane (0.406 M in CH_2Cl_2, 4.8 mL, 1.97 mmol) was slowly added. The reaction mixture was stirred until complete conversion (TLC control). Then the mixture was diluted with Et_2O (15 mL),

filtered through a short Celite® column and the filtrate was evaporated. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 15:1) to give ketone **7a**–**7e**.

Compounds **7b**,[37] and **7e**[38] are known.

1-[(*tert*-Butyldimethylsilyl)oxy]pent-3-yn-2-one (7a): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30 (s, 2 H, -CH_2OTBS), 2.03 (s, 3 H, -CH_3), 0.92 [s, 9 H, -SiC(CH_3)$_3$], 0.10 [s, 6 H, -Si(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.8, 93.3, 78.2, 70.6, 25.9, 18.6, 4.3, –5.2 ppm.

5-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)pent-3-yn-2-one (7c): Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.28 (m, 5 H, -C$_6H_5$), 4.62 (s, 2 H, -CH_2OTBS), 4.38–4.31 (m, 4 H, two signals overlapping, -CH_2OBn, -OCH_2Ph), 0.93 [s, 9 H, -SiC(CH_3)$_3$], 0.11 [s, 6 H, -Si(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.1, 136.8, 128.7, 128.3, 128.2, 90.6, 83.4, 72.3, 70.5, 57.1, 25.9, 18.5, –5.3 ppm.

6-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)hex-3-yn-2-one (7d): Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.14 (m, 5 H, -C$_6H_5$), 4.45 (s, 2 H, -CH_2OTBS), 4.22 (s, 2 H, -OCH_2Ph), 3.54 (t, J = 6.8 Hz, 2 H, -CH$_2$CH_2OBn), 2.58 (t, J = 6.8 Hz, 2 H, -CH_2CH$_2$OBn), 0.83 [s, 9 H, -SiC(CH_3)$_3$], 0.00 [s, 6 H, -Si(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.4, 137.8, 128.5, 127.9, 127.8, 93.7, 79.3, 73.2, 70.6, 67.1, 25.8, 20.7, 18.5, –5.3 ppm.

General Procedure for the Synthesis of Enantioenriched Alcohols *R*-5a–5e: To a solution of catalyst **8** (20 mg, 0.03 mmol) in degassed *i*PrOH (8 mL) a solution of ketone **7a**–7**e** (0.49 mmol) in *i*PrOH (2 mL) was added. The reaction mixture was stirred until TLC showed complete conversion (from 40 min to 15 h). Then the reaction mixture was evaporated and the residue was purified by flash column chromatography (petroleum ether/EtOAc, 15:1) to give diol ***R*-5a**–**5e**.

1-[(*tert*-Butyldimethylsilyl)oxy]pent-3-yn-2-ol (*R*-5a): Enantiomeric excess (90%) was determined by chiral GC analysis [β-DEX™ 120; 30 m × 0.25 mm, d_f 0.25 μm; 160 °C to 220 °C; t_r (major) 19.4 min, t_r (minor) 19.6 min].

1-[(*tert*-Butyldimethylsilyl)oxy]-4-(trimethylsilyl)but-3-yn-2-ol (*R*-5b): $[\alpha]_D^{20}$ = –9.0 (c = 1.0, CH_2Cl_2). Enantiomeric excess (96%) was determined by chiral GC analysis [β-DEX™ 120; 30 m × 0.25 mm, d_f 0.25 μm; 160 °C to 220 °C; t_r (major) 26.5 min, t_r (minor) 26.2 min].

5-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)pent-3-yn-2-ol (*R*-5c): $[\alpha]_D^{20}$ = –2.6 (c = 0.4, CH_2Cl_2). Enantiomeric excess (92%) was determined by supercritical fluid chromatography (SFC) analysis on chiral phase [Lux Cellulose 1; 4.6 × 150 mm; F = 2 mL/min, 10% IPA + 90% Hex; T = 25 °C; t_r (major) 9.3 min, t_r (minor) 7.2 min].

6-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)hex-3-yn-2-ol (*R*-5d): $[\alpha]_D^{20}$ = –2.6 (c = 0.3, CH_2Cl_2). Enantiomeric excess (93%) was determined by SFC analysis on chiral phase [Chiralpak IB; 4.6 × 250 mm; F = 1 mL/min, 10% IPA + 90% Hex; T = 25 °C; t_r (major) 7.6 min, t_r (minor) 6.6 min].

1-[(*tert*-Butyldimethylsilyl)oxy]-5,5-dimethylhex-3-yn-2-ol (*R*-5e): $[\alpha]_D^{20}$ = –4.2 (c = 0.3, CH_2Cl_2) Enantiomeric excess (93%) was determined by chiral GC analysis [β-DEX™ 120; 30 m × 0.25 mm, d_f 0.25 μm; 160 °C to 220 °C; t_r (major) 31.0 min, t_r (minor) 30.8 min].

General Procedure for the Synthesis of Enantioenriched Alcohols *R*-5h–5j: Zn(OTf)$_2$ (2.0 mmol, 2.0 equiv.) was dried under vacuum at 125 °C for 2 h. Then the flask was cooled to room temperature, the vacuum was released and (–)-*N*-methylephedrine (2.2 mmol, 2.2 equiv.) was added. The vacuum was applied for 30 min and then released. Toluene (3 mL) and triethylamine (2.2 mmol, 2.2 equiv.) were added and the reaction mixture was stirred at room temperature for 2 h (in some cases overnight). Alkyne (3.0 mmol, 3.0 equiv.) was added dropwise and the reaction mixture was stirred at room temp. for 15 min. A solution of aldehyde (1.0 mmol, 2.2 equiv.) in toluene (1 mL) was added slowly by means of a syringe pump (within 1 h). The reaction mixture was stirred until TLC showed complete conversion. The reaction mixture was filtered through a short silica gel column (toluene) to afford products **5h**–**5j**.

4-Phenyl-1-(trityloxy)but-3-yn-2-ol (*R*-5h): $[\alpha]_D^{20}$ = 12.4 (c = 1.0, CH_2Cl_2). Enantiomeric excess (88%) was determined by SFC analysis on chiral phase [Chiralpak IB; 4.6 × 250 mm; F = 1 mL/min, 10% IPA + 90% Hex; T = 25 °C; t_r (major) 11.0 min, t_r (minor) 8.0 min].

4-(3-Chlorophenyl)-1-(trityloxy)but-3-yn-2-ol (*R*-5i): $[\alpha]_D^{20}$ = 2.6 (c = 1.2, CH_2Cl_2). Enantiomeric excess (90%) was determined by SFC analysis on chiral phase [Lux Cellulose 1; 4.6 × 150 mm; F = 1 mL/min, 10% IPA + 90% Hex; T = 25 °C; t_r (major) 7.0 min, t_r (minor) 9.1 min].

4-(3,5-Dichlorophenyl)-1-(trityloxy)but-3-yn-2-ol (*R*-5j): $[\alpha]_D^{20}$ = 19.9 (c = 1.7, CH_2Cl_2). Enantiomeric excess (93%) was determined by SFC analysis on chiral phase [Lux Cellulose 1; 4.6 × 150 mm; F = 2 mL/min, 10% IPA + 90% Hex; T = 25 °C; t_r (major) 6.1 min, t_r (minor) 10.2 min].

General Procedure for the Synthesis of Bis-imidates 1: To a solution of diol **6a**–**6m** (1.0 mmol) in CH_2Cl_2 or THF (10 mL) molecular sieves (4 Å) were added. The reaction mixture was cooled to 0 °C and DBU (0.25 mmol, 25 mol-%) was added. The solution was stirred at 0 °C for 30 min, trichloroacetonitrile (4 mmol, 4 equiv.) was added. The reaction mixture was stirred until complete conversion of the starting material (TLC control). The solvent was removed and the residue was purified by filtering through a short silica-gel column (CH_2Cl_2). If needed, the product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 10:1) to give bis-trichloroacetimidate **1a**–**1m**.

Pent-3-yne-1,2-diyl Bis-trichloroacetimidate (1a): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 1 H, =N*H*), 8.43 (s, 1 H, =N*H*), 5.88–5.84 (m, 1 H, -C*H*O-), 4.67–4.53 (m, 2 H, CH_2O-), 1.89 (s, 3 H, -CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 161.6, 91.1, 91.1, 84.7, 71.9, 69.2, 66.6, 3.7 ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_9H_9Cl_6N_2O_2$ [M + H]$^+$ 386.8790; found 386.8786.

4-(Trimethylsilyl)but-3-yne-1,2-diyl Bis-trichloroacetimidate (1b): White powder, m.p. 46–48 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (s, 1 H, =N*H*), 8.43 (s, 1 H, =N*H*), 5.93 (dd, J = 7.7, 4.1 Hz, 1 H, -C*H*O-), 4.68–4.57 (m, 2 H, -CH_2O-), 0.17 [s, 9 H, -Si(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 161.5, 97.3, 93.8, 77.4, 69.0, 66.6, –0.2 ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{11}H_{15}Cl_6N_2O_2Si$ [M + H]$^+$ 444.9028; found 444.9029.

5-(Benzyloxy)pent-3-yne-1,2-diyl Bis-trichloroacetimidate (1c): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (s, 1 H, =N*H*), 8.46 (s, 1 H, =N*H*), 7.37–7.26 (m, 5 H, -C$_6H_5$), 6.00–5.94 (m, 1 H, -C*H*O-), 4.68 (dd, J = 11.7, 3.9 Hz, 1 H, -CH_2O-), 4.62 (dd, J = 11.7, 7.7 Hz, 1 H, -CH_2O-), 4.58 (s, 2 H, -CH_2Ph), 4.21 (d, J = 1.7 Hz, 2 H, -CH_2OBn) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 161.4, 137.2, 128.6, 128.3, 128.1, 90.9, 84.0, 79.5, 71.6, 68.8, 66.0, 57.2 ppm. Unstable under HRMS analysis conditions.

6-(Benzyloxy)hex-3-yne-1,2-diyl Bis-trichloroacetimidate (1d): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 1 H, =N*H*),

8.42 (s, 1 H, =N*H*), 7.37–7.24 (m, 5 H, -C_6H_5), 5.90 (ddt, *J* = 5.9, 4.0, 2.0 Hz, 1 H, -C*H*O-), 4.64–4.56 (m, 2 H, -CH_2O-), 4.52 (s, 2 H, -OCH_2Ph), 3.57 (t, *J* = 7.0 Hz, 2 H, -CH_2CH_2OBn), 2.55 (td, *J* = 7.0, 2.0 Hz, 2 H, -CH_2CH_2OBn) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 162.7, 161.9, 138.4, 128.9, 128.2, 128.1, 91.3, 86.2, 74.3, 73.4, 69.5, 68.3, 66.9, 20.7 ppm. Unstable under HRMS analysis conditions.

5,5-Dimethylhex-3-yne-1,2-diyl Bis-trichloroacetimidate (1e): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 8.49 (s, 1 H, =N*H*), 8.41 (s, 1 H, =N*H*), 5.91 (dd, *J* = 7.0, 4.8 Hz, 1 H, -C*H*O-), 4.61–4.53 (m, 2 H, -CH_2O-), 1.21 [s, 9 H, -C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 162.6, 161.5, 97.2, 91.2, 91.1, 71.4, 69.4, 66.7, 30.8, 27.6 ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{12}H_{15}Cl_6N_2O_2$ [M + H]$^+$ 428.9259; found 428.9248.

Non-3-yne-1,2-diyl Bis-trichloroacetimidate (1f): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 8.49 (s, 1 H, =N*H*), 8.40 (s, 1 H, =N*H*), 5.87 (dd, *J* = 9.2, 4.3 Hz, 1 H, -C*H*O-), 4.63–4.56 (m, 2 H, -CH_2O-), 2.21 [td, *J* = 7.1, 2.0 Hz, 2 H, -$CH_2(CH_2)_3CH_3$], 1.54–1.45 [m, 2 H, -$CH_2CH_2(CH_2)_2CH_3$], 1.38–1.22 [m, 4 H, -$CH_2CH_2(CH_2)_2CH_3$], 0.87 [t, *J* = 7.1 Hz, 3 H, -$(CH_2)_4CH_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 162.5, 161.7, 89.4, 72.9, 69.4, 66.9, 31.1, 28.1, 22.3, 18.9, 14.1 (-CCl_3 not detected) ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{13}H_{17}Cl_6N_2O_2$ [M + H]$^+$ 442.9416; found 442.9408.

4-(Triisopropylsilyl)but-3-yne-1,2-diyl Bis-trichloroacetimidate (1g): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 8.53 (s, 1 H, =N*H*), 8.41 (s, 1 H, =N*H*), 5.90 (dd, *J* = 7.6, 4.2 Hz, 1 H, -C*H*O-), 4.70–4.55 (m, 2 H, -CH_2O-), 1.04 {s, 21 H, -Si[C*H*(CH_3)$_2$]$_3$} ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 162.5, 161.3, 110.2, 99.4, 91.1, 90.2, 69.0, 66.7, 18.6, 11.2 ppm. Unstable under HRMS analysis conditions.

4-Phenylbut-3-yne-1,2-diyl Bis-trichloroacetimidate (1h): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 8.57 (s, 1 H, =N*H*), 8.45 (s, 1 H, =N*H*), 7.56–7.41 (m, 2 H, -C_6H_5), 7.41–7.25 (m, 3 H, -C_6H_5), 6.13 (dd, *J* = 7.6, 4.1 Hz, 1 H, -C*H*O-), 4.79–4.65 (m, 2 H, -CH_2O-) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 162.5, 161.6, 132.2, 129.2, 128.5, 121.8, 91.1, 87.8, 81.7, 69.0, 66.9 ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{12}H_9Cl_3NO$ [M – C_2HNOCl_3]$^+$ 287.9752; found 287.9750.

4-(2-Chlorophenyl)but-3-yne-1,2-diyl Bis-trichloroacetimidate (1i): Colorless oil. ^{1}H NMR (400 MHz, cdcl$_3$): *δ* = 8.55 (s, 1 H, =N*H*), 8.41 (s, 1 H, =N*H*), 7.40 (d, *J* = 7.6 Hz, 1 H, -C_6H_4Cl), 7.31 (d, *J* = 8.0 Hz, 1 H, -C_6H_4Cl), 7.24–7.17 (m, 1 H, -C_6H_4Cl), 7.17–7.10 (m, *J* = 7.5 Hz, 1 H, -C_6H_4Cl), 6.12 (dd, *J* = 7.7, 4.0 Hz, 1 H, -C*H*O-), 4.76–4.63 (m, 2 H, -CH_2O-) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 162.4, 161.5, 136.5, 133.8, 130.2, 129.5, 126.5, 121.8, 91.0, 91.0, 86.9, 84.4, 68.8, 66.8 ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{12}H_8NOCl_4$ [M – C_2HNOCl_3]$^+$ 321.9360; found 321.9360.

4-(3,5-Dichlorophenyl)but-3-yne-1,2-diyl Bis-trichloroacetimidate (1j): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 8.60 (s, 1 H, =N*H*), 8.48 (s, 1 H, =N*H*), 7.39–7.27 (m, 3 H, -C_6H_3), 6.10 (dd, *J* = 7.5, 4.1 Hz, 1 H, -C*H*O-), 4.72 (dd, *J* = 11.7, 4.1 Hz, 1 H, -CH_2O-), 4.68 (dd, *J* = 11.7, 7.5 Hz, 1 H, -CH_2O-) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 162.4, 161.5, 135.1, 130.3, 129.7, 124.5, 91.0, 90.9, 85.0, 84.2, 68.6, 66.5 ppm. Unstable under HRMS analysis conditions.

Undeca-3,5-diyne-1,2-diyl Bis-trichloroacetimidate (1k): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 8.57 (s, 1 H, =N*H*), 8.46 (s, 1 H, =N*H*), 5.94 (dd, *J* = 7.8, 3.9 Hz, 1 H, -C*H*O-), 4.71–4.57 (m, 2 H, -CH_2O-), 2.28 [t, *J* = 7.1 Hz, 2 H, -$CH_2(CH_2)_3CH_3$], 1.58–1.48 [m, 4 H, -$(CH_2)_2(CH_2)_2CH_3$], 1.41–1.24 [m, 4 H, -$CH_2CH_2(CH_2)_2CH_3$], 0.90 [t, *J* = 7.1 Hz, 3 H, -$(CH_2)_4CH_3$] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): *δ* = 162.4, 161.4, 90.9, 90.8, 83.3, 73.0, 68.7, 67.7, 66.7, 64.2, 31.1, 27.8, 22.3, 19.4, 14.0 ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{15}H_{17}Cl_6N_2O_2$ [M + H]$^+$ 466.9416; found 466.9413.

6-(Triisopropylsilyl)hexa-3,5-diyne-1,2-diyl Bis-trichloroacetimidate (1l): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 8.53 (s, 1 H, =N*H*), 8.40 (s, 1 H, =N*H*), 5.91 (dd, *J* = 8.0, 3.8 Hz, 1 H, -C*H*O-), 4.62 (dd, *J* = 11.7, 3.8 Hz, 1 H, -CH_2O-), 4.56 (dd, *J* = 11.7, 8.0 Hz, 1 H, -CH_2O-), 1.01 {s, 21 H, -Si[C*H*(CH_3)$_2$]$_3$} ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 162.1, 161.2, 90.7, 90.6, 88.2, 86.7, 72.9, 68.6, 68.4, 66.3, 18.5, 11.2 ppm. Unstable under HRMS analysis conditions.

Hex-5-en-3-yne-1,2-diyl Bis-trichloroacetimidate (1m): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = ppm. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 8.55 (s, 1 H, =N*H*), 8.45 (s, 1 H, =N*H*), 6.03 (ddd, *J* = 7.7, 4.1, 1.6 Hz, 1 H, -C*H*O-), 5.82 (ddd, *J* = 17.5, 10.8, 1.6 Hz, 1 H, -C*H*=CH_2), 5.72 (dd, *J* = 17.5, 2.5 Hz, 1 H, -CH=C*H*$_2$), 5.57 (dd, *J* = 10.8, 2.5 Hz, 1 H, -C*H*=C*H*$_2$), 4.70–4.60 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 162.5, 161.6, 129.4, 116.1, 91.0, 91.0, 86.4, 82.2, 68.9, 66.7 ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{10}H_8Cl_6N_2O_2$ [M + H]$^+$ 398.8790; found 398.8793.

General Procedure for the Cyclization Reaction of Bis-trichloroacetimidates 1a–1m: Molecular sieves (4 Å) and a Lewis acid catalyst (0.05 mmol, 10 mol-%) were added to a stirred solution of bis-imidate **1a**–**1m** (0.50 mmol) in solvent (5 mL) at room temp. After the reaction was complete (TLC control in the first minute of the reaction), TEA (50 mol-%) was added to the reaction mixture and the solvent was evaporated. The residue was purified by chromatography on a short silica-gel column (light petroleum ether/ethyl acetate, 10:1) to afford product **2a**–**2m**.

4-(Prop-1-yn-1-yl)-2-(trichloromethyl)oxazoline (2a): Colorless oil. ^{1}H NMR (400 MHz, [D$_6$]dimethyl sulfoxide): *δ* = 5.19–5.12 (m, 1 H, -C*H*N-), 4.86 (dd, *J* = 10.0, 8.2 Hz, 1 H, -CH_2O-), 4.47 (t, *J* = 8.2 Hz, 3 H, -CH_2O-), 1.84 (d, *J* = 2.3 Hz, 3 H, -CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ dried with K_2CO_3): *δ* = 163.7, 86.5, 82.7, 75.8, 58.0, 3.9 ppm. GC–MS (EI): *m*/*z* = 225 [M]$^+$. Enantiomeric excess (90%) was determined by chiral GC analysis [β-DEX™ 120; 30 m × 0.25 mm, d_f 0.25 μm; 160 °C to 220 °C; t_r (major) 19.2 min, t_r (minor) 18.8 min].

4-[(Trimethylsilyl)ethynyl]-2-(trichloromethyl)oxazoline (2b): White powder, m.p. 53–54 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 5.07 (dd, *J* = 10.2, 9.1 Hz, 1 H, -C*H*N-), 4.82 (dd, *J* = 10.2, 8.2 Hz, 1 H, -CH_2O-), 4.54 (dd, *J* = 9.1, 8.2 Hz, 1 H, -CH_2O-), 0.19 [s, 9 H, -Si(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 164.0, 101.2, 91.2, 86.2, 76.4, 58.3, –0.3 ppm. GC–MS (EI): *m*/*z* = 283 [M]$^+$. HRMS (ESI-TOF): *m*/*z* calcd. for $C_9H_{13}Cl_3NOSi$ [M + H]$^+$ 283.9827; found 283.9833. Enantiomeric excess (96%) was determined by chiral GC analysis [β-DEX™ 120; 30 m × 0.25 mm, d_f 0.25 μm; 160 °C to 220 °C; t_r (major) 23.4 min, t_r (minor) 22.9 min].

4-[3-(Benzyloxy)prop-1-yn-1-yl]-2-(trichloromethyl)oxazoline (2c): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.37–7.27 (m, 5 H, -C_6H_5), 5.12 (ddt, *J* = 10.3, 8.7, 1.8 Hz, 1 H, -C*H*O-), 4.82 (dd, *J* = 10.3, 8.3 Hz, 1 H, -CH_2O-), 4.59–4.53 (two signals overlapping, 3 H, -OCH_2Ph, -CH_2O-), 4.23 (d, *J* = 2.0 Hz, 2 H, -CH_2OBn) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 164.4, 137.3, 128.6, 128.2, 128.1, 82.9, 82.3, 77.4, 76.5, 72.1, 57.9, 57.6 ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{14}H_{13}Cl_3NO_2$ [M + H]$^+$ 332.0006; found 332.0011. Enantiomeric excess (92%) was determined by SFC analysis on chiral

phase [Chiralpak IB; 4.6 × 250 mm; F = 1 mL/min, 10% IPA + 90% Hex; T = 25 °C; t_r (major) 13.0 min, t_r (minor) 14.0 min].

4-[4-(Benzyloxy)but-1-yn-1-yl]-2-(trichloromethyl)oxazoline (2d): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H, -C$_6H_5$), 5.04 (ddt, J = 10.1, 9.0, 2.1 Hz, 1 H, -CHN-), 4.78 (dd, J = 10.1, 8.2 Hz, 1 H, -CH_2O-), 4.56–4.46 (two signals overlapping, 3 H, -CH_2O-, -OCH_2Ph), 3.59 (t, J = 6.9 Hz, 2 H, -CH$_2$CH_2OBn), 2.55 (td, J = 6.9, 2.1 Hz, 2 H, -CH_2CH$_2$OBn) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 138.1, 128.6, 127.9, 127.8, 86.4, 83.8, 77.7, 76.8, 73.1, 68.1, 58.0, 20.4 ppm. HRMS (ESI-TOF): m/z calcd. for $C_{15}H_{15}Cl_3NO_2$ [M + H]$^+$ 346.0163; found 346.0160. Enantiomeric excess (92%) was determined by SFC analysis on chiral phase [Chiralpak IB; 4.6 × 250 mm; F = 1 mL/min, 10% IPA + 90% Hex; T = 25 °C; t_r (major) 11.9 min, t_r (minor) 9.7 min].

4-(3,3-Dimethylbut-1-yn-1-yl)-2-(trichloromethyl)oxazoline (1e): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.02 (dd, J = 10.0, 9.1 Hz, 1 H, -CHN-), 4.78 (dd, J = 10.0, 8.1 Hz, 1 H, -CH_2O-), 4.43 (dd, J = 9.1, 8.1 Hz, 1 H, -CH_2O-), 1.20 [s, 9 H, -C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 95.0, 86.5, 77.1, 75.1, 58.1, 30.9, 27.6 ppm. HRMS (ESI-TOF): m/z calcd. for $C_{10}H_{13}Cl_3NO$ [M + H]$^+$ 268.0057; found 268.0064. Enantiomeric excess (93%) was determined by chiral GC analysis [β-DEX™ 120; 30 m × 0.25 mm, d_f 0.25 μm; 160 °C to 220 °C; t_r (major) 26.3 min, t_r (minor) 26.1 min].

4-(Hept-1-yn-1-yl)-2-(trichloromethyl)oxazoline (2f): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.02 (ddt, J = 9.9, 8.8, 2.1 Hz, 1 H, -CHN-), 4.77 (dd, J = 9.9, 8.2 Hz, 1 H, -CH_2O-), 4.47 (dd, J = 8.8, 8.2 Hz, 1 H, -CH_2O-), 2.19 [td, J = 7.2, 2.1 Hz, 3 H, -CH_2(CH$_2$)$_3$CH$_3$], 1.50 [p, J = 7.2 Hz, 2 H, -CH$_2$CH_2(CH$_2$)$_2$CH$_3$], 1.38–1.22 [m, 4 H, -(CH$_2$)$_2$(CH_2)$_2$CH$_3$], 0.92–0.81 [m, 3 H, -(CH$_2$)$_4$-CH_3] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 87.3, 86.5, 77.0, 76.6, 58.1, 31.2, 28.2, 22.3, 18.9, 14.1 ppm. HRMS (ESI-TOF): m/z calcd. for $C_{11}H_{15}Cl_3NO$ [M + H]$^+$ 282.0214; found 282.0219.

4-[(Triisopropylsilyl)ethynyl]-2-(trichloromethyl)oxazoline (2g): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.06 (dd, J = 9.9, 8.2 Hz, 1 H, -CHN-), 4.79 (dd, J = 9.9, 8.2 Hz, 1 H, -CH_2O-), 4.53 (t, J = 8.2 Hz, 1 H, -CH_2O-), 1.05 {s, 21 H, -Si[CH(CH$_2$)]$_3$} ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 103.6, 87.9, 86.5, 77.1, 58.6, 18.7, 11.2 ppm. GC–MS: 368 [M]$^+$.

4-(Phenylethynyl)-2-(trichloromethyl)oxazoline (2h): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.43 (m, 2 H, o-C$_6H_5$-), 7.37–7.28 (m, 3 H, p,m-C$_6H_5$-), 5.30 (dd, J = 10.0, 8.5 Hz, 1 H, -CHN-), 4.90 (dd, J = 10.0, 8.5 Hz, 1 H, -CH_2O-), 4.66 (t, J = 8.5 Hz, 1 H, -CH_2O-) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 132.0, 129.0, 128.5, 122.2, 86.4, 86.1, 85.4, 76.7, 58.5 ppm. HRMS (ESI-TOF): m/z calcd. for $C_{12}H_9Cl_3NO$ [M + H]$^+$ 287.9750; found 287.9749. Enantiomeric excess (36%) was determined by SFC analysis on chiral phase [Chiralpak IB; 4.6 × 250 mm; F = 1 mL/min, 10% IPA + 90% Hex; T = 25 °C; t_r (major) 6.9 min, t_r (minor) 11.8 min].

4-[(3-Chlorophenyl)ethynyl]-2-(trichloromethyl)oxazoline (2i): Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (dd, J = 7.4, 2.0 Hz, 1 H, -C$_6H_4$), 7.32 (dd, J = 7.9, 1.3 Hz, 1 H, -C$_6H_4$), 7.25–7.10 (m, 2 H, -C$_6H_4$), 5.27 (dd, J = 10.0, 8.5 Hz, 1 H, -CHN-), 4.85 (dd, J = 10.0, 8.5 Hz, 1 H, -CH_2O-), 4.63 (t, J = 8.5 Hz, 1 H, -CH_2O-) ppm. ^{13}C NMR: δ = 164.5, 136.4, 133.8, 130.0, 129.4, 126.6, 122.2, 90.6, 86.4, 82.8, 58.6 ppm. HRMS (ESI-TOF): m/z calcd. for $C_{12}H_7Cl_4NO$ [M + H]$^+$ 321.9355; found 321.9346. Enantiomeric excess (52–57%) was determined by SFC analysis on chiral phase [Chiralpak IB; 4.6 × 250 mm; F = 1 mL/min, 10% IPA + 90% Hex; T = 25 °C; t_r (major) 9.7 min, t_r (minor) 10.9 min].

4-[(3,5-Dichlorophenyl)ethynyl]-2-(trichloromethyl)oxazoline (2j): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 3 H, -C$_6H_3$), 5.24–5.17 (m, 1 H, -C$_6H_3$), 4.83 (dd, J = 10.1, 8.4 Hz, 1 H, -CHN-), 4.62–4.54 (m, 1 H, -CH_2O-) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 135.1, 130.2, 129.4, 124.9, 87.8, 86.2, 83.4, 76.4, 58.2 ppm. Unstable under HRMS analysis conditions. Enantiomeric excess (76–89%) was determined by SFC analysis on chiral phase [Chiralpak IB; 4.6 × 250 mm; F = 1 mL/min, 10% IPA + 90% Hex; T = 25 °C; t_r (major) 5.8 min, t_r (minor) 6.4 min].

4-(Nona-1,3-diyn-1-yl)-2-(trichloromethyl)oxazoline (2k): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.13–5.07 (m, 1 H, -CHN-), 4.79 (dd, J = 10.1, 8.4 Hz, 1 H, -CH_2O-), 4.56 (t, J = 8.4 Hz, 1 H, -CH_2O-), 2.27 [td, J = 7.1, 0.8 Hz, 2 H, -CH_2(CH$_2$)$_3$CH$_3$], 1.53 [p, J = 7.1 Hz, 2 H, -CH$_2$CH_2(CH$_2$)$_2$CH$_3$], 1.42–1.24 [m, 4 H, -(CH$_2$)$_2$(CH_2)$_2$CH$_3$], 0.89 [t, J = 7.1 Hz, 3 H, -(CH$_2$)$_4$CH_3] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 86.2, 82.7, 76.2, 71.4, 71.3, 64.5, 58.3, 31.1, 27.9, 22.3, 19.4, 14.1 ppm. GC–MS (EI): m/z 290 [M$^+$ – Me]. Unstable under HRMS analysis conditions.

4-[(Triisopropylsilyl)buta-1,3-diyn-1-yl]-2-(trichloromethyl)oxazoline (2l) Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.13 (dd, J = 10.2, 8.5 Hz, 1 H, -CHN-), 4.81 (dd, J = 10.2, 8.5 Hz, 1 H, -CH_2O-), 4.60 (t, J = 8.5 Hz, 1 H, -CH_2O-), 1.08 {s, 21 H, -Si[CH-(CH_3)$_2$]$_3$} ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 88.5, 86.0, 85.9, 75.8, 72.2, 71.2, 58.0, 18.5, 11.2 ppm. Unstable under HRMS analysis conditions.

4-(But-3-en-1-yn-1-yl)-2-(trichloromethyl)oxazoline (2m): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (ddd, J = 17.6, 10.9, 1.8 Hz, 1 H, -CH=CH$_2$), 5.70 (dd, J = 17.6, 2.3 Hz, 1 H, -CH=CH_2), 5.54 (dd, J = 10.9, 2.3 Hz, 1 H, -CH=CH_2), 5.18 (ddd, J = 10.1, 8.6, 1.8 Hz, 1 H, -CHN-), 4.83 (dd, J = 10.1, 8.6 Hz, 1 H, -CH_2O-), 4.56 (t, J = 8.6 Hz, 1 H, -CH_2O-) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 128.6, 116.4, 86.4, 86.0, 84.7, 76.6, 58.3 ppm. HRMS (ESI-TOF): m/z calcd. for $C_8H_7Cl_3NO$ [M + H]$^+$ 237.9593; found 237.9593.

General Procedure for the Synthesis of Alkynyl-Glycinols (*S*-3): Aqueous HCl (6 M, 1 mL) was added dropwise to a solution of oxazoline *S*-**2** (0.15 mmol) in MeOH (1.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h and the solvent was evaporated. Toluene (1 mL) was added to the reaction mixture and the solvents evaporated. This procedure was repeated one more time. The residue was suspended in EtOAc and filtered to give amino alcohol *S*-**3**.

2-Amino-4-(trimethylsilyl)but-3-yn-1-ol Hydrochloride (*S*-3b): White powder, yield 90%, m.p. 136–139 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 4.11 (dd, J = 8.2, 4.2 Hz, 1 H, -NCH-), 3.85 (dd, J = 11.6, 4.2 Hz, 1 H, -CH_2OH), 3.65 (dd, 1 H, -CH_2OH), 0.20 [s, 9 H, -Si(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 98.5, 94.4, 63.2, 49.6, 46.6, –0.5 ppm. HRMS (ESI-TOF): m/z calcd. for $C_7H_{16}NOSi$ [M]$^+$ 158.1001; found 158.0994. $[\alpha]_D^{20}$ = 15.6 (c = 1.0, MeOH).

2-Amino-7-(benzyloxy)hepta-3,5-diyn-1-ol Hydrochloride (*S*-3c): White powder, yield 75%, m.p. 110–114 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.39–7.27 (m, 5 H, -C$_6H_5$), 4.59 (s, 2 H, -OCH_2Ph), 4.26 (d, J = 1.8 Hz, 2 H, -CH_2OBn), 4.18 (ddt, J = 7.7, 4.0, 1.8 Hz, 1 H, -CHN-), 3.87 (dd, J = 11.6, 4.0 Hz, 1 H, -CH_2O), 3.70 (dd, J = 11.6, 7.7 Hz, 1 H, -CH_2O) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 137.3, 128.0, 127.7, 127.6, 84.0, 78.3, 71.5, 61.7, 56.5, 44.7 ppm. HRMS (ESI-TOF): m/z calcd. for $C_{12}H_{16}NO_2$ [M]$^+$ 206.1181; found 206.1175. $[\alpha]_D^{20}$ = 4.1 (c = 0.4, MeOH).

2-Amino-8-(benzyloxy)octa-3,5-diyn-1-ol Hydrochloride (*S*-3d): White powder, yield 81%, m.p. 120–124 °C. ^{1}H NMR (400 MHz,

CD_3OD): δ = 7.38–7.25 (m, 5 H, -C_6H_5), 4.54 (s, 2 H, -OCH_2Ph), 4.05 (ddt, J = 8.3, 4.1, 2.1 Hz, 1 H, -C*H*OH), 3.83 (dd, J = 11.6, 4.1 Hz, 1 H, -CH_2N-), 3.69–3.57 (m, 3 H, -CH_2CH_2OBn, -CH_2OH), 2.57 (td, J = 6.5, 2.1 Hz, 2 H, -CH_2CH_2OBn) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 137.9, 128.0, 127.5, 127.4 ppm.

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[1] G. Reginato, A. Mordini, M. Caracciolo, *J. Org. Chem.* **1997**, *62*, 6187–6192.
[2] G. T. Crisp, Y.-L. Jiang, P. J. Pullman, C. De Savi, *Tetrahedron* **1997**, *53*, 17489–17500.
[3] M. Falorni, G. Giacomelli, E. Spanu, *Tetrahedron Lett.* **1998**, *39*, 9241–9244.
[4] B. M. Trost, M. T. Rudd, *J. Am. Chem. Soc.* **2005**, *127*, 4763–4776.
[5] J. Pietruszka, A. Witt, W. Frey, *Eur. J. Org. Chem.* **2003**, 3219–3229.
[6] H. Lin, U. Kazmaier, *Eur. J. Org. Chem.* **2007**, 2839–2843.
[7] S. P. Govek, L. E. Overman, *Tetrahedron Prize Creat. Org. Chem. New React. Catal. Dev. Appl.* **2007**, *63*, 8499–8513.
[8] D. Chen, F. Brahimi, Y. Angell, Y.-C. Li, J. Moscowicz, H. U. Saragovi, K. Burgess, *ACS Chem. Biol.* **2009**, *4*, 769–781.
[9] G. Verniest, D. England, N. De Kimpe, A. Padwa, *Tetrahedron* **2010**, *66*, 1496–1502.
[10] K. Goswami, I. Duttagupta, S. Sinha, *J. Org. Chem.* **2012**, *77*, 7081–7085.
[11] P. Meffre, L. Gauzy, E. Branquet, P. Durand, F. Le Goffic, *Tetrahedron* **1996**, *52*, 11215–11238.
[12] P. Meffre, S. Hermann, P. Durand, G. Reginato, A. Riu, *Tetrahedron* **2002**, *58*, 5159–5162.
[13] D. Clark, D. A. Travis, *Bioorg. Med. Chem.* **2001**, *9*, 2857–2862.
[14] T. P. Tang, S. K. Volkman, J. A. Ellman, *J. Org. Chem.* **2001**, *66*, 8772–8778.
[15] P. A. Evans, M. J. Lawler, *Angew. Chem. Int. Ed.* **2006**, *45*, 4970–4972; *Angew. Chem.* **2006**, *118*, 5092–5094.
[16] A. G. H. Wee, B. Zhang, *Tetrahedron Lett.* **2007**, *48*, 4135–4138.
[17] B.-L. Chen, B. Wang, G.-Q. Lin, *J. Org. Chem.* **2010**, *75*, 941–944.
[18] Q. Liang, J. K. De Brabander, *Strateg. Synth. Tetrahydropyran-Contain. Nat. Prod.* **2011**, *67*, 5046–5053.
[19] R. D. Grigg, J. W. Rigoli, S. D. Pearce, J. M. Schomaker, *Org. Lett.* **2012**, *14*, 280–283.
[20] H. D. Dickson, S. C. Smith, K. W. Hinkle, *Tetrahedron Lett.* **2004**, *45*, 5597–5599.
[21] A. Temperini, A. Capperucci, A. Degl'Innocenti, R. Terlizzi, M. Tiecco, *Tetrahedron Lett.* **2010**, *51*, 4121–4124.
[22] L. Grigorjeva, A. Jirgensons, *Eur. J. Org. Chem.* **2011**, 2421–2425.
[23] L. Grigorjeva, A. Maleckis, K. Klimovica, M. Skvorcova, N. Ivdra, G. Leitis, A. Jirgensons, *Chem. Heterocycl. Compd.* **2012**, *48*, 919–924.
[24] A. Jirgensons, L. Grigorjeva, A. Maleckis, K. Klimovica, *Synlett* **2013**, *24*, 2345–2349.
[25] K. Klimovica, L. Grigorjeva, A. Maleckis, J. Popelis, A. Jirgensons, *Synlett* **2011**, *22*, 2849–2851.
[26] L. Grigorjeva, A. Kinens, A. Jirgensons, *J. Org. Chem.* **2015**, *80*, 920–927.
[27] V. Kumar, K. Klimovica, D. Rasina, A. Jirgensons, *J. Org. Chem.* **2015**, *80*, 5934–5943.
[28] J. Waser, B. Gaspar, H. Nambu, E. M. Carreira, *J. Am. Chem. Soc.* **2006**, *128*, 11693–11712.
[29] K. Matsumura, S. Hashigushi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.
[30] F. Kleibeck, G. J. Fettes, L. D. Fader, E. M. Carreira, *Chem. Eur. J.* **2012**, *18*, 3598–3610.
[31] F. Feire, J. M. Seco, E. Quinoa, R. Riguera, *Chem. Eur. J.* **2005**, *11*, 5509–5522.
[32] K. Harada, Y. Shimizu, K. Fujii, *Tetrahedron Lett.* **1998**, *39*, 6245–6248.
[33] K. J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285–288; *Angew. Chem.* **1997**, *109*, 297–300.
[34] J. A. Lafontaine, D. P. Provencal, C. Gardelli, J. W. Leahy, *J. Org. Chem.* **2003**, *68*, 4215–4234.
[35] A. N. Roehrle, H. Schmidhammer, *Helv. Chim. Acta* **1998**, *81*, 1070–1076.
[36] M. Yaseen, A. Mosa, I. Fuyuhiko, T. Ryohei, M. Chisato, *Tetrahedron* **2011**, *67*, 5133–5141.
[37] X. Z. Shu, X. Li, D. Shu, S. Huang, C. M. Schienebeck, X. Zhou, P. J. Robichaux, W. Tang, *J. Am. Chem. Soc.* **2012**, *134*, 5211–5221.
[38] E. M. Carreira, C. A. Hastings, M. S. Shepard, L. A. Yerkey, D. B. Millward, *J. Am. Chem. Soc.* **1994**, *116*, 6622–6630.
[39] O. S. Ascenso, J. C. Marques, A. R. Santos, K. B. Xavier, M. R. Ventura, C. D. Maycock, *Bioorg. Med. Chem.* **2011**, *19*, 1236–1241.
[40] K. C. Nicolaou, V. A. Adsool, C. R. H. Hale, *Org. Lett.* **2010**, *12*, 1552–1555.
[41] X. Tang, S. Woodward, N. Krause, *Eur. J. Org. Chem.* **2009**, 2836–2844.

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Microreview

Unnatural Amino Acids

Synthesis of α-Ethynyl Glycines

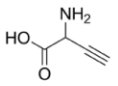
Jekaterina Bolsakova[a] and Aigars Jirgensons*[a]

Abstract: α-Ethynyl glycine derivatives have a high potential for functionalization by derivatization of the amino acid or acetylene moiety, and, as a result, are important intermediates in the construction of biologically active compounds, including natural products. The main methods for the synthesis of ethynyl glycines and glycinols can be divided into six different transformations: (a) homologations of serinal derivatives, (b) nucleophilic alkynylations of α-imino esters/alcohols or their precursors α-halo glycinates, (c) derivatizations of alkynyl imino esters, (d) electrophilic alkynylations of α-nitro esters and azlactones by using hypervalent iodine reagents, (e) intra- and intermolecular aminolysis reactions of epoxides, and (f) propargylic aminations through the cyclization of bis(imidate). This microreview summarizes the methods that were published from 1996 to 2015.

Introduction

The simplest α-ethynyl glycine, 2-aminobut-3-ynoic acid (**1**, FR-900130), was isolated in 1980 from *Streptomyces catenulae* and was shown to exhibit antimicrobial activity against *Streptomyces aureus* strains (Figure 1).[1–3] It has been proposed that amino acid **1** covalently binds to bacterial alanine racemase after the formation of its imine conjugate with pyridoxal phosphate (PLP) cofactor. Several other alkynyl glycines are also known as mechanism-based inhibitors of PLP-dependent enzymes, including ornithine decarboxylase[4] and L-amino acid decarboxylase.[5]

In addition to the biological activity of α-ethynyl glycines, their derivatives are versatile building blocks for biologically active compounds as exemplified by the syntheses of β-erythroidine (**2**),[6] fluoromethyl thalidomide **3**,[7,8] tumor necrosis factor-alpha converting enzyme (TACE) inhibitors **4**,[9] and (+)-lactacystin (**5**)[10] from key intermediates **6**–**9**, respectively (Figure 2). The potential for alkynyl group derivatization in α-ethynyl glycines has also been demonstrated in the construction of diverse five-membered heterocycles such as 1,2,3-triazoles,[11,12] oxazoles,[13] isoxazoles,[14] dehydroprolines,[15] and benzoprolines.[16]



1 (FR-900130)

Figure 1. α-Ethynyl glycine (**1**).

This wide range of applications has enabled the development of methods for the syntheses of α-ethynyl glycines and their synthetically equivalent ethynyl glycinols (Figure 3). These approaches can be divided into six different transformations:

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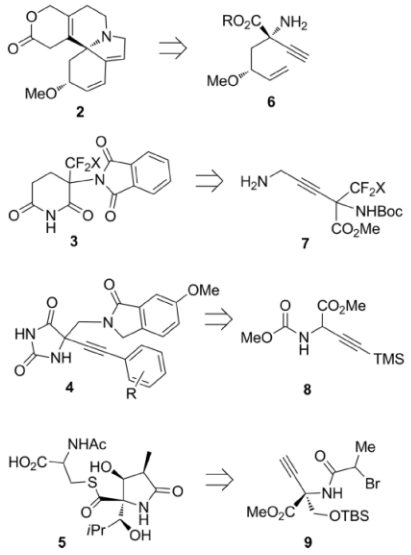


Figure 2. Examples of biologically active compounds prepared from α-ethynyl glycine derivatives (Boc = *tert*-butyloxycarbonyl, TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl).

(a) homologations of serinal derivatives **10** and **11**, (b) nucleophilic alkynylations of α-imino esters/alcohols **12** or their precursors α-halo glycinates **13**, (c) derivatizations of alkynyl imino esters **14**, (d) electrophilic alkynylations of α-nitro esters **15** and azlactones **16** by using hypervalent iodine reagents, (e) intra- and intermolecular aminolysis reactions of epoxides **17** and **18**, and (f) propargylic aminations through the cyclization of bis(imidate) **19**.

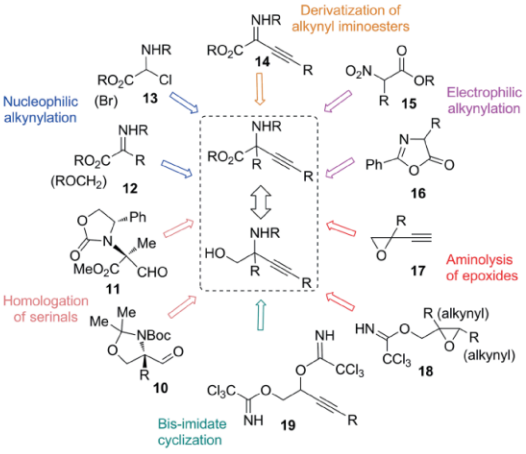


Figure 3. General synthetic approaches toward α-ethynyl glycines.

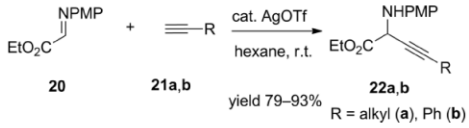
Several minireviews have been published that focus on the syntheses and applications of serinals **10** as alkynyl glycinol building blocks.[17,18] The last comprehensive review of synthetic approaches to alkynyl glycines and glycinols was published in 1996 by Meffre and Goffic.[19] Since then, a number of new methods have been developed, which was the impetus for us to summarize them in a review article. Herein, we provide an overview of the methods for the syntheses of α-ethynyl glycines and glycinols in racemic and enantioenriched form that were reported from 1996 to 2015. Previously reviewed methods regarding serinals **10**, however, have been excluded.

1. Alkyne Addition to Imines

1.1. Addition to *N*-Aryl and *N*-Acyl Imines

The addition of terminal alkynes to α-imino esters is a straightforward approach for the synthesis of racemic and optically active α-alkynyl glycine derivatives.[20] Because of the low stability of most α-imino esters, however, their synthesis, purification, and handling can be difficult.[21] For this reason, relatively stable *N*-*para*-methoxyphenyl-substituted (*N*-PMP-substituted) imino esters are often used as substrates for the addition reactions of alkynes. The PMP group in the product can then be cleaved by treatment with cerium ammonium nitrate (CAN).

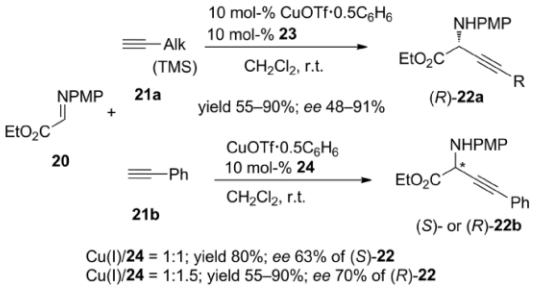
Chan's group developed the addition of alkyl acetylenes **21a** and phenylacetylene **21b** to *N*-PMP-substituted ethyl glyoxylate imine (**20**) under Ag^I (10 mol-%, Scheme 1) catalysis.[22] Among the examined catalysts, AgOTf (OTf = trifluoromethanesulfonate), $AgNO_3$, $AgPF_6$, and $AgClO_4$ showed acceptable activity, whereas AgOAc was less effective. With AgOTf as the catalyst and hexane as the solvent at room temperature, five examples of α-alkynyl glycine derivatives **22** were prepared in good to excellent yields. McNulty et al. observed that prolonged exposure of alkynyl glycine **22b** to the AgOTf catalyst led to the formation of the quinoline-2-carboxylic acid derivative. This renders Ag-mediated tandem imine alkynylation/annulation as a useful method for the construction of quinolines.[23]

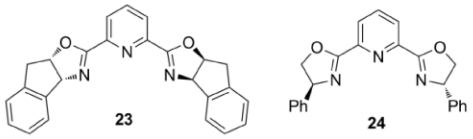


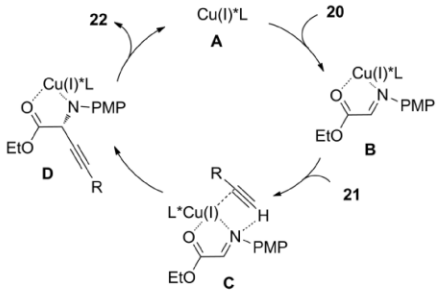
Scheme 1. AgOTf-catalyzed alkynylation of *N*-PMP-substituted ethyl glyoxylate imine (**20**).

Enantioselective alkynylations of glyoxylate imines can be problematic because of the racemization of the product under basic conditions. Chan's group was the first to demonstrate the asymmetric addition of alkynes to glyoxylate imine **20** by using a nonbasic catalytic system that consisted of $CuOTf{\cdot}0.5C_6H_6$ and chiral bis(oxazoline)-pyridine (PyBOX) ligands **23** and **24** (Scheme 2).[24–26] This procedure allowed for the synthesis of enantioenriched amino acid derivatives **22** in high yields with high enantiomeric excess values. The lowest yield (55 %) and enantioselectivity (48 % *ee*) was obtained by using trimethylsilylacetylene **21a** (R = TMS). However, the addition of phenylacetylene was less enantioselective than that of the alkyl acetylenes.[25] PyBOX **23** was the best ligand for the addition of alkylacetylenes **21a**, whereas PyBOX **24** was best for that of

phenylacetylene **21b**. Interestingly, for the addition of phenylacetylene **21b**, a change of the Cu catalyst/ligand **24** ratio from 1:1 to 1:1.5 reversed the enantioselectivity to lead to the opposite enantiomer (*R*)-**22b** as the major product.[25] The proposed reaction mechanism involves complexation of imine ester **20** and alkyne **21** to the Cu^{I}–PyBOX catalyst **A** (Scheme 2, to form intermediates **B** and **C**). The imine group of the ester activates the alkyne to act as a base for proton transfer. The protonated imine becomes more electrophilic, which facilitates the addition of the alkyne to the C=N bond and leads to complex **D**, which releases product **22** and copper–ligand complex **A**.[24]

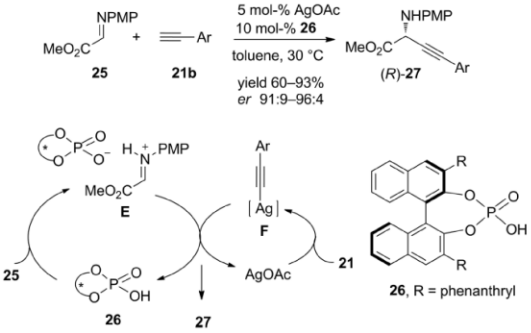






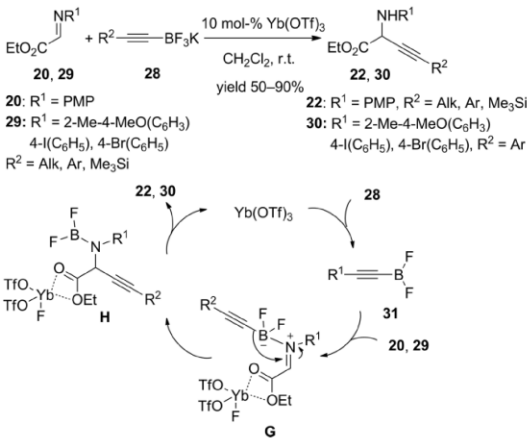
Scheme 2. Cu^{I}–PyBOX complex catalyzed alkynylation of glyoxylate imine **20**.

Rueping's group reported a procedure for the enantioselective addition of aryl alkynes **21b** to methyl glyoxylate imine **25** by using the catalytic system that consisted of AgOAc and chiral 1,1′-bi-2-naphthol (BINOL) derived phosphoric acid **26** (Scheme 3).[27] Catalyst screenings revealed phenanthryl-substituted phosphoric acid **26** as the optimal cocatalyst to lead to the formation of (*R*)-**27** in good yields high enantioselectivity. According to the proposed mechanism, chiral phosphoric acid **26** activates imine **25** to form chiral ion pair **E**. In a concurrent catalytic cycle, AgOAc activates alkyne **21** to form silver acetylide **F**, which then undergoes a reaction with complex **E** to give product **27** (Scheme 3).



Scheme 3. AgOAc/chiral phosphoric acid catalyzed enantioselective alkynylation of glyoxylate imine **25**.

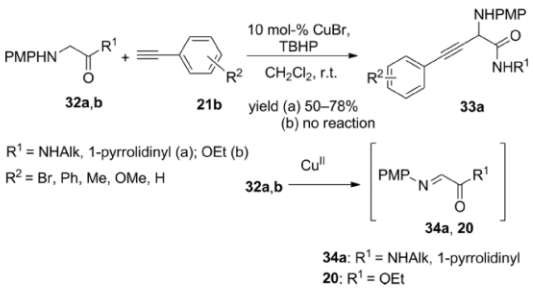
Stefani et al. have shown that more reactive potassium alkynyltrifluoroborate salts **28** can be used, instead of terminal alkynes, in the addition reaction to glyoxylate imines **20** and **29** to give α-alkynyl glycine derivatives **22** and **30** (Scheme 4).[28] The reaction requires $Yb(OTf)_3$ as the Lewis acid catalyst, which was superior among the catalysts that were screened. There was also a broad scope of substrates that could be employed with alkynyl borates **28**. Besides *N*-PMP imines **20**, some *N*-aryl-imines **29** were used as substrates. For a reaction mechanism, the authors proposed that $Yb(OTf)_3$ acts as a defluorinating agent. $Yb(OTf)_3$ converts alkynyltrifluoroborate **28** into the more electrophilic alkynyldifluoroborate **31**, which coordinates to imine **20** or **29** to form nitrogen–boron complex **G**. The migration of the alkynyl group of **G** leads to the formation of the C–C bond. Dissociation of resulting complex **H** releases the corresponding product and the catalyst to initiate the next reaction cycle (Scheme 4).



Scheme 4. $Yb(OTf)_3$-catalyzed addition of potassium alkynyltrifluoroborates to glyoxylate imines **20** and **29**.

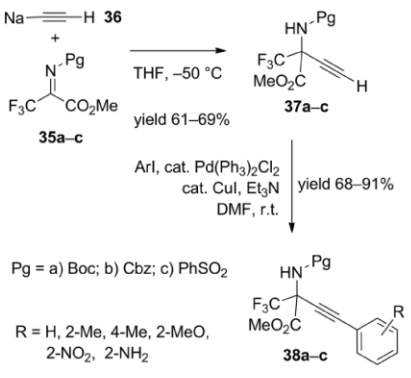
Li's group reported synthesis of α-alkynyl glycines **33a** by the C–H bond functionalization of *N*-PMP-protected glycine amides **32a** using a cross-dehydrogenative coupling reaction with aromatic alkynes (Scheme 5).[29] In this case, the reaction

conditions involved CuBr as the catalyst and *tert*-butyl hydroperoxide (TBHP) as an oxidant. According to the proposed mechanism, Cu^{I} has a dual role in this reaction. It is involved in the oxidation of amine **32** to give the corresponding imine **34** and the formation of the copper acetylide nucleophile from alkyne **21b**. Notably, only glycine amides **32a** were suitable substrates for this transformation, whereas glycine ester **32b** gave a complex mixture of products. The higher oxidation potential of ester **32b** compared with amides **32a** and the lower stability of imine intermediates **20** formed from the ester may be an explanation. Only aryl-substituted acetylenes **21b**, which were used in threefold excess amounts, were reported as the alkyne components.



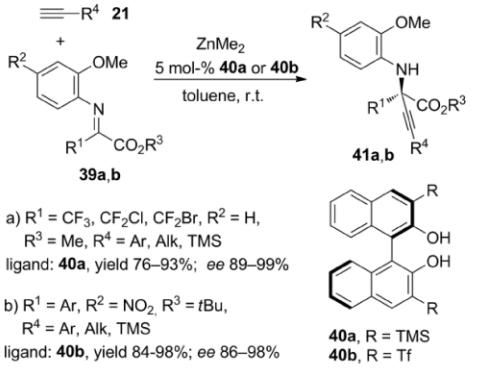
Scheme 5. Functionalization of glycine amides by cross-dehydrogenative coupling with aromatic alkynes.

In general, ketimino esters are much less reactive than aldimine esters towards the addition of alkynes. However, ketimines that are derived from fluoropyruvates are considered activated substrates. Osipov's group reported the synthesis of racemic α-ethynyl trifluoroalanine esters **37** by using the addition of sodium acetylide **36** to *N*-protected imines **35**, which were derived from α-trifluoropyruvate (Scheme 6).[30] The best yield (67 %) was obtained from *N*-Cbz-protected (Cbz = carbobenzyloxy) imine **35b**. The protected α-ethynyl trifluoroalanine esters **37** were then subjected to Sonogashira coupling reactions with a range of iodobenzenes to give derivatives **38**.



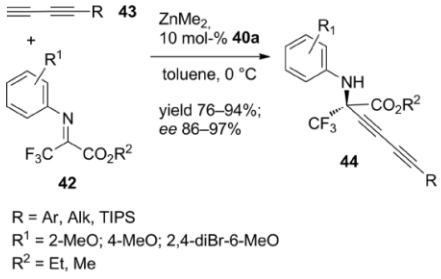
Scheme 6. Addition of sodium acetylide to trifluoropyruvate imines **35a**–**35c** (Pg = protecting group, THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide).

Zhang's group reported the first enantioselective BINOL (**40**) catalyzed alkynylations of α-fluoroalkyl ketimine esters **39a**, which were promoted by a stoichiometric amount of $ZnMe_2$, to give amino acid esters **41** (Scheme 7).[31] Less reactive α-phenyl ketimine esters **39b** could also successfully undergo the enantioselective alkynylation when a nitro group was introduced as an aryl substituent to enhance the electrophilicity.[32] For this substrate, the enantioselectivity considerably improved when the substrate contained a *tert*-butyl ester group. Notably, substituents at the 3,3′-positions of BINOL catalyst **40** had a crucial effect on the enantioselectivity of the reaction. The best ligand for the enantioselective addition of the alkyne to fluorinated substrates **39a** was trimethylsilyl (TMS)-substituted BINOL **40a**, whereas for aryl imino esters **39b**, it was trifluoromethanesulfonyl (Tf)-substituted BINOL **40b**.



Scheme 7. Zn/substituted BINOL catalyzed acetylene addition to ketimine esters **39a** and **39b**.

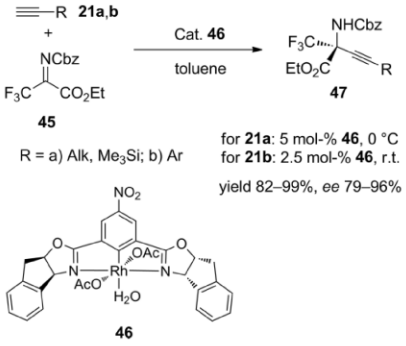
A slight modification to the reaction conditions along with an increased loading of both $ZnMe_2$ (2 equiv.) and ligand **40a** (10 mol-%) was then used for the highly enantioselective addition of diynes **43** to trifluoroalkyl imine esters **42** (Scheme 8).[33]



Scheme 8. Zn/substituted BINOL catalyzed diyne addition to ketimine esters **42** (TIPS = triisopropylsilyl).

Ohshima's group developed an enantioselective procedure for the synthesis of α-alkynyl glycine derivatives **47**, which avoids the use of stoichiometric amounts of organometallic reagents. The addition of terminal alkynes **21** to trifluoropyruvate imine **45** was achieved by using rhodium–bis(oxazolinyl)phenyl (Rh–PheBOX) catalyst complex **46** (Scheme 9).[8] For addition of

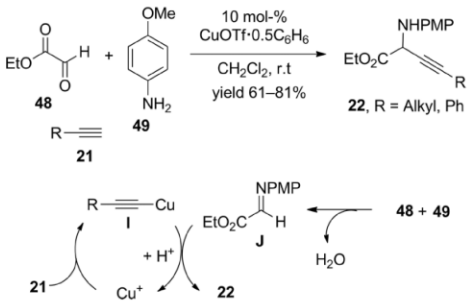
alkyl- and silyl-substituted acetylenes **21a**, the loadings of the catalyst and alkyne components were increased twofold relative to those for reaction with aryl-substituted acetylene **21b** to afford product **47** with high enantioselectivity. Moreover, for alkyl-substituted acetylene **21a**, premixing the Rh–PheBOX catalyst with the alkyne component at 30 °C followed by the addition of imine **45** at 0 °C was very important to achieve high enantioselectivity. A reason for this may be that a higher temperature was needed to form the catalytically active Rh–acetylide complex, whereas a lower temperature was required for the enantioselective addition step.



Scheme 9. Rh–PheBOX catalyzed addition of alkynes to pyruvate imine **45**.

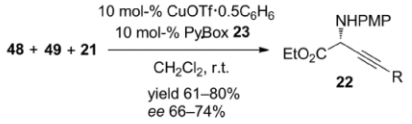
1.2. Three-Component Coupling Reaction of Aldehyde, Amine, and Alkyne

Chan's group was the first to describe the synthesis of protected alkynyl amino acids by employing the copper(I)-catalyzed three-component reaction of ethyl glyoxylate (**48**), *p*-anisidine (**49**), and terminal alkynes **21** (Scheme 10).[34] Both alkyl-substituted alkynes and phenylacetylene were suitable reagents to provide products **22** in good yields. For the reaction mechanism, the authors proposed that the copper(I) catalyst activates the C–H bond of terminal alkyne **21** to form the corresponding copper acetylide **I**. The further reaction of **I** with α-imino esters **J**, which are generated in situ from ethyl glyoxylate (**48**) and *p*-anisidine (**49**), then release **22** and the copper(I) catalyst (Scheme 10).



Scheme 10. Copper(I)-catalyzed three-component coupling reaction of ethyl glyoxylate (**48**), *p*-anisidine (**49**), and terminal alkynes **21**.

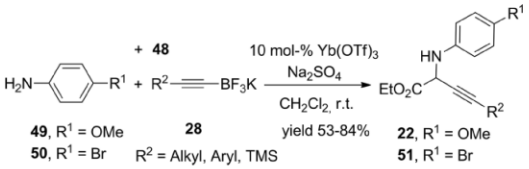
The same group also reported an enantioselective version of the above reaction by using PyBOX ligand **23** and a copper(I) triflate-benzene complex as the catalyst (Scheme 11).[35] The enantioselectivity of this reaction was similar for both alkyl- and phenyl-substituted alkynes **21**.



Scheme 11. Copper(I)/PyBOX complex catalyzed enantioselective three-component reaction.

Singh's group investigated the use of several PyBOX **23** analogues in the three-component reaction of ethyl glyoxylate (**48**), *p*-anisidine (**49**), and terminal alkynes **21**.[36] High yields of the product **22** were achieved, but the *ee* values did not exceed 56 %.

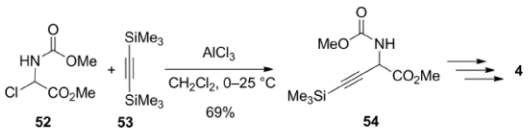
Stefani et al. reported the $Yb(OTf)_3$-catalyzed three-component reaction of alkynyltrifluoroborate salts **28** with ethyl glyoxylate (**48**), and either aniline **49** or **50** to give protected alkynyl amino acids **22** and **51**, respectively (Scheme 12).[37] Both alkyl- and aryl-substituted alkynyltrifluoroborates were suitable components in the reaction.



Scheme 12. $Yb(OTf)_3$-catalyzed coupling of alkynyl trifluoroborates with ester **48** and anilines **49** and **50**.

1.3. Addition to α-Halo Glycinates

Early approaches to the synthesis of racemic alkynyl amino acids were carried out by coupling α-halo glycinate **52** either with bis(trimethylsilyl)acetylene (**53**) and promoted by $AlCl_3$ (Scheme 13),[38] with alkynyl tin reagents in the presence of $ZnCl_2$,[39] or with alkynyl Grignard reagents.[40] These methods have been previously reviewed.[19]



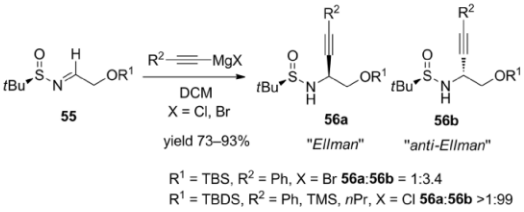
Scheme 13. Addition of bis(trimethylsilyl)acetylene to α-chloro glycinate **52**.

A recent application of α-chloro glycinate **52** alkynylation involved the synthesis of TACE inhibitor **4**, which was reported by Girijavallabhan et al., and includes $AlCl_3$-promoted coupling of compound **52** with bis(trimethylsilyl)acetylene **53** to give key intermediate **54** (Scheme 13).[9] Ren et al. used the same condi-

tions to prepare ^{13}C- and ^{15}N-labeled intermediate **54** for the synthesis of a labeled analogue of another TACE inhibitor.[41]

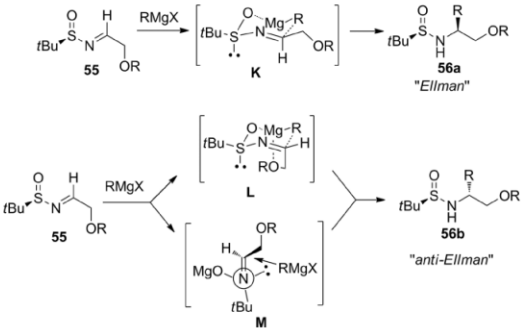
1.4. Addition to *N*-Sulfinylimines

Barrow et al. showed the first example of the diastereoselective addition of phenylacetylene to an *N*-*tert*-butylsulfinyl aldimine **55** to obtain the *N*-sulfinyl-protected ethynyl glycinol derivative **56a** and **56b** in high yield but with moderate diastereoselectivity (Scheme 14).[42] Later, Wang's group developed an improved version of this reaction by changing the hydroxyl protecting group of sulfinimine **55** to the *tert*-butyldiphenylsilyl (TBDS) group and using alkynylmagnesium chloride instead of the bromide.[43] These modifications resulted in almost exclusive formation of *anti*-Ellman diastereomer **56b** (*dr* >1:99) in the addition reactions of Grignard reagents derived from phenyl-, TMS-, and *n*-propylacetylene to sulfinimine **55**. Importantly, the chiral auxiliary in addition products **56** can be conveniently removed under mild acidic conditions.



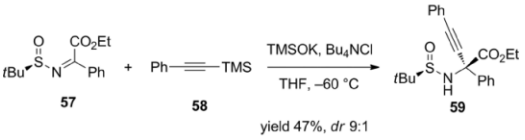
Scheme 14. Addition of alkynyl Grignard reagents to *N*-*tert*-butylsulfinyl aldimines **55** (DCM = dichloromethane).

According to the stereoinduction model that was proposed by Ellman, the addition of Grignard reagents to *N*-sulfinyl aldimines proceeds through chair-like transition state **K**, which results from the coordination of imine (*E*)-**55** with the organometallic reagent, to lead to diastereomer **56a** (Scheme 15). When sulfinyl imine **55** contains a protected hydroxyl group, the selectivity is reversed. To explain, Barrow et al. proposed the formation of bicyclic-chelated transition state **L**, which involves the coordination of the imine (*Z*)-**55** and the additional coordination of the oxy group with the magnesium atom of the incoming nucleophile. Alternatively, *anti*-Ellman selectivity can be explained by open transition state **M**, which was proposed by Davis. In this case, the six-membered transition state is hindered by the chelation of the magnesium atom of the Grignard reagent to the sufinyl group, which results in an acyclic transition state and the addition of another organomagnesium molecule.



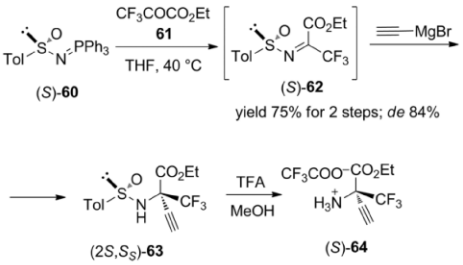
Scheme 15. Stereoinduction models for Grignard addition to sulfinyl aldimines.

O'Shea's group reported one example of the alkynylation of *N*-*tert*-butylsulfinimine ester **57** with alkynylsilane **58** by employing the $TMSO^-/Bu_4N^+$ system as the Lewis base activator (Scheme 16).[44] As a result, α-alkynyl glycine derivative **59** was produced in moderate yield and good diastereoselectvity.



Scheme 16. Addition of alkynylsilane **58** to *N*-*tert*-butylsulfinimine ester **57**.

Zanda's group performed the synthesis of enantiomerically pure α-ethynyl trifluoroalanine ester (*S*)-**64** by using the stereoselective addition of ethynylmagnesium bromide to *N*-tolylsulfinimine ester **62** (Scheme 17).[45] Sulfinimine (*S*)-**62** was prepared by a Staudinger (aza-Wittig) reaction of ethyl 3,3,3-trifluoropyruvate (**61**) with iminophosphorane (*S*)-**60** and then used, without isolation, in the alkynylation. The reaction proceeded with good diastereoselectivity and overall yield. After purification, major diastereomer (2*S*,S_S)-**63** was obtained with a diastereomeric excess value of 97.5 %. The cleavage of the *p*-toluenesulfinyl group from (*S*,S_S)-**63** was successfully accomplished by treatment with TFA/MeOH to give α-ethynyl trifluoroalanine ethyl ester **64**.

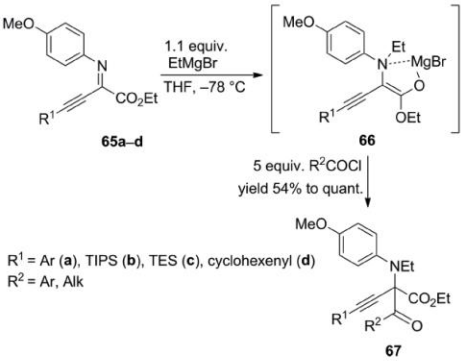


Scheme 17. Synthesis of α-ethynyl trifluoroalanine through the stereoselective ethynylation of *N*-tolylsulfinimine (Tol = *p*-tolyl, TFA = trifluoroacetic acid).

2. Derivatization of Alkynyl Imino Esters

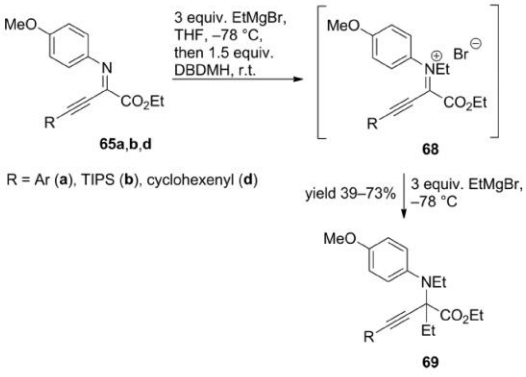
Shimizu et al. developed a tandem reaction that involves an umpolung of imino esters **65a–d** by the addition of the Grignard reagent to the nitrogen atom followed by an α-acylation of intermediate **66** (Scheme 18).[46] The one-pot procedure provided quaternary α-ethynyl glycine derivatives **67** in moderate to good yields. Sterically hindered pivaloyl or isobutyryl chloride either gave very low yields or failed to react. It was also

observed that **67** was unstable under the reaction conditions. However, by decreasing the reaction time, the yield of **67** considerably improved.



Scheme 18. Tandem *N*-alkylation and α-acylation of alkynyl imino esters **65a–d** (TES = triethylsilyl).

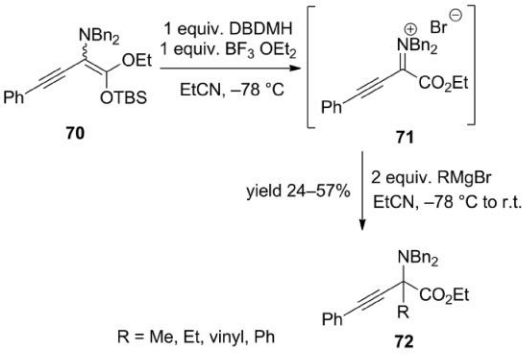
When *N*-alkylation intermediate **66** was oxidized with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), iminium ion **68** was generated in situ (Scheme 19). This intermediate was then treated with EtMgBr to give products **69** in moderate yields.



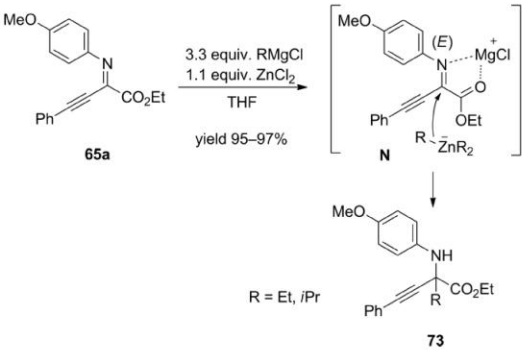
Scheme 19. Tandem *N*-alkylation, oxidation, and α-alkylation of β,γ-alkynyl α-imino esters **65a**,**b**,**d**.

The same group reported a related approach for the in situ generation of iminium salt **71** by oxidation of amino silyl ketene acetal **70** with DBDMH. This was followed by treatment with Grignard reagents to give *C*-quaternary ethynyl glycine derivatives **72** in low to moderate yields (Scheme 20).[47]

Ishihara's group developed a synthesis for alkynyl glycines **73** by using a highly regio- and diastereoselective alkyl addition to the carbon atom of the imino group in ester **65a** (Scheme 21). The addition reaction was achieved by using a zinc(II)ate complex ($[R_3Zn]^-[MgX]^+[\{MgX_2\}_2]$), which was prepared in situ from a Grignard reagent (RMgX) and $ZnCl_2$.[48] It was proposed that the Lewis acidic $[MgX]^+$ ion activates the carbon atom of the imino group by *N*- and *O*-chelation of the (*E*) isomer (complex **N**, Scheme 21) to promote attack by the



Scheme 20. Tandem oxidation/α-alkylation of amino silyl ketene acetal **70**.



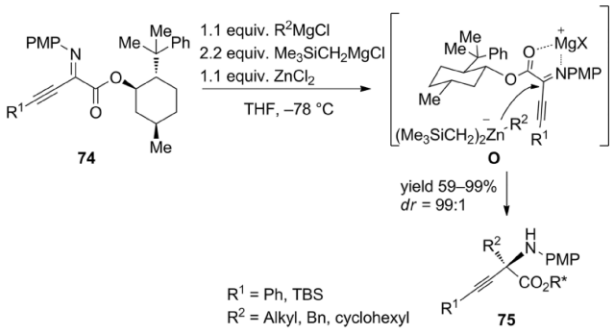
Scheme 21. *C*-Selective addition of zinc(II)ate reagents to alkynyl imino esters **65a**.

nucleophilic zinc(II)ate $[R_3Zn]^-$. These conditions were also successfully used in the case of the less reactive *i*PrMgCl Grignard reagent.

The diastereoselective addition of zincate reagents to chiral 8-phenylmenthyl esters **74** was also developed (Scheme 22). However, for this type of substrate, the regioselectivity of the addition decreased significantly to lead to *N*-alkylation products along with the desired product **75**. To suppress the *N*-alkylation, a more reactive mixed zinc(II)ate complex ($[R(Me_3SiCH_2)_2Zn]^-[MgX]^+[\{MgX_2\}_2]$) was used. In some cases, the use of LiCl as an additive or the use of Me_3SiCH_2Li, instead of the Grignard reagent, improved the reactivity and regioselectivity of the reaction. These modified procedures made it possible to obtain **75** in good yield and high diastereoselectivity.

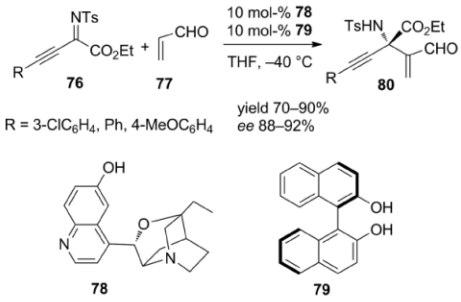
In proposed stereoinduction model **O**, the bulky 8-phenylmenthyl group shields the *re* face of imino group to direct attack of the nucleophilic $[R_3Zn]^-$ moiety exclusively from the *si* face (Scheme 22).

Chen's group has reported synthesis of three alkynyl glycine derivatives **80** by employing an enantioselective aza-Morita–Baylis–Hillman reaction of *N*-tosyl alkynyl imino esters **76** with



Scheme 22. Diastereoselective zinc(II)ate addition to chiral imines **74**.

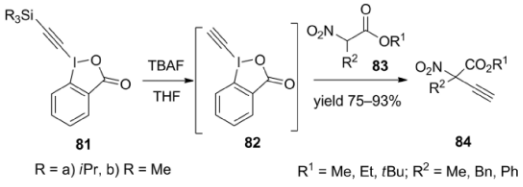
acrolein (**77**, Scheme 23).[49] Good yields and high chiral induction was achieved by using a combined catalytic system that consisted of β-isocupreidine (**78**) and (*R*)-BINOL (**79**).



Scheme 23. Enantioselective aza-Morita–Baylis–Hillman reaction of alkynyl imino esters **76** with acrolein (Ts = *para*-toluenesulfonyl).

3. Alkynyl Iodonium Salt Mediated Alkynylation

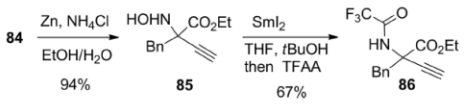
Waser's group reported the first electrophilic alkynylation of α-nitro esters **83** by using the hypervalent iodine reagent TMS-ethynyl-1,2-benziodoxol-3(1*H*)-one (**81b**) to give nitro esters **84** (Scheme 24).[50] For the alkynylation reaction, tetra-*n*-butylammonium fluoride (TBAF) was used both as a base for the enolate formation and as a desilylating agent for the generation of reagent **82**. A control experiment showed that desilylation does not occur at the product stage, which led the authors to



Scheme 24. Alkynylation of α-nitro esters **83** with ethynyl benziodoxolone **81**.

propose that reagent **82** is involved in the ethynylation reaction.

α-Nitro ester **84** (R^1 = Et, R^2 = Bn) was converted into the corresponding α-ethynyl α-amino acid derivative **86** by employing a two-step sequence (Scheme 25). First, the reduction of **84** by using Zn dust afforded hydroxylamine **85**. Forcing this reaction to obtain the amine resulted in the concomitant reduction of the triple bond. However, a selective reduction could be performed by using SmI_2 in a THF/*t*BuOH solution. The acylation of the amino group provided derivative **86**.

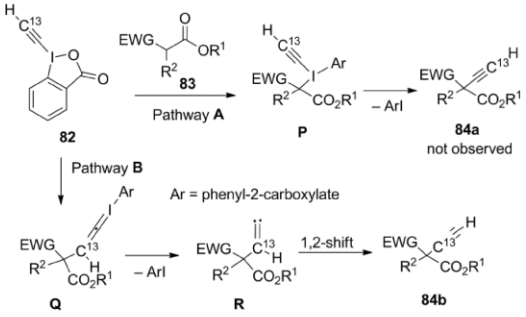


Scheme 25. Reduction of propargylic nitro ester **84** to give α-amino acid derivative **86** (TFAA = trifluoroacetic anhydride).

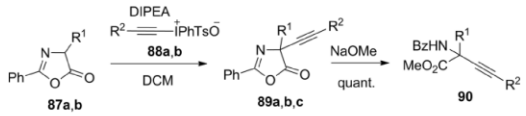
The reaction mechanism of the alkynylation was investigated by using ^{13}C-labeled hypervalent iodonium reagent **82** to discriminate between two possible reaction pathways (Scheme 26). Pathway A involves the addition of the enolate of ester **83** to the iodine atom in reagent **82**. The resulting intermediate **P** then undergoes a reductive elimination to produce ^{13}C-labeled **84a**. The authors, however, did not observe the formation of this product, and ^{13}C-labeled **84b** was detected instead. The formation of such a product can be explained by Pathway B, which involves the conjugate addition of the enolate to the alkyne to form intermediate **Q**. Elimination of the aryl iodide gives carbene **R**, which undergoes a 1,2-hydride shift to lead to product **84b**.

Nachtsheim et al. developed the efficient alkynylation of azlactones **87a**,**b** by using phenyl iodonium salt **88a**,**b** as an electrophilic alkyne source (Scheme 27).[51] The resulting alkynylation product **89a**–**c** can then be readily converted into *C*-quaternary amino acid derivatives **90** through a methanolysis of the azlactone ring.

During the reaction mechanism, the authors propose the formation of vinylidene carbene intermediate **S** followed by a [1,2]-migration to give product **89b**–**d** (Scheme 28, Pathway A). Products **92** and **93**, which were generated from a [1,5]-insertion of carbene into the C–H bond of the side chain, were also



Scheme 26. Proposed mechanism of alkynylation with ethynyl benziodoxolone **82** (EWG = electron-withdrawing group).



87a: R^1 = Alk, CH_2Ar **88a**: R^2 = TMS
87b: R^1 = *i*Bu **88b**: R^2 = Ph

89a: R^1 = Alk, Ar R^2 = TMS; yield 60–94%
89b: R^1 = *i*Bu, R^2 = Ph; yield 84%
89c: R^1 = *i*Bu, R^2 = TMS; yield 96%

Scheme 27. Alkynylation of azlactones **87a,b** with alkynyl iodonium salt **88a,b** (DIPEA = *N*,*N*-diisopropylethylamine).

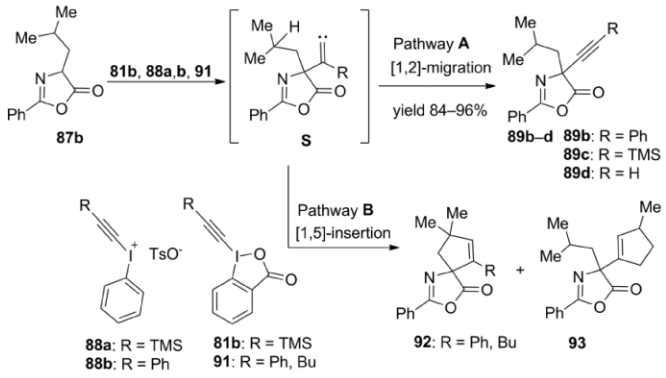
observed (Scheme 28, Pathway B). The chemoselectivity of the reaction was dependent on the hypervalent iodane reagent that was employed. TMS-ethynyl-substituted iodane **88a** (R = TMS) gave the best results and exclusively formed [1,2]-migration products **89c** in up to 96 % yield. Interestingly, TMS-ethynyl-1,2-benziodoxol-3(1*H*)-one (**81b**) formed desilylated product **89d** (R = H) in 85 % yield. Phenylacetylene-containing iodanes **88b** and **91** preferably formed the desired product **89b** (R = Ph). In contrast, 1-hexyne-substituted iodinane **91** (R = Bu) gave a mixture of [1,5]-insertion products.

An additional example of the alkynylation of azlactone **87** (R^1 = Bn, Scheme 27) with benziodoxolone **81b** was reported by Kamlar et al.[52] Under the optimized reaction conditions (20 mol-% triethylamine as the base and chloroform as the solvent), desilylated alkynylation product **89** (R^1 = Bn, R^2 = H, Scheme 27) was obtained in 85 % yield.

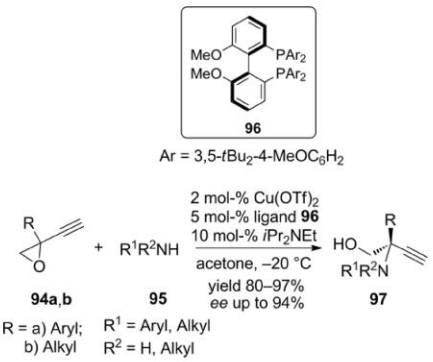
4. Ring-Opening Reaction of Ethynyl Epoxides

Nishibayashi's group reported the enantioselective copper-ligand complex catalyzed ring-opening of racemic ethynyl epoxides **94** with amines **95** to give ethynyl amino alcohols **97** (Scheme 29).[53] Product **97** was obtained in high enantiomeric excess from model substrates **94a** and **95** (R^1 = Ph, R^2 = H) by using several axially chiral biphenyldiphosphine ligands. Among these ligands, (*R*)-DTBM-MeO-BIPHEP **96** (DTBM = 3,5-di-*tert*-butyl-4-methoxyphenyl, BIPHEP = biphenylphosphine) was used to explore the scope of substrates for the reaction. The enantioselectivity markedly depended on the substituents of epoxide **94** and amine **95**. Anilines **95** afforded moderate to high enantioselectivities (57–94 % *ee*) in reactions with epoxide **94a**. The best results were obtained by amines **95** that contained electron-withdrawing groups such as 4-trifluoromethylaniline and 4-methoxycarbonylaniline (93–94 % *ee*). In the case of primary aliphatic amines **95** such as *tert*-butylamine and 1-adamantylamine or secondary amines, the enantioselectivity of the reaction significantly dropped (26–52 % *ee*). The ring-opening reaction of 2-aryl-2-ethynyloxiranes **94a** with anilines proceeded to give considerably higher enantioselectivities (87–94 % *ee*) than those obtained by 2-alkyl analogues **94b** (54–77 % *ee*).

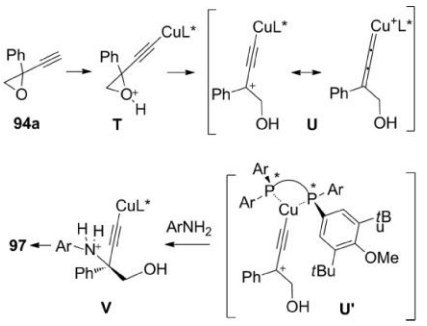
Resonance stabilized copper-allenylidene complex **U** is proposed as a key intermediate of this reaction (Scheme 30) and is a tautomer of protonated copper acetylide **T**, which is formed from alkyne **94** and a chiral copper-ligand complex. The preferred conformer **U′**, which minimizes the interaction between the phenyl group of the acetylide and the bulky aryl group of the phosphine ligand, is also proposed. Aniline addition then occurs from the *si* face of carbenium ion **U′** to give intermediate **V**, which undergoes a proton transfer and releases the copper catalyst to provide product **97**.



Scheme 28. The proposed pathways (A and B) for the reaction of azlactones **87** with iodinanes **81b**, **88a,b**, and **91**.



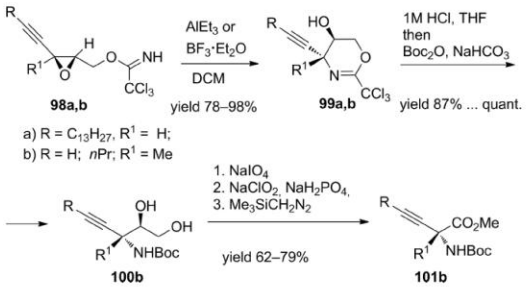
Scheme 29. Enantioselective ring-opening reaction of ethynyl epoxides **94** with amines **95**.



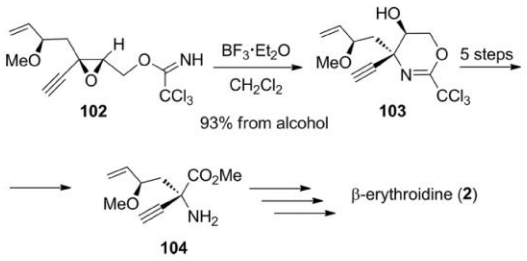
Scheme 30. Proposed mechanism for enantioselective aminolysis of epoxides **94**.

Vasella's group was the first to report the intramolecular aminolysis of chiral 3-ethynyl epoxide **98a**, which contained a trichloroacetimidate moiety, by employing an excess amount of $AlEt_3$. The reaction proceeded with inversion of configuration at the propargylic carbon atom of the epoxide to lead to enantioenriched dihydrooxazine **99a** (R^1 = H, Scheme 31).[54] Later, Schmidt et al. developed a procedure for the synthesis of optically active α-amino acids from 3-ethynyl-substituted epoxides **98b**.[55] These substrates, when exposed to a catalytic amount of BF_3·Et_2O, underwent a regioselective aminolysis with an inversion of configuration to provide enantioenriched dihydrooxazines **99b**, which contain a *C*-quaternary stereocenter. 1,3-Dihydrooxazines **99b** were hydrolyzed into amino alcohols **100b**, which were then converted into the corresponding amino acid derivatives **101b** by using a three-step sequence that involving diol cleavage by treatment with $NaIO_4$, a Pinnick oxidation, and esterification reactions.

Hatakeyama's group employed the cyclization of trisubstituted epoxide **102** into 1,3-dihydrooxazine **103** to obtain enantioenriched amino acid derivative **104**, which served as key intermediate in the total synthesis of β-erythroidine (Scheme 32).[6]



Scheme 31. Intramolecular aminolysis of epoxides that have a trichloroacetimidate moiety.

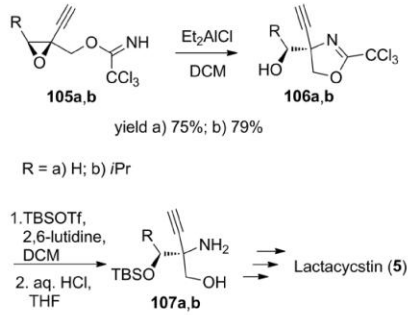


Scheme 32. Synthesis of 1,3-dihydrooxazine **103**, a precursor of β-erythroidine, through the aminolysis of epoxides.

On the basis of previous work by Hatakeyama et al. on the aminolysis of epoxides that have a trichloroacetimidate moiety,[56] Pattenden's group performed the Et_2AlCl-promoted regioselective cyclization of enantioenriched 3-ethynyl epoxide **105a** (Scheme 33). The reaction proceeded with complete inversion to provide enantioenriched oxazoline **106a**. Protection of the silyl group followed by hydrolysis gave amino alcohol **107a**, which was used as the key intermediate in the total synthesis of lactacystin (**5**).[57] In an alternative approach towards lactacystin (**5**), Pattenden and Rescourio accessed key amino alcohol **107b** in enantiomerically and diastereomerically pure form through the cyclization of trisubstituted epoxide **105b** to afford oxazoline **106b**.[10]

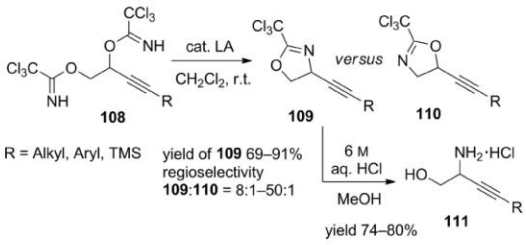
5. Lewis Acid Catalyzed Propargylic Substitution of Bis(imidate)s

Our group has developed an approach for the synthesis of oxazolines **109** by employing a Lewis acid catalyzed propargylic substitution reaction of bis(imidate)s **108** (Scheme 34).[58] A wide range of Lewis acids, including TMSOTf, BF_3·Et_2O, $AlCl_3$, and $FeCl_3$, were suitable for this transformation. The cyclization reaction of bis(imidate)s **108** proceeded with high regioselectivity and in good yields to provide a mixture of propargylic substitution isomers **109** and **110**. In the case of trimethylsilyl-substituted bis(imidate) **108** (R = TMS), the regioselectivity of the reaction improved from 9:1 to 35:1 by employing TMSOTf in-



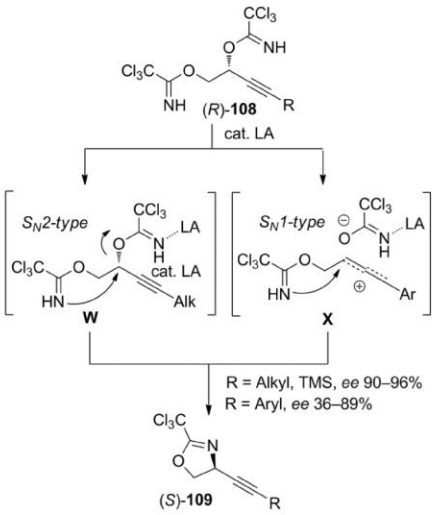
Scheme 33. Synthesis of oxazolines **106a** and **106b**, precursors to lactacytin, through the aminolysis of epoxides.

stead of $AlCl_3$, respectively, as the catalyst. The resulting oxazolines **109** were then hydrolyzed under acidic conditions to give ethynyl glycinols **111**.



Scheme 34. Synthesis of ethynylglycinols **111** by the propargylic substitution reaction of bis(imidate)s **108**.

The chirality transfer in the cyclization of enantioenriched bis(imidate) (*R*)-**108** has also been investigated (Scheme 35). In the case of alkyl- and trimethylsilyl-substituted bis(imidate)s (*R*)-**108**, the cyclization reaction proceeded with complete inversion of configuration at the stereocenter. This indicates that an S_N2-type of reaction mechanism may be occurring through transition state **W**. In contrast, the cyclization of aryl-substituted bis(imidate)s **108** proceeded with a considerable degree of racemization, which is presumably from the contribution of an S_N1-type mechanism through cationic intermediate **X**. The introduction of two electron-withdrawing atoms to the benzene ring of substrate (*R*)-**108** (R = 3,5-$Cl_2C_6H_3$) decreased the carbenium ion stabilizing effect of the aryl group and considerably suppressed the racemization process (89 % *ee*).



Scheme 35. Chirality transfer in the cyclization reaction of enantioenriched bis(imidate)s (*R*)-**108**.

Conclusions

During the last two decades, a number of new methods have been developed to synthesize α-ethynyl glycine derivatives. Notable progress has been achieved to access enantioenriched α-ethynyl glycines and synthetically equivalent glycinols by using substrate-controlled (chiral auxiliary and chirality transfer) and catalyst-controlled asymmetric induction. These are milestone discoveries that enable the use of ethynyl glycines/glycinols as multifunctional intermediates in the syntheses of value-added products. However, there is still a need for improved methods for the synthesis of ethynyl glycines/glycinols. It is expected that new approaches will emerge to overcome the limitations of substrate scope, particularly regarding the *N*-protecting group, to rely on less expensive catalytic systems, and to provide greener alternatives.

Acknowledgments

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Keywords: Synthetic methods · Enantioselectivity · Reaction mechanisms · Amino acids · Amino alcohols · Alkynes

[1] Y. Kuroda, M. Okuhara, T. Goto, E. Iguchi, M. Kohsaka, H. Aoki, H. Imanaka, *J. Antibiot.* **1980**, *33*, 125–131.
[2] Y. Kuroda, M. Okuhara, T. Goto, M. Kohsaka, H. Aoki, H. Imanaka, *J. Antibiot.* **1980**, *33*, 132–136.
[3] R. M. Williams, D. J. Aldous, S. C. Aldous, *J. Chem. Soc. Perkin Trans. 1* **1990**, 171–172.
[4] C. Danzin, P. Casara, N. Claverie, B. W. Metcalf, *J. Med. Chem.* **1981**, *24*, 16–20.
[5] G. Ribéreau-Gayon, C. Danzin, M. G. Palfreyman, M. Aubry, J. Wagner, B. W. Metcalf, M. J. Jung, *Biochem. Pharmacol.* **1979**, *28*, 1331–1335.
[6] H. Fukumoto, K. Takahashi, J. Ishihara, S. Hatakeyama, *Angew. Chem. Int. Ed.* **2006**, *45*, 2731–2734; *Angew. Chem.* **2006**, *118*, 2797.
[7] S. N. Osipov, P. Tsouker, L. Hennig, K. Burger, *Tetrahedron* **2004**, *60*, 271–274.
[8] K. Morisaki, M. Sawa, J. Nomaguchi, H. Morimoto, Y. Takeuchi, K. Mashima, T. Ohshima, *Chem. Eur. J.* **2013**, *19*, 8417–8420.
[9] V. M. Girijavallabhan, L. Chen, C. Dai, R. J. Feltz, L. Firmansjah, D. Li, S. H. Kim, J. A. Kozlowski, B. J. Lavey, A. Kosinski, J. J. Piwinski, J. Popovici-Muller, R. Rizvi, K. E. Rosner, B. B. Shankar, N.-Y. Shih, M. A. Siddiqui, L. Tong, M. K. C. Wong, D.-y. Yang, L. Yang, W. Yu, G. Zhou, Z. Guo, P. Orth, V. Madison, H. Bian, D. Lundell, X. Niu, H. Shah, J. Sun, S. Umland, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7283–7287.
[10] G. Pattenden, G. Rescourio, *Org. Biomol. Chem.* **2008**, *6*, 3428–3438.

[11] H. Johansson, D. S. Pedersen, *Eur. J. Org. Chem.* **2012**, 4267–4281.
[12] D. V. Vorobyeva, N. V. Sokolova, V. G. Nenajdenko, A. S. Peregudov, S. N. Osipov, *Tetrahedron* **2012**, *68*, 872–877.
[13] G. Bartoli, C. Cimarelli, R. Cipolletti, S. Diomedi, R. Giovannini, M. Mari, L. Marsili, E. Marcantoni, *Eur. J. Org. Chem.* **2012**, 630–636.
[14] D. V. Vorobyeva, N. M. Karimova, I. L. Odinets, G.-V. Roschenthaler, S. N. Osipov, *Org. Biomol. Chem.* **2011**, *9*, 7335–7342.
[15] D. Semeril, J. Le Notre, C. Bruneau, P. H. Dixneuf, A. F. Kolomiets, S. N. Osipov, *New J. Chem.* **2001**, *25*, 16–18.
[16] G. T. Shchetnikov, S. N. Osipov, C. Bruneau, P. H. Dixneuf, *Synlett* **2008**, 578–582.
[17] G. Reginato, P. Meffre, F. Gaggini, *Amino Acids* **2005**, *29*, 81–87.
[18] Z. Benfodda, D. Bénimélis, G. Reginato, P. Meffre, *Amino Acids* **2015**, *47*, 271–279.
[19] P. Meffre, F. Le Goffic, *Amino Acids* **1996**, *11*, 313–328.
[20] G. Blay, A. Monleón, J. R. Pedro, *Curr. Org. Chem.* **2009**, *13*, 1498–1539.
[21] A. E. Taggi, A. M. Hafez, T. Lectka, *Acc. Chem. Res.* **2003**, *36*, 10–19.
[22] J.-X. Ji, T. T.-L. Au-Yeung, J. Wu, C. W. Yip, A. S. C. Chan, *Adv. Synth. Catal.* **2004**, *346*, 42–44.
[23] J. McNulty, R. Vemula, C. Bordon, R. Yolken, L. Jones-Brando, *Org. Biomol. Chem.* **2014**, *12*, 255–260.
[24] J.-X. Ji, J. Wu, A. S. C. Chan, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11196–11200.
[25] Z. Shao, J. Wang, K. Ding, A. S. C. Chan, *Adv. Synth. Catal.* **2007**, *349*, 2375–2379.
[26] F. Peng, Z. Shao, A. S. C. Chan, *Tetrahedron: Asymmetry* **2010**, *21*, 465–468.
[27] M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem. Int. Ed.* **2007**, *46*, 6903–6906; *Angew. Chem.* **2007**, *119*, 7027.
[28] H. A. Stefani, F. Manarin, A. N. Khan, S. N. S. Vasconcelos, *Eur. J. Org. Chem.* **2014**, 1236–1240.
[29] L. Zhao, C.-J. Li, *Angew. Chem. Int. Ed.* **2008**, *47*, 7075–7078; *Angew. Chem.* **2008**, *120*, 7183.
[30] G. T. Shchetnikov, M. A. Zotova, C. Bruneau, P. H. Dixneuf, S. N. Osipov, *Eur. J. Org. Chem.* **2010**, 1587–1592.
[31] G. Huang, J. Yang, X. Zhang, *Chem. Commun.* **2011**, *47*, 5587–5589.
[32] G. Huang, Z. Yin, X. Zhang, *Chem. Eur. J.* **2013**, *19*, 11992–11998.
[33] F.-G. Zhang, H. Ma, Y. Zheng, J.-A. Ma, *Tetrahedron* **2012**, *68*, 7663–7669.
[34] Z. Shao, A. S. C. Chan, *Synthesis* **2008**, 2868–2870.
[35] Z. Shao, X. Pu, X. Li, B. Fan, A. S. C. Chan, *Tetrahedron: Asymmetry* **2009**, *20*, 225–229.
[36] A. Bisai, V. K. Singh, *Tetrahedron* **2012**, *68*, 3480–3486.
[37] H. A. Stefani, F. Manarin, A. C. S. Sousa, F. B. Souza, W. R. Ferraz, *Tetrahedron* **2014**, *70*, 3243–3248.
[38] P. Casara, B. W. Metcalf, *Tetrahedron Lett.* **1978**, *19*, 1581–1584.
[39] R. M. Williams, D. J. Aldous, S. C. Aldous, *J. Org. Chem.* **1990**, *55*, 4657–4663.
[40] A. L. Castelhano, S. Horne, G. J. Taylor, R. Billedeau, A. Krantz, *Tetrahedron* **1988**, *44*, 5451–5466.
[41] S. Ren, D. Hesk, P. McNamara, D. Koharski, S. Borges, *J. Labelled Compd. Radiopharm.* **2014**, *57*, 632–636.
[42] J. C. Barrow, P. L. Ngo, J. M. Pellicore, H. G. Selnick, P. G. Nantermet, *Tetrahedron Lett.* **2001**, *42*, 2051–2054.
[43] B.-L. Chen, B. Wang, G.-Q. Lin, *J. Org. Chem.* **2010**, *75*, 941–944.
[44] M. Das, D. F. O'Shea, *Chem. Eur. J.* **2015**, *21*, 18717–18723.
[45] M. Crucianelli, F. De Angelis, F. Lazzaro, L. Malpezzi, A. Volonterio, M. Zanda, *J. Fluorine Chem.* **2004**, *125*, 573–577.
[46] I. Mizota, Y. Matsuda, S. Kamimura, H. Tanaka, M. Shimizu, *Org. Lett.* **2013**, *15*, 4206–4209.
[47] S. Hata, H. Koyama, M. Shimizu, *J. Org. Chem.* **2011**, *76*, 9670–9677.
[48] M. Hatano, K. Yamashita, M. Mizuno, O. Ito, K. Ishihara, *Angew. Chem. Int. Ed.* **2015**, *54*, 2707–2711; *Angew. Chem.* **2015**, *127*, 2745.
[49] Y. Yao, J.-L. Li, Q.-Q. Zhou, L. Dong, Y.-C. Chen, *Chem. Eur. J.* **2013**, *19*, 9447–9451.
[50] D. Fernández González, J. P. Brand, J. Waser, *Chem. Eur. J.* **2010**, *16*, 9457–9461.
[51] P. Finkbeiner, N. M. Weckenmann, B. J. Nachtsheim, *Org. Lett.* **2014**, *16*, 1326–1329.
[52] M. Kamlar, I. Cisarova, J. Vesely, *Org. Biomol. Chem.* **2015**, *13*, 2884–2889.
[53] G. Hattori, A. Yoshida, Y. Miyake, Y. Nishibayashi, *J. Org. Chem.* **2009**, *74*, 7603–7607.
[54] B. Bernet, A. Vasella, *Tetrahedron Lett.* **1983**, *24*, 5491–5494.
[55] U. Schmidt, M. Respondek, A. Lieberknecht, J. Werner, P. Fischer, *Synthesis* **1989**, 256–261.
[56] S. Hatakeyama, H. Matsumoto, H. Fukuyama, Y. Mukugi, H. Irie, *J. Org. Chem.* **1997**, *62*, 2275–2279.
[57] C. J. Brennan, G. Pattenden, G. Rescourio, *Tetrahedron Lett.* **2003**, *44*, 8757–8760.
[58] J. Sirotkina, L. Grigorjeva, A. Jirgensons, *Eur. J. Org. Chem.* **2015**, 6900–6908.

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