

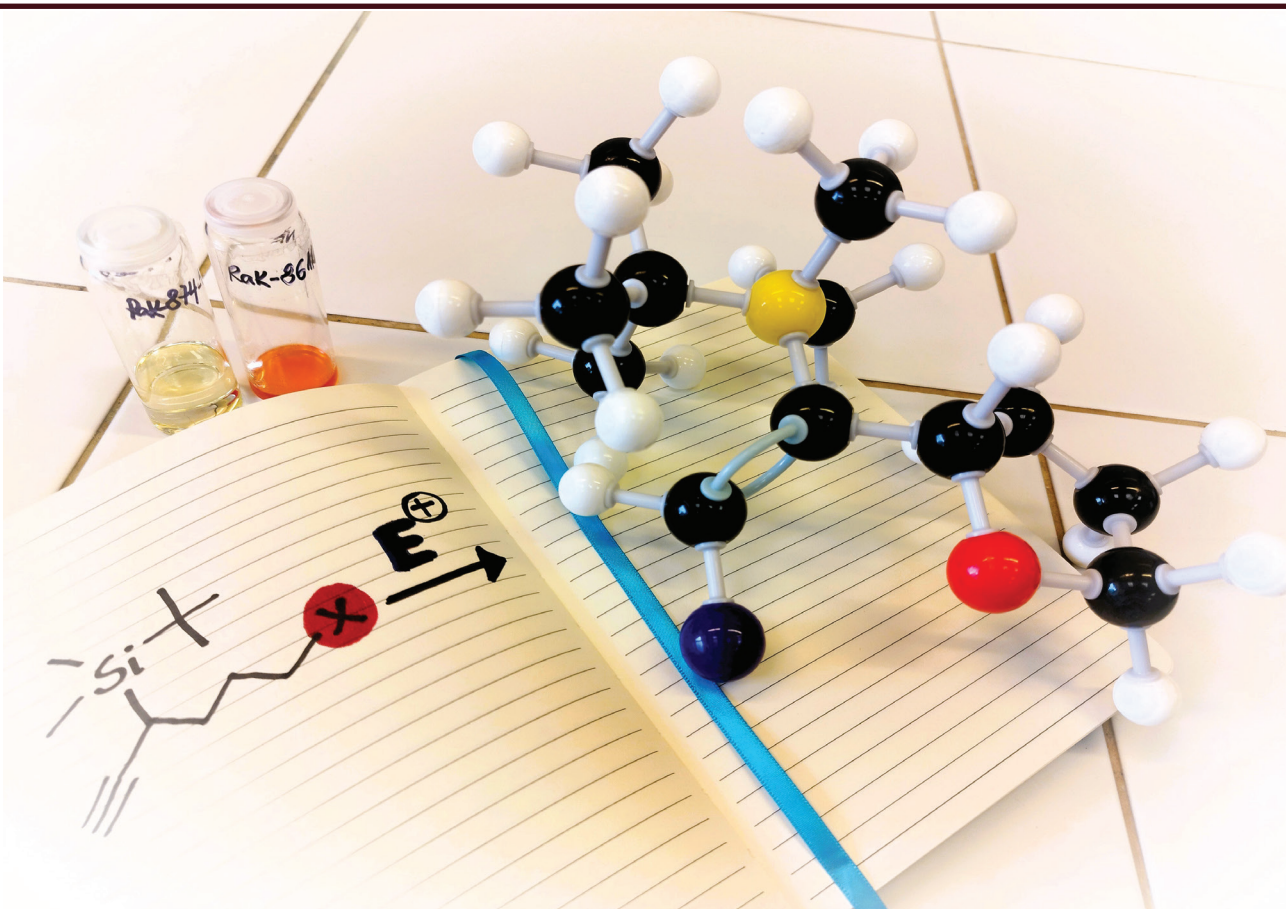
Rasma Kroņkalne

**SILILGRUPAS 1,2-NOBĪDE PROPARGILSILĀNOS
KĀ JAUNA METODOLOĢIJA HETEROCIKLU
UN AIZVIETOTU OLEFĪNU SINTĒZEI**

Promocijas darba kopsavilkums

**1,2-SILYL SHIFT IN PROPARGYL SILANES
AS A NOVEL METHODOLOGY FOR THE SYNTHESIS
OF HETEROCYCLES AND SUBSTITUTED OLEFINS**

Summary of the Doctoral Thesis



RĪGAS TEHNISKĀ UNIVERSITĀTE

Dabaszinātņu un tehnoloģiju fakultāte
Ķīmijas un ķīmijas tehnoloģijas institūts

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SILILGRUPAS 1,2-NOBĪDE PROPARGILSILĀNOS KĀ JAUNA METODOLOĢIJA HETEROCIKLU UN AIZVIETOTU OLEFĪNU SINTĒZEI

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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.

Rasma Kronkalne

(*paraksts*)

Datums

Promocijas darbs sagatavots kā tematiski vienotu zinātnisko publikāciju kopa ar kopsavilkumu latviešu un angļu valodā. Tajā ietvertas trīs oriģinālpublikācijas *SCI* žurnālos, viens apskatraksts, viens sagatavošanā esošais manuskripts un nepublicētie rezultāti. Publikācijas zinātniskajos žurnālos uzrakstītas angļu valodā.

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LIETOTIE SAĪSINĀJUMI

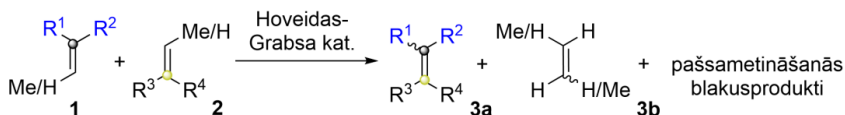
Ac	acetil-
Ar	aril-
B:	bāze
Boc	<i>t</i> -butiloksikarbonil-
Bu	butil-
Bz	benzoil-
Cbz	benziloksikarbonil-
DBU	1,8-diazabicklo(5.4.0)undec-7-ēns
DCE	1,2-dihlorekāns
DCM	dihlormetāns
DIAD	diizopropilazodikarboksilāts
DMAP	<i>N,N</i> -Dimetilpyridīn-4-amine
DMF	<i>N,N</i> -dimetilformamīds
ECAC	etil-2-(3,4-dihlorfenil)diazēn-1-karboksilāts
Et	etil-
Hal	halogēns
HFIP	1,1,1,3,3,3-heksafluorpropan-2-ols
KMR	kodolu magnētiskā rezonanse
Me	metil-
Mes	mezitil-
Ms	metilsulfonil-
NBS	<i>N</i> -bromsukcinimīds
NCS	<i>N</i> -hlorsukcinimīds
NIS	<i>N</i> -jodsukcinimīds
PCC	piridīnija hlorkromāts
Ph	fenil-
Pr	propil-
Py	piridīns
Ns	<i>p</i> -nitrobenzolsulfonil-, nozil-
Su	sukcinimīds
TEMPO	(2,2,6,6-tetrametilpiperidīn-1-il)oksil
TFE	2,2,2-trifluoetān-1-ols
Tf	trifluometānsulfonil-
THF	oksolāns
Ts	4-metilbenzolsulfonil-
XPhos	dicikloheksil[2',4',6'-tris(propān-2-il)[1,1'-bifenil]-2-il]fosfāns

PROMOCIJAS DARBA VISPĀRĒJS RAKSTUROJUMS

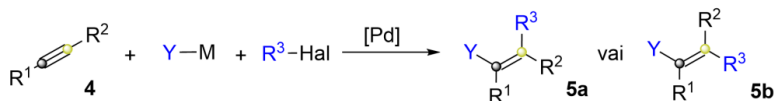
Tēmas aktualitāte

Alkēni ir izplatīta karbofunkcionālo savienojumu klase – tie kā struktūrelementi ir plaši sastopami gan dabasvielās, gan sintētiskajos savienojumos.^[1–3] Alkēni kalpo kā prekursori neskaitāmām organiskajām pārvērtībām, kas ļauj iegūt plašu vērtīgu produktu spektru.^[4, 5] Alkēnu ģeometrija un to aizvietotāji tieši ietekmē produktu īpašības, kas ir nozīmīgs faktors gan bioaktīvos savienojumos, gan polimēros, gan asimetriskās katalīzes substrātos.^[6] Neskatoties uz to, trīs- un čtraizvietotu olefīnu stereoselektīva iegūšana pat 21. gadsimtā mēdz būt izaicinoša.^[7] (*E/Z*)-selektivitāti bieži nosaka relatīvais aizvietotāju izmērs.^[8] (*E*)-izomēru tipiski iegūst kā termodinamisko produktu, taču enerģētiski neizdevīgāko (*Z*)-alkēnu sintēze ir problemātiskāka. Turklāt daudzu klasisko alkēnu sintēzes metožu, piemēram, Vitiga (*Wittig*) reakcijas, Žiliā-Kočińska (*Julia-Kocienski*) olefinēšanas u. c., piemērotība stereoselektīvai trīs- un čtraizvietotu alkēnu sintēzei ir ierobežota.^[6, 9] Tas motivē alternatīvu olefīnu sintēzes, piemēram, olefīnu metatēzes^[10–12] stratēģiju attīstību (1. shēma). Augsti funkcionālizētu alkēnu sintēzei izmanto arī pārvērtību rindas, kas apvieno alkīnu hidrometalēšanu, karbometalēšanu vai halogēnborēšanu ar šķērssametinašanās reakcijām,^[13–16] kā arī pārejas metālu katalizētu alkīnu hidroalkilēšanu.^[6] Diemžēl šīs metodes bieži vien nav pietiekami stereoselektīvas.^[6] Tāpat aktuāls mērķis ir arī masas efektivitātes paaugstināšana trīs- un čtraizvietotu olefīnu sintēzē.^[17]

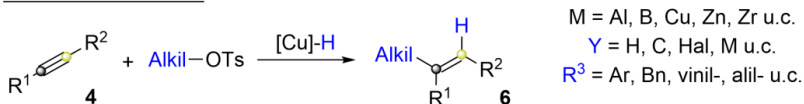
A) Olefīnu metatēze



B) Alkīnu 1,2-difunkcionalizēšana



C) Alkīnu hidroalkilēšana

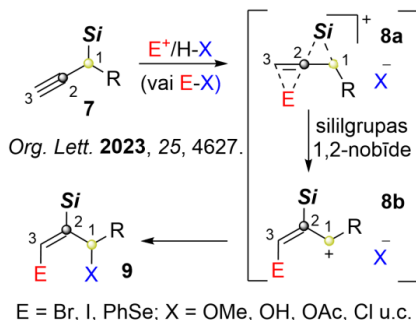


1. shēma. Mūsdienīgās stratēģijas stereoselektīvai augsti funkcionālizētu olefīnu sintēzei.

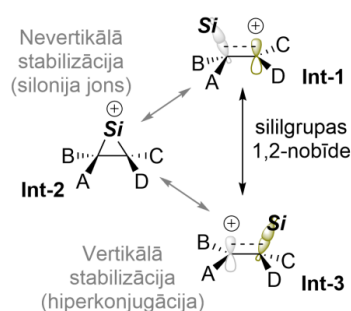
Darba autores un kolēģu zinātniskajā grupā nesen tika demonstrēta jauna pieeja stereoselektīvai trīsaizvietotu olefīnu **9** sintēzei, izmantojot propargilsilānu **7** 1,3-

difunkcionalizāciju (2. shēma).^[18, 19] Šī pieeja tika balstīta propargilsistēmas aktivēšanā ar ārējiem elektrofilu (Hal⁺, RSe⁺), kam sekoja sililgrupas 1,2-migrācija.^[19] Daudzos gadījumos β-sililkarbēnija jona kā iespējamā starpsavienojuma veidošanos veicina nevertikālā stabilizācija (**Int-2**), kas sekmē sililgrupas migrāciju un izraisa stabilākā alilkatjona veidošanos.^[20, 21] Šie β-silīcija stabilizētie alilkatjoni **8b** tālāk kalpoja kā būvbloki trīsaizvietotu alkēna fragmentu ievadīšanai molekulā **9** ar augstu stereoselektivitāti.^[19]

d) Alkīnu 1,3-difunkcionalizēšana



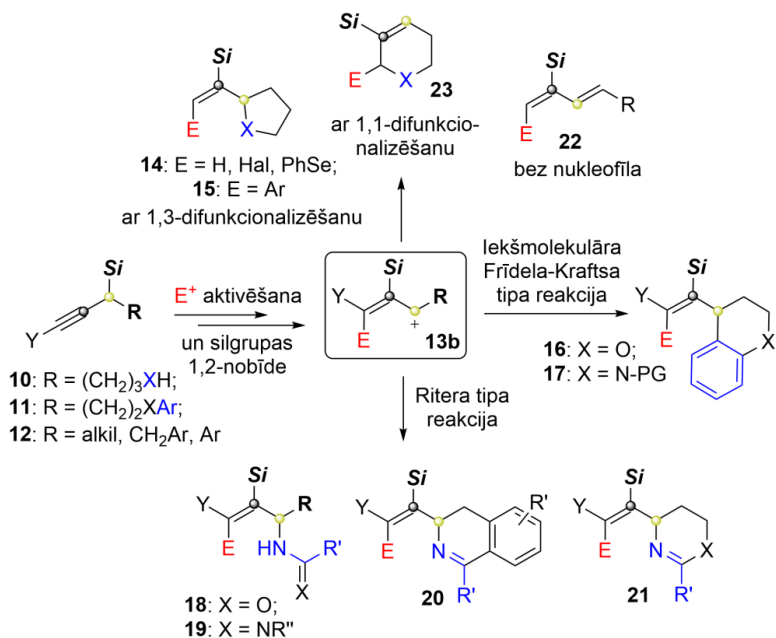
Karbēnija jonu stabilizēšana ar β-silīciju:



2. shēma. Alkīnu difunkcionalizēšana ar sililgrupas 1,2-migrāciju.

Lai gan sintētiskās metodes, kas ietver sililgrupas 1,2-nobīdi, ir pazīstamas jau kopš 20. gadsimta 80. gadiem, piemēri to lietojumam stereodefinētu alkēnu, kas satur trīs vai vairāk aizvietotājus, sintēzē joprojām ir ierobežoti. Silīcija pārgrupēšanās koncepcija heterociklisko struktūru sintēzei arī ir salīdzinoši maz pētīta.^[20, 21] Heterociklu nozīmība organiskajā ķīmijā ir nenoliedzama. Statistika rāda, ka lielākā daļa moderno zāļu vielu un agroķīmijas vielu satur vismaz vienu heterociklisku struktūrfragmentu.^[22] Piemēram, 2019. gadā vismaz pusi no jaunajām ASV Pārtikas un zāļu pārvaldes (FDA) apstiprinātajām zāļu vielām veidoja heterociklu atvasinājumi.^[23, 24] Tas veicina interesi par jaunu un efektīvu sintētisko stratēģiju izstrādi funkcionālizētu heterociklisko struktūru sintēzei, arvien vairāk paplašinot iegūstamo sintētisko atvasinājumu daudzveidību.^[25, 26]

Ņemot vērā to, ka silīcija pārgrupēšanās propargilsilānos ir relatīvi maz izpētīta tēma organiskajā ķīmijā,^[20, 21] kā arī nepieciešamību pēc jaunu metožu izstrādes stereodefinētu augsti funkcionālizētu olefinu un mazmolekulāro heterociklu sintēzei, tika nolemts attīstīt tālāk propargilsilānu 1,3-difunkcionalizācijas konceptu heterociklisku struktūru, kas satur stereodefinētu olefinu sānu virkni, sintēzei (3. shēma).



3. shēma. Vispārējais koncepts heterociklu un augsti funkcionālizētu C=C saiti saturošu savienojumu sintēzei no propargilsilāniem **10-12**.

Pētījuma mērķis un uzdevumi

Promocijas darba mērķis ir izstrādāt jaunu organiskās sintēzes metodoloģiju piesātinātu un daļēji piesātinātu heterociklu, kas sānu ķēdē satur stereokīmiski definētu augsti funkcionālizētu dubultsaiti, ieguvei. To plānots panākt, ar elektrofilu aktivējot propargilsilānus, kas sililgrupas 1,2-nobīdes rezultātā dod alilkatjonu vai tā ekvivalentu. Tam seko iekšējā O-, N-, S- vai C-nukleofila uzbrukums, kā rezultātā tiek iegūti cikliski produkti. Papildus tiks apskatīts propargilsilānu lietojums Ritera tipa reakcijas apstākļos, kur kā primārais nukleofils ar β-silīcija stabilizētu karbkatjonu reaģē nitrils, bet iegūtais nitrīlija jons tiek dzēsts ar iekšējiem un ārējiem nukleofiliem, lai iegūtu stereokīmiski definētus, alilamīna fragmentu saturošus produktus.

Darba mērķa īstenošanai definēti vairāki uzdevumi.

- 1) Izpētīt literatūrā zināmās metodes piesātinātu heterociklu ieguvei iekšmolekulāras ciklizācijas ceļā, identificējot līdzšinējo metožu priekšrocības un trūkumus, un apkopot tās apskatraksta veidā.
- 2) Piedalīties kopprojektā par metodes izstrādi pieclocēkļu heterociklu **14** – tetrahydrofurānu (X = O), pirolidīnu (X = N-PG) un tiolānu (X = S) – sintēzei no

propargilsilāniem **10**, kas ietver elektrofilu inducētu sililgrupas 1,2-nobīdi reaģētspējīgu, β -silīcija stabilizētu alilkatjonu **13b** veidošanai ar sekojošu cikla saslēgšanu, veidojot C-Het saiti iekšmolekulāra *O*-, *N*-, vai *S*-nukleofila uzbrukuma rezultātā.

- 3) Piedalīties kopprojektā par propargilsilānu heterociklizācijas metodes pielāgošanu Frīdela-Kraftsa (*Friedel-Crafts*) tipa reakcijai, kur β -silīcija stabilizēts alilkatjons **13b** iekšmolekulāri reaģē ar arilsistēmām (*C*-nukleofīls), veidojot bicikliskus daļēji piesātinātus heterociklus **17**. Veikt iegūto tetrahidrohinolīnu **17** ($X = N-PG$) un to skābekļa analogu **16** ($X = O$) tālākās modifikācijas, kas demonstrētu iegūto produktu sintētisko lietojumu.
- 4) Piedalīties kopprojektā par diaril- λ^3 -jodānu kā formālu *C*-elektrofilu izmantošanu propargilsilānu **10** un **12** aktivēšanai vara katalīzes apstākļos arilētu heterociklisko produktu **15** un **23**, kā arī arilētu silidiēnu **22** sintēzei.
- 5) Pētīt sililgrupas 1,2-nobīdes izraisīšanu propargilsilānos **10-12** Ritera (*Ritter*) tipa reakcijas apstākļos dažādu aciklisko **18-19** ($X = O, N-PG$) un ciklisko **20-21** produktu sintēzei, kas satur augsti funkcionalizētu $C=C$ saiti.

Zinātniskā novitāte un galvenie rezultāti

Veikto pētījumu rezultātā ir izstrādāta sintētiskā metodoloģija piesātinātu un daļēji piesātinātu heterociklu sintēzei no propargilsilāniem, ievadot sistēmā augsti funkcionalizētu alkēnu sānu virkni. Šīs pārvērtības pamatā ir β -silīcija stabilizētu alilkatjonu ģenerēšana caur sililgrupas 1,2-nobīdi, ko izraisa propargilsilānu trīskāršās saites aktivēšana ar spēcīgiem elektrofilu. *In situ* ģenerētos alilkatjonus dzēšot ar iekšējiem nukleofiliem, tika iegūta virkne heterociklisku struktūru – tetrahidrofurāni, pirolidīni, tiolāni, tetrahidrohinolīni u. c.

Lai īstenotu tetrahidrofurānu, pirolidīnu un tiolānu sintēzi, no komerciāli pieejamā heks-5-īn-1-ola tika iegūti iekšmolekulārā *O*-, *N*-, un *S*-nukleofila saturoši propargilsilāni. Iegūtās iekšējo nukleofila saturošās izejvielas tālāk tika aktivētas spēcīgu elektrofilu (H^+ , Hal^+ , RSe^+) klātbūtnē, izraisot sililgrupas 1,2-nobīdes – heterociklizācijas pārvērtību virkni, kurā cikla saslēgšana, veidojot C-Het saiti, notiek, iekšmolekulāram nukleofilam uzbrūkot β -silīcija stabilizētam alilkatjonam. Iegūtie produkti satur vienus no izplatākajiem heterocikliskajiem struktūrelementiem (tetrahidrofurāna, pirolidīna vai tiolāna cikls) zāļvielās, kā arī augsti funkcionalizētus alkēnu struktūrfragmentus ar izcilu (*E*)-selektivitāti.

Biciklisku, daļēji piesātinātu heterociklu – tetrahidrohinolīnu – sintēzei propargilsilānu heterociklizācijas koncepts tika pielāgots iekšmolekulārai Frīdela-Kraftsa tipa reakcijai, kur sililgrupas 1,2-nobīdes rezultātā radītais alilkatjons tiek iekšmolekulāri dzēsts ar elektroniem

bagātu arilsistēmu, kas šajā reakcijā kalpo kā C-nukleofils. Lai nodrošinātu šo pārvērtību, propargilsilāna struktūrā caur slāpekļa tiltiņu tika ievadīta arilgrupa. Funkcionalizēti arilamīda atvasinājumi tika iegūti no komerciālā pent-4-īn-1-ola. Iegūto biciklisko heterociklu sānu ķēdē tika ievadīti augsti funkcionālizētu alkēnu fragmenti ar (Z)-selektivitāti.

Diaril- λ^3 -jodānu kā formālu C-elektrofila avotu izmantošana vara katalīzes apstākļos tika attīstīta propargilsilānu arilēšanas-heterociklizācijas reakciju virknei, kurā tika iegūti sānu ķēdē arilēti tetrahidrofurāna, pirolidīna un tetrahidropiridīna atvasinājumi. Šī metode sniedz efektīvu pieeju ar stīrilgrupu funkcionālizētu heterociklu iegūšanai, saīsinot kopējo sintētisko soļu skaitu, salīdzinot ar iepriekš zināmajām pieejām.

Ar elektrofilu aktivējot propargilsilānus Ritera tipa reakcijas apstākļos, tika iegūti dihidroizohinolīna un tetrahidropirimidīna atvasinājumi, kā arī acikliski produkti – amidīni un alilamīdi, kas satur augsti funkcionālizētu C=C saiti. No entropijas viedokļa propargilsilānu pārvērtības Ritera tipa apstākļos ir īpaši komplicētas – daudzkomponentu reakcijā tika panākta secīga četru jaunu kovalento saišu veidošanās vienā stadijā, kas tika izmantotas dažādu komplicētu struktūru iegūšanai no vienkāršām izejvielām.

Darba struktūra un apjoms

Promocijas darbs sagatavots kā tematiski vienotu zinātnisko publikāciju kopa, kas veltīta pētījumiem par propargilsilānu izmantošanu mazmolekulāro heterociklu, kas satur augsti funkcionālizētu olefīnu sānu virkni, sintēzei, izmantojot sililgrupas 1,2-nobīdi β -silīcija stabilizētu alilkatjonu starpsavienojumu ģenerēšanai. Šis darbs ietver vienu apskatrakstu un trīs oriģinālpublikācijas *SCI* žurnālos, vienu sagatavošanā esošo manuskriptu, kā arī nepublicētos rezultātus.

Darba aprobācija un publikācijas

Promocijas darba galvenie rezultāti publicēti trīs zinātniskajos oriģinālrakstos. Promocijas darba izstrādes laikā sagatavots viens apskatraksts. Par pētījumu rezultātiem ziņots 20 zinātniskajās konferencēs.

Zinātniskās publikācijas

1. **Kronkalne, R.**; Beļunieks, R.; Ubaidullajevs, A.; Mishnev, A.; Turks, M. 1,2-Silyl Shift-Induced Heterocyclization of Propargyl Silanes: Synthesis of Five-Membered Heterocycles Containing a Functionalized Olefin Side Chain. *J. Org. Chem.*, **2023**, *88* (19), 13857–13870. Available from: <https://doi.org/10.1021/acs.joc.3c01481>.

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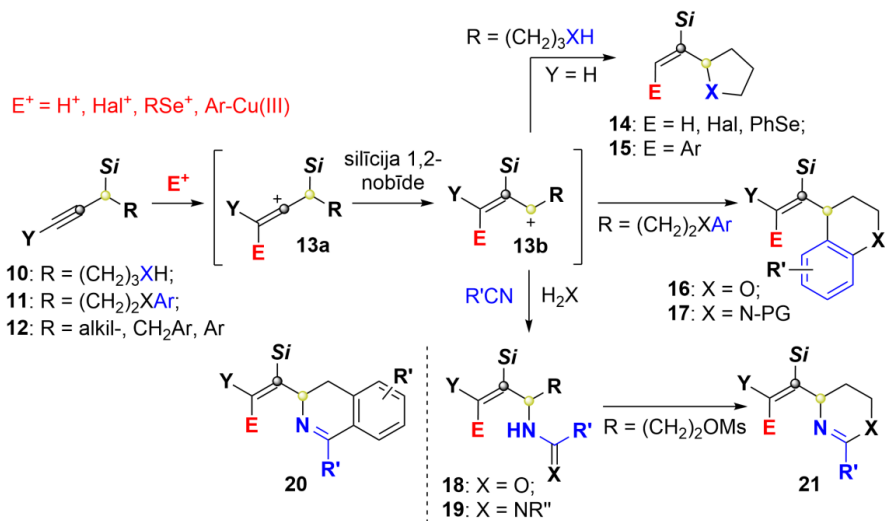
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3. **Kroņkalne, R.**; Beļunieks, R.; Sebris, A.; Mishnev, A.; Turks, M. Copper-Catalyzed Arylation of Propargyl Silanes with Iodanes Featuring 1,2-Silyl Shift and Cascade Cyclization. In: *ISySyCat: International Symposium on Synthesis and Catalysis 2025: Book of Abstracts*, Portugal, Coimbra, September 2–5, **2025**. Coimbra: 2025, p. 206. ISBN 978-989-95050-9-4
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13. Turks, M.; **Kronkalne, R.**; Ubaidullajevs, A.; Beļunieks, R.; Sebris, A.; Puriņš, M.; Rogaļevs, R. One, Two, Three, Go: Novel Applications of 1,2-Silyl Shift for 1,3-Difunctionalization of Propargyl Silanes. In: *Balticum Organicum Syntheticum 2024: Abstract Book*, Latvia, Riga, July 7–10, **2024**. Riga: 2024, p. 156.

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17. **Kronkalne, R.**; Beļunieks, R.; Ubaidullajevs, A.; Turks, M. Use of Terminally Functionalized Propargyl Silanes for the Synthesis of Various 5-Membered Heterocycles via 1,2-Silyl Migration. In: *81st International Scientific Conference of the University of Latvia: Organic Chemistry Session*, Latvia, Riga, March 17, **2023**. Riga: 2023, p. 14.
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PROMOCIJAS DARBA GALVENIE REZULTĀTI

Propargilsilānu heterociklizācijas koncepts balstās β -silīcija stabilizētu karbkatjonu ģenerēšanā, spēcīgam elektrofilam (E^+) pievienojoties trīskāršajai saitei. Sākotnēji ģenerētais vinilkatjons **13a** 1,2-sililmigrācijas rezultātā pārgrupējas par stabilāko alilkatjonu **13b**, kuru dzēšot ar iekšējiem nukleofīliem (heteroatomiem vai $C(sp^2)$) rodas cikliskas struktūras ar funkcionalizētu alkēnu sānu ķēdi (4. shēma).



4. shēma. Galvenie pētījuma virzieni heterociklu sintēzei no propargilsilāniem **10-12**.

Šajā promocijas darbā tiek apskatīta:

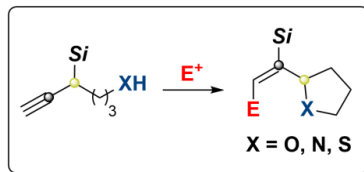
a) pieclocēkļu heterociklu **14** sintēze, ar elektrofilu ierosinot silīcija 1,2-nobīdes-heterociklizācijas reakciju kaskādi propargilsilānos, kas funkcionalizēti ar iekšējiem *O*-, *N*- vai *S*-nukleofīliem;

b) iekšmolekulāra Frīdela-Kraftsa tipa reakcija tetrahidrohinolīnu **17** ($X = N-PG$) sintēzei, kā arī to tālākās sintētiskās modifikācijas, apskatot arī to struktūranalogu **16** ($X = O$) modificēšanas iespējas;

c) vara katalizētas arilēšanas-heterociklizēšanas reakcijas, izmantojot diaril- λ^3 -jodānus kā formālus Ar^+ sintonus ($E^+ = Ar-Cu(III)$);

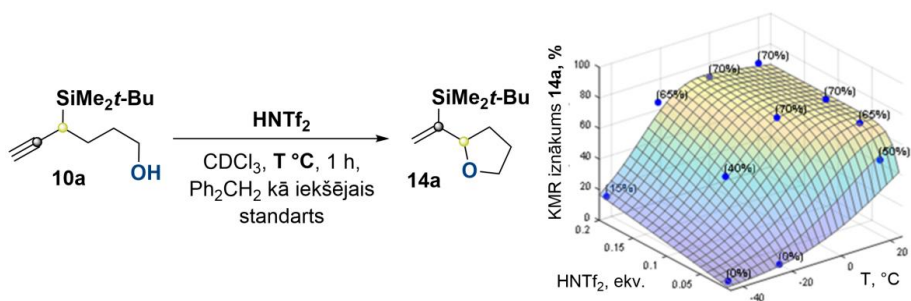
d) Ritera tipa reakcijas funkcionalizētu alilamīnu **18** ($X = O$), amidīnu **19** ($X = NR''$), dihidroizohinolīnu **20** un tetrahidropirimidīnu **21** ($X = N-PG$) sintēzei.

1.1. Propargilsilānu heterociklizācija, iekšējam *O*-/*N*-/*S*-nukleofilam reaģējot ar β -silīcija stabilizētu alilkatjonu



Iepriekšējos pētījumos tika demonstrēts, ka elektrofilu (Brensteda skābes vai Hal^+) aktivācijas apstākļos propargilsilāni var darboties kā reaģētspējīgi alilkatjona sintoni, kurus var izmantot silildiēnu vai indēnu,^[18] 1,3-funkcionalizētu olefinu,^[19] sulfolēnu^[27] un citu vērtīgu produktu sintēzē.^[28] Šī darba mērķis bija paplašināt propargilsilānu lietojuma konceptu, pielāgojot to mazmolekulāro heterociklu sintēzei. Šim nolūkam autore kopā ar Rūdolfu Beļāunieku un Artjomu Ubaidullajevu izstrādāja metodoloģiju dažādu pieclocēkļu heterociklu sintēzei, kur heterociklizācija tika panākta, iekšmolekulāri dzēšot no propargilsilāniem ģenerētos β -silīcija stabilizētos alilkatjonus ar nukleofīliem heteroatomiem (*O*, *N*, *S*).^[29] Iegūtie rezultāti tika daļēji apspriesti R. Beļāunieka promocijas darbā.^[30]

Par stratēģisko izejvielu tetrahydrofurānu sintēzei tika izvēlēts 4-(*tert*-butildimetilsilil)heks-5-īn-1-ols **10a**, kas tika iegūts no *O*-sililēta komerciālā heks-5-īn-1-ola pēc Vanga (*Wang*) aprakstītās retro-Brūka (*Brook*) pārgrupēšanās procedūras.^[31] Tālāka propargilsilāna **10a** aktivēšana ar Brensteda skābēm (HNTf_2 vai TfOH) deva heterociklizācijas produktu **14a**.

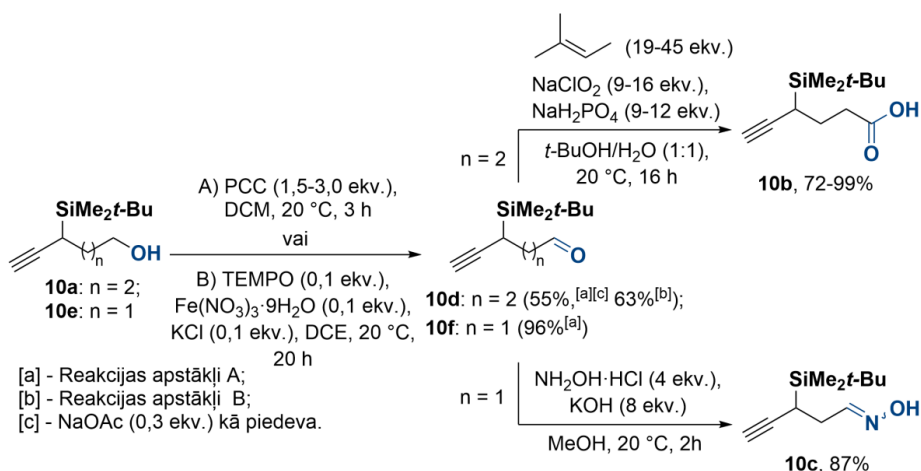


5. shēma. Apstākļu optimizācija Brensteda skābes katalizētai propargilsilāna **10a** heterociklizācijai.

Galvenie secinājumi no reakcijas apstākļu optimizācijas Brensteda skābes katalizētai pārvērtībai **10a**→**14a** bija šādi: 1) optimālā reakcijas temperatūra bija 0–20 °C; 2) optimālais skābes katalizatora daudzums bija 10–20 mol%; 3) šķīdinātāju izvēli noteica to nivelējošais

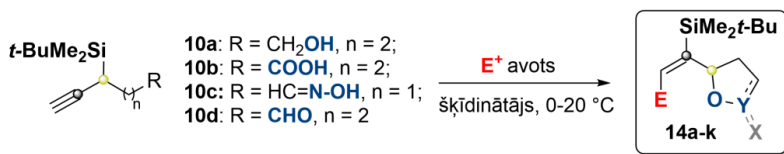
efekts, kur aprotiskajos šķīdinātājos CDCl_3 un CD_2Cl_2 tika iegūti augstākie iznākumi (**14a**, 70 % KMR, bet benzolā- d_6 un CD_3NO_2 iznākumi bija zemāki (attiecīgi 65 % un 50 % **14a**); 4) optimālajos reakcijas apstākļos (0,2 ekv. H^+ , CDCl_3 , 0 °C, 1 h) HNTf_2 un TfOH deva līdzīgi labus iznākumus (70 % KMR), savukārt ar konc. H_2SO_4 reakcija nenotika. Detalizēta skābes katalizatora daudzuma (HNTf_2 , ekv.) un temperatūras ietekme uz tetrahidrofurāna **14a** sintēzes iznākumu grafiski attēlota 5. shēmā.

Citi skābekļa nukleofīlu saturoši propargilsilāni **10b-f** tika iegūti, modificējot spirtu **10a** un tā C5-ķēdi saturošo analogu **10e**, kā tas redzams 6. shēmā. Spirts **10e** tika pagatavots pēc analogiskas procedūras C6-ķēdi saturošajam spirtam **10a**, izmantojot komerciāli pieejamo pent-4-īn-1-olu.^[31]

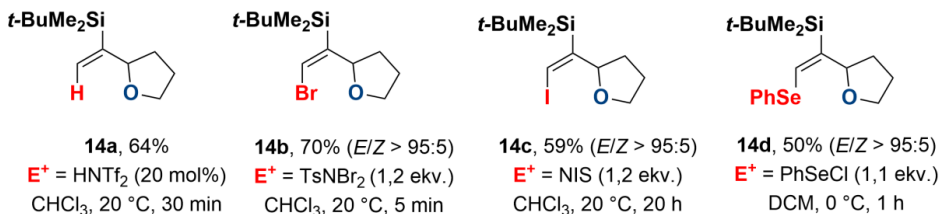


6. shēma. Iekšējo skābekļa nukleofīlu saturošu propargilsilānu **10b-f** iegūšana.

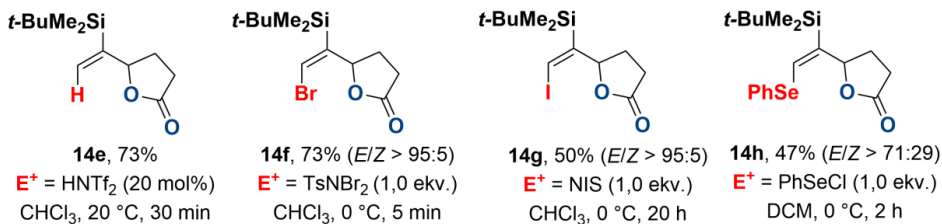
Optimizētajos apstākļos tika veikta iekšējo skābekļa nukleofīlu saturošu propargilsilānu **10a-d** ciklizēšana (7. shēma). Sililgrupas 1,2-nobīdes inducēšanai izmantojot elektrofilos halogenēšanas reaģentus (TsNBr_2 , NBS, NIS) vai elektrofilo selēna ievadīšanas reaģentu PhSeCl , tika iegūti heterocikli ar trīsaizvietotu alkēnu sānu virknē. No spirta **10a** iegūto tetrahidrofurānu **14a-d** iznākumi bija 50–70 % robežās, savukārt karbonskābe **10b** ciklizējās par laktona atvasinājumiem **14e-h** ar iznākumiem 47–73 % robežās. Oksīms **10c** deva 4,5-dihidroizoksazola atvasinājumus **14i-j** (29–32 % iznākumi), savukārt aldehīds **10d**, ciklizējoties ar NBS ūdens klātbūtnē, deva hemiacetālu **14k** (30 % iznākums).



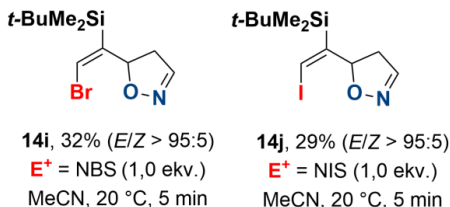
No spirta **10a** (R = CH₂OH, n = 2):



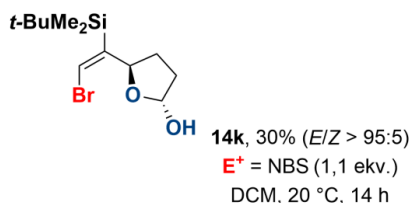
No karbonskābes **10b** (R = COOH, n = 2):



No oksīma **10c** (R = HC=N-OH, n = 1):



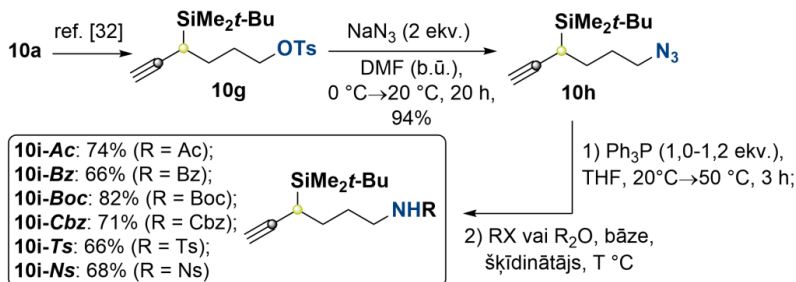
No aldehīda **10d** (R = CHO, n = 2):



7. shēma. Iekšējo skābekļa nukleofilu saturošu propargilsilānu **10a-d** heterociklizēšana.

Spirtu saturošais propargilsilāns **10a** tālāk tika modificēts par slāpekļa nukleofilu saturošām izejvielām (1. tabula). Tozīlāts **10g** tika iegūts pēc literatūrā aprakstītās metodes.^[32] Sekojoša azidēšana, azīda **10h** reducēšana Štaudingera (*Staudinger*) apstākļos un *N*-aizsarggrupas uzlikšana deva amīdus **10i-Ac** un **10i-Bz**, karbamātus **10i-Boc** un **10i-Cbz**, kā arī sulfonamīdus **10i-Ts** un **10i-Ns**.

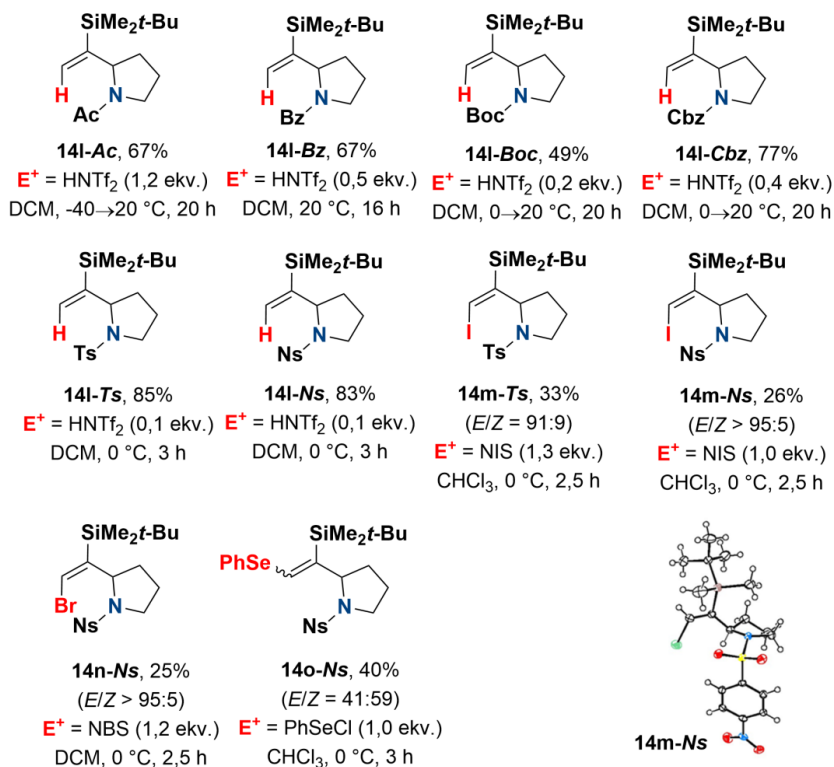
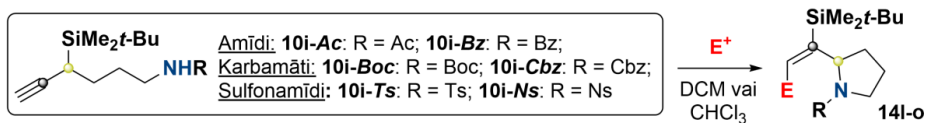
Ar iekšējo slāpekļa nukleofilu funkcionalizētu propargilsilānu **10i** sintēze



Nr. p. k.	RX/R ₂ O (ekv.)	Bāze/piedeva (ekv.)	Šķīdinātājs	T (°C)	t (h)	Produkta iznākums
1.	Ac ₂ O (2,0)	DMAP (0,5)	Py	0–20	16	10i-Ac , 74 %
2.	Bz ₂ O (2,0)	DMAP (1,0)	DMF	60	22	10i-Bz , 66 %
3.	Boc ₂ O (1,2)	NaHCO ₃ (3,0)	THF/H ₂ O (1:1)	0–20	14	10i-Boc , 82 % ^[a]
4.	Cbz-OSu (1,2)	NaHCO ₃ (2,7)	MeCN/H ₂ O (1:1)	0–20	16	10i-Cbz , 71 %
5.	TsCl (2,0)	Et ₃ N (5,0)	DCM	0–20	6	10i-Ts , 66 %
6.	NsCl (2,0)	Et ₃ N (5,0)	DCM	0–20	6	10i-Ns , 68 %

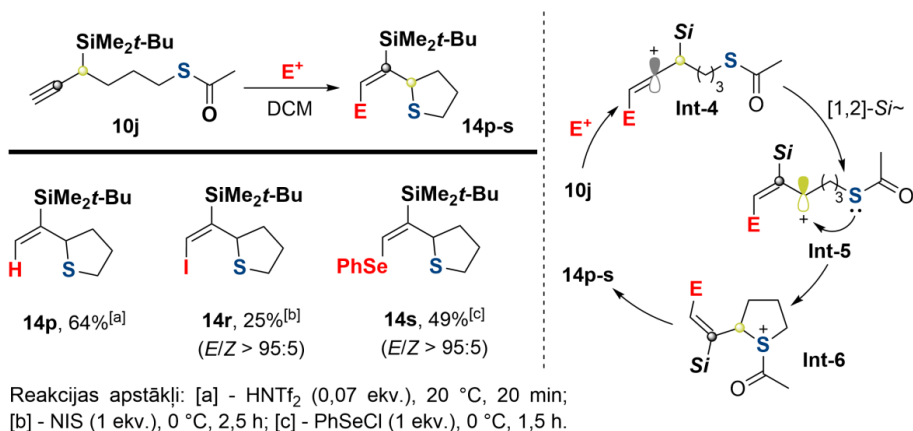
[a] – THF/H₂O (1:1) šķīdinātāju sistēma un 1 h maisīšana reducēšanas solim.

Spēcīgu elektrofilu (H⁺, Hal⁺, RSe⁺) klātbūtnē *N*-nukleofilu saturošie propargilsilāni **10i** ciklizējas par pirolidīna atvasinājumiem **14l-o** (8. shēma). Brensteda skābes HNTf₂ katalizētās heterociklizēšanas reakcijās sulfonamīdi (R = Ts, Ns) deva augstākos pirolidīnu **14l** iznākumus (83–85 %). Karbamātu (R = Boc, Cbz) un amīdu (R = Ac, Bz) gadījumā pirolidīnu **14l** iznākumi variēja 49–77 % robežās. Izmantojot elektrofilos halogenēšanas reaģentus (NIS, NBS) propargilsistēmas aktivēšanai, iznākumi bija zemāki (**14m-n**, 25–33 %), taču iegūtie produkti saturēja augsti funkcionalizētu C=C saiti, kur (*E/Z*)-selektivitāte bija robežās no 91:9 līdz 95:5. Trīsaizvietoto C=C saišu (*E*)-ģeometriju apstiprināja gan KMR 2D kodolu Overhauzera efekta spektroskopija (NOESY, korelācija starp C=C-H un *t*-BuMe₂Si-), gan arī monokristālu rentgenstaru difrakcijas (SCXRD) analīze pirolidīnam **14m-Ns**. Savukārt, izmantojot PhSeCl kā elektrofilu avotu, tika iegūts pirolidīns **14o** (40 % izdalīts) kā (*E/Z*)-izomēru maisījums (41:59). Iespējams, ka selenilgrupas gadījumā izveidotais alilkatjons ir papildus stabilizēts ar α-selēna efektu, kas var dot tam laiku izomerizēties pirms nukleofila uzbrukuma.



8. shēma. Slāpekļa heterociklu **14l-o** sintēze.

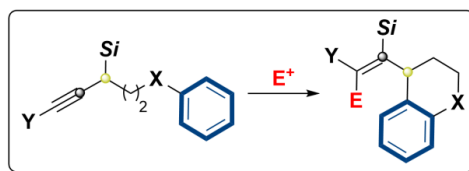
Tālāk tika apskatīta sēra heterociklu ieguve (9. shēma). Tiolānu **14p-s** sintēzei par izejvielu tika izmantots tioacetāts **10j**, ko iegūst, maisot tozilātu **10g**^[32] ar KSAc (1,4 equiv) acetonitrilā (20°C , 16 h, 87 % iznākums **10j**). Vislabāk ciklizēšanās noritēja HNTf₂ katalizētos apstākļos (**14p**, 64 %). Ar zemāku iznākumu bija iespējams iegūt arī trīsaizvietotu alkēnu sānu ķēdi saturošus tiolānus **14r-s** (25–49 %), izmantojot NIS (I⁺) un PhSeCl (PhSe⁺) propargilsistēmas aktivēšanai. Ciklizēšanās tioacetāta **10j** gadījumā, visticamāk, notiek ar sulfonija jonu **Int-6**, kas sabrūk par tiolānu **14p-s**.



9. shēma. Tiolānu sintēze no tioacetāta **10j**.

Iegūtie rezultāti liecina, ka β -silīcija stabilizētus alilkatjonus var iekšmolekulāri dzēst ar dažādiem *O*-, *N*- un *S*-nukleofiliem, lai iegūtu pieclocēkļu heterociklus, kas satur gemināli divaizvietotas vai stereodefinētas trīsaizvietotas alkēnu sānu virknes. Izmantojot elektrofilos halogenēšanas reaģentus (NBS, NIS) propargilsilānu aktivēšanai, tika iegūtas alkēnu sānu virknes ar (*E/Z*)-selektivitāti līdz pat 95:5. Pilns pētījuma rezultātu izklāsts ir pieejams publikācijā Kroņkalne, R.; Beļainieks, R.; Ubaidullajevs, A.; Mishnev, A.; Turks, M. 1,2-Silyl Shift-Induced Heterocyclization of Propargyl Silanes: Synthesis of Five-Membered Heterocycles Containing a Functionalized Olefin Side Chain. *J. Org. Chem.*, **2023**, 88 (19), 13857-13870. (1. pielikums).^[29]

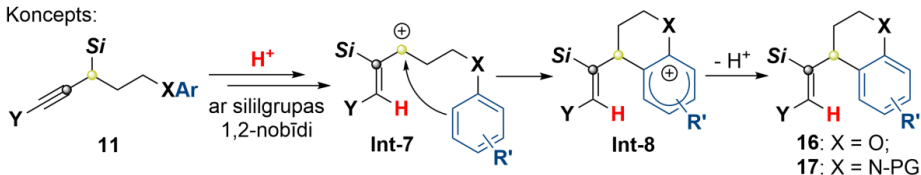
1.2. Propargilsilānu heterociklizācija arēniem kā iekšējiem C-nukleofiliem, reaģējot ar β -silīcija stabilizētu alilkatjonu



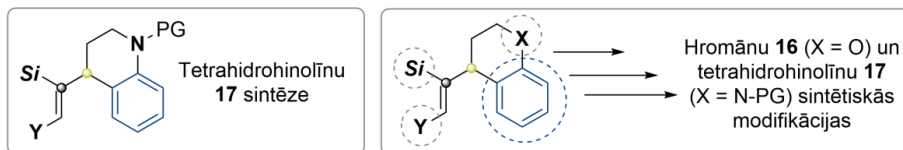
Iepriekšējā nodaļā demonstrēts, kā sililgrupas 1,2-migrācijas rezultātā ģenerētu alilkatjonu var dzēst iekšmolekulāri, veidojot jaunas C-O, C-N un C-S saites. Šī nodaļa veltīta analogiskai pārvērtībai, kurā heterociklizācija norit ar iekšmolekulāru C-C saites veidošanu Frīdela-Kraftsa tipa reakcijā (10. shēma). Alilkatjona **Int-7** iekšmolekulāra dzēšana ar elektroniem bagātu arilsistēmu paver iespējas biciklisku savienojumu sintēzei. Kopā ar Artjomu Ubaidullajevu tika izstrādāta metode biciklisku heterociklu – hromānu **16** (X = O) un tetrahidrohinolīnu **17** (X = N-

PG) sintēzei.^[33] Šajā promocijas darbā apskatīta tetrahidrohinolīnu **17** (X = N-PG) iegūšana no propargilsilāniem, kā arī demonstrēts hromānu **16** (X = O) un tetrahidrohinolīnu **17** (X = N-PG) lietojums tālākās sintētiskās modifikācijās.

Koncepts:



Šajā darbā:



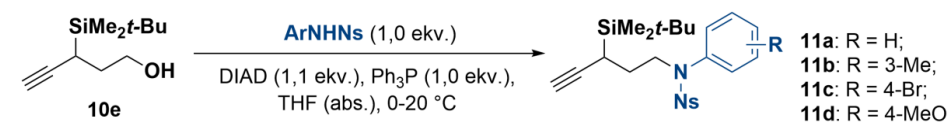
10. shēma. Koncepts propargilsilānu **11** ciklizēšanai Frīdela-Kraftsa tipa reakcijā un produktu **16-17** tālākās modifikēšanas iespējas.

1.2.1. Tetrahidrohinolīnu sintēze no propargilsilāniem

Par stratēģiskajām izejvielām tetrahidrohinolīnu sintēzei tika izvēlēti anilīna funkcionālo grupu saturoši propargilsilāni **11a-f**. Viena no stratēģijām to iegūšanai bija Micunobu (*Mitsunobu*) reakcija starp nozilgrupu saturošiem anilīniem (ArNHNS) un spirta funkcionālo grupu saturošo silānu **10e**, kas deva stratēģiskās izejvielas **11a-d** ar 66–75 % iznākumu (2. tabula).

2. tabula

N-Nozilēta anilīna funkcionalitāti saturošu propargilsilānu sintēze Micunobu reakcijas apstākļos

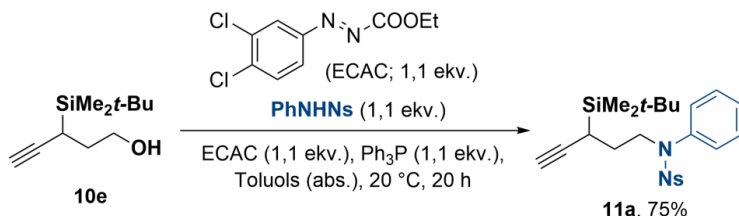


Nr. p. k. ^[a]	Ar	Laiks (h)	Produkts (%) ^[b]
1.	Ph	21,0	11a , 66
2.	<i>m</i> -MeC ₆ H ₄	15,0	11b , 67
3.	<i>p</i> -BrC ₆ H ₄	15,5	11c , 75
4.	<i>p</i> -MeOC ₆ H ₄	17,0	11d , 74

[a] Visas reakcijas tika veiktas 2,5 mmol mērogā. [b] Izdalītais iznākums.

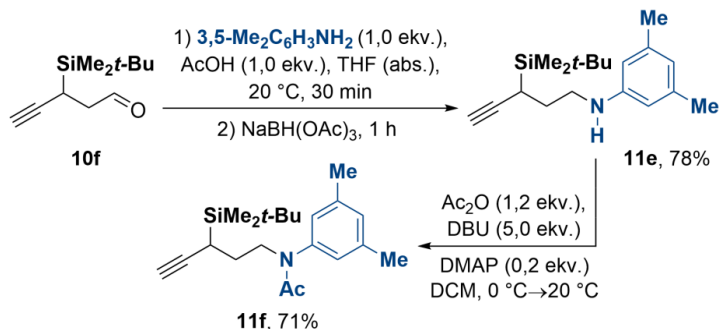
DIAD vietā izmantojot ECAC, kas ir otrās paaudzes Micunobu reaģents, trešējā amīda iznākumi palielinājās (11. shēma). Piemēram, savienojuma **11a** gadījumā iznākums pieauga no

66 % (ar DIAD) līdz 75 % (ar ECAC). Identiskus apstākļus A. Ubaidullajevs izmantoja skābekļa tilpņu saturošu izejvielu **11** (Y = H, X = O) iegūšanai.^[33]



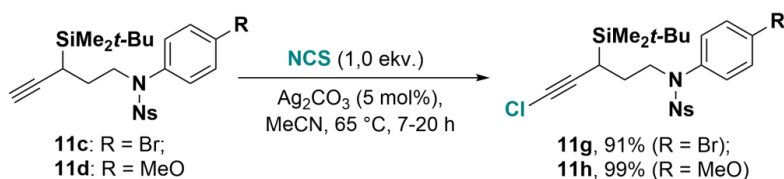
11. shēma. *N*-Nozilēta anilīna funkcionalitāti saturoša propargilsilāna **11a** pagatavošana, izmantojot ECAC reāģentu.

Micunobu stratēģija bija piemērojama tikai ar sulfonilgrupu aizsargātu anilīnu gadījumā. Lai iegūtu ar acetamīda grupu funkcionalizētus propargilsilānus **11f**, tika izmantota aldehīdu reducējošās aminēšanas stratēģija (12. shēma). Aldehīdam **10f** etiķskābes klātbūtnē pievienojot 3,5-dimetilanilīnu, kā starpprodukts izveidojās imīns, kuru reducējot ar NaBH(OAc)₃, tika iegūts produkts **11e**. Sekojoša acetilgrupas uzlikšana ļāva iegūt *N*-acetilētu produktu **11f**.



12. shēma. Ar acetamīda grupu funkcionalizēta propargilsilāna **11f** sintēze, izmantojot reducējošās aminēšanas paņēmieni.

Termināli halogenētu izejvielu **11g-h** iegūšanai propargilsilāni **11c-d** tika apstrādāti ar NCS sudraba katalizatora (Ag₂CO₃, 5 mol%) klātbūtnē. Tas deva vēlamos produktus **11g-h** ar 91–99 % iznākumu (13. shēma).

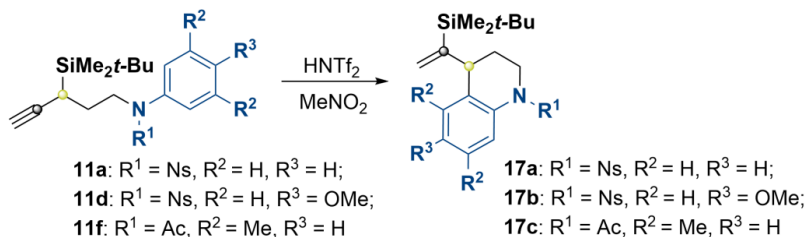


13. shēma. Termināli halogenētu propargilsilānu **11g-h** iegūšana.

Tālāk tika veikti ciklizēšanas eksperimenti ar funkcionalizētiem propargilsilāniem **11**, tos pārvēršot par tetrahidrohinolīna atvasinājumiem **17** (3. tabula). Reakcijas tika veiktas nitrometānā (MeNO₂), izmantojot bistriflimīdu (HNTf₂) kā Brensteda skābi. Reakcijas optimizācija parādīja, ka HNTf₂ ir vēlams pievienot ekvimolārā daudzumā vai nelielā pārkumā – tas saīsināja reakcijas laiku un palielināja produkta **17a** iznākumu. To pašu novēroja A. Ubaidullajevs hromānu sintēzes optimizācijā, kur reakcijas iznākums palielinājās līdz ar pievienotā HNTf₂ daudzumu.^[33]

3. tabula

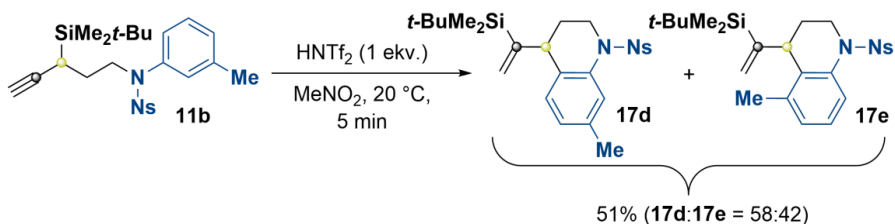
Tetrahidrohinolīnu **17a-c** sintēze no propargilsilāniem **11a**, **11d** un **11f**



Nr. p. k.	Silāns	HNTf ₂ (ekv.)	T (°C)	Laiks (min)	11 (%) ^[a]	Produkts (%)
1.	11a	0,2	50	10	53	17a , 15 ^[a]
2.	11a	0,2	0→20	70	55	17a , 15 ^[a]
3.	11a	0,2	0→20	1020	11	17a , 12 ^[a]
4.	11a	1,0	0	60	0	17a , 41 ^[a] (40 ^[b])
5.	11d	1,0	20	5	0	17b , 47 ^[a] (43 ^[b])
6.	11f	1,0	20	5	40	17c , 10 ^[a]
7.	11f	3,0	20	30	0	17c , 47 ^[a] (45 ^[b])

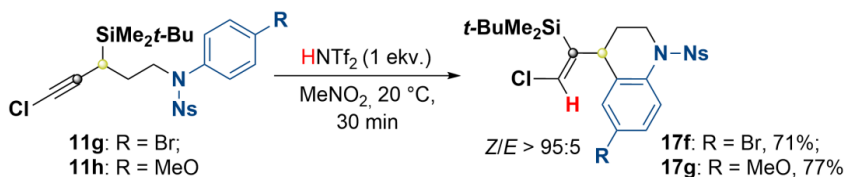
[a] KMR iznākums. [b] Izdalītais iznākums.

Nesimetriski aizvietota anilīna **11b** gadījumā ciklizācija ar HNTf₂ deva reģioizomēru **17d/17e** maisījumu attiecībā 58:42 (14. shēma).



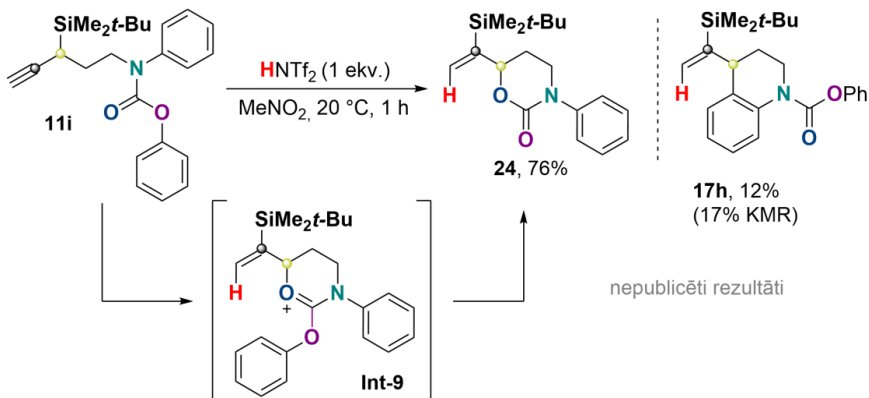
14. shēma. Tetrahidrohinolīnu sintēze no propargilsilāna **11b**, kas satur nesimetriski aizvietotu anilīna fragmentu.

Termināli halogenētu propargilsilānu **11g-h** ciklizēšanas reakcija noritēja ar izcilu *Z/E* selektivitāti, ļaujot iegūt tetrahidrohinolīnus **17f-g** ar 71–77 % iznākumu (15. shēma).



15. shēma. Tetrahidrohinolīnu **17f-g** sintēze no termināli halogenētiem propargilsilāniem.

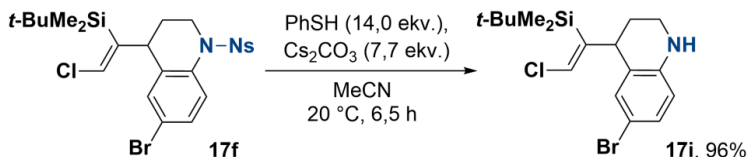
Cita tipa reakcija tika novērota, mēģinot ciklizēt ar karbamāta grupu aizsargātu anilīnu **11i**, kas kā galveno produktu deva 1,3-oksazinān-2-onu **24** ar 76 % iznākumu (16. shēma). Reakcija, visticamāk, notiek ar starpstāvoli **Int-9**. Tetrahidrohinolīns **17h** tika novērots kā minora produkts ar 17 % KMR iznākumu.



16. shēma. 1,3-Oksazinān-2-ona **24** sintēze.

1.2.2. Iegūto tetrahydrohinolīnu un hromānu modificēšanas iespējas

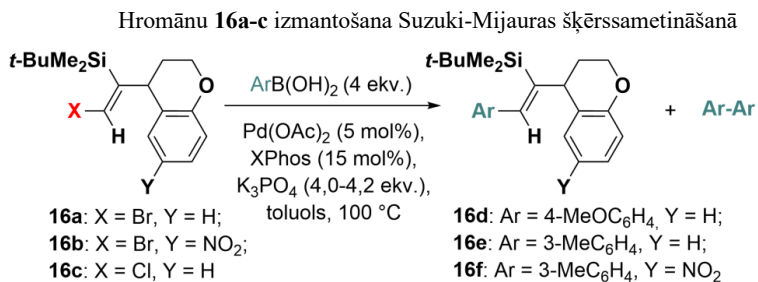
Kā pirmā iespējamā modifikācija tika parādīta *N*-aizsarggrupas noņemšanas iespēja tetrahydrohinolīnos. Klasiskos apstākļos, izmantojot tiofenolu (PhSH) bāzes (Cs_2CO_3) klātbūtnē, ar 96 % iznākumu tika iegūts tetrahydrohinolīns **17i**, kam ir iespējama tālāka *N*-funkcionalizēšana (17. shēma).



17. shēma. Nozilgrupas nošķelšana tetrahydrohinolīna **17i** iegūšanai.

Tālāk ar Suzuki-Mijauras šķērssametināšanas reakciju tika modificēti hromāna atvasinājumi **16a-c** (4. tabula). Vinilbromīda **16a** reakcijā ar 4-metoksifenilborskābi iegūto stirola atvasinājumu **16d** bija grūti atdalīt no pašsametināšanās blakusprodukta (Ar-Ar) abu līdzīgās polaritātes dēļ, līdz ar to hromatogrāfiski izdalītais iznākums bija zems (**16d**, 6 %). Turpretim 3-metilfenilborskābe ar vinilbromīdiem **16a-b** deva vieglāk izdalāmus produktus, un stirolī **16e-f** tika iegūti ar 92–97 % iznākumu. Kā sagaidāms, reakcijas iznākums vinilhlorīda **16c** gadījumā bija būtiski zemāks (**16e**, 27 %) nekā to bromu saturošajiem analogiem **16a-b**.

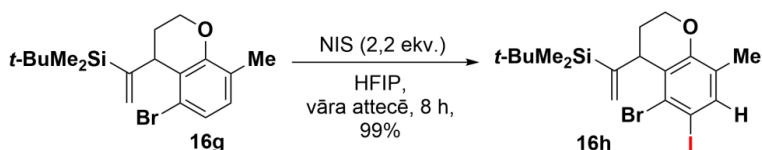
4. tabula



Nr. p. k.	X	Y	Ar	t (h)	Produkts (%)
1. ^[c, d]	Br	H	4-MeOC ₆ H ₄	14	16d , 45 ^[a] , 6 ^[b]
2.	Br	H	3-MeC ₆ H ₄	44	16e , 97 ^[b]
3.	Br	NO ₂	3-MeC ₆ H ₄	22	16f , 92 ^[b]
4.	Cl	H	3-MeC ₆ H ₄	26	16e , 27 ^[b]

[a] KMR iznākums (%). [b] Izdalītais iznākums (%). [c] Šķērssametināšanas produkts **16d** veidoja nesadalāmu maisījumu ar pašsametināšanās blakusproduktu (Ar-Ar). [d] Modificēti reakcijas apstākļi: 3 ekv. $\text{ArB}(\text{OH})_2$, 7 mol% $\text{Pd}(\text{OAc})_2$, 21 mol% XPhos, 4,9 ekv. K_3PO_4 .

Līdzīgi, kā tas aprakstīts promocijas darba autores un kolēģu grupas iepriekšējos darbos,^[19, 29] tika veikta sililgrupas-halogēna apmaiņa hromānam **16g**, izmantojot NIS heksafluorizopropanolā (HFIP). Pārsteidzošā kārtā, pat izmantojot NIS pārākumu (2,2 ekv.) un reakciju vārot, *Si*→*I* apmaiņa nenotika. Tā vietā tika iegūts arilgredzenā monojodētais produkts **16h** ar kvantitatīvu iznākumu (18. shēma).

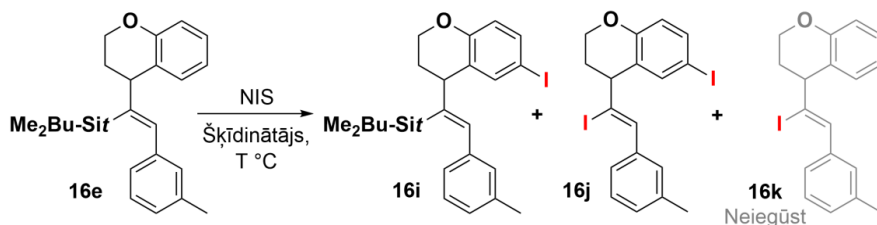


18. shēma. Arilsistēmā monojodētā produkta **16h** iegūšana.

Si→*Hal* apmaiņa notiek caur silīcija-virzītu elektrofila (Hal^+) pievienošanās vinilsilānam $\text{R}_2\text{C}=\text{C}(\text{Si})-\text{R}'$, veidojot β -silīcija stabilizētu karbēnija jona starpsavienojumu $\text{R}_2\text{C}^+-\text{C}(\text{Si})(\text{Hal})-\text{R}'$.^[34] Terminālu vinilsilānu gadījumā veidotos destabilizēts pirmējais karbēnija jons, kas padara reakciju nevēlamu. Savukārt stirola atvasinājuma **16e** gadījumā reakcija var noritēt, veidojoties iespējamam benzilkatjona starpsavienojumam. Jodēšanas eksperimenti stirola atvasinājumam **16e** apstiprināja šo hipotēzi, kur tika novērota gan arilsistēmas jodēšanās, gan *Si*→*I* apmaiņa (5. tabula).

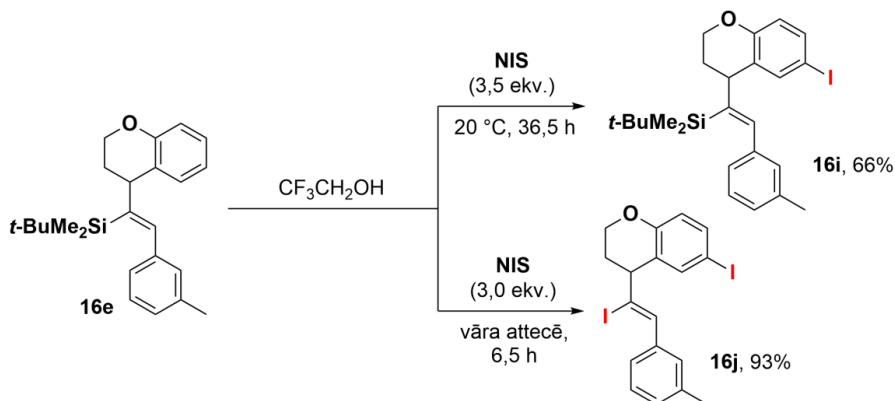
5. tabula

Jodēšanas eksperimenti stirola atvasinājumam **16e**



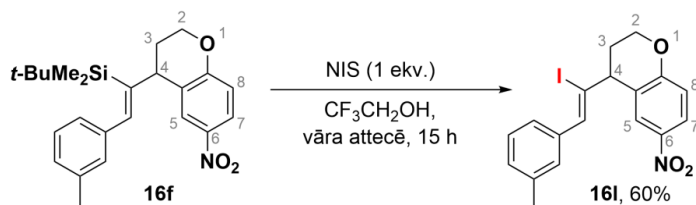
Nr. p. k.	NIS (ekv.)	Šķīdinātājs	T °C	Laiks (h)	Izejvielas 16e / produktu 16i-j molārā attiecība KMR		
					16e	16i	16j
1.	1,0	HFIP	20	0,5	31	49	20
2.	2,5			1,5	0	0	100
3.	1,0	TFE		18,0	33	67	0
4.	2,0			17,5	20	80	0
5.	3,5			36,5	13	87	0
6.	10,8			1,5	5	35	60
7.	1,0		75–80	6,5	38	62	0
8	3,0	71,0		28	72	0	
		6,5		0	0	100	

Jodējot stirola atvasinājumu **16e** ar ekvimolāru daudzumu NIS, izmantojot HFIP kā šķīdinātāju, tika iegūts maisījums ar monojodēto produktu **16i** un diiodēto produktu **16j** (49:20), bet NIS pārākumā (2,5 ekv.) tika iegūts vienīgi diiodētais produkts **16j**. Izmantojot TFE kā šķīdinātāju, reakcija notika ievērojami lēnāk, kas ļāva vieglāk kontrolēt produktu veidošanos atkarībā no reakcijas laika. Apstādinot reakciju pēc 36,5 h, tika iegūts monojodētais produkts **16i** ar 66 % iznākumu (71 % KMR). Augsts diiodētā produkta **16j** iznākums (93 % izdalīts) tika iegūts, hromānam **16e** pievienojot NIS pārākumu (3 ekv.) un karsējot 75–80 °C (spiediena mēģenē) 6,5 h (19. shēma).



19. shēma. Hromāna **16e** mono- un diiodēšanas eksperimenti optimizētos apstākļos.

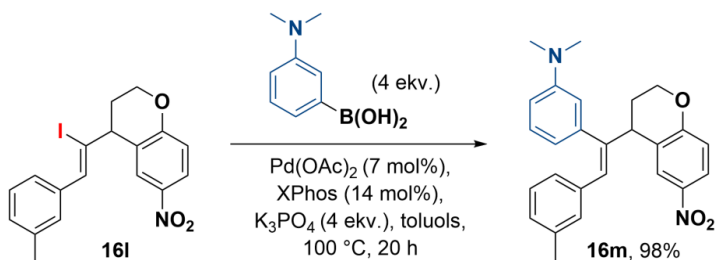
Ievadot hromāna 6. pozīcijā elektronatvelkošo nitrogrupu, aromātiskā gredzena jodēšanās iepriekš minētajos apstākļos vairs netika novērota. Hromānam **16f** paaugstinātā temperatūrā reaģējot ar NIS (1 ekv.) trifluoetanolā, selektīvi notika silīcija – joda apmaiņa, kas ļāva iegūt viniljodīdu **16l** ar 60 % iznākumu (20. shēma).



20. shēma. Si→I apmaiņas reakcija hromānā **16f**.

Noslēdzot hromānu tālāko modifikāciju tēmu, tika demonstrēts iegūtā viniljodīda **16l** lietojums šķērssametīnāšanā Suzuki-Mijauras apstākļos (21. shēma). Izmantojot (3-

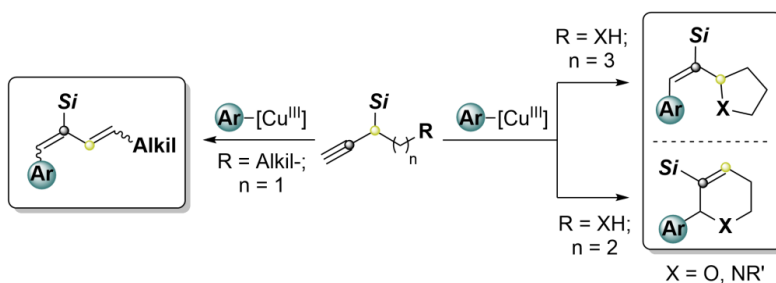
(dimetilamino)fenil)borskābi kā reaģentu, pallādija katalīzes apstākļos tika iegūts šķērssametināšanas produkts **16m** ar iznākumu tuvu kvantitatīvam (98 % izdalīts).



21. shēma. Viniljodīda **16l** lietojums Suzuki-Mijauras šķērssametināšanā.

Šajā nodaļā parādīts, ka Brensteda skābes katalīzes apstākļos propargilsilāni, kas caur slāpekļa tiltiņu ir funkcionalizēti ar arilgrupu, Frīdela-Kraftsa tipa reakcijā ciklizējas par tetrahidrohinolīna **17** atvasinājumiem. Termināli hlorētu propargilsilānu **11g-h** gadījumā ciklizēšanās reakcija ir augsti stereoselektīva, un tiek iegūti produkti **17f-g** ar (*Z*)-ģeometriju alkēnu sānu virknē. Rezultējošās vinilhalīdu sānu virknes var modificēt Suzuki-Mijauras šķērssametināšanas reakcijās, savukārt sililgrupu var aizstāt ar jodu elektrofilās apmaiņas reakcijā sintētiski noderīgu viniljodīda fragmentu iegūšanai. Pilns pētījuma rezultātu izklāsts pieejams publikācijā Ubaidullajevs, A.; Kronkalne, R.; Mishnev, A.; Turks, M. Synthesis of Substituted Chromanes and Tetrahydroquinolines *via* Tandem 1,2-Silyl Shift – Friedel–Crafts cyclization. *J. Org. Chem.*, **2026**, *91* (17), 5785–5810 (2. pielikums).^[33]

1.3. Arilētu heterociklu un diēnu sintēze reakcijā ar diaril- λ^3 -jodāniem vara katalīzes apstākļos

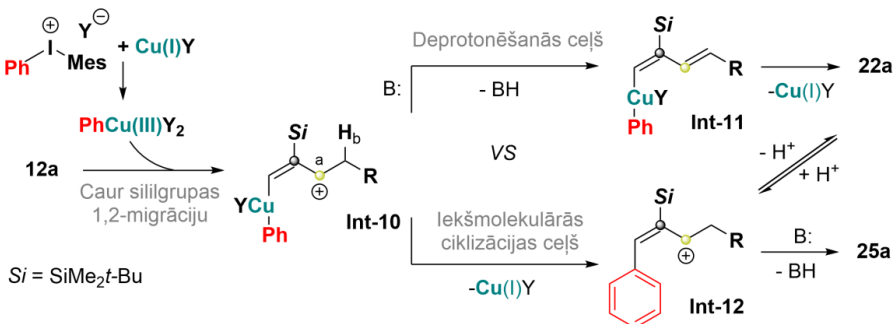
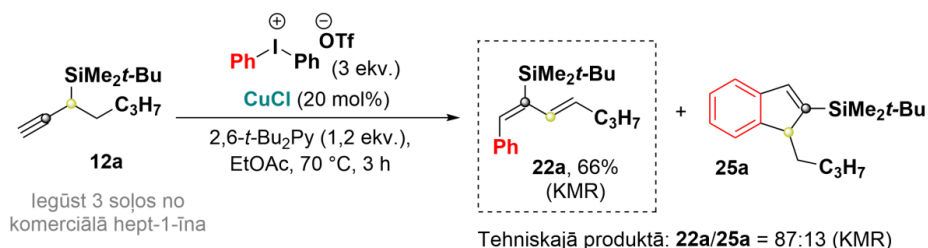


Iepriekš tika apskatīta propargilsilānu aktivēšana heterociklu sintēzei, izmantojot Brensteda skābes vai elektrofilos halogenēšanas reaģentus. Oglekļa elektrofilu izmantošana analogiskas

pārvērtības īstenošanai ir atsevišķs pētījumu virziens, kas tika izstrādāts kopā ar Rūdolfu Beļunieku un Armandu Sebri.^[35]

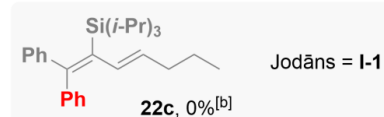
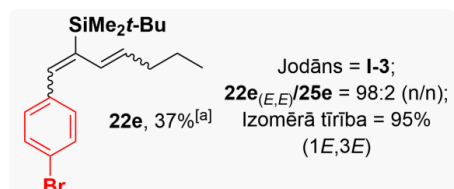
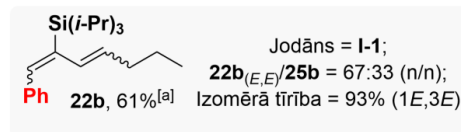
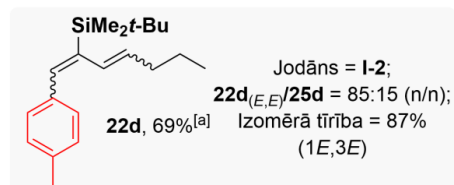
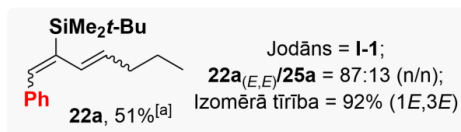
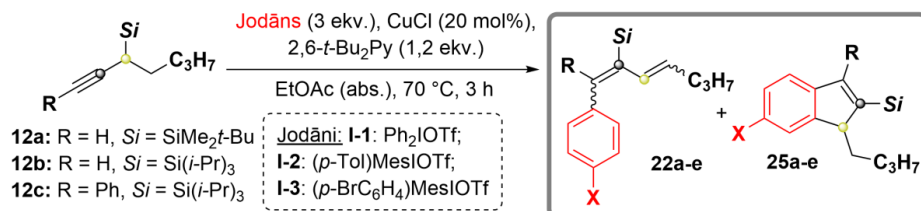
Diaryl- λ^3 -jodānus izmanto arilgrupas ievadīšanai π -sistēmās, kur arilgrupa nodrošina formālo Ar^+ sintonu, tostarp alkīnu 1,2-difunkcionalizēšanas reakcijās.^[36] Šādos gadījumos hipervalentā joda(III) reaģentus aktivē ar vara vai pallādija katalizatoriem.^[37, 38] Tā kā propargilsilāni elektrofilās aktivācijas apstākļos spēj dod formālus 1,3-dipolus, ko nodrošina sililgrupas 1,2-nobīde, var panākt 1,3-difunkcionalizēšanu, kas ir daudz retāk sastopama par 1,2-difunkcionalizēšanu. Šajā darbā tika izstrādāta vara katalizēta metode diaryl- λ^3 -jodānu izmantošanai propargilsilānu 1,3-difunkcionalizēšanas reakcijās dažādu sānu virknē arilētu heterociklu un silildiēnu iegūšanai.

Meklējot piemērotus reakcijas apstākļus propargilsilānu arilēšanai, tika nolemts iesākt ar vienkāršākajiem substrātiem – alkilvirkni saturošiem silāniem **12a**.^[18] Tika novērots, ka reakcijas gaitā veidojās arilēta silildiēna **22a** un sililindēna **25a** maisījums (22. shēma). Šo produktu veidošanos var skaidrot ar divu konkurējošu reakciju norisi, kur vienā no gadījumiem eliminējas alilkatjona **Int-10** β -pozīcijas protons, veidojot diēnu **22a**. Otrā gadījumā notiek starpsavienojuma **Int-12** iekšmolekulāra ciklizēšanās, kas rezultējas sililindēnos **25a**. Optimizētos apstākļos (3 ekv. Ph_2IOTf , 20 mol% $CuCl$, 1,2 ekv. 2,6-*t*-Bu₂Py, EtOAc, 70 °C) silildiēna **22a**/indēna **25a** attiecība reakcijas maisījumā bija 87:13, diēna **22a** iznākums – 66 % pēc KMR. Izmantojot $PhMesIOTf$, tika iegūts līdzīgs diēna **22a** iznākums (59 % pēc KMR), bet diēna **22a** veidošanās selektivitāte bija zemāka ($PhMesIOTf$: **22a**/**25a** = 71:22).



22. shēma. Arilēta silildiēna **22a** sintēze – reakcijas koncepts un konkurējošās reakcijas.

Izmantojot apstākļus, kuros var iegūt augstākos diēna **22a** iznākumus, tika turpināts apskatīt substrātu klāstu (23. shēma). Arilēšanas reakcijā ar elektroniem bagātu arilsistēmu (*p*-Tol) saturošo jodānu **I-2** tika iegūti augstākie iznākumi (**22d**, 69 %). Visaugstākā selektivitāte attiecībā pret diēna veidošanos (**22e/25e** = 98:2) tika iegūta reakcijā ar *p*-bromaizvietoto jodānu **I-3**. No substrātiem **12b**, kas saturēja stēriski apjomīgo triizopropilsililgrupu (TIPS), tika iegūts maisījums ar palielinātu indēna proporciju (**22b/25b** = 67:33). Visos gadījumos (1*E*,3*E*)-diēni **22a-e** tika iegūti kā mažorie izomēri, kur (1*E*,3*E*)-izomēra saturs maisījumā bija 87–95 %. Nelielos daudzumos varēja detektēt arī pārējos izomērus ((1*Z*,3*E*)-, (1*E*,3*Z*)- un (1*Z*,3*Z*)-**22**) pēc to raksturīgajiem signāliem ¹H-KMR spektros. Iekšējais alkīns **12c** (R = Ph, Si = TIPS) nereaģēja ne standarta reakcijas apstākļos (EtOAc, 70 °C), ne arī paaugstinātā temperatūrā (*n*-BuOAc, 110 °C). Abos gadījumos tika atgūta izejviela bez degradācijas pazīmēm. Tas liecināja, ka šī metode ir izmantojama tikai propargilsilāniem, kas satur terminālas alkīna grupas.



[a] - Iznākums **22** + **25** maisījumam.
 [b] - Reakcija nenotiek arī 110 °C BuOAc (17 h).

23. shēma. Substrātu klāsts arilētiem silildiēniem.

Iepriekš tika demonstrēts, ka iekšējus nukleofilus saturoši substrāti paver iespējas heterociklizācijai. Piemēram, terminālo spirta grupu saturošais propargilsilāns **10a** tika izmantots tetrahidrofurānu sintēzei.^[29] Sānu virknē arilētu tetrahidrofurānu sintēzei tika testēti dažādi Cu(I) katalizatori (6. tabula), kur CuCl un CuOTf benzola komplekss deva līdzīgi labus iznākumus

(**15a**, 82–84 % KMR), CuBF₄ acetonitrila komplekss bija nākamā labākā izvēle (**15a**, 77 %), savukārt heterogēnās katalīzes apstākļos ar Cu₂O tika iegūts maisījums ar arilēto produktu **15a** un protodemetalēšanas blakusproduktu **14a**, kur abiem bija zems iznākums. Nepievienojot reakcijas maisījumam nenukleofilu bāzi (2,6-di-*tert*-butilpiridīnu = 2,6-*t*-Bu₂Py), iespējams selektīvi iegūt protodemetalēšanas produktu **14a** (69 % KMR iznākums). Strukturāli līdzīgais, bet mazāk stēriski traucētais lutidīns, kā arī Et₃N, arilēšanas-heterociklizēšanas reakcijā nedeķa vēlamo produktu **15a**.

Iegūtās C=C saites ģeometrija produktā **15a** tika pierādīta ar 2D-KMR NOESY spektroskopiju. Arilēšanas-ciklizēšanas kaskādes reakcija uzrādīja augstu stereoselektivitāti – vienīgais ar spektroskopiskām metodēm detektējais C=C saites izomērs bija (*E*)-**15a**.

6. tabula

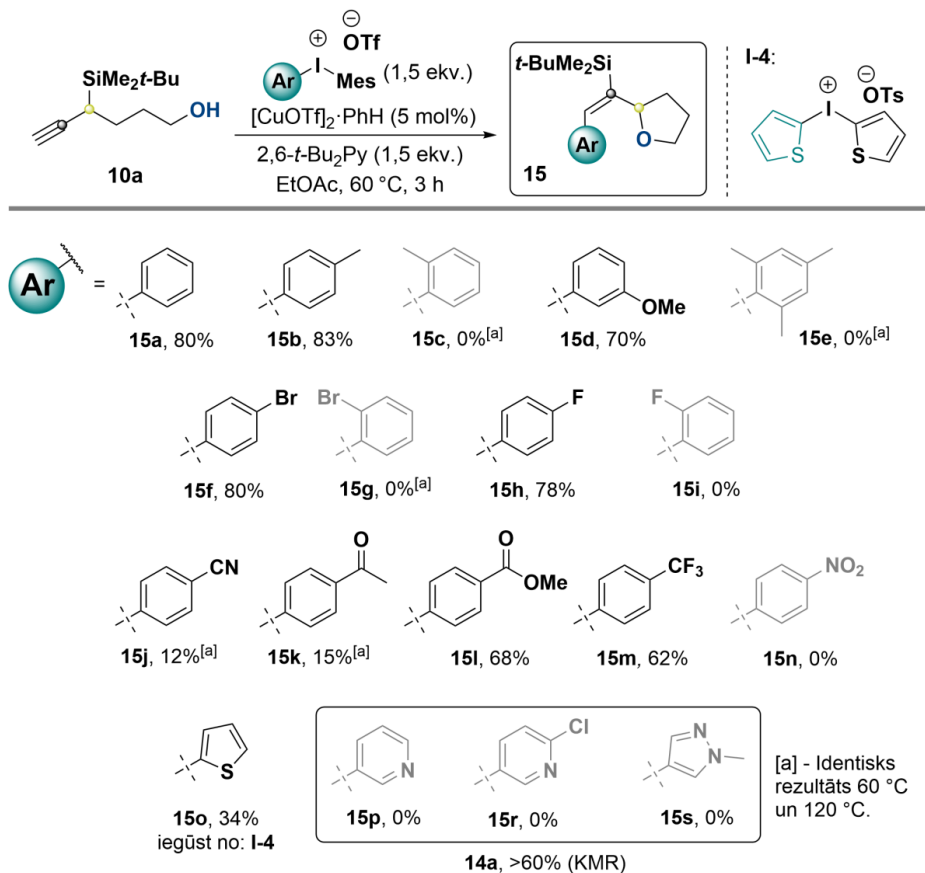
Propargilsilāna **10a** arilēšanas-heterociklizēšanas reakcijas optimizācija, variējot Cu(I) katalizatorus un temperatūru

Nr. p. k.	CuX (mol%)	T (°C)	15a , % (KMR)	14a , % (KMR)
1. ^[a]	CuCl (2,5)	20	0	69
2.	CuCl (2,5)	20	0	0
3.	CuCl (5)	60	82, 76^[c]	0
4.	CuI (5)	60	0	0
5. ^[b]	[CuOTf] ₂ ·PhH (5)	60	84	0
6.	Cu(MeCN) ₄ BF ₄ (5)	70	77	0
7.	Cu ₂ O (5)	70	6	2
8.	[CuOTf] ₂ ·PhH (2,5)	70	70	0
9. ^[d]	[CuOTf] ₂ ·PhH (2,5)	70	43	0
10.	[CuOTf] ₂ ·PhH (11)	70	47	0

[a] Bez 2,6-*t*-Bu₂Py. [b] Reakcijas laiks – 2 h (pilna konversija). [c] Izdalītais iznākums (%). [d] 15 mol% of H₂O kā piedeva.

Optimizētajos apstākļos ar dažādiem diaril-λ³-jodāniem tika panākta arī citu arilgrupu ievadišana molekulā (24. shēma). Jodāni, kas saturēja elektroniem bagātas arilgrupas (*p*-Tol, *m*-MeOC₆H₄, Ph) vai halogēnus (Br, F), deva labus arilēto tetrahidrofurānu **15** iznākumus (70–83 %). Turpretim elektronatvelkošas grupas saturoši jodāni, īpaši tie, kas satur nukleofilus

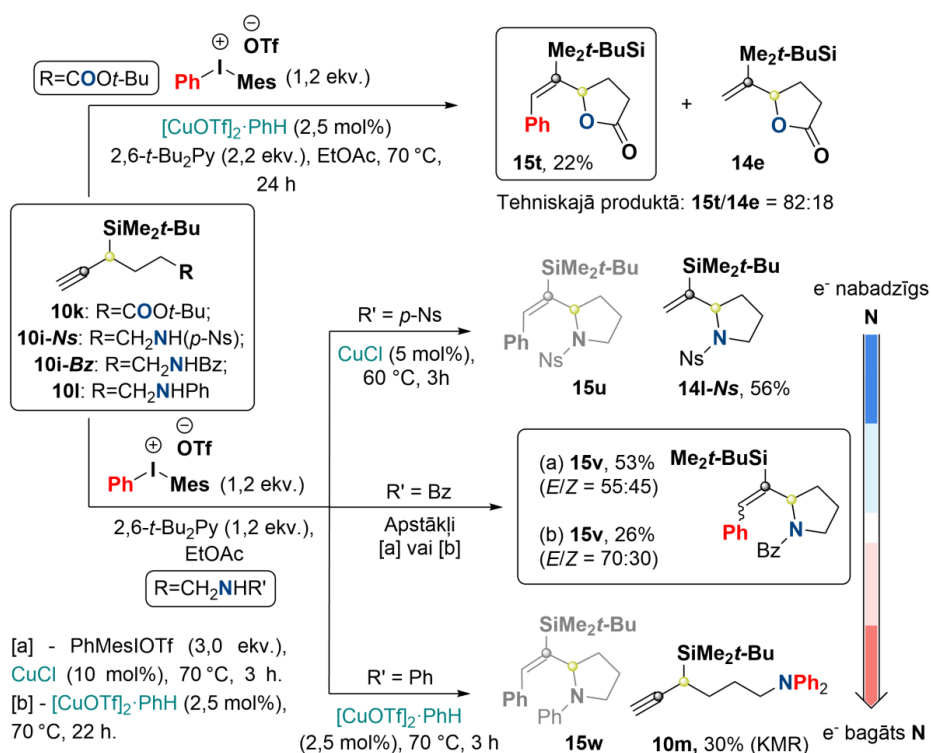
heteroatomus ($CN \approx COR \gg NO_2$), reaģēja vāji. Savukārt jodāni, kas saturēja citas elektronatvelkošas grupas (CF_3 , CO_2Me), deva vidējus iznākumus (62–68 %). *Orto*-aizvietoti jodāni neatkarīgi no to elektroniskajām īpašībām nereaģēja vispār. Jodāni, kas saturēja *N*-heterociklus, kā piridīnu vai pirazolu, deva nearilēto tetrahidrofurānu **14a** kā galveno reakcijas produktu, kas, visticamāk, radās pēc protodekuperēšanas mehānisma. Tiofēnilgrupu gan varēja veiksmīgi izmantot propargilsilānu hetarilēšanai, par reaģentu lietojot simetrisko ditiofēn-2-iljodonija *p*-tozilātu (**I-4**). Ir vērts pieminēt, ka visi arilētie tetrahidrofurāni tika iegūti ar ekskluzīvu (*E*)-selektivitāti alkēnu sānu ķēdē.



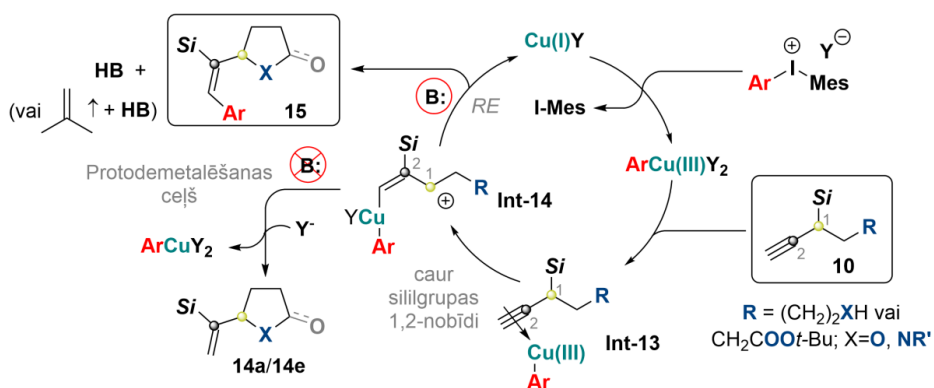
24. shēma. Substrātu klāsts stīrilaizvietotu tetrahidrofurānu sintēzei.

Interesanti, ka iepriekš aprakstītajos arilēšanas apstākļos tikai iekšēji *O*-nukleofīli reakcijā deva 1,3-difunkcionalizētus produktus. Arēju *O*-nukleofīlu R-OX (5 ekv.) klātbūtnē alifātisko sānu ķēdi saturošā propargilsilāna **12b** arilēšanas mēģinājums rezultējās *O*-nukleofīla arilēšanā. Tas tika novērots spirtiem, karbonskābēm, to nātrija sāļiem un sililētām karbonskābēm.

Tālāk autore un kolēģi vēlējās noskaidrot, kādi citi iekšējie nukleofili ir savietojami ar arilēšanas-heterociklizācijas reakcijas apstākļiem (25. shēma). Karbonskābi saturošais silāns **10b** nedeva vēlamo laktona **15t** produktu karbonskābes *O*-arilēšanās dēļ. Savukārt *tert*-butilesteris **10t** deva gaidīto arilēšanas produktu **15t** kopā ar protodekuprēšanas produktu **14e**, kas tika iegūts pārākumā standarta arilēšanas apstākļos (1,2 ekv. ArMesIOTf, 5 mol% [CuOTf]₂·PhH, 1,2 ekv. 2,6-*t*-Bu₂Py, EtOAc, 60 °C, 3h). Lielāks pievienotās bāzes daudzums (kopā 2,2 ekv. 2,6-*t*-Bu₂Py) palīdzēja iegūt arilēto laktonu **15t** kā galveno reakcijas produktu. *N*-Nozilētā izejviela **10i-Ns** standarta arilēšanas reakcijas apstākļos deva fenilgrupu nesaturošo pirolidīnu **14i-Ns** ar 56 % iznākumu. Šajā gadījumā sulfonamīda N-H bija pārāk skābs, un tas veicināja protodekuprēšanos. Turpretī benzamīds **10i-Bz** arilējošos apstākļos deva arilēto pirolidīna atvasinājumu **15v** kā C=C saites izomēru maisījumu (*E/Z* = 55:45). Anilīna **10l** (R = CH₂NHPh) gadījumā notika N-H arilēšanās, nevis heterociklizācija, kas liecina par pārāk augstu *N*-nukleofilītāti. No šiem rezultātiem var secināt, ka acilamīdiem piemīt optimāls pK_a un nukleofilītāte, lai reaģētu atbilstoši vēlamo arilēšanas-heterociklizācijas mehānismam.

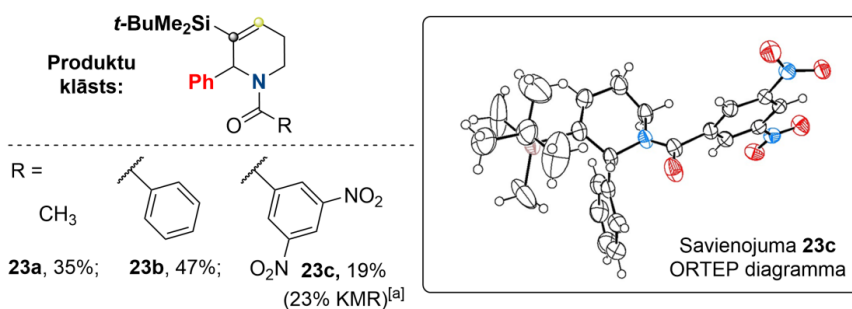
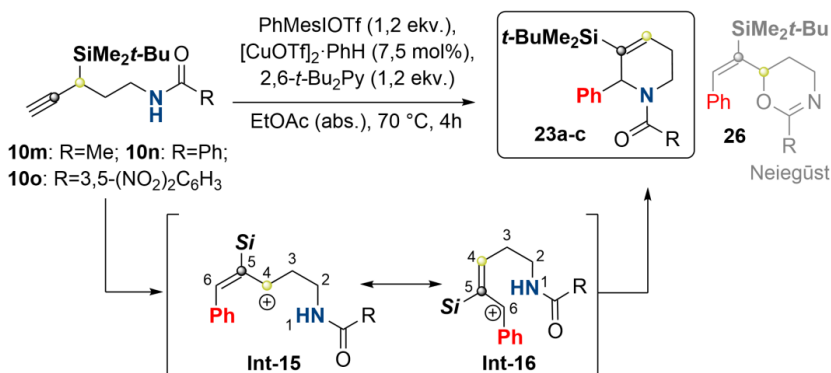


Pētot arilētu silildiēnu **22a** sintēzi (3. pielikums), tika noskaidrots, ka šī tipa reakcijā Cu(I) sāļi ir reaģētspējīgāki nekā Cu(II) sāļi. Tas netieši liecina par to, ka, visticamāk, reakcija notiek ar Cu(I/III) katalītisko ciklu. Balstoties eksperimentālajos novērojumos, kā arī literatūrā iztirtajos mehānismos π -sistēmu arilēšanai vara katalīzes apstākļos,^[37] tika piedāvāts arilēšanas-heterociklizēšanas reakcijas mehānisms (26. shēma). Vispirms vara(I) sāls reaģē ar diaril- λ^3 -jodānu (ArMesIY), lai ģenerētu arilvaru(III), kas kā spēcīgs elektrofilis aktivē propargilsistēmu, inducējot sililgrupas 1,2-nobīdi. Tas rezultējas β -silīcija efekta stabilizētā alilkatjona starpstāvoklī **Int-14**. Sekojošs iekšējā nukleofila (O-, N-) uzbrukums un reducējošā eliminācija dod arilētus heterociklus **15** ar vienlaicīgu Cu(I) katalizatora reģenerāciju. Pievienotā bāze (B = 2,6-*t*-Bu₂Py) neitralizē katalītiskajā ciklā ģenerēto H⁺. *Terc*-butilestera **10k** gadījumā papildus tiek ģenerēts viens ekvivalents izobutilēna gāzes. Ja reakcijā netiek pievienota bāze, protodekuprēšanas mehānisms ir dominējošais un galvenokārt veidojas arilgrupu nesaturoši heterocikli **14a/14e**.



26. shēma. Piedāvātais mehānisms propargilsilānu arilēšanas-heterociklizēšanas reakciju kaskādei.

Mainot oglekļa atomu virknes izmēru, ir iespējamas reakcijas mehānisma variācijas, kā tas tika novērots, veicot reakcijas ar acilamīdiem **10m-o**. Sākotnēji tika sagaidīta imidāta **26** veidošanās,^[39] taču tika iegūti tetrahidropiridīni **23a-c**, kas veidojās caur nukleofila uzbrukumu alilkatjona rezonanses formai **Int-16**, kurai piemīt papildu arilgrupas stabilizācija (27. shēma). Iegūtā tetrahidropiridīna **23c** struktūra viennozīmīgi tika pierādīta ar rentgenstruktūranalīzes palīdzību.

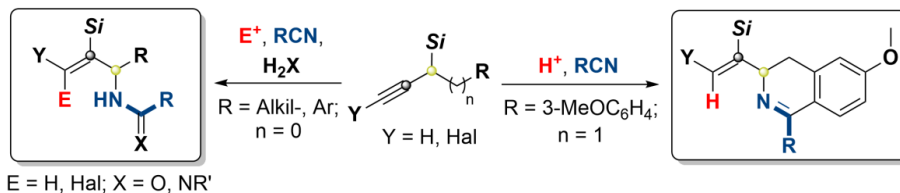


[a] - Modificēti apstākļi: **Ph₂IOTf** (3,0 ekv.), 20 h.

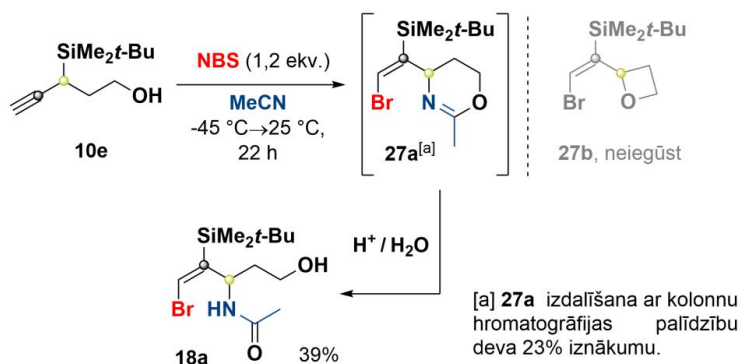
27. shēma. Tetrahidropiridīnu **23** sintēze no propargilsilāniem.

No iegūtajiem rezultātiem var secināt, ka alilkatjonu, kurus iegūst no iekšēju nukleofilu saturošiem propargilsilāniem **10**, iekšmolekulāras dzēšanas reģioselektivitāti nosaka izejvielas oglekļa atomu virknes izmērs. Substrātiem, kur ir iespējama pieclocekļu cikla veidošanās, tiek novērota 1,3-difunkcionalizēšana, kur rodas tetrahidrofurāni **15** (X = O) vai pirolidīni **15** (X = N-PG), kas sānu ķēdē funkcionalizēti ar stirilgrupu. Substrātiem **10m-o**, kas satur īsākas sānu virknes, tika novērota 1,1-difunkcionalizēšana, kur veidojās tetrahidropiridīni **23**. Demonstrētā pieeja izrādījās efektīvāka stirilgrupu saturošu heterociklu **15** sintēzei, salīdzinot ar iepriekš zināmajām stratēģijām.^[29] Pilns pētījuma rezultātu izklāsts ir pieejams publikācijā Kronkalne, R.; Beļunnieks, R.; Sebris, A.; Mishnev, A.; Turks, M. Aryl Iodane-Induced Cascade Arylation–1,2-Silyl Shift–Heterocyclization of Propargylsilanes under Copper Catalysis. *Beilstein J. Org. Chem.*, **2025**, *21*, 1984–1994 (3. pielikums).^[35]

1.4. Ritera tipa reakcija ar β -silīcija stabilizētu alilkatjonu

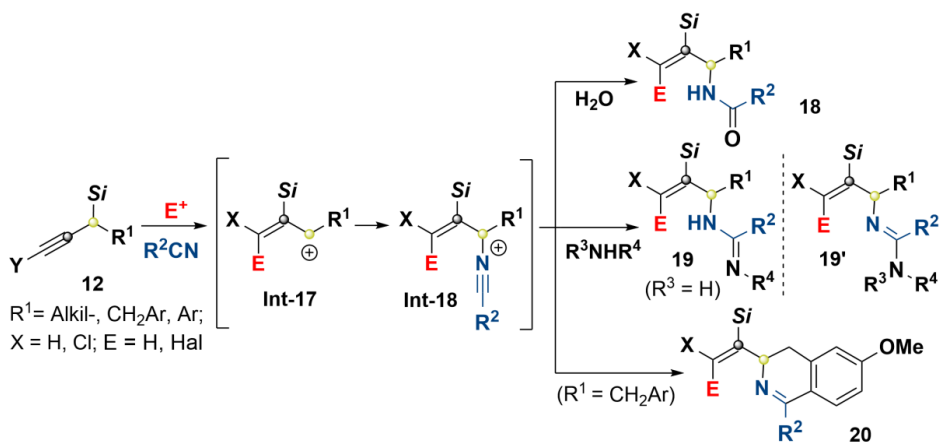


Mēģinot heterociklizēt spirtu **10e** NBS klātbūtnē analogiski 1.1. nodaļā aprakstītajām pārvērtībām, taču izmantojot acetonitrilu (MeCN) kā šķīdinātāju, tika novērota Ritera tipa reakcija, kur tika iegūts oksazīna atvasinājums **27a**, nevis gaidītais oksetāna atvasinājums **27b** (28. shēma). Cikliskais produkts **27a** viegli hidrolizējās par acetamīdu **18a** – klasisko Ritera reakcijas produktu.



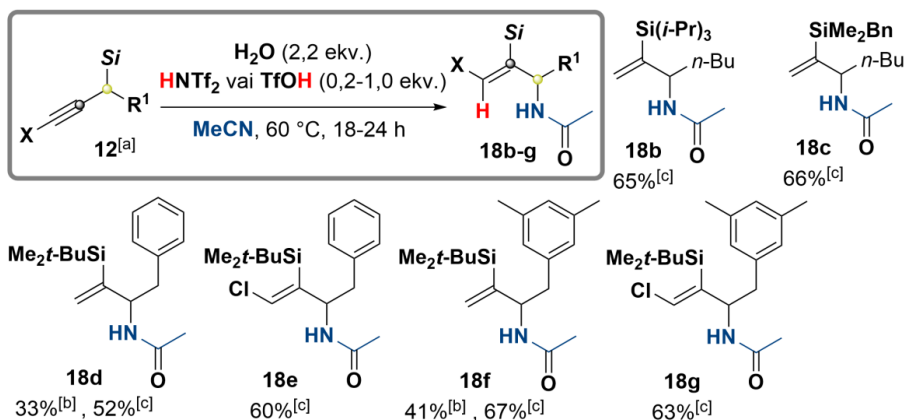
28. shēma. Spirta **10e** heterociklizēšana Ritera tipa reakcijas apstākļos.

Lietojot nitrilus, tie kā primārais nukleofils pievienojas alilkatjonam **Int-17**, veidojot nitrilija jonu **Int-18**, kas tiek dzēsts ar sekundāro nukleofīlu (H_2O , R^1R^2NH , Ar). Tas dod iespēju sintezēt gan cikliskus, gan acikliskus produktus, ko vieno funkcionālizētas alkēnu sānu virknes klātbūtne (29. shēma). Apskatītā daudzkomponentu reakcija ir izaicinoša no entropijas skatupunkta, jo ir jāpanāk secīga četru kovalento saišu veidošanās, reakcijas komponentēm reaģējot vēlamajā secībā. Neskatoties uz sistēmas sarežģītību, kopā ar Sandru Turku,^[40] Raimonu Rogaļevu^[41] un Miku Puriņu^[42] tika izstrādāta metodoloģija propargilsilānu izmantošanai funkcionālizētu alilamīdu **18**, amidīnu **19** un dihidroizohinolīnu **20** sintēzei Ritera tipa reakcijas apstākļos.



29. shēma. Propargilsilānu lietojums Ritera tipa reakcijā.

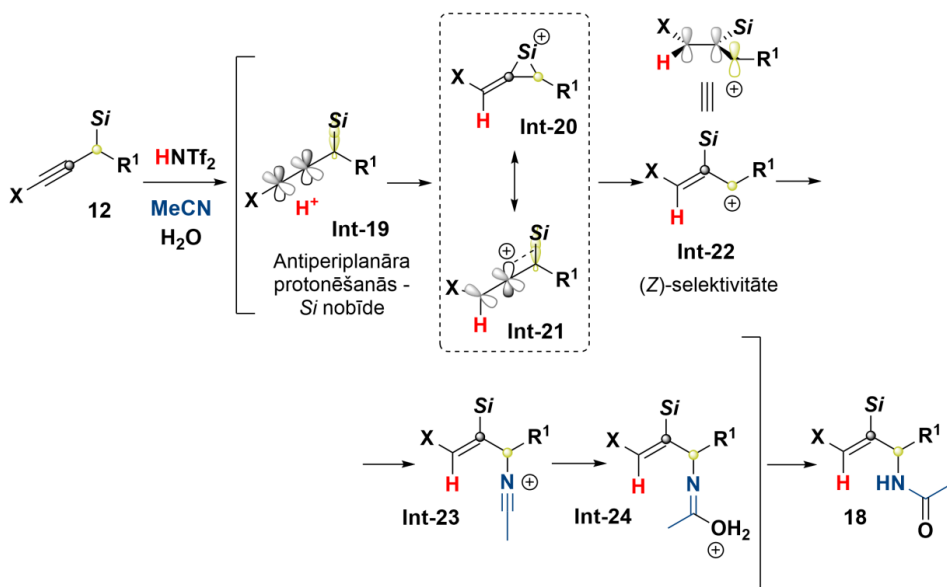
Vispirms tika apskatītas sistēmas, kur reakcijas apstākļi ir visvairāk pietuvināti klasiskajiem Ritera reakcijas apstākļiem, kas apvieno Brensteda skābi (TfOH vai HNTf₂) karbkatjona ģenerēšanai, MeCN kā primāro nukleofilu un šķīdinātāju, kā arī ūdeni kā sekundāro nukleofilu. Šādos apstākļos tika iegūti alilamīda funkcionalitāti saturoši produkti **18b-g** (30. shēma). Tika novērots, ka, izmantojot ekvimolāru daudzumu skābes (1 ekv. HNTf₂: **18f**, 67 %), produktu iznākumi bija augstāki nekā ar katalītisku skābes daudzumu (0,2 ekv. TfOH: **18f**, 41 %). Termināli halogenētu propargilsilānu **12** (X = Cl) gadījumā tika iegūti trīsaizvietotu C=C saiti saturoši produkti **18e** un **18g**, kas reakcijas maisījuma ¹H-KMR spektrā tika novēroti kā (Z/E)-isomēru maisījums (9:1). Mažorais (Z)-izomērs tika izdalīts ar kolonnu hromatogrāfijas palīdzību.



[a] Silāni: **12b** ($\text{X} = \text{H}$, $\text{R}^1 = n\text{-Bu}$, $\text{Si} = (i\text{-Pr})_3\text{Si}$), **12d** ($\text{X} = \text{H}$, $\text{R}^1 = n\text{-Bu}$, $\text{Si} = \text{BnMe}_2\text{Si}$), **12e** ($\text{X} = \text{H}$, $\text{R}^1 = \text{Bn}$, $\text{Si} = t\text{-BuMe}_2\text{Si}$), **12f** ($\text{X} = \text{Cl}$, $\text{R}^1 = \text{Bn}$, $\text{Si} = t\text{-BuMe}_2\text{Si}$), **12g** ($\text{X} = \text{H}$, $\text{R}^1 = \text{CH}_2(3,5\text{-Me}_2\text{C}_6\text{H}_3)$, $\text{Si} = t\text{-BuMe}_2\text{Si}$), **12h** ($\text{X} = \text{Cl}$, $\text{R}^1 = \text{CH}_2(3,5\text{-Me}_2\text{C}_6\text{H}_3)$, $\text{Si} = t\text{-BuMe}_2\text{Si}$). [b] 0.2 ekv. TfOH kā H^+ avots. [c] 1 ekv. HNTf_2 kā H^+ avots.

30. shēma. Alilamīdu sintēze no propargilsilāniem.

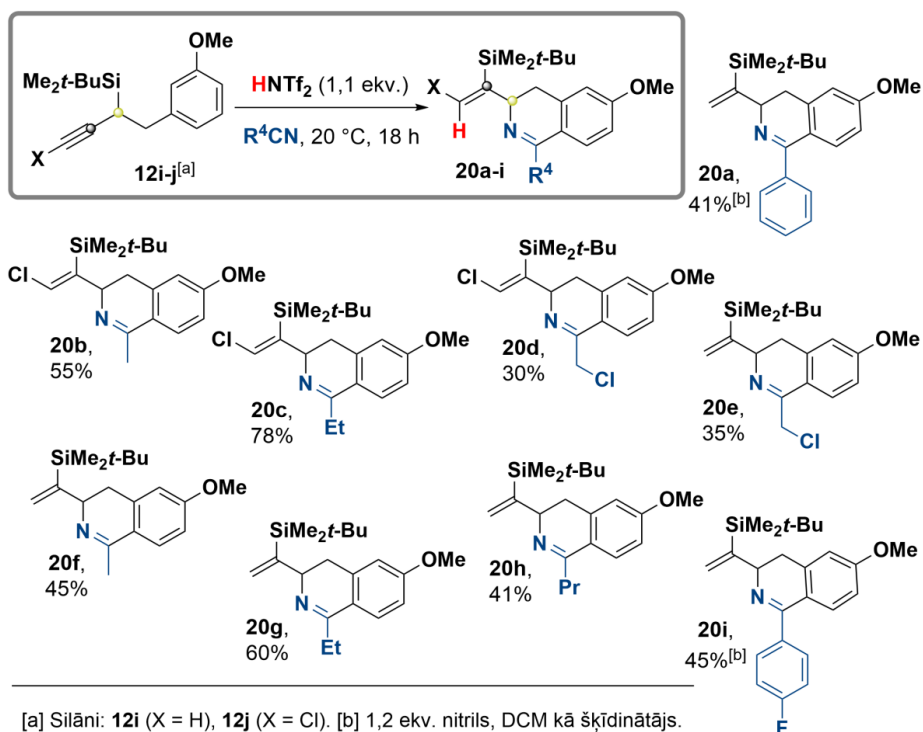
(Z)-Dubultsaites veidošanos alilamīdu **18e/18g** gadījumā var skaidrot ar alkīna protonēšanos antiperiplanārā pozīcijā attiecībā pret migrējošo sililgrupu (31. shēma).



31. shēma. Produktu (Z)-ģeometrijas racionalizācija propargilsilānu Ritera reakcijā.

Elektroniem bagātu arilsistēmu **12i-j** gadījumā tika novērota Bišlera–Napirālska (*Bischler–Napieralski*) tipa reakcija, kur arilsistēma reaģēja kā sekundārais nukleofils nitrīlija jona dzēšanai,

kā rezultātā tika iegūti dihidroizohinolīna atvasinājumi **20a-i** (32. shēma). Analógiski iepriekš novērotajai sakarībai alilamīdu sintēzē, no termināli halogenētā silāna **12j** tika iegūti produkti **20b-d** ar (*Z*)-ģeometriju alkēnu sānu ķēdē. Halogenētais silāns **12j** deva augstākus produkta **20** iznākumus (līdz 78 %) nekā tā nehalogenētais analogs **12i** (līdz 60 %). Atšķirtībā no alilamīdu **18** sintēzes (kurai bija nepieciešama karsēšana līdz 60 °C), dihidroizohinolīnu **20** sintēze efektīvi noritēja istabas temperatūrā (20 °C). Lietojot alifātiskos (MeCN, EtCN, PrCN) un halogenētos nitrilus (ClCH₂CN) kā šķīdinātājus, tika iegūti dihidroizohinolīni **20b-h** ar 30–78 % iznākumu. Aromātiskos nitrilus Ritera-tipa reakcijās kā šķīdinātājus izmanto reti^[43] – tie visbiežāk ir augsti virstoši šķidrums vai cietvielas.^[44, 45] Šādos gadījumos kā šķīdinātājs tika izmantots DCM, pievienojot augsti virstošos nitrilus (PhCN, 4-FC₆H₄CN) nelielā pārkumā (1,2 ekv.). Tas ļāva iegūt dihidroizohinolīnus **20a/20i** ar iznākumiem 41–45 % robežās.



32. shēma. Dihidroizohinolīnu sintēze no propargilsilāniem Bišlera–Napiraļska tipa reakcijā.

Tālāk tika apskatītas komplicētākas sistēmas – Ritera tipa reakcija, kur nitrīlija jona dzēšanai tiek pievienots ārējais slāpekļa nukleofils. Brensteda skābes aktivācijas apstākļos amidīna **19** tipa produkti netika iegūti. Silānam **12b** reaģējot ar 1,2 ekv. TfOH un 2,0 ekv. TsNH₂ acetonitrilā (T = –45 °C), vienīgais identificētais produkts bija (*E*)-hepta-1,3-diēn-2-iltriizopropilsilāns^[18] (30 % KMR iznākums). Savukārt ar HNTf₂ reakcija nenotika, un tika

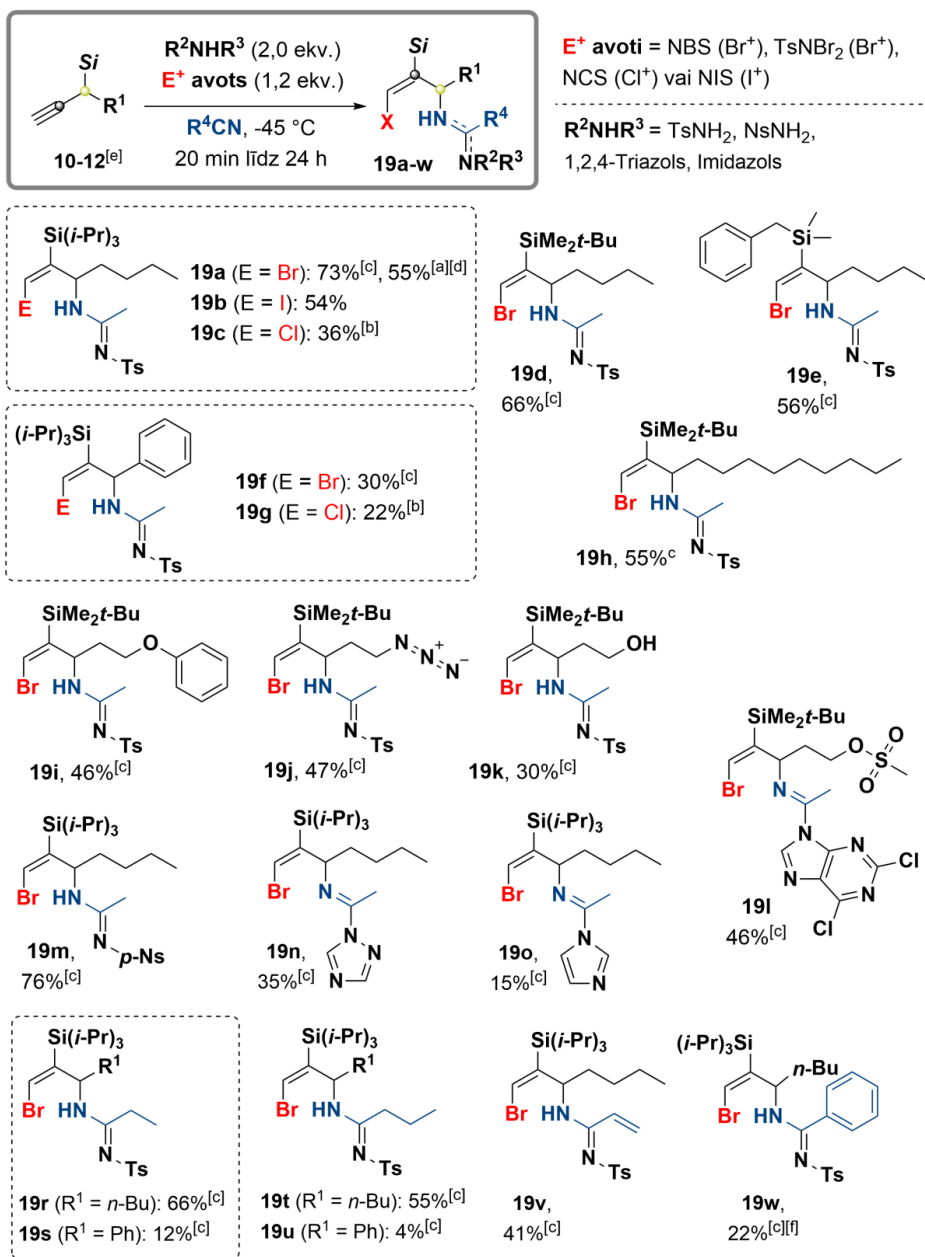
atgūtas izejvielas. Toties, aktivējot propargilsistēmu ar NBS, kā galvenais reakcijas produkts tika iegūts amidīns **19a** ar 56 % KMR iznākumu (apstākļi: 1,2 ekv. NBS, 1,1 ekv. TsNH₂, MeCN, 20 °C). Veicot tālāku reakcijas optimizāciju, tika noskaidrots, ka augstākos amidīna **19a** iznākumus (75 % KMR) var iegūt šādos apstākļos: T = -45 °C, MeCN kā šķīdinātājs, 2 ekv. TsNH₂ un 1,2 ekv. NBS.

Optimizētajos reakcijas apstākļos tika turpināta substrātu klāsta izpēte (33. shēma). Halogēna aizvietotāju dažādība pie produktu **19a-c** C=C saites tika panākta, izmantojot dažādus elektrofilās halogenēšanas reaģentus: NBS, NCS un NIS. Augstākie amidīnu **19** iznākumi (līdz 76 %) tika iegūti ar propargilsilāniem **12a,b,d**, kas satur vienkāršas alifātiskās virknes. Arilgrupu saturošais propargilsilāns **12k**^[18] Ritera tipa reakcijas apstākļos deva zemus amidīnu iznākumus (22–30 %). Iespējams, ka papildu stabilizācija alilkatjonam, ko dod blakus esošā arilgrupa (R¹ = Ar), palēnina nitrila pievienošanos, ko netieši apstiprina papildus nepieciešamais reakcijas laiks. Piemēram, alkilsilāns **12b** bija pilnībā izreaģējis jau pēc 45 minūtēm, savukārt arilsilānam **12k** bija nepieciešama 1,5 stunda.

Substrāti, kas saturēja terminālu arilētera grupu **11i**, azīdu **10p**, mezilātu **10r** un pat brīvu spirta grupu **10e**, Ritera tipa reakcijā deva amidīna produktus **19** ar iznākumiem 30–47 % robežās.

Starp alternatīviem sekundārajiem nukleofiliem amidīnu **19** sintēzei, sulfonamīdi (NsNH₂, TsNH₂) deva augstākos produktu **19** iznākumus (73–76 %). Daži slāpekļa heterocikli, lai arī ar zemāku iznākumu (15–46 %), arī bija izmantojami šīm mērķim, piemēram, 2,6-dihlorpurīns, 1,2,4-triazols un imidazols. Spēcīgāki nukleofili, kā cikloheksanols, cikloheksiltiols un cikloheksilamīns, standarta reakcijas apstākļos (silāns **12b**, 1,2 ekv. NBS, -45 °C, MeCN kā šķīdinātājs) nedeva gaidītos imidāta/tioimidāta/amidīna produktus.

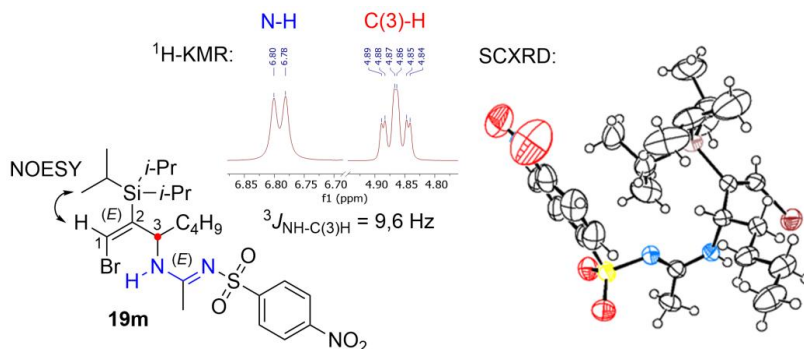
Garākas alkilvirknes (C₃-C₄) saturoši nitrili, kā arī akrilnitrils reakcijā ar alifātisko silānu **12b** deva salīdzinoši zemākus amidīnu **19** iznākumus (41–66 %), nekā iepriekš tika iegūti ar acetonitrilu. Benzonitrila gadījumā bija nepieciešams izvairīties no tā kristalizēšanās reakcijas apstākļos (-45 °C), tādēļ tika izmantota jaukta šķīdinātāju sistēma: PhCN/DCM (4:3 v/v). Benzonitrils šajos apstākļos nebija pietiekami reaģētspējīgs (amidīns **19w** tika iegūts tikai ar 22 % iznākumu), un galvenokārt notika deprotonēšanās, veidojot diēnu.^[18]



[a] KMR iznākums. [b] T = -45→20 °C. [c] NBS kā Br⁺ avots. [d] TsNBr₂ kā Br⁺ avots. [e] Silani: **12a** (R¹ = n-Bu, Si = t-BuMe₂Si), **12k** (R¹ = Ph, Si = (i-Pr)₃Si), **12l** (R¹ = C₉H₁₉, Si = t-BuMe₂Si), **11i** (R¹ = CH₂CH₂OPh, Si = t-BuMe₂Si), **10p** (R¹ = CH₂CH₂N₃, Si = t-BuMe₂Si), **10e** (R¹ = CH₂CH₂OH, Si = t-BuMe₂Si), **10r** (R¹ = CH₂CH₂OMs, Si = t-BuMe₂Si). [f] Tika izmantota modificēta šķīdinātāju sistēma: PhCN/DCM (4:3 v/v).

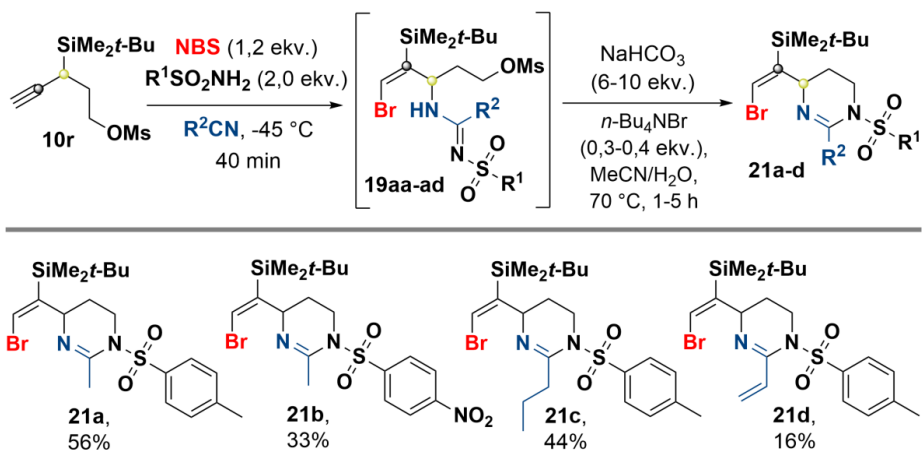
33. shēma. Amidiņu sintēze Ritera tipa reakcijā no propargilsilāniem.

Amidīniem šķīdumā ir iespējams novērot gan konfigurācijas izomērus (C=N saitei ir iespējama (*E*)- vai (*Z*)-konfigurācija), gan rotācijas izomērus (sin/anti), kas veidojas, rotējot ap C-N saiti. Tautomērija arī ir būtisks faktors, kas apgrūtina šo savienojumu analīzi.^[46] Analizējot amidīnus **19a-w** ar KMR spektroskopijas palīdzību, CDCl₃ visbiežāk tika novēroti divi signālu komplekti, savukārt DMSO-*d*₆ bija redzams tikai viens izomērs. Amidīna **19m** gadījumā mažorā/minorā izomēra attiecība CDCl₃ bija 96:4 (integrāļu attiecība ¹H KMR). N-H signāls ¹H-KMR deva dubletu ar ³*J* = 9,6 Hz sadarbības konstanti ar C(3)-H, kas liecina par N-H vicinālo pozīciju attiecībā pret C(3)-H (1. attēls). Tas pats tika novērots visiem pārējiem amidīniem, kas saturēja brīvu N-H grupu. Kamēr atbilstošo amidīna tautomēru varēja noteikt ar spektroskopiskām metodēm, C=N saites ģeometrijas noteikšana bija sarežģītāka. Produkta **19m** gadījumā C=N saites (*E*)-izomērs tika pierādīts ar rentgenstruktūranalīzi. (*E*)-ģeometrija tika apstiprināta arī C=C dubultsaitei, un tas saskan ar iepriekšējiem novērojumiem propargilsilānu elektrofilās halogenēšanas reakcijās.^[19]



1. attēls. Amidīna **19m** struktūras pierādīšana.

Noslēgumā darba autore un kolēģi apskatīja aciklisko Ritera tipa produktu lietojumu heterociklu sintēzē. Standarta Ritera tipa reakcijas apstākļos (1,2 ekv. NBS, 2,0 ekv. R¹SO₂NH₂, R²CN kā šķīdinātājs, T = -45 °C) no mezilāta **10r** tika iegūti amidīni **19aa-ad**, kas bāzes klātbūtnē (NaHCO₃) ciklizējās iekšmolekulārā S_N2 tipa reakcijā par tetrahidropirimidīna atvasinājumiem **21a-d** (34. shēma).

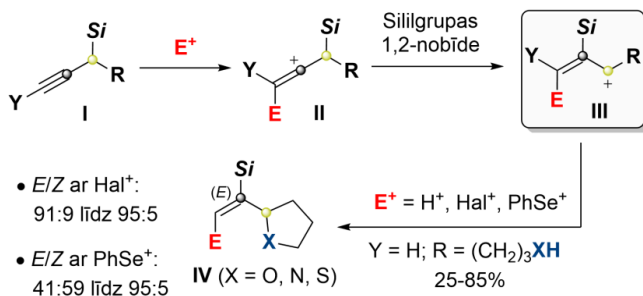


34. shēma. Ritera tipa reakcija tetrahidropirimidīnu **21** sintēzei.

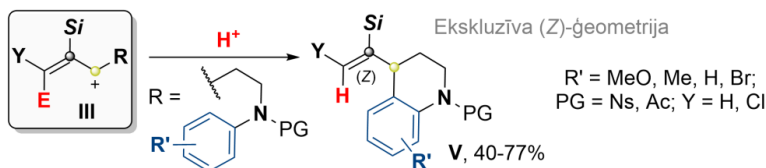
Šajā nodaļā tika demonstrēts, ka propargilsilānu pārvērtības Ritera tipa apstākļos var sniegt plašu produktu klāstu, sākot no acikliskām struktūrām – alilamīdiem **18** un amidīniem **19** –, līdz pat heterocikliem **20-21**. Apvienojot ārēju elektrofilu pievienošanas propargilsilāna trīskāršajai saitei ar vinil-alilkatjonu pārgrupēšanas sililgrupas 1,2-migrācijas rezultātā un divu secīgu nukleofilu uzbrukumu, tika iegūtas komplicētas, alilamīna struktūrfragmentu saturošas struktūras no vienkāršām izejvielām. Pilns pētījuma rezultātu izklāsts pieejams 6. pielikumā: Turka S.; Kroņkalne R.; Rogaļevs R.; Puriņš M.; Mishnev A.; Turks M. 1,2-Silyl Shift – Ritter Reaction Cascade for the Synthesis of Dihydroisoquinolines and Allylamine Derivatives (nepublicēts manuskripts).

SECINĀJUMI

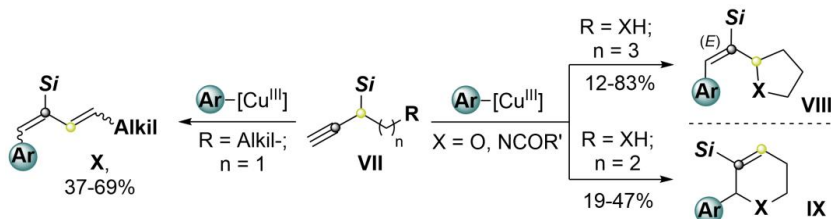
1. Elektrofīli propargilsilānos **I** ierosina sililgrupas 1,2-nobīdi, veidojot reaģētspējīgus alilkatjonus **III**. Tos dzēšot ar iekšējiem *O*-, *N*- un *S*-nukleofiliem, tiek iegūti piesātināti pieclocēkļu heterocikli **IV** – tetrahidrofurāni ($X = O$), pirolidīni ($X = N\text{-PG}$) un tiolāni ($X = S$) –, kas funkcionalizēti ar gemināli divaizvietotu ($E = H$) vai stereodefinētu trīsaizvietotu ($E = \text{Hal}, \text{PhSe}$) alkēnu sānu ķēdi.



2. Iekšmolekulāri dzēšot β -silīcija stabilizēto alilkatjonu **III** ar elektroniem bagātām arilsistēmām Brensteda skābes ierosinātā Frīdela-Kraftsa tipa reakcijā, tiek iegūti bicikliski, daļēji piesātināti heterocikli **V**, kas satur stereodefinētu (*Z*)-ģeometrijas alkēnu sānu ķēdi.

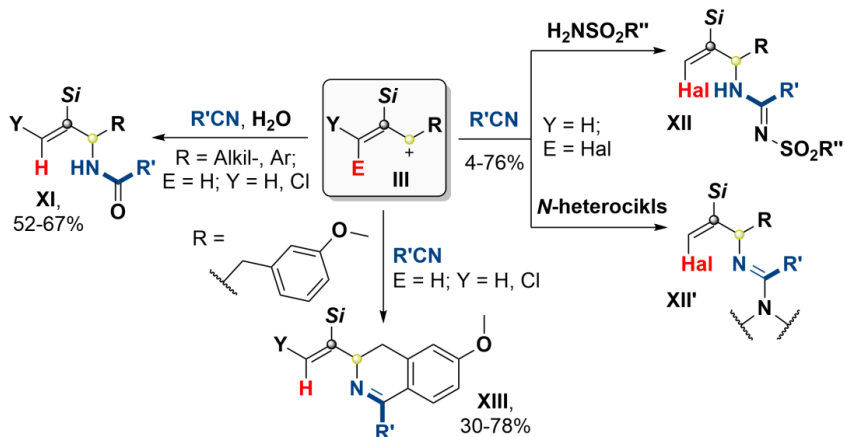


3. Kombinējot diaril- λ^3 -jodānus ar Cu(I) katalizatoru, var ģenerēt elektrofīlus Ar-Cu(III) reaģentus, kas kā formāli Ar^+ sintoni pievienojas propargilsilānu trīskāršajai saitei un ierosina arilēšanas – sililgrupas 1,2-nobīdes – heterociklizēšanas sekvenču **VII**→**VIII** un **VII**→**IX** atkarībā no sānu virknes izmēra. Savukārt, ja propargilsilāns nesatur reaģētspējīgus iekšējos nukleofilus, tiek iegūti arilēti silīdiēni **X**.

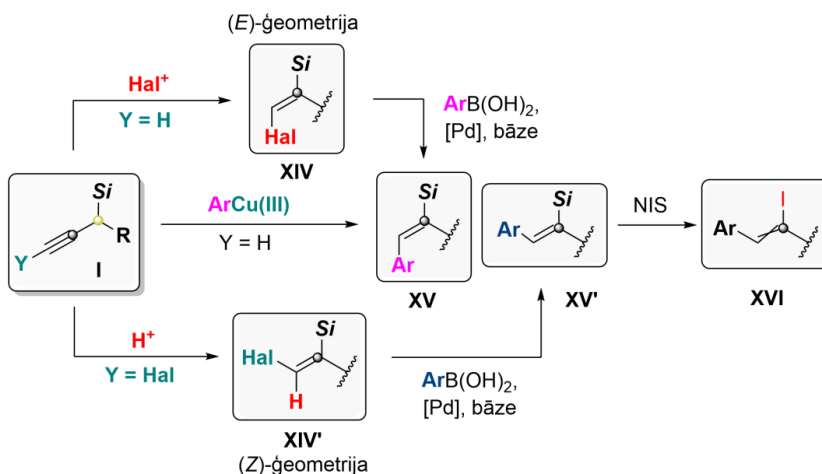


4. Ritera tipa reakcijas apstākļos propargilsilānus var kombinēt ar divu secīgu nukleofīlu uzbrukumu, iegūstot alilamīdus **XI** ($X = O$) un amidīnus **XII** ($X = N\text{-PG}$), kas satur augsti funkcionalizētu olefīnu struktūrfragmentu. Propargilsilānus ar elektroniem bagātām

arilsistēmām sānu virknē var pakļaut Bišlera–Napiraļska tipa reakcijai, kurā ir iegūstami dihidroizohinolīnu atvasinājumi **XIII**.



5. Dubultsaišu ģeometriju var kontrolēt, kombinējot: (a) nehalogenētus propargilsilānus **I** ($Y = H$) ar elektrofilās halogenēšanas reagentiem ($E^+ = Hal^+$) (**E**)-ģeometrijas iegūšanai vai (b) halogenētus propargilsilānus **I** ($Y = Hal$) ar Brensteda skābes aktivāciju ($E^+ = H^+$) (**Z**)-ģeometrijas iegūšanai. Olefīnu sānu ķēdi var tālāk modificēt šķērssametināšanas reakcijās, kā arī veicot $Si \rightarrow I$ apmaiņu, saglabājot alkēna konfigurāciju. Propargilsilānu **I** aktivējot ar $Ar-Cu(III)$, stirola atvasinājumus **XV** var iegūt vienā stadijā, izlaižot Pd -katalizēto vinilhalīdu šķērssametināšanas soli.



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

To be granted the scientific degree of Doctor of Science (PhD), the present Doctoral Thesis has been submitted for defense at the open meeting of the RTU Promotion Council on 23 September 2026 at the Faculty of Natural Sciences and Technology of Riga Technical University, Paula Valdena iela 3/7, Room 272.

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DECLARATION OF ACADEMIC INTEGRITY

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

Rasma Kronkalne

(signature)

Date

The Doctoral Thesis has been prepared as a collection of thematically related scientific publications complemented by summaries in Latvian and English. The Doctoral Thesis unites three original research articles in SCI journals, one review, one manuscript in preparation and unpublished results. The scientific publications have been written in English.

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ABBREVIATIONS

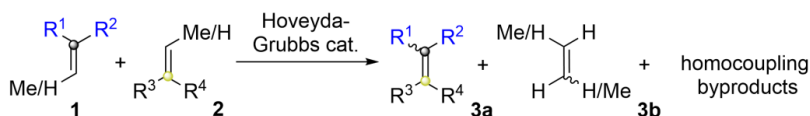
Ac	acetyl
Ar	aryl
B:	base
Boc	<i>t</i> -butyloxycarbonyl
Bu	butyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
DBU	2,3,4,6,7,8,9,10-octahydropyrimido[1,2- <i>a</i>]azepine
DCE	1,2-dichloroethane
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DMAP	<i>N,N</i> -dimethylpyridin-4-amine
DMF	<i>N,N</i> -dimethylformamide
ECAC	ethyl 2-(3,4-dichlorophenyl)diazene-1-carboxylate
Et	ethyl
Hal	halogen
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol
NMR	nuclear magnetic resonance
Me	methyl
Mes	mesityl
Ms	methanesulfonyl
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NIS	<i>N</i> -iodosuccinimide
PCC	pyridinium chlorochromate
Ph	phenyl
Pr	propyl
Py	pyridine
Ns	<i>p</i> -nitrobenzenesulfonyl, nosyl
Su	succinimide
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFE	2,2,2-trifluoroethan-1-ol
Tf	trifluoromethanesulfonyl
THF	oxolane
Ts	<i>p</i> -toluenesulfonyl
XPhos	dicyclohexyl[2',4',6'-tris(propan-2-yl)[1,1'-biphenyl]-2-yl]phosphane

GENERAL OVERVIEW OF THE THESIS

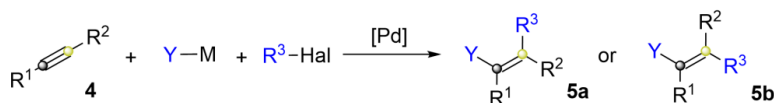
Relevance of the Topic

Olefins are a class of widespread carbofunctional compounds – they are ubiquitous motifs in both natural products and synthetic compounds.^[1–3] Olefins serve as precursors for countless organic transformations, enabling access to a broad spectrum of valuable products.^[4,5] The geometry of olefins and their substituents directly influences the properties of the resulting products, which is an important factor in bioactive compounds, polymers, and substrates for asymmetric catalysis.^[6] Despite this, the stereoselective synthesis of tri- and tetrasubstituted olefins remains challenging even in the 21st century.^[7] (*E/Z*)-selectivity is often determined by the relative size of substituents.^[8] The (*E*)-isomer is typically obtained as the thermodynamic product, whereas the synthesis of the energetically less favorable (*Z*)-alkenes is more problematic. Furthermore, many classical olefin synthesis methods, such as the Wittig reaction or the Julia-Kocienski olefination, exhibit limited applicability in the stereoselective synthesis of tri- and tetrasubstituted olefins.^[6,9] This motivates the development of alternative strategies for olefin synthesis, such as olefin metathesis (Scheme 1).^[10–12] For the synthesis of highly functionalized double bonds, reaction sequences that combine alkyne hydrometallation, carbometallation, or haloboration with cross-coupling reactions,^[13–16] as well as transition-metal-catalyzed alkyne hydroalkylation are also employed.^[6] Unfortunately, these methods are often not sufficiently stereoselective.^[6] Increasing mass efficiency in the synthesis of tri- and tetrasubstituted olefins also remains an important objective.^[17]

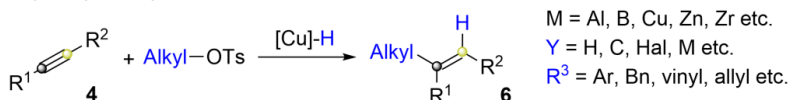
A) Olefin metathesis



B) Alkyne 1,2-difunctionalization

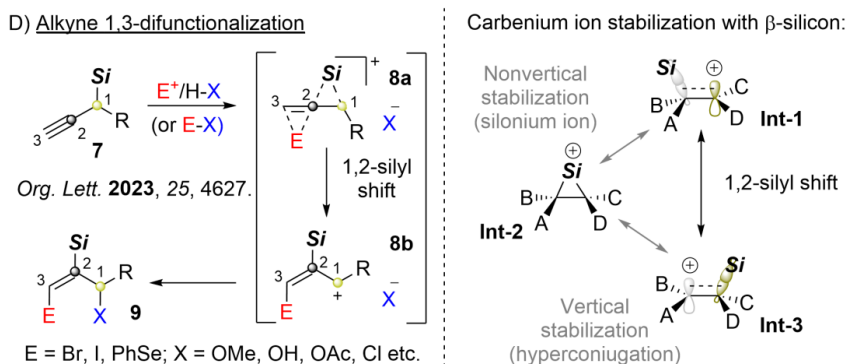


C) Alkyne hydroalkylation



Scheme 1. Contemporary strategies for stereoselective highly functionalized olefin synthesis.

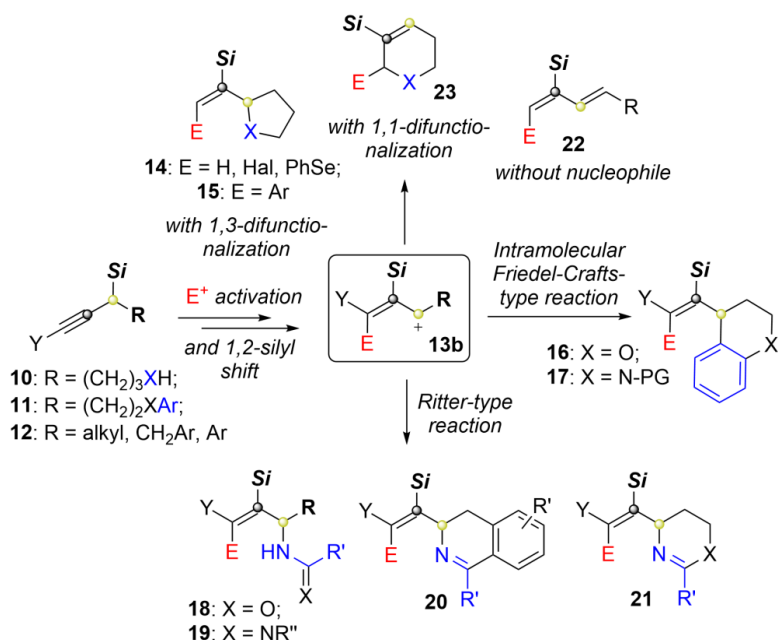
A new approach for the stereoselective synthesis of trisubstituted olefins **9** by 1,3-difunctionalization of propargyl silanes **7** was recently demonstrated by our group (Scheme 2).^[18, 19] In this approach, the propargylic system is activated with external electrophiles (Hal⁺, RSe⁺) to induce the 1,2-silyl shift.^[19] In many cases, formation of a β -silyl carbocation as the possible intermediate is facilitated by non-vertical stabilization (**Int-2**), which promotes migration of the silyl group toward formation of a more stabilized allyl cation.^[20, 21] These β -silicon-stabilized carbocation intermediates **8b** subsequently serve as building blocks for the incorporation of trisubstituted olefin fragments with high stereoselectivity.^[19]



Scheme 2. Alkyne difunctionalization by 1,2-silyl shift.

Although synthetic methods involving the 1,2-silyl shift have been known since the 1980s, examples of their application in the synthesis of stereodefined olefins containing three or more substituents remain limited. The concept of silicon rearrangement in the synthesis of heterocyclic structures has also been relatively underexplored.^[20, 21] The importance of heterocycles in organic chemistry is undeniable. Statistical data show that the majority of modern pharmaceuticals and agrochemicals contain at least one heterocyclic structural fragment.^[22] For example, in 2019, at least half of the drugs approved by the U.S. Food and Drug Administration (FDA) were heterocycle derivatives.^[23, 24] This drives continued interest in the development of new and efficient synthetic strategies for the preparation of functionalized heterocyclic structures, thereby expanding the diversity of accessible synthetic derivatives.^[25, 26]

Taking into account that silicon rearrangement in propargyl silanes remains a relatively underexplored topic in organic chemistry,^[20, 21] as well as the need for new methods for the synthesis of stereodefined, highly functionalized olefins and small-molecule heterocycles, the author set out to further develop the concept of 1,3-difunctionalization of propargyl silanes for the synthesis of heterocyclic structures containing a stereodefined olefin side chain (Scheme 3).



Scheme 3. General concept for the synthesis of highly functionalized olefin side chain-containing heterocycles from propargyl silanes **10-12**.

Aims and objectives

This Doctoral Thesis aims to develop a new methodology in organic synthesis for obtaining saturated and partially saturated heterocycles that contain a stereochemically defined, highly functionalized double bond in the side chain. This will be achieved by activating propargyl silanes with electrophiles to induce the 1,2-silyl shift, thus generating an allyl cation intermediate or its equivalent. Ring-closure will be achieved by subsequent attack of internal *O*-, *N*-, *S*-, or *C*-centered nucleophiles. In addition, the application of propargyl silanes under Ritter-type reaction conditions will be investigated, where a nitrile acts as the primary nucleophile toward a β -silicon-stabilized carbocation. The resulting nitrilium ion intermediate will be quenched by internal or external nucleophiles to afford products containing stereochemically defined allylamine fragments.

To achieve the aim of the study, several tasks were defined.

- 1) To investigate literature-reported methods for the synthesis of saturated heterocycles *via* intramolecular cyclization, identifying the advantages and limitations of existing methodologies, and to compile these findings in the form of a review article.

- 2) To participate in a collaborative project, directed towards the development of a synthetic methodology, which incorporates the 1,2-silyl shift and subsequent C-Het bond formation *via* internal *O*-, *N*-, or *S*-nucleophile attack on reactive β -silicon-stabilized allyl cation intermediates **13b**, to transform propargyl silanes **10** into five-membered heterocycles **14** – tetrahydrofurans (X = O), pyrrolidines (X = N-PG), and thiolanes (X = S).
- 3) To participate in a collaborative project aimed at adapting the propargyl silane heterocyclization methodology to a Friedel-Crafts-type reaction, in which the β -silicon-stabilized allyl cation **13b** reacts intramolecularly with aryl systems (C-nucleophiles) to form bicyclic partially saturated heterocycles **17**. To perform further modifications of the obtained tetrahydroquinolines **17** (X = N-PG) and their oxygen analogs **16** (X = O) to demonstrate their potential for further synthetic applications.
- 4) To participate in a collaborative project investigating the use of diaryl- λ^3 -iodanes as formal C-electrophiles for activation of propargyl silanes **10** and **12** under copper-catalyzed conditions, enabling the synthesis of arylated heterocyclic products **15** and **23**, as well as arylated silyl dienes **22**.
- 5) To study the induction of 1,2-silyl shift in propargyl silanes **10-12** under Ritter-type reaction conditions for the synthesis of various acyclic products **18-19** (X = O, N-PG) and cyclic products **20-21** containing highly functionalized C=C bonds.

Scientific novelty and main results

As a result of the conducted research, a synthetic methodology has been developed for the preparation of saturated and partially saturated heterocycles from propargyl silanes, incorporating a highly functionalized olefin side chain into the molecular framework. The key transformation underlying this methodology is the generation of β -silicon-stabilized allyl cations *via* 1,2-silyl shift, which occurs upon activation of the propargyl silane triple bond by strong electrophiles. The resulting reactive allyl cation intermediates are subsequently quenched by intramolecular nucleophiles, leading to the formation of a series of heterocyclic structures – tetrahydrofurans, pyrrolidines, thiolanes, tetrahydroquinolines, etc.

For the synthesis of tetrahydrofurans, pyrrolidines, and thiolanes, propargyl silanes containing internal *O*-, *N*-, and *S*-nucleophiles were synthesized starting from commercially available hex-5-yn-1-ol. These substrates were then activated in the presence of strong electrophiles (H⁺, Hal⁺, RSe⁺), inducing a 1,2-silyl migration-heterocyclization sequence. Ring closure by formation of a C-Het bond occurs *via* intramolecular nucleophilic attack on the β -silicon-stabilized allyl cation. The obtained products contain heterocyclic motifs, such as

tetrahydrofuran, pyrrolidine and thiolane derivatives, which are prevalent in pharmaceuticals, and highly functionalized C=C bonds with excellent (*E*)-selectivity.

For the synthesis of bicyclic, partially saturated heterocycles – namely tetrahydroquinolines – the propargyl silane heterocyclization concept was adapted to an intramolecular Friedel-Crafts-type reaction. In this transformation, the allyl cation generated *via* 1,2-silyl migration is intramolecularly quenched by an electron-rich aryl system acting as a *C*-nucleophile. To enable this transformation, an aryl unit was introduced into the propargyl silane structure *via* a nitrogen linker. Functionalized aryl amide derivatives were synthesized from commercially available pent-4-yn-1-ol. The resulting bicyclic heterocycles contained highly functionalized olefin side chains with defined (*Z*)-geometry.

The use of diaryl- λ^3 -iodanes as formal *C*-electrophile sources under copper-catalyzed conditions was developed for arylation-heterocyclization sequences of propargyl silanes. This approach enabled the synthesis of tetrahydrofuran, pyrrolidine, and tetrahydropyridine derivatives bearing arylated side chains. This method provides an efficient route to heterocycles containing a functionalized styryl side chain, while reducing the total number of required synthetic steps compared to previously known strategies.

Activation of propargyl silanes with electrophiles under Ritter-type reaction conditions enabled the synthesis of dihydroisoquinoline and tetrahydropyrimidine derivatives, as well as acyclic products – amidines and allylamides – featuring highly functionalized C=C bonds. From an entropic standpoint, these transformations are particularly complex: in a multicomponent reaction, the sequential formation of four new covalent bonds was achieved in a single step, resulting in the formation of complex molecular structures from simple starting materials.

Structure and volume of the Thesis

The Doctoral Thesis is structured as a collection of thematically unified scientific publications dedicated to the use of propargyl silanes in the synthesis of small-molecule heterocycles containing highly functionalized olefin side chains, utilizing 1,2-silicon shift to generate β -silicon-stabilized allyl cation intermediates. The Thesis comprises one review article and three original research publications in SCI-indexed journals, one publication manuscript in preparation and related unpublished results.

Publications and approbation of the Thesis

The main results of the Doctoral Thesis have been published in three original scientific research articles. During the course of the doctoral study, one review article was also prepared. The research findings have been presented at 20 scientific conferences.

Scientific publications

1. **Kronkalne, R.**; Beļunieks, R.; Ubaidullajevs, A.; Mishnev, A.; Turks, M. 1,2-Silyl Shift-Induced Heterocyclization of Propargyl Silanes: Synthesis of Five-Membered Heterocycles Containing a Functionalized Olefin Side Chain. *J. Org. Chem.*, **2023**, *88* (19), 13857–13870. Available from: <https://doi.org/10.1021/acs.joc.3c01481>
2. **Kronkalne, R.**; Beļunieks, R.; Sebris, A.; Mishnev, A.; Turks, M. Aryl Iodane-Induced Cascade Arylation–1,2-Silyl Shift–Heterocyclization of Propargylsilanes under Copper Catalysis. *Beilstein J. Org. Chem.*, **2025**, *21*, 1984–1994. Available from: <https://doi.org/10.3762/bjoc.21.154>
3. Ubaidullajevs, A.; **Kronkalne, R.**; Mishnev, A.; Turks, M. Synthesis of Substituted Chromanes and Tetrahydroquinolines *via* Tandem 1,2-Silyl Shift – Friedel–Crafts Cyclization. *J. Org. Chem.* **2026**, *91* (17), 5785–5810. Available from: <https://doi.org/10.1021/acs.joc.5c03136>
4. **Kronkalne, R.**; Turks, M. Recent Advances in Intramolecular C-N Bond Formation for Pyrrolidine Synthesis. *ChemistryOpen*, **2026**, *15* (6), e70182. Available from: <https://doi.org/10.1002/open.70182>
5. Turka, S.; **Kronkalne, R.**; Rogaļevs, R.; Puriņš, M.; Mishnev, A.; Turks, M. 1,2-Silyl Shift – Ritter Reaction Cascade for the Synthesis of Dihydroisoquinolines and Allylamine Derivatives. (*Manuscript in preparation*)

The results of the Thesis were presented at 20 conferences

1. **Kronkalne, R.**; Ubaidullajevs, A.; Turks, M. Synthesis of Fused Heterocycles by a Novel Cascade 1,2-Silyl Shift – Friedel–Crafts Cyclization. In: *Balticum Organicum Syntheticum 2026: Program and Abstract Book*, Estonia, Tallinn, June 28 – July 1, **2026**. Tallinn: 2026.
2. **Kronkalne, R.**; Beļunieks, R.; Sebris, A.; Turks, M. Copper-Catalyzed Arylation and Subsequent Cyclization of Terminally Functionalized Propargyl Silanes. In: *83rd International Scientific Conference of the University of Latvia 2025, Chemistry Section and Section of Institute of Chemical Physics: Book of Abstracts*, Latvia, Riga, February 14, **2025**. Riga: University of Latvia, 2025, p. 40. ISBN 978-9934-36-369-6. Available from: <https://doi.org/10.22364/iscul.83.cs.ba>
3. **Kronkalne, R.**; Beļunieks, R.; Sebris, A.; Mishnev, A.; Turks, M. Copper-Catalyzed Arylation of Propargyl Silanes with Iodanes Featuring 1,2-Silyl Shift and Cascade Cyclization. In: *ISySyCat: International Symposium on Synthesis and Catalysis 2025*:

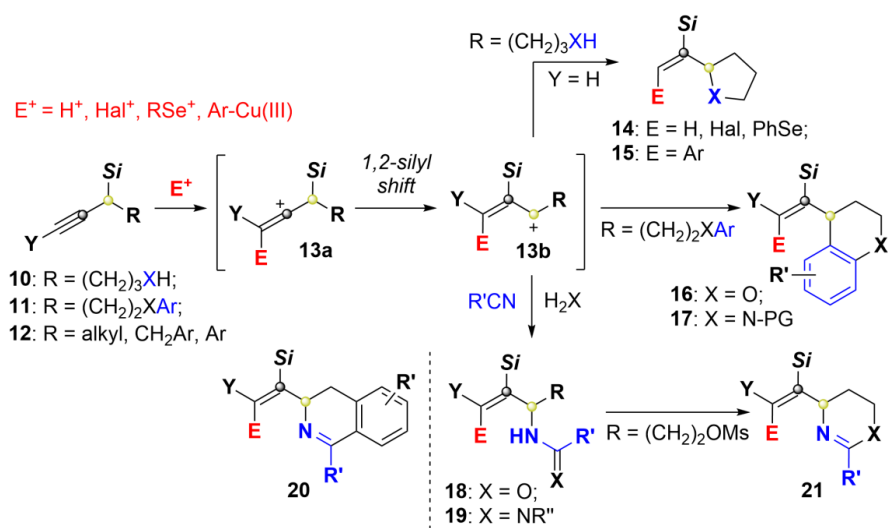
- Book of Abstracts*, Portugal, Coimbra, September 2–5, **2025**. Coimbra: 2025, p. 206. ISBN 978-989-95050-9-4
4. **Kronkalne, R.**; Turks, M. Copper-Catalyzed Arylation of Propargyl Silanes with Iodanes Featuring the 1,2-Silyl Shift. In: *Paul Walden 14th Symposium on Organic Chemistry: Program and Abstract Book*, Latvia, Riga, September 25–26, **2025**. Riga: 2025, p. 63.
 5. Rogaļevs, R.; Turka, S.; **Kronkalne, R.**; Ubaidullajevs, A.; Puriņš, M.; Turks, M. 1,2-Silyl Shift – Ritter Reaction Cascade for the Synthesis of Dihydroisoquinolines and Allylamine Derivatives. In: *International Symposium on Synthesis and Catalysis (ISySyCat 2025): Book of Abstracts*, Portugal, Coimbra, September 2–5, **2025**. Coimbra: 2025, p. 200.
 6. Ubaidullajevs, A.; **Kronkalne, R.**; Turks, M. Synthesis of Substituted Chromanes via Tandem 1,2-silyl shift – Friedel–Crafts Cyclization. In: *82nd International Scientific Conference of the University of Latvia: Organic Chemistry Session*, Latvia, Riga, March 15, **2024**. Riga: 2024, p. 8.
 7. Ubaidullajevs, A.; **Kronkalne, R.**; Turks, M. Synthesis of Vinyl Chromanes from Propargyl Silanes via Tandem Electrophilic Activation – 1,2-Silyl Shift – Friedel–Crafts Cyclization. In: *24th Tetrahedron Symposium*, France, Montpellier, June 18–21, **2024**. Montpellier: 2024.
 8. Ubaidullajevs, A.; **Kronkalne, R.**; Gercāns, K.; Mishnev, A.; Turks, M. Synthesis of Fused Heterocycles by a Novel 1,2-Silyl Shift – Friedel–Crafts Domino Process. In: *29th International Society of Heterocyclic Chemistry Congress: Program*, Portugal, Aveiro, July 21–26, **2024**. Aveiro: 2024, p. 5.
 9. Ubaidullajevs, A.; **Kronkalne, R.**; Gercāns, K.; Turks, M. Synthesis of Fused Heterocycles via Cascade 1,2-Silyl Shift – Friedel–Crafts Cyclization. In: *Balticum Organicum Syntheticum 2024: Program and Abstract Book*, Latvia, Riga, July 7–10, **2024**. Riga: 2024, p. 157.
 10. **Kronkalne, R.**; Ubaidullajevs, A.; Beļāunieks, R.; Turks, M. Expanding the Possibilities for Heterocycle Synthesis by Propargyl Silane Cyclization via the 1,2-Silyl Shift. In: *Balticum Organicum Syntheticum 2024: Abstract Book*, Latvia, Riga, July 7–10, **2024**. Riga: 2024, p. 79.
 11. **Kronkalne, R.**; Ubaidullajevs, A.; Beļāunieks, R.; Turks, M. Inducing 1,2-Silyl Migration in Propargyl Silanes for the Synthesis of 5- and 6-Membered Heterocycles. In: *24th Tetrahedron Symposium*, France, Montpellier, June 18–21, **2024**. Montpellier: 2024.

12. Sebris, A.; Beļunieks, R.; **Kronkalne, R.**; Turks, M. Copper-Catalyzed Arylation of Propargyl Silanes with Consequent Internal Cyclization. In: *Balticum Organicum Syntheticum 2024: Abstract Book*, Latvia, Riga, July 7–10, **2024**. Riga: 2024, p. 139.
13. Turks, M.; **Kronkalne, R.**; Ubaidullajevs, A.; Beļunieks, R.; Sebris, A.; Puriņš, M.; Rogaļevs, R. One, Two, Three, Go: Novel Applications of 1,2-Silyl Shift for 1,3-Difunctionalization of Propargyl Silanes. In: *Balticum Organicum Syntheticum 2024: Abstract Book*, Latvia, Riga, July 7–10, **2024**. Riga: 2024, p. 156.
14. Turks, M.; Beļunieks, R.; **Kronkalne, R.**; Ubaidullajevs, A.; Līpiņa, R. Synthesis of Allylic Systems and Heterocycles with Highly Functionalized Olefin Side Chain from Propargyl Silanes via 1,2-Silyl Shift. In: *International Symposium on Synthesis and Catalysis 2023: Program and Abstract Book*, Portugal, Evora, September 5–8, **2023**. Evora: 2023, p. 16.
15. **Kronkalne, R.**; Beļunieks, R.; Turks, M. Electrophile-Induced 1,2-Silyl Migration in Propargyl Silanes: a Pathway towards Saturated Heterocycles. In: *13th Paul Walden Symposium on Organic Chemistry: Program and Abstract Book*, Latvia, Riga, September 14–15, **2023**. Riga: 2023, p. 45.
16. **Kronkalne, R.**; Ubaidullajevs, A.; Beļunieks, R.; Turks, M. Electrophile-Induced 1,2-Silyl Shift in Terminally Functionalized Propargyl Silanes for the Synthesis of Small Heterocycles. In: *International Symposium on Synthesis and Catalysis 2023: Book of Abstracts*, Portugal, Evora, September 5–8, **2023**. Evora: 2023, p. 244.
17. **Kronkalne, R.**; Beļunieks, R.; Ubaidullajevs, A.; Turks, M. Use of Terminally Functionalized Propargyl Silanes for the Synthesis of Various 5-Membered Heterocycles via 1,2-Silyl Migration. In: *81st International Scientific Conference of the University of Latvia: Organic Chemistry Session*, Latvia, Riga, March 17, **2023**. Riga: 2023, p. 14.
18. Turks, M.; Beļunieks, R.; **Kronkalne, R.**; Puriņš, M.; Līpiņa, R.; Ubaidullajevs, A.; Rogaļevs, R. Synthesis of Allylic Systems or Heterocycles with Highly Functionalized Olefin Side Chain from Propargyl Silanes via 1,2-Silyl Migration. In: *ACS Fall 2023 – Sessions*, United States of America, San Francisco, August 13–17, **2023**. San Francisco: 2023, p. 3915259.
19. Ubaidullajevs, A.; **Kronkalne, R.**; Turks, M. Tandem 1,2-silyl shift – Friedel–Crafts Synthetic Approach to Substituted Vinyl Chromanes. In: *13th Paul Walden Symposium: Program and Abstracts*, Latvia, Riga, September 14–15, **2023**. Riga: 2023, p. 35.
20. **Kronkalne, R.**; Beļunieks, R.; Turks, M. Heterocyclization of Terminally Functionalized C6-Chain Containing Propargyl Silanes via 1,2-Silyl Shift.

In: *Materials Science and Applied Chemistry 2022: Programme and Abstract Book*,
Latvia, Riga, October 21, **2022**. Riga: 2022, p. 4.

MAIN RESULTS OF THE THESIS

The concept of propargyl silane heterocyclization is based on the generation of β -silicon-stabilized carbocations through the addition of a strong electrophile (E^+) to the triple bond. The initially formed vinyl cation **13a** undergoes rearrangement *via* 1,2-silyl shift to form the more stable allyl cation **13b**. Subsequent quenching by intramolecular nucleophiles (heteroatoms or $C(sp^2)$) leads to cyclic structures bearing a functionalized olefin side chain (Scheme 4).

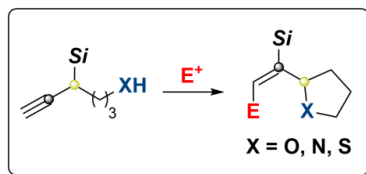


Scheme 4. Main research directions for heterocycle synthesis from propargyl silanes **10-12**.

Within the scope of this Thesis, the following transformations are investigated:

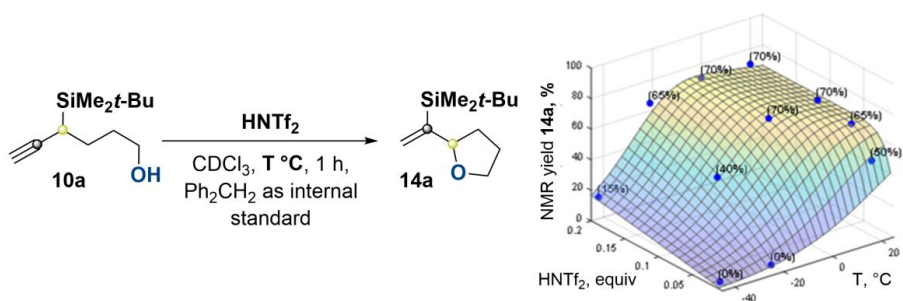
- electrophile-induced 1,2-silyl shift-heterocyclization of propargyl silanes containing internal *O*-, *N*-, or *S*-nucleophiles for the synthesis of five-membered heterocycles **14** – tetrahydrofurans ($X = O$), pyrrolidines ($X = N-PG$), and thiolanes ($X = S$);
- intramolecular Friedel-Crafts-type reactions for the synthesis of tetrahydroquinolines **17** ($X = N-PG$), and further synthetic modifications of the obtained products **17** and their oxygen analogs **16**;
- copper-catalyzed arylation-heterocyclization reactions using diaryl- λ^3 -iodanes as formal Ar^+ synthons ($E^+ = Ar-Cu(III)$);
- Ritter-type reactions for the synthesis of functionalized allylamines **18** ($X = O$), amidines **19** ($X = NR''$), dihydroisoquinolines **20**, and tetrahydropyrimidines **21** ($X = N-PG$).

1.1. Propargyl silane heterocyclization by intramolecular O-/N-/S-nucleophile attack on β -silicon-stabilized allyl cation



In previous studies, it was demonstrated that under electrophilic activation conditions (Brønsted acids or Hal^+), propargyl silanes can generate reactive allyl cation synthons. These intermediates can be further utilized in the synthesis of silyl dienes or indenenes,^[18] 1,3-difunctionalized olefins,^[19] sulfolenes,^[27] and other valuable products.^[28] Within the scope of this study, the author sought to expand the application of propargyl silanes by adapting this concept to the synthesis of small-molecule heterocycles. For this purpose, in collaboration with Rūdolfs Beļāunieks and Artjoms Ubaidullajevs, a heterocyclization strategy was developed in which an allyl cation is generated *via* electrophile-induced 1,2-silyl migration and then intramolecularly trapped by a heteroatom nucleophile (*O*, *N*, *S*). This enables the synthesis of various five-membered heterocycles.^[29] The findings of this study were partially discussed within the framework of R. Beļāunieks' Thesis, but the core process of synthetic methodology was developed within this Thesis.^[30]

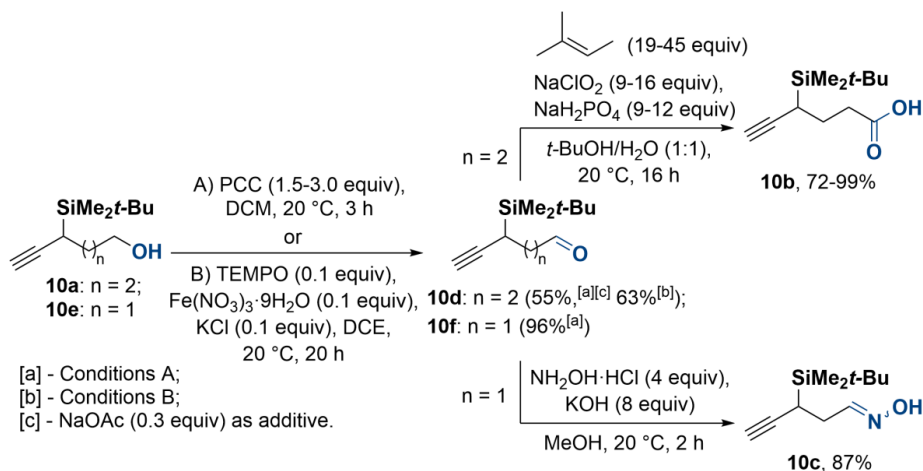
The key starting material for tetrahydrofuran synthesis was 4-(tert-butyldimethylsilyl)hex-5-yn-1-ol (**10a**), which was obtained from *O*-silylated commercially available hex-5-yn-1-ol using the retro-Brook rearrangement procedure described by Wang and Gao.^[31] Subsequent activation of propargyl silane **10a** with Brønsted acids (HNTf_2 or TfOH) afforded the heterocyclization product **14a**.



Scheme 5. Optimization of reaction conditions for Brønsted acid-catalyzed propargyl silane **10a** heterocyclization.

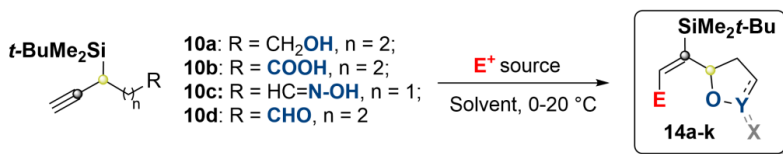
The main conclusions from the Brønsted acid-catalyzed reaction optimization were as follows: 1) the optimal temperature for tetrahydrofuran synthesis was 0–20 °C; 2) the optimal catalyst loading was 10–20 mol%; 3) the solvent choice was influenced by their leveling effects, where aprotic solvents CDCl_3 and CD_2Cl_2 afforded the highest yields (**14a**, 70 % NMR), but in benzene- d_6 and CD_3NO_2 the yields were lower (65 % and 50 % of **14a**, respectively); 4) under optimal reaction conditions (0.2 equiv H^+ , CDCl_3 , 0 °C, 1 h) HNTf_2 and TfOH afforded similar yields (70 % by NMR), whereas conc. H_2SO_4 was unreactive. A detailed correlation between acid catalyst loading (Tf_2NH , equiv) and reaction temperature with tetrahydrofuran **14a** NMR yield is graphically depicted in Scheme 5.

Other oxygen nucleophile-containing propargyl silanes **10b–f** were synthesized by modifying alcohol **10a** and its C5-chain analogue **10e**, as it is depicted in Scheme 6. Alcohol **10e** itself was prepared according to the method described by Wang and Gao using commercial pent-4-yn-1-ol.^[31]

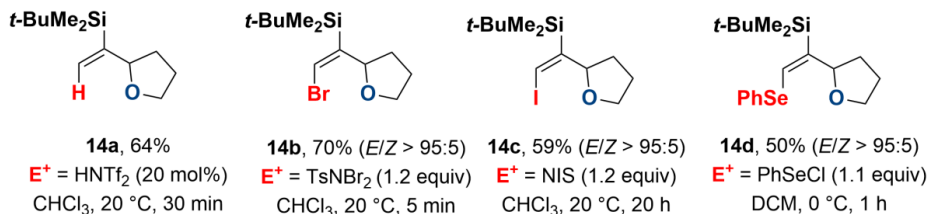


Scheme 6. Synthesis of oxygen nucleophile-containing propargyl silanes **10b–f**.

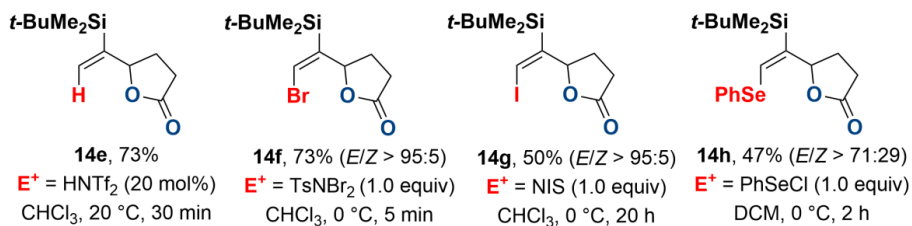
Under optimized conditions, cyclization of propargyl silanes **10a–d** containing internal oxygen nucleophiles was performed (Scheme 7). Using electrophilic halogenating reagents to induce 1,2-silyl migration, such as TsNBr_2 , *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS) or PhSeCl , heterocycles bearing functionalized vinyl halide or vinyl selenide side chains were obtained. Alcohol **10a** afforded tetrahydrofuran derivatives **14a–d** in yields of 50–70 %, carboxylic acid **10b** cyclized to lactone derivatives **14e–h** (47–73 % yields), whereas oxime **10c** gave 4,5-dihydroisoxazole derivatives **14i–j** (29–32 % yields). Aldehyde **10d**, upon cyclization with NBS in the presence of water, produced hemiacetal **14k** (30 % yield).



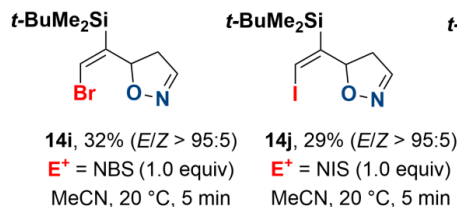
From alcohol **10a** (R = CH₂OH, n = 2):



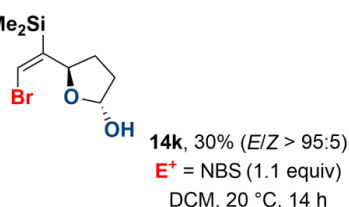
From carboxylic acid **10b** (R = COOH, n = 2):



From oxime **10c** (R = HC=N-OH, n = 1):



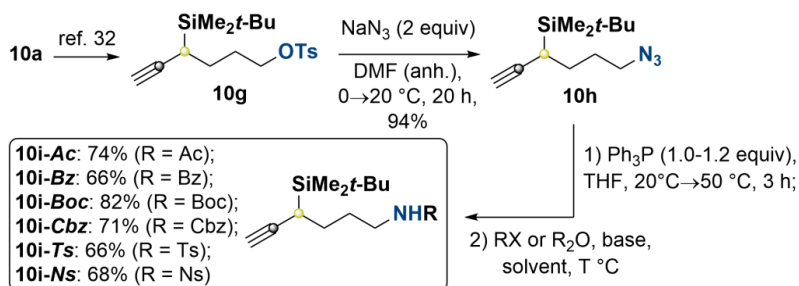
From aldehyde **10d** (R = CHO, n = 2):



Scheme 7. Heterocyclization of oxygen nucleophile-containing propargyl silanes **10a-d**.

The alcohol-containing propargyl silane **10a** was further modified to obtain substrates bearing nitrogen nucleophiles **10i** (Table 1). Tosylate **10g** was prepared according to a literature procedure.^[32] Subsequent azidation followed by reduction of azide **10h** under Staudinger conditions, and installation of an *N*-protecting group, yielded amides **10i-Ac** and **10i-Bz**, carbamates **10i-Boc** and **10i-Cbz**, as well as sulfonamides **10i-Ts** and **10i-Ns**.

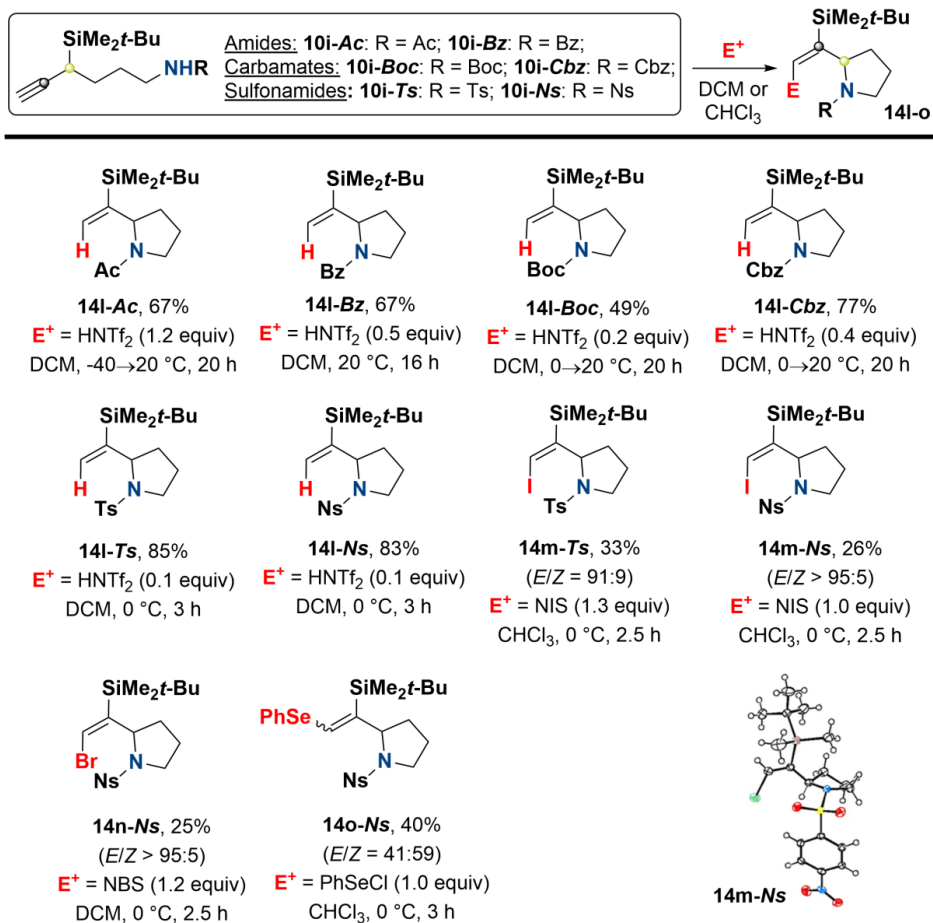
Table 1

Synthesis of propargyl silanes **10i** bearing internal nitrogen nucleophiles

Entry	RX/R ₂ O (equiv)	Base/additive (equiv)	Solvent	T (°C)	t (h)	Product yield
1	Ac ₂ O (2.0)	DMAP (0.5)	Py	0–20	16	10i-Ac , 74 %
2	Bz ₂ O (2.0)	DMAP (1.0)	DMF	60	22	10i-Bz , 66 %
3	Boc ₂ O (1.2)	NaHCO ₃ (3.0)	THF/H ₂ O (1:1)	0–20	14	10i-Boc , 82 % ^[a]
4	Cbz-OSu (1.2)	NaHCO ₃ (2.7)	MeCN/H ₂ O (1:1)	0–20	16	10i-Cbz , 71 %
5	TsCl (2.0)	Et ₃ N (5.0)	DCM	0–20	6	10i-Ts , 66 %
6	NsCl (2.0)	Et ₃ N (5.0)	DCM	0–20	6	10i-Ns , 68 %

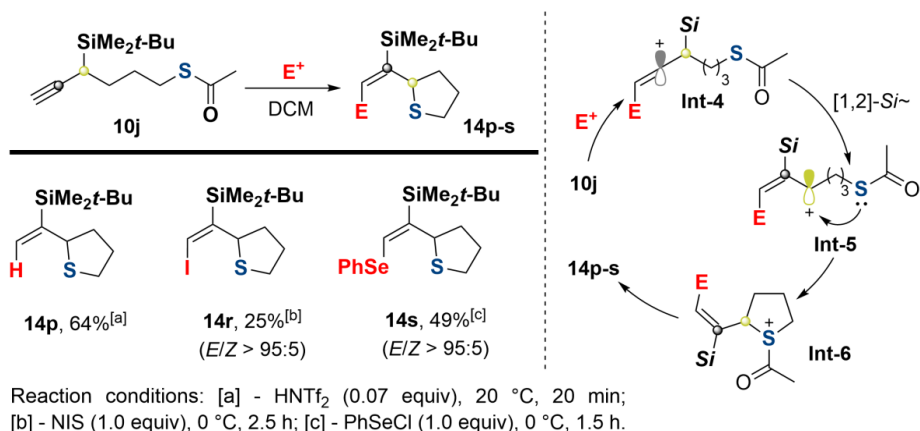
^[a] THF/H₂O (1:1) solvent system and 1 h stirring time for the reduction step.

In the presence of strong electrophiles (H⁺, Hal⁺, RSe⁺), N-nucleophile-containing propargyl silanes **10i** cyclized to give pyrrolidine derivatives **14l-o** (Scheme 8). Under HNTf₂-catalyzed conditions, sulfonamides **10i** (R = Ts, Ns) gave the highest yields of pyrrolidine **14l** (83–85 %). Carbamates **10i** (R = Boc, Cbz) and amides **10i** (R = Ac, Bz) gave yields in the range of 49–77 %. By using electrophilic halogenating reagents (NIS, NBS) to activate the propargylic system, the obtained yields were lower (25–33 %), but the products **14m-n** contained highly functionalized olefin side chains with (*E/Z*)-selectivity of 91:9 to 95:5. The absolute geometry of the trisubstituted double bonds in products **14m-n** was confirmed using 2D NOESY nuclear Overhauser effect spectroscopy (NOESY), where a correlation signal between C=C-H and *t*-BuMe₂Si-group was observed for the (*E*)-isomer. Single-crystal X-ray diffraction (SCXRD) analysis of compound **14m-Ns** confirmed the previous findings. When PhSeCl was used as the electrophile source, pyrrolidine **14o** was obtained as an (*E/Z*) mixture (41:59). This can be explained by the additional stabilization provided by the α-selenium effect to the intermediate allyl cation, which affords more time for isomerization before the allyl cation is quenched by an internal nucleophile.



Scheme 8. Synthesis of nitrogen heterocycles **14l-o**.

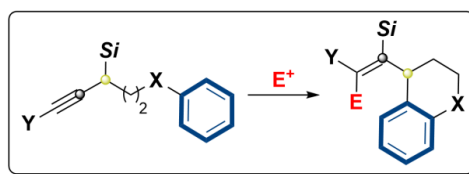
For the synthesis of sulfur-containing heterocycles, thioacetate **10j** was used as the starting material (Scheme 9). It was obtained by reacting tosylate **10g** with potassium thioacetate (KSAC) in acetonitrile (20 °C, 16 h, 87 % yield). Cyclization proceeded most efficiently under HNTf₂-catalyzed conditions, yielding thiolane **14p** (64 %). Lower yields of thiolanes **14r-s** (25–49 %) were obtained when electrophilic reagents (NIS, PhSeCl) were used to generate products **14r-s** containing trisubstituted olefin side chains. The cyclization likely proceeds *via* a sulfonium ion intermediate **Int-6**, which releases the thiolane product **14p-s**.



Scheme 9. Synthesis of thiolanes from thioacetate **10j**.

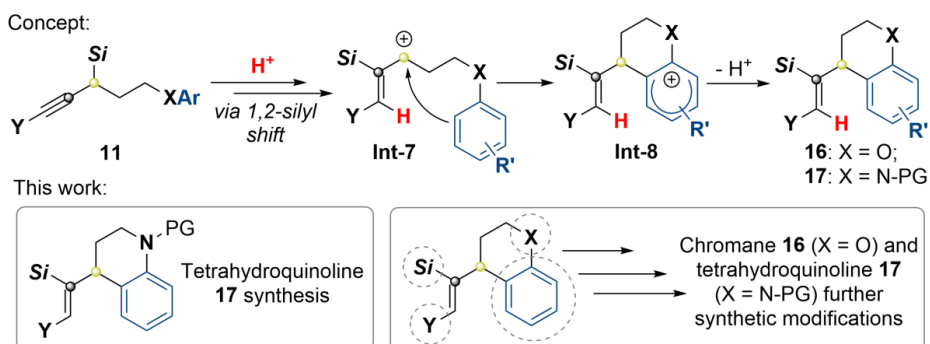
The author can conclude from these results that β -silicon-stabilized allyl cations may be quenched intramolecularly by *O*-, *N*- and *S*-nucleophiles to obtain five-membered heterocycles, which contain geminally disubstituted or stereodefined trisubstituted olefin side chains. By activating propargyl silanes with electrophilic halogenating reagents (NBS, NIS), olefins with high (*E/Z*)-selectivity (up to 95:5) are obtained. Full details of this research are described in the publication Kropkalne, R.; Beļunieks, R.; Ubaidullajevs, A.; Mishnev, A.; Turks, M. 1,2-Silyl Shift-Induced Heterocyclization of Propargyl Silanes: Synthesis of Five-Membered Heterocycles Containing a Functionalized Olefin Side Chain. *J. Org. Chem.*, **2023**, 88 (19), 13857–13870 (Appendix 1).^[29]

1.2. Propargyl silane heterocyclization by reacting β -silicon stabilized allyl cations with arenes as internal C-nucleophiles



In the previous section, it was demonstrated that allyl cations generated *via* 1,2-silyl migration can be intramolecularly quenched to form new C-O, C-N, and C-S bonds. This section is devoted to an analogous transformation in which heterocyclization proceeds *via* intramolecular C-C bond formation in a Friedel-Crafts-type reaction (Scheme 10). Intramolecular trapping of the

allyl cation intermediate **Int-7** by an electron-rich aryl system enables the synthesis of bicyclic structures. In collaboration with A. Ubaidullajevs, a method was developed for the synthesis of bicyclic heterocycles, namely chromanes **16** (X = O) and tetrahydroquinolines **17** (X = N-PG).^[33] Within this Thesis, the focus is on the synthesis of tetrahydroquinolines **17** from propargyl silanes, as well as the demonstration of further synthetic transformations of both chromanes **16** (X = O) and tetrahydroquinolines **17** (X = N-PG).



Scheme 10. The concept for propargyl silane **11** cyclization in a Friedel-Crafts-type reaction and further modification possibilities of products **16** and **17**.

1.2.1. Synthesis of tetrahydroquinolines from propargyl silanes

Propargyl silanes **11a-f** bearing an aniline functionality were identified as the key starting materials for tetrahydroquinoline synthesis. One approach to their preparation involved the Mitsunobu reaction between nosyl group-bearing anilines (ArNHNs) and the alcohol functionality-bearing silane **10e**. This allowed the preparation of key intermediates **11a-d** in yields of 66–75 % (Table 2).

Table 2

Synthesis of propargyl silanes bearing the *N*-nosylaniline functionality under Mitsunobu reaction conditions

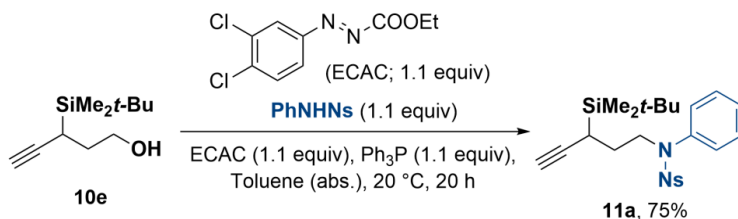
10e $\xrightarrow[\text{DIAD (1.1 equiv), Ph}_3\text{P (1.0 equiv), THF (abs.), 0-20 } ^\circ\text{C}]{\text{ArNHNs (1.0 equiv)}}$ 11a-d

11a: R = H;
11b: R = 3-Me;
11c: R = 4-Br;
11d: R = 4-MeO

Entry ^[a]	Ar	Time (h)	Product (%) ^[b]
1	Ph	21.0	11a , 66
2	<i>m</i> -MeC ₆ H ₄	15.0	11b , 67
3	<i>p</i> -BrC ₆ H ₄	15.5	11c , 75
4	<i>p</i> -MeOC ₆ H ₄	17.0	11d , 74

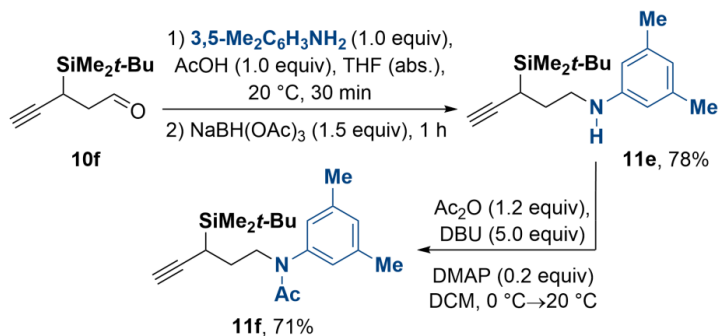
^[a] All reactions were performed on a 2.5 mmol scale. ^[b] Isolated yield.

It was later found that replacing DIAD with ECAC, which is a second-generation Mitsunobu reagent, improved the yields of tertiary amines (Scheme 11). For example, in the case of compound **11a**, the yield increased from 66 % (with DIAD) to 75 % (with ECAC). The same conditions were used by A. Ubaidullajevs for the preparation of oxygen-bridged analogues **11** (Y = H, X = O).^[33]



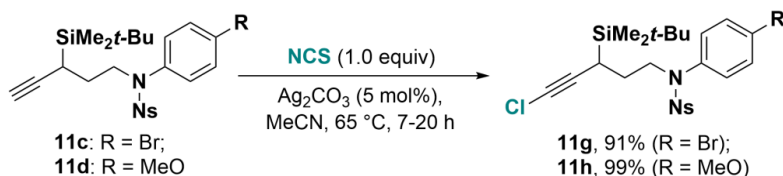
Scheme 11. Synthesis of propargyl silane **11a** bearing the *N*-nosylaniline functionality using the ECAC reagent.

The Mitsunobu strategy was applicable only to anilines bearing strongly electron-withdrawing sulfonyl protecting groups. When less electron-withdrawing groups (e.g., Ac) were used, the reaction did not proceed. To obtain propargyl silanes **11f** functionalized with acetamide groups, a reductive amination strategy was employed (Scheme 12). Aldehyde **10f** was reacted with 3,5-dimethylaniline in the presence of acetic acid to form an imine intermediate. The imine was reduced using NaBH(OAc)₃ to give product **11e**. Subsequent acetylation afforded the *N*-acetylated product **11f**.



Scheme 12. Synthesis of propargyl silanes **11f** bearing the acetamide functionality by employing the reductive amination strategy.

To obtain terminally halogenated substrates **11g-h**, propargyl silanes **11c-d** were treated with an equimolar amount of NCS in the presence of a silver catalyst (Ag_2CO_3 , 5 mol%). The chlorinated propargyl silanes **11g-h** were obtained in excellent yields (91–99 %) (Scheme 13).

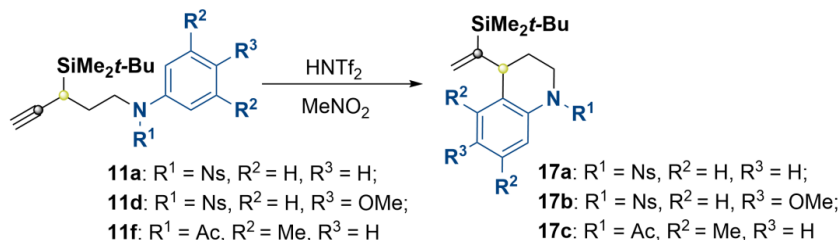


Scheme 13. Synthesis of terminally halogenated propargyl silanes **11g-h**.

Next, the author explored the cyclization reactions of aniline-functionalized propargyl silanes **11** to transform them into tetrahydroquinoline **17** derivatives (Table 3). The reactions were performed in nitromethane (MeNO_2), using HNTf_2 for activation of the propargylic moiety. Reaction optimization revealed that HNTf_2 is most effective when used in equimolar amounts or even in slight excess. Similar trends were observed in chromane **16** synthesis by A. Ubaidullajevs, where the reaction yields improved by increasing the HNTf_2 loading.^[33]

Table 3

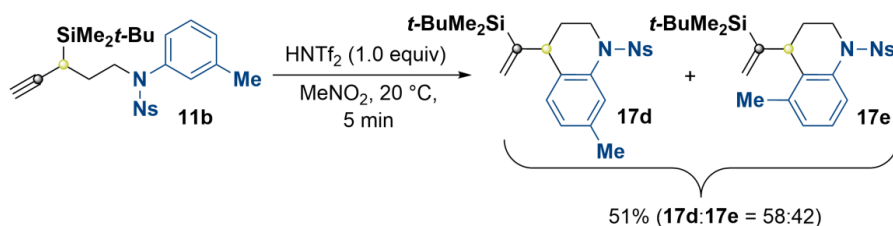
Synthesis of tetrahydroquinolines **17a-c** from propargyl silanes **11a**, **11d** and **11f**



Entry ^[c]	Silane	HNTf_2 (equiv)	T (°C)	t (min)	11 (%) ^[a]	Product (%)
1	11a	0.2	50	10	53	17a , 15 ^[a]
2	11a	0.2	0→20	70	55	17a , 15 ^[a]
3	11a	0.2	0→20	1020	11	17a , 12 ^[a]
4	11a	1.0	0	60	0	17a , 41 ^[a] (40 ^[b])
5	11d	1.0	20	5	0	17b , 47 ^[a] (43 ^[b])
6	11f	1.0	20	5	40	17c , 10 ^[a]
7	11f	3.0	20	30	0	17c , 47 ^[a] (45 ^[b])

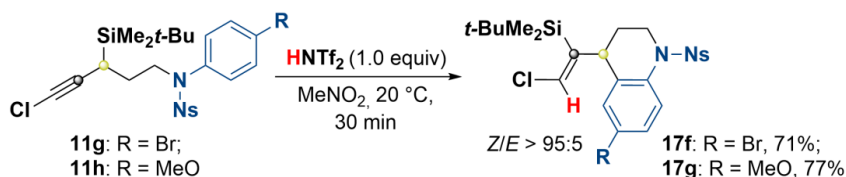
^[a] NMR yield. ^[b] Isolated yield. ^[c] All reactions were performed on a 0.1–0.4 mmol scale.

In the case of unsymmetrically substituted aniline **11b**, cyclization with HNTf_2 produced a mixture of regioisomers **17d/17e** in a ratio of 58:42 (Scheme 14).



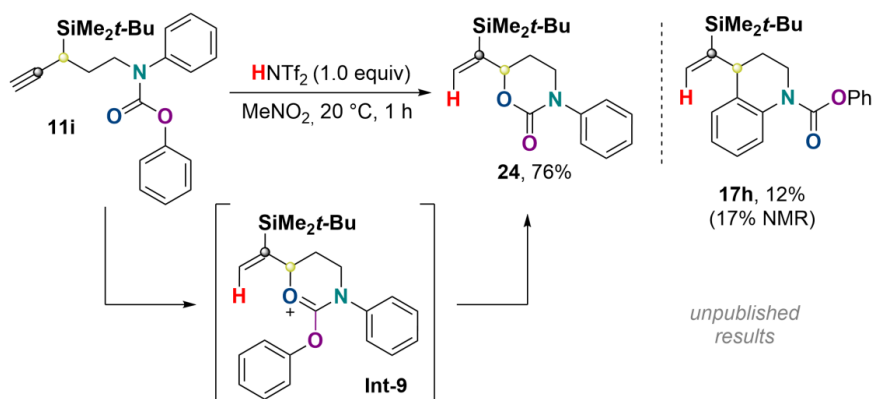
Scheme 14. Synthesis of isomeric tetrahydroquinolines from unsymmetrically substituted aniline **11b**.

Cyclization of terminally halogenated substrates **11g-h** proceeded with excellent *Z/E* selectivity, yielding tetrahydroquinolines **17f-g** in 71–77 % yields (Scheme 15).



Scheme 15. Synthesis of tetrahydroquinolines **17f-g** from terminally halogenated propargyl silanes.

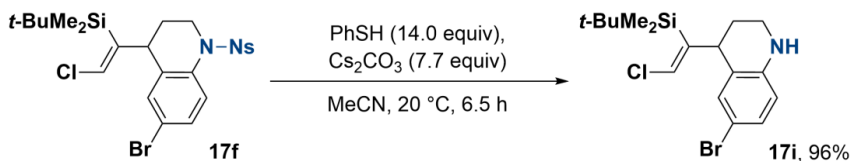
Unexpected reactivity was observed during the attempts to cyclize the carbamate-protected aniline **11i**. The major reaction product was 1,3-oxazinan-2-one derivative **24**, which was isolated in 76 % yield, whereas only small quantities of tetrahydroquinoline **17h** were obtained (17 % by NMR). This suggests that under these conditions, an alternative cyclization pathway becomes favorable, likely involving intermediate **Int-9**, which decomposes to product **24** (Scheme 16).



Scheme 16. Synthesis of 1,3-oxazinan-2-one derivative **24**.

1.2.2. Further modifications of the obtained tetrahydroquinoline and chromane derivatives

Firstly, the author aimed to access tetrahydroquinoline products containing a free N-H group from the previously synthesized tetrahydroquinoline **17f**. Under typical nosyl group deprotection conditions, combining thiophenol (PhSH) and a base (Cs₂CO₃), tetrahydroquinoline **17i** was obtained in 96 % yield, which possesses potential for further *N*-functionalization (Scheme 17).

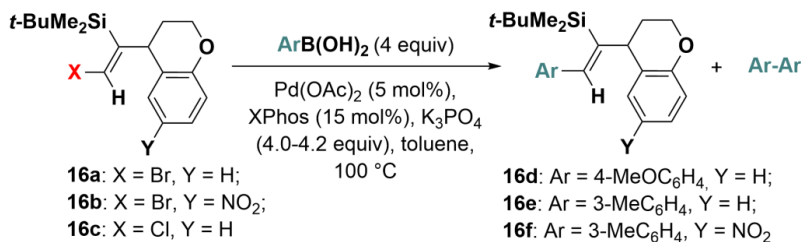


Scheme 17. Synthesis of tetrahydroquinoline **17i** by nosyl group deprotection.

For the modification of chromanes **16a-c**, Suzuki-Miyaura cross-coupling reactions were performed (Table 4). Cross-coupling of vinyl bromide **16a** with 4-methoxyphenylboronic acid afforded styrene derivative **16d**. The latter was difficult to separate from the homocoupling by-product (4,4'-dimethoxy-1,1'-biphenyl) due to similar polarity, resulting in a low isolated yield (**16d**, 6 %). In contrast, 3-methylphenylboronic acid reacted with vinyl bromides **16a-b** to give more easily separable products, and styrenes **16e-f** were isolated in high yields (92–97 %). As expected, vinyl chloride **16c** afforded significantly lower cross-coupling product yields (**16e**, 27 %) than its brominated analogues **16a-b**.

Table 4

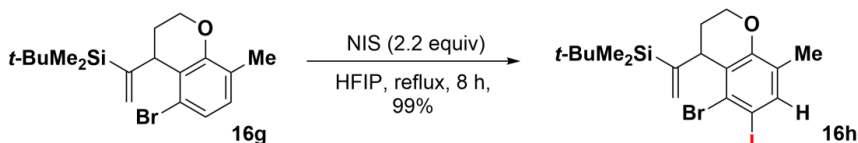
The application of chromanes **16a-c** in Suzuki-Miyaura cross-coupling reactions



Entry	X	Y	Ar	Time (h)	Product (%)
1 ^{[c][d]}	Br	H	4-MeOC ₆ H ₄	14	16d , 45 ^[a] , 6 ^[b]
2	Br	H	3-MeC ₆ H ₄	44	16e , 97 ^[b]
3	Br	NO ₂	3-MeC ₆ H ₄	22	16f , 92 ^[b]
4	Cl	H	3-MeC ₆ H ₄	26	16e , 27 ^[b]

^[a] NMR yield (%). ^[b] Isolated yield (%). ^[c] The cross-coupling product **16d** formed an inseparable mixture with the homocoupling product (Ar-Ar). ^[d] Modified reaction conditions were used: 3 equiv ArB(OH)₂, 7 mol% Pd(OAc)₂, 21 mol% XPhos, 4.9 equiv K₃PO₄.

Similarly to previous studies,^{[19], [29]} the author attempted a silicon-halogen exchange in chromane **16g** using NIS in hexafluoroisopropanol (HFIP). Unexpectedly, even with an excess of NIS (2.2 equiv) and under reflux conditions, *Si*→*I* exchange did not occur. Instead, monoiodination of the aromatic ring afforded product **16h** in quantitative yield (Scheme 18).

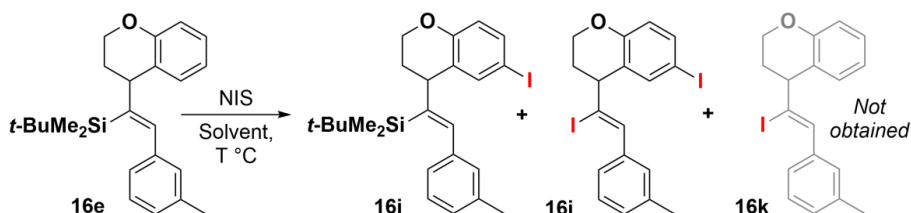


Scheme 18. Synthesis of monoiodinated product **16h**.

The electrophilic *Si*→*Hal* exchange is achieved through silicon-directed addition of an electrophilic species (Hal^+) to the vinyl silane $\text{R}_2\text{C}=\text{C}(\text{Si})\text{-R}'$, forming a β -silicon-stabilized carbenium ion intermediate $\text{R}_2\text{C}^+-\text{C}(\text{Si})(\text{Hal})\text{-R}'$.^[34] In the case of terminal $\text{C}=\text{C}$ bonds, a destabilized primary carbenium ion would be formed, making the reaction unfavorable. For styrene derivatives, however, the reaction becomes feasible due to a plausible benzylic cation intermediate. Iodination experiments performed on styrene derivative **16e** support this hypothesis (Table 5).

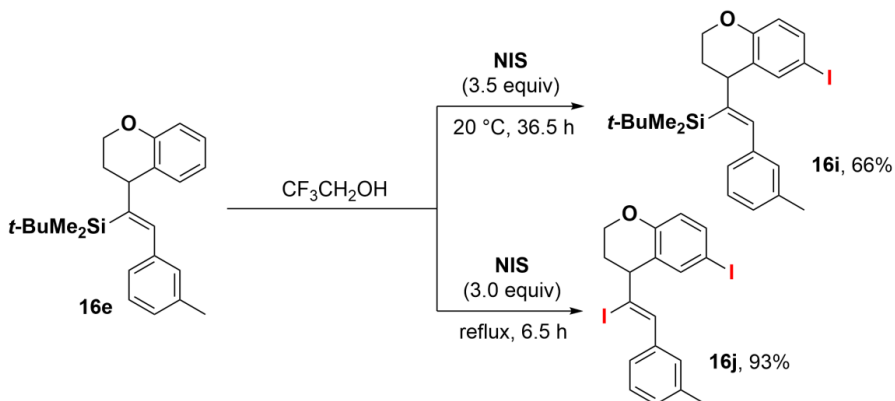
Table 5

Iodination experiments on styrene derivative **16e**



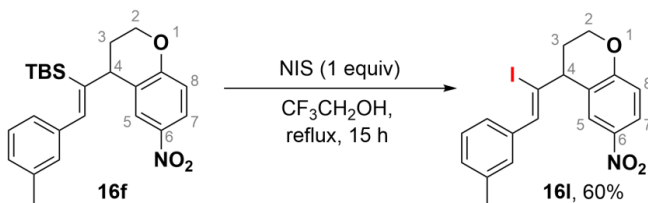
Entry	NIS (equiv)	Solvent	T °C	Time (h)	Starting material 16e/product 16i-j molar ratio by NMR		
					16e	16i	16j
1	1.0	HFIP	20	0.5	31	49	20
2	2.5			1.5	0	0	100
3	1.0	TFE		18.0	33	67	0
4	2.0			17.5	20	80	0
5	3.5			36.5	13	87	0
6	10.8			1.5	5	35	60
7	1.0		75–80	6.5	38	62	0
				71.0	28	72	0
8	3.0	6.5		0	0	100	

Using equimolar NIS in HFIP, a mixture of mono-iodinated product **16i** and diiodinated product **16j** (49:20) was obtained. With excess NIS (2.5 equiv), only the diiodinated product **16j** was formed. Using TFE as solvent, the reaction proceeded more slowly, allowing better control over product formation. By stopping the reaction after 36.5 h, mono-iodinated product **16i** was isolated in 66 % yield (71 % by NMR). High yields of diiodinated product **16j** (93 % isolated) were obtained using excess NIS (3 equiv) at elevated temperatures (75–80 °C, pressure flask, 6.5 h). Optimized conditions for selective mono- or diiodination are depicted in Scheme 19.



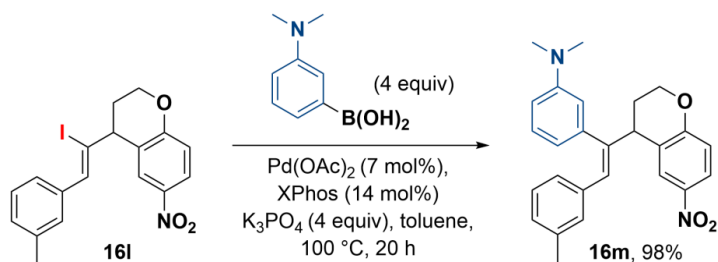
Scheme 19. Chromane **16e** mono- and diiodination experiments under optimized conditions.

Introduction of an electron-withdrawing nitro group at the chromane 6-position suppressed aromatic iodination, as observed by reacting nitro chromane **16f** with NIS (1 equiv) in trifluoroethanol at reflux temperature. In this case, selective *Si*→*I* exchange was achieved, yielding vinyl iodide **16l** in 60 % yield (Scheme 20).



Scheme 20. *Si*→*I* exchange reaction using chromane **16f**.

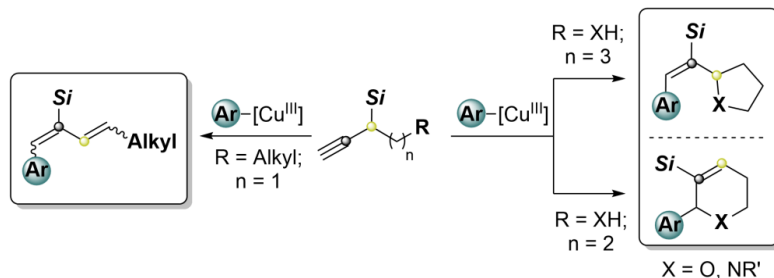
Finally, the synthetic utility of vinyl iodide **16l** was demonstrated in Suzuki-Miyaura cross-coupling reactions (Scheme 21). Using (3-(dimethylamino)phenyl)boronic acid as coupling partner under palladium catalysis, product **16m** was obtained in nearly quantitative yield (98 % isolated).



Scheme 21. Vinyl iodide **16l** application in Suzuki-Miyaura cross-coupling.

In this chapter, the author demonstrated propargyl silane heterocyclization *via* a Friedel-Crafts type reaction, where the propargylic system was activated by a Brønsted-acid. For terminally chlorinated propargyl silanes **11g-h**, cyclization occurred stereoselectively, affording tetrahydroquinolines **17** with exclusive (*Z*)-geometry for the resulting olefin side chain. The formed vinyl halide fragments were further modified by Suzuki-Miyaura cross-coupling and electrophilic silicon-iodine exchange to obtain synthetically useful vinyl iodides. Full details of this research are described in publication Ubaidullajevs, A.; Kroņkalne, R.; Mishnev, A.; Turks, M. Synthesis of Substituted Chromanes and Tetrahydroquinolines *via* Tandem 1,2-Silyl Shift – Friedel-Crafts cyclization. *J. Org. Chem.*, **2026**, 91 (17), 5785–5810 (Appendix 2).^[33]

1.3. Synthesis of arylated heterocycles and dienes using diaryl- λ^3 -iodanes under copper-catalyzed conditions

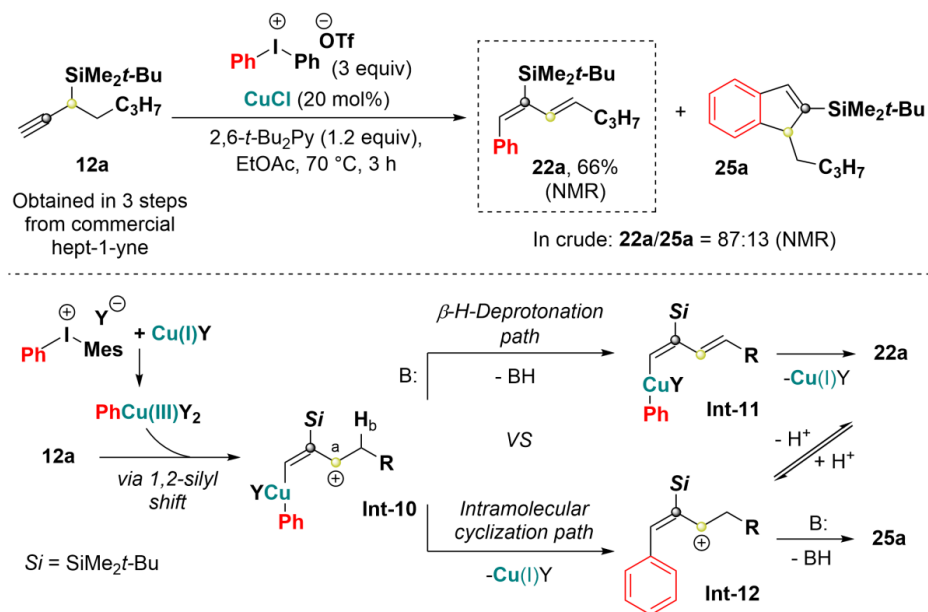


Previously, the author described activation of propargyl silanes for heterocycle synthesis using Brønsted acids or electrophilic halogenating reagents. The use of carbon electrophiles for analogous transformations represents a separate research direction developed in collaboration with Rūdolfs Beļāunieks and Armands Sebris.^[35]

Diaryl- λ^3 -iodanes are commonly used to introduce aryl groups into π -systems, particularly in transformations requiring a formal Ar^+ species. This approach has been applied for 1,2-difunctionalization of alkynes.^[36] In the latter context, hypervalent iodine(III) reagents are

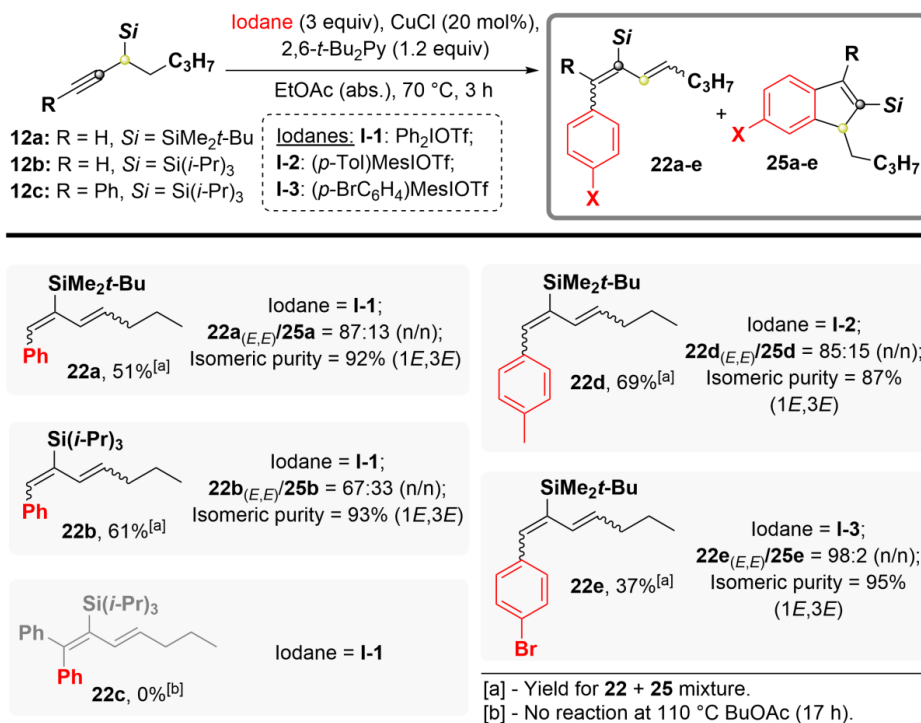
typically activated by copper or palladium catalysts.^{[37], [38]} Since propargyl silanes under electrophilic activation conditions can act as formal 1,3-dipoles due to 1,2-silyl migration, it is possible to achieve 1,3-difunctionalization, which is significantly less common than its 1,2-counterpart. In this study, the author developed a copper-catalyzed method for the 1,3-difunctionalization of propargyl silanes using diaryl- λ^3 -iodanes to obtain arylated heterocyclic structures and silyl dienes.

While searching for suitable reaction conditions for the arylation of propargyl silanes, the author began with simple silanes **12a**^[18] bearing an alkyl side chain. Its reaction gave a mixture of arylated silyl diene **22a** and silylindene **25a** (Scheme 22). The formation of these products can be explained by two competing reaction pathways: (a) elimination of a β -proton from allyl cation intermediate **Int-10** leads to formation of diene **22a**; (b) intramolecular cyclization of intermediate **Int-12** occurs, resulting in silylindene **25a**. Under optimized conditions (3.0 equiv Ph₂IOTf, 20 mol% CuCl, 1.2 equiv 2,6-*t*-Bu₂Py, EtOAc, 70 °C), the diene **22a**/indene **25a** ratio in the crude reaction mixture was 87:13, with a 66 % NMR yield of diene **22a**. Use of PhMesIOTf gave similar yields of diene **22a** (59 % by NMR), but lower selectivity toward diene formation (**22a**/**25a** = 71:22).



Scheme 22. Synthesis of arylated silyl diene **22a**: reaction concept and competing reaction pathways.

Using the conditions that provided the highest diene **22a** yield, the substrate scope was further investigated (Scheme 23). Arylation of silane **12a** with iodane **I-2**, which contains an electron-rich aryl system (*p*-tolyl), afforded the highest diene yields (**22d**, 69 %). The highest selectivity toward diene formation (**22e/25e** = 98:2) was observed with a *p*-bromo-substituted iodane **I-3**. Substrate **12b** bearing a bulky triisopropylsilyl (TIPS) group gave a mixture with a higher proportion of indene (**22b/25b** = 67:33). In all cases, (1*E*,3*E*)-dienes **22a-e** were obtained as the major isomers, with 87–95 % content. Minor amounts of other isomers ((1*Z*, 3*E*)-, (1*E*, 3*Z*)-, and (1*Z*, 3*Z*)-**22**) were detected by their characteristic signals in ¹H NMR spectra. Internal alkyne **12c** (R = Ph, Si = TIPS) did not react under standard (EtOAc, 70 °C) or elevated temperature conditions (*n*-BuOAc, 110 °C), and the starting material was recovered unchanged. This indicates that the method is limited to propargyl silanes containing terminal alkyne groups.



Scheme 23. Substrate scope for arylated silyl dienes.

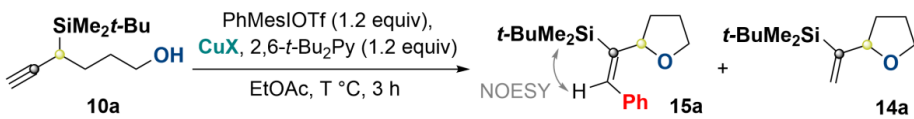
It was previously demonstrated that substrates containing internal nucleophiles enable heterocyclization. For example, propargyl silane **10a** bearing a terminal alcohol group was used for tetrahydrofuran synthesis.^[29] To achieve an arylation-heterocyclization cascade reaction, various alternative Cu(I) catalysts were tested (Table 6). CuCl and the CuOTf benzene complex

gave similarly high yields (**15a**, 82–84 % by NMR), while Cu(MeCN)₄BF₄ gave a slightly lower yield (**15a**, 77 %). Heterogeneous catalysis using Cu₂O afforded a mixture of arylated product **15a** and protodemetalation by-product **14a**, both in low yields. In the absence of a non-nucleophilic base (2,6-di-*tert*-butylpyridine = 2,6-*t*-Bu₂Py), selective formation of the protodemetalation product **14a** (69 % by NMR) was observed. Other, less sterically hindered bases (lutidine, Et₃N) did not afford the desired product.

The geometry of the olefin side chain in **15a** was confirmed using 2D NOESY NMR spectroscopy. The reaction exhibited high stereoselectivity, with only the (*E*)-isomer detected.

Table 6

Copper(I)-catalyst and temperature screening for the arylation-heterocyclization reaction of propargyl silane **10a**

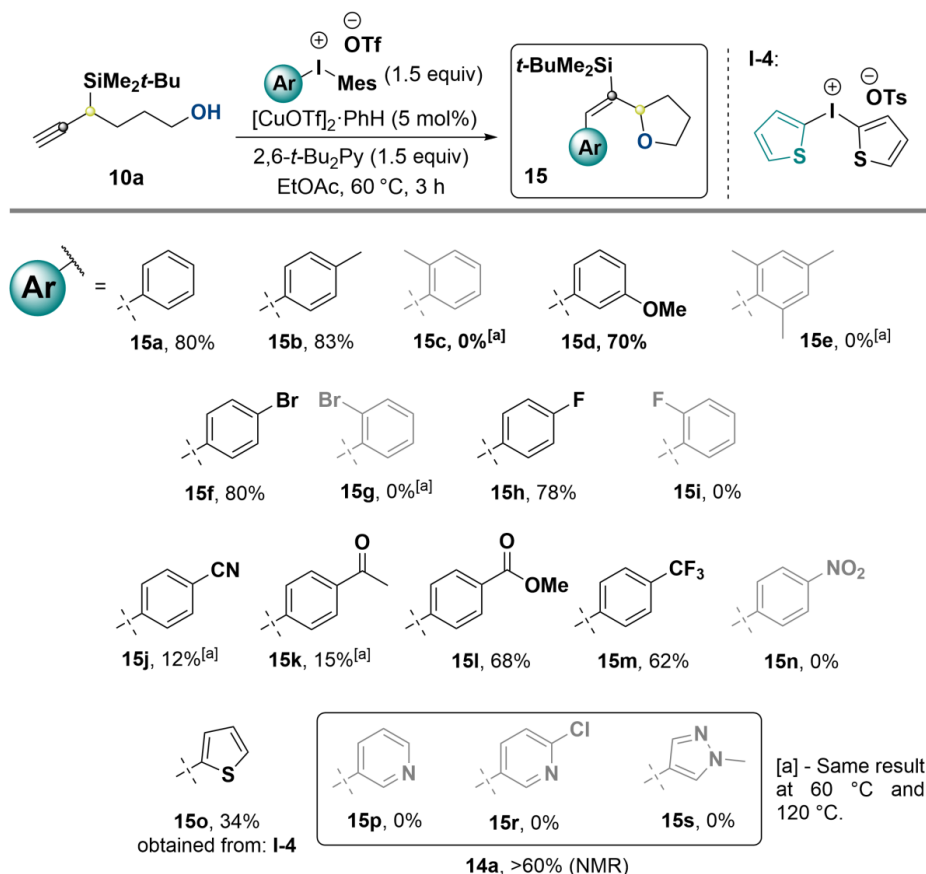


N°	CuX (mol%)	T (°C)	15a, % (NMR)	14a, % (NMR)
1 ^[a]	CuCl (2.5)	20	0	69
2	CuCl (2.5)	20	0	0
3	CuCl (5)	60	82, 76^[c]	0
4	CuI (5)	60	0	0
5 ^[b]	[CuOTf] ₂ ·PhH (5)	60	84	0
6	Cu(MeCN) ₄ BF ₄ (5)	70	77	0
7	Cu ₂ O (5)	70	6	2
8	[CuOTf] ₂ ·PhH (2.5)	70	70	0
9 ^[d]	[CuOTf] ₂ ·PhH (2.5)	70	43	0
10	[CuOTf] ₂ ·PhH (11)	70	47	0

^[a] Without 2,6-*t*-Bu₂Py. ^[b] Reaction time – 2 h (full conv.). ^[c] Isolated yield (%). ^[d] 15 mol% of H₂O as additive.

Under optimized conditions, the scope of arylated tetrahydrofurans **15** was examined (Scheme 24). Iodonium salts with electron-rich aryl groups (Ar = *p*-tolyl, *m*-methoxyphenyl, phenyl) and those containing halogens (Br, F) gave the highest yields (**15**, 70–83 %). In contrast, iodonium salts bearing electron-poor aryl groups, especially those containing nucleophilic heteroatoms (CN ≈ COR >> NO₂), reacted poorly. Aryl iodanes, bearing other electron-

withdrawing groups (CF₃, CO₂Me) gave moderate yields (62–68 %). Ortho-substituted iodonium salts were unreactive. Iodonium salts containing *N*-heterocycles (e.g., pyridine, pyrazole) gave predominantly non-arylated product **14a** via protodecupration. The only heterocycle-containing iodane, which led to heteroarylated tetrahydrofuran derivatives **15o**, was the thiophenyl group-containing symmetrical iodane **I-4**. It should be noted that all arylated tetrahydrofurans **15a-o** were obtained with exclusive (*E*)-selectivity for the olefin side chain.

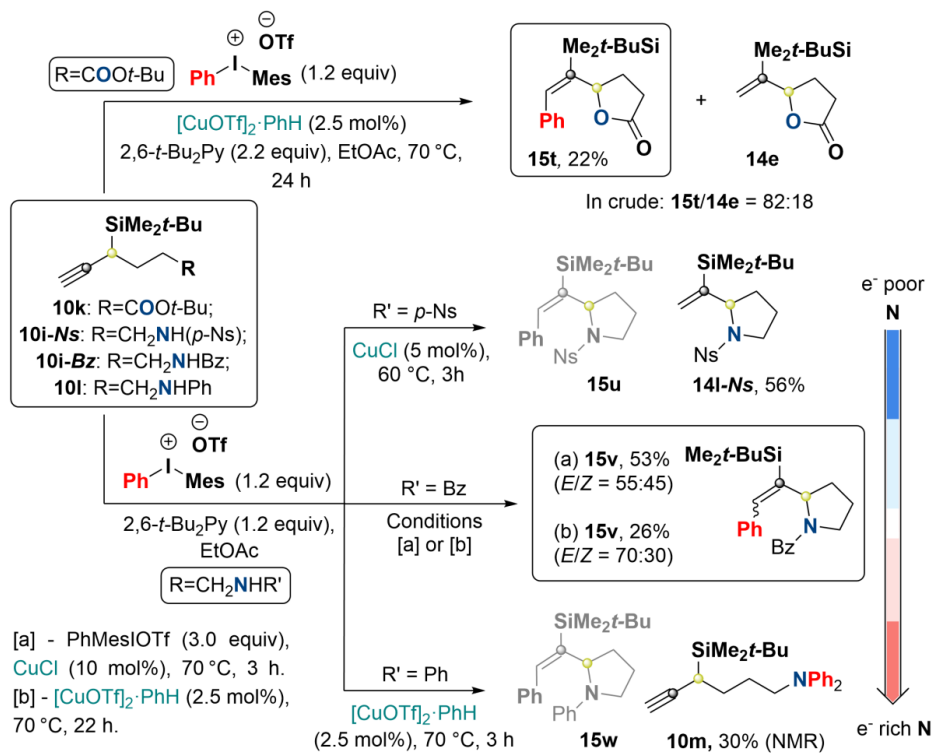


Scheme 24. Substrate scope for arylated tetrahydrofurans.

It was found that under the described arylation conditions, only internal *O*-nucleophiles reacted to afford 1,3-carbofunctionalized products. Attempts to perform arylation of propargyl silane **12b** in the presence of external *O*-nucleophiles (alcohols, carboxylic acids or their salts, silylated acids) resulted in arylation of the nucleophile itself, rather than formation of the desired product.

The author proceeded to explore other propargyl silanes as starting materials, bearing internal nucleophiles (Scheme 25). Carboxylic acid-containing substrate **10b** did not yield the

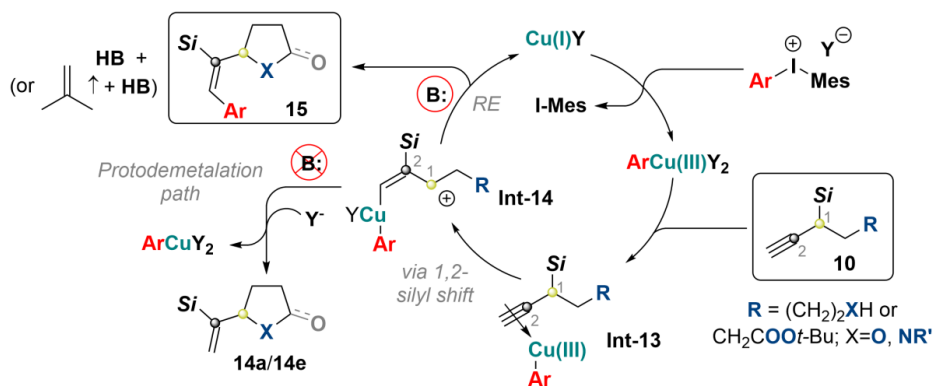
desired lactone **15t**, due to competing *O*-arylation forming phenyl alkyl esters. Its *tert*-butyl ester analogue **10t**, however, yielded the desired product **15t**, although the protodecupration product **14e** was also formed. Increasing the base loading reduced formation of **14e** and improved selectivity toward **15t**. *N*-Nosyl substrate **10i-Ns** yielded the non-arylated pyrrolidine **14i-Ns** (56 %) due to excessive acidity promoting protodecupration, whereas benzamide **10i-Bz** gave the arylated pyrrolidine **15v** as an *E/Z* mixture (55:45). Highly nucleophilic amine **10l** ($R = \text{CH}_2\text{NHPh}$) underwent *N*-arylation instead of forming heterocycles. These results indicate that acylamides possess optimal pKa and nucleophilicity for the desired arylation-heterocyclization reaction pathway.



Scheme 25. Arylation of amides **10i**, **10l** and carboxylic acid ester **10k**.

From previous optimization studies (see Appendix 3), it was established that Cu(I) salts are more reactive than Cu(II) salts, suggesting a Cu(I/III) catalytic cycle. Therefore, for the arylation-heterocyclization sequence, a Cu(I/III) catalytic cycle is proposed, which we based on experimental observations and mechanistic rationalizations for copper-catalyzed arylations in other π -systems.^[37] In the proposed mechanism, Cu(I) reacts with the diaryl- λ^3 -iodane to generate a highly electrophilic Ar-Cu(III) species, which activates the propargyl system (Scheme 26).

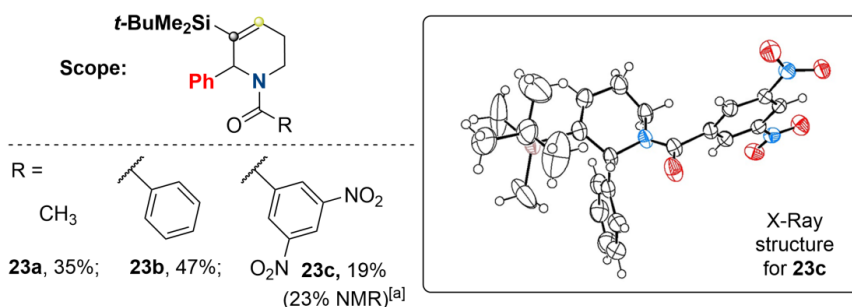
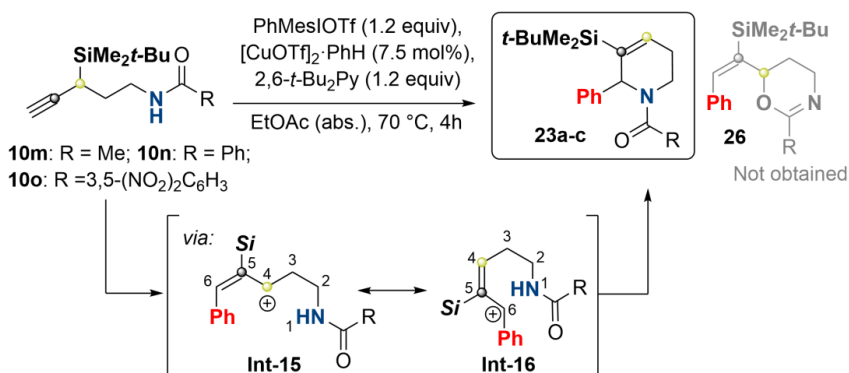
Silicon 1,2-migration affords a β -silicon-stabilized allyl cation intermediate **Int-14**. Next events include cyclization with the internal nucleophile and reductive elimination leading to arylated heterocycle **15** and regenerating Cu(I). In the case of *tert*-butyl ester **10k** ($R = \text{CH}_2\text{COO}t\text{-Bu}$), 1 equiv of isobutylene gas is also generated. The external base ($B = 2,6\text{-}t\text{-Bu}_2\text{Py}$) neutralizes the acid generated in the catalytic cycle and suppresses the formation of undesired protodecupration side-products **14a/14e**.



Scheme 26. Proposed mechanism for propargyl silane arylation-heterocyclization.

For substrates with shorter carbon chains **10m-o**, an alternative mechanism was observed (Scheme 27). Instead of the initially expected imidates **26**,^[39] tetrahydropyridines **23a-c** were formed *via* nucleophilic attack on the allyl cation resonance form **Int-16**, which was additionally stabilized by the aryl group. The structure of product **23c** was unambiguously confirmed by X-ray structure analysis.

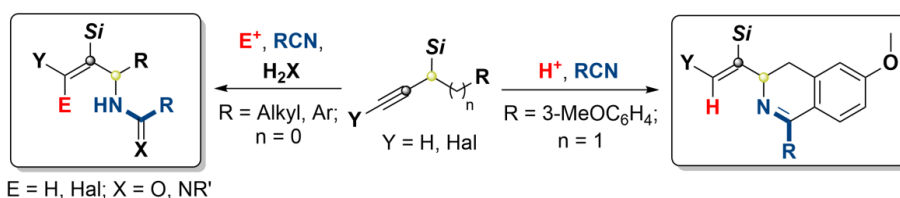
From this, the author concludes that the regioselectivity of propargyl silane **10** arylation-heterocyclization depends on the substrate carbon chain size. In systems where five-membered cycle formation is possible, 1,3-difunctionalization is observed, resulting in tetrahydrofurans **15** ($X = \text{O}$) and pyrrolidines **15** ($X = \text{N-PG}$). Substrates **10m-o** bearing shorter carbon chains undergo 1,1-difunctionalization, forming tetrahydropyridines **23**. The author's demonstrated approach offers a more efficient route towards heterocycles bearing a styryl side chain compared to previously explored strategies.^[29] Full details of this research are described in the publication Kronkalne, R.; Beļāunieks, R.; Sebris, A.; Mishnev, A.; Turks, M. Aryl Iodane-Induced Cascade Arylation–1,2-Silyl Shift–Heterocyclization of Propargylsilanes under Copper Catalysis. *Beilstein J. Org. Chem.*, **2025**, *21*, 1984–1994 (Appendix 3).^[35]



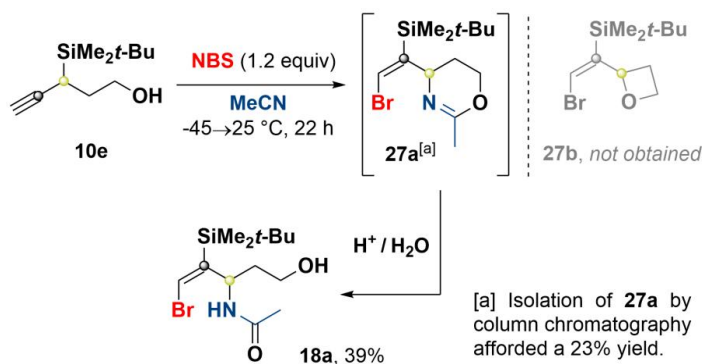
[a] - Modified conditions: **Ph₂IOTf** (3.0 equiv), 20 h.

Scheme 27. Tetrahydropyridine **23** synthesis from propargyl silanes.

1.4. Ritter-type reaction with β-silicon stabilized allyl cations

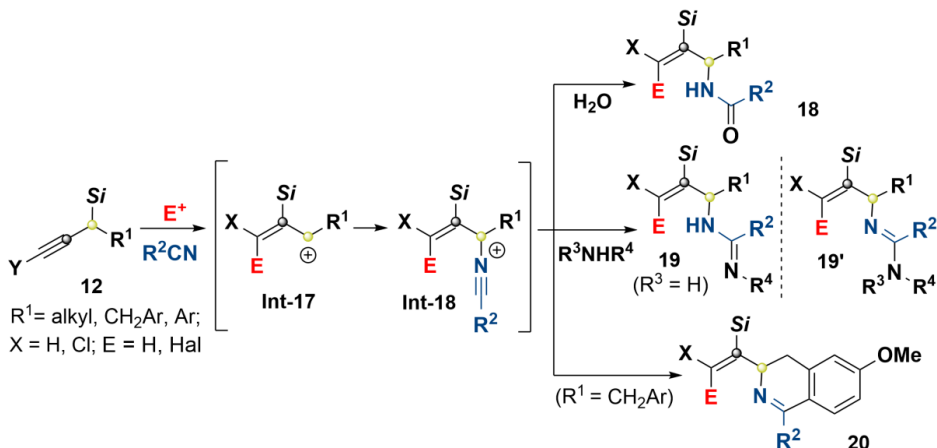


Attempts to perform heterocyclization of alcohol **10e** using NBS, analogously to the transformations described earlier in Section 1.1, but with acetonitrile (MeCN) as solvent, resulted in the formation of oxazine derivative **27a** rather than the expected oxetane derivative **27b** (Scheme 28). The cyclic product **27a** readily underwent hydrolysis to give acetamide **18a** – a classical Ritter reaction product. This observation encouraged further investigations into the application of 1,2-silyl shift in Ritter-type reactions.



Scheme 28. Heterocyclization of alcohol **10e** under Ritter reaction conditions.

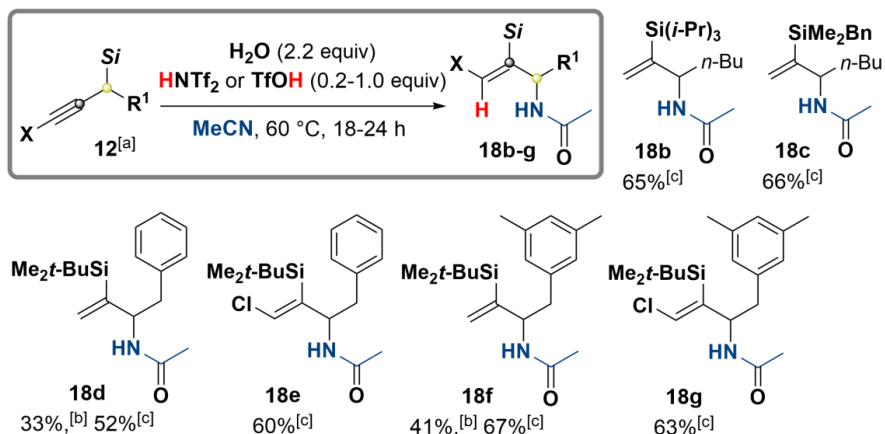
In this transformation, the nitrile acts as the primary nucleophile, attacking the allyl cation intermediate **Int-17** to form a nitrilium ion **Int-18** (Scheme 29). This intermediate is subsequently quenched by a secondary nucleophile (H₂O, ROH, R₁R₂NH, Ar), leading to the formation of cyclic or acyclic products that share a common feature – a functionalized olefin side chain. From an entropic perspective, this multicomponent reaction is particularly complex, as it involves the sequential formation of four covalent bonds in a single step. Despite this complexity, a methodology was developed for the use of propargyl silanes **12** in the synthesis of functionalized allylamides **18**, amidines **19**, and dihydroisoquinolines **20** under Ritter-type conditions. This study was conducted in collaboration with Sandra Turka,^[40] Raimonds Rogaļevs^[41] and Mikus Purīņš,^[42] and the results are yet to be published.



Scheme 29. The application of propargyl silanes in Ritter-type reaction.

Initially, systems most closely resembling classical Ritter reaction conditions were investigated. These conditions combined a Brønsted acid (TfOH or HNTf₂) for carbocation

generation, MeCN as both solvent and primary nucleophile, and water as a secondary nucleophile. Under these conditions, products **18b-g** bearing the allylamide functionality were obtained (Scheme 30).

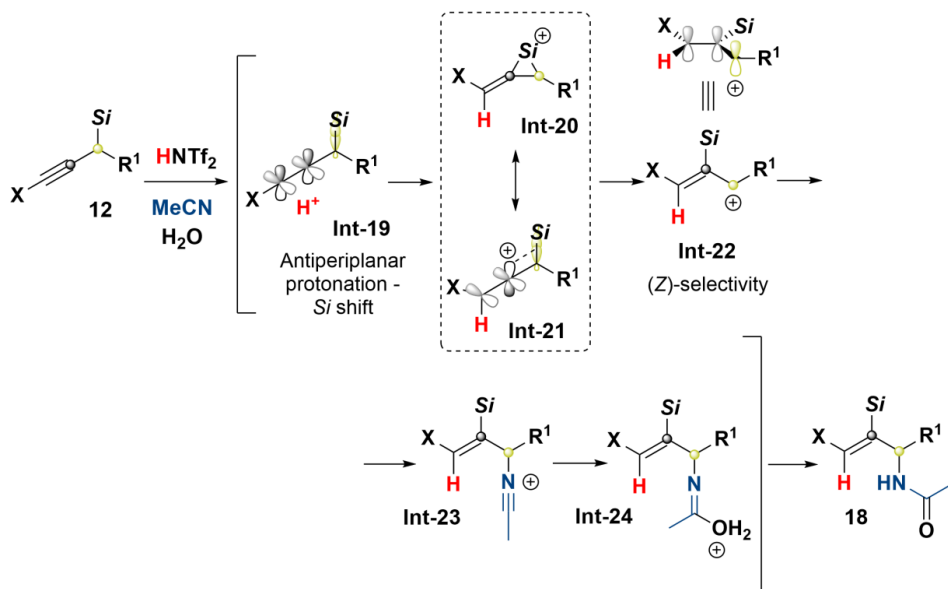


[a] Silanes: **12b** (X = H, R¹ = *n*-Bu, Si = (*i*-Pr)₃Si), **12d** (X = H, R¹ = *n*-Bu, Si = BnMe₂Si), **12e** (X = H, R¹ = Bn, Si = *t*-BuMe₂Si), **12f** (X = Cl, R¹ = Bn, Si = *t*-BuMe₂Si), **12g** (X = H, R¹ = CH₂(3,5-Me₂C₆H₃), Si = *t*-BuMe₂Si), **12h** (X = Cl, R¹ = CH₂(3,5-Me₂C₆H₃), Si = *t*-BuMe₂Si). [b] 0.2 equiv TfOH as H⁺ source. [c] 1.0 equiv HNTf₂ as H⁺ source.

Scheme 30. Synthesis of allylamides from propargyl silanes.

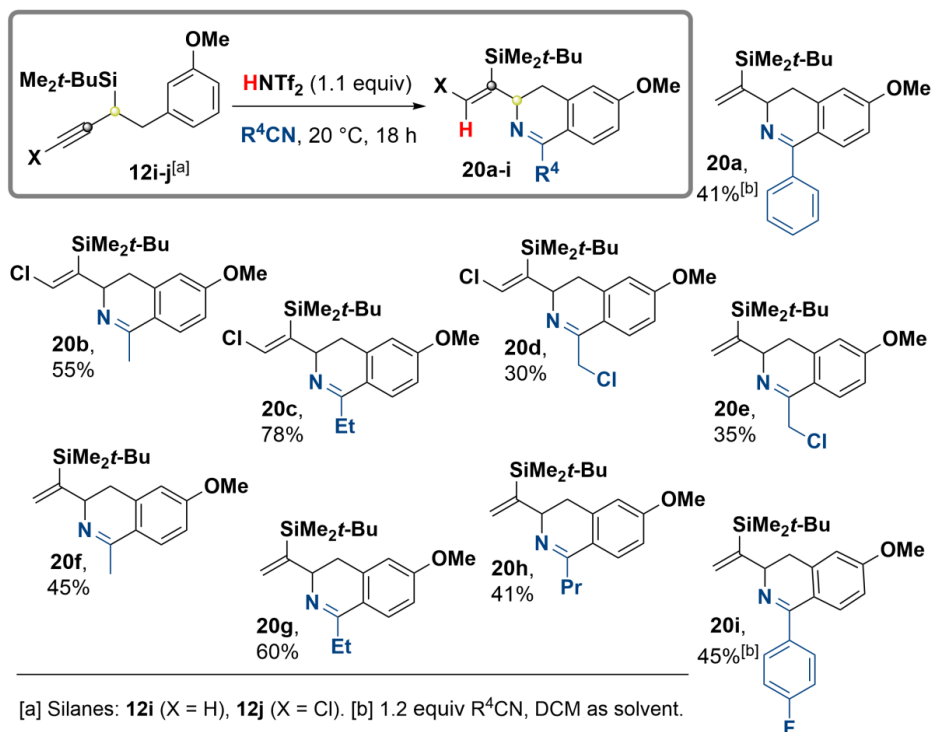
It was observed that using stoichiometric amounts of acid (1.0 equiv HNTf₂: **18f**, 67 % yield) resulted in higher yields compared to catalytic amounts (0.2 equiv TfOH: **18f**, 41 % yield). In the case of terminally halogenated propargyl silanes **12** (X = Cl), products **18e** and **18g** were obtained with trisubstituted olefin side chains, showing a (*Z/E*)-isomer ratio of 9:1 prior to purification. The major (*Z*)-isomer could be isolated by column chromatography.

The formation of the (*Z*)-configured double bond in allylamides **18e/18g** can be explained by protonation of the alkyne in an antiperiplanar orientation relative to the migrating silyl group (Scheme 31).



Scheme 31. Mechanistic rationalization for the formation of olefin (Z)-geometry.

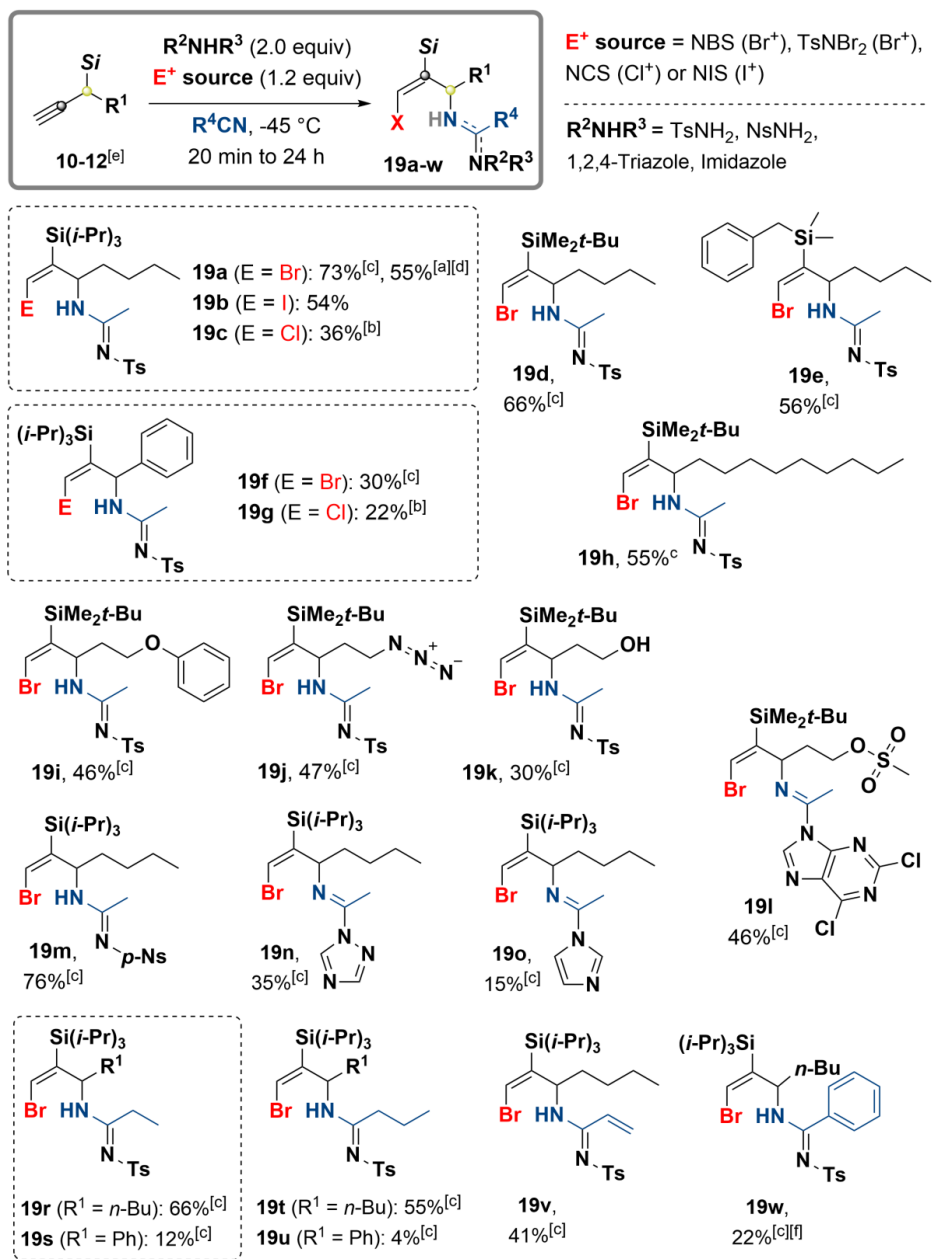
For substrates **12i-j** bearing electron-rich aromatic systems, a Bischler-Napieralski-type transformation was observed (Scheme 32). In this case, the aromatic ring acts as the secondary nucleophile, quenching the nitrilium ion and forming dihydroisoquinoline derivatives **20a-i**. Consistent with earlier observations, terminally halogenated substrate **12j** yielded products **20b-d** with (Z)-configured olefin side chains. The halogenated substrate **12j** also gave higher product **20** yields (up to 78 %) compared to the non-halogenated analogue **12i** (up to 60 %). Unlike the synthesis of allylamide **18** (which required heating to 60 °C), the synthesis of dihydroisoquinolines **20** proceeded efficiently at room temperature (20 °C). Using various aliphatic (MeCN, EtCN, PrCN) and halogenated (ClCH₂CN) nitriles, products **20b-h** were obtained in 30–78 % yields. Aromatic nitriles are less commonly used as solvents in Ritter-type reactions due to their high boiling points or solid state.^{[43], [44], [45]} To overcome this issue, dichloromethane (DCM) was used as solvent, with aromatic nitriles (PhCN, 4-FC₆H₄CN) added in quantities near stoichiometric ones (1.2 equiv). Under these conditions, products **20a** and **20i** were obtained in 41–45 % yields.



Scheme 32. Synthesis of dihydroisoquinolines from propargyl silanes in a Bischler-Napieralski-type reaction.

Next, more complex systems were investigated, where an external nitrogen nucleophile participates in nitrilium ion quenching. Under Brønsted acid activation conditions, the reaction either produced only diene by-products or did not proceed. For example, (*E*)-hepta-1,3-dien-2-yltriisopropylsilane^[18] was formed with 30 % NMR yield when silane **12b** (1.0 equiv) was reacted with TfOH (1.2 equiv) and TsNH_2 (2.0 equiv) in MeCN ($T = -45\text{ }^\circ\text{C}$), whereas with HNTf_2 (1.2 equiv) under identical conditions the reaction did not proceed. However, activation using the electrophilic brominating reagent NBS led to formation of amidine **19a** with 56 % yield by NMR (conditions: 1.2 equiv NBS, 1.1 equiv TsNH_2 , MeCN, $20\text{ }^\circ\text{C}$). Further optimization demonstrated that the highest amidine **19a** yields (75 % by NMR) were obtained under the following conditions: $T = -45\text{ }^\circ\text{C}$, MeCN as solvent, 2 equiv TsNH_2 and 1.2 equiv NBS.

Using the optimized reaction conditions ($T = -45\text{ }^\circ\text{C}$, RCN as solvent, 2 equiv TsNH_2), the author proceeded with the investigation of the substrate scope (Scheme 33).



[a] NMR yield. [b] T = -45→20 °C. [c] NBS as Br⁺ source. [d] TsNBr₂ as Br⁺ source. [e] Silanes: **12a** (R¹ = *n*-Bu, Si = *t*-BuMe₂Si), **12k** (R¹ = Ph, Si = (*i*-Pr)₃Si), **12l** (R¹ = C₉H₁₉, Si = *t*-BuMe₂Si), **11i** (R¹ = CH₂CH₂OPh, Si = *t*-BuMe₂Si), **10p** (R¹ = CH₂CH₂N₃, Si = *t*-BuMe₂Si), **10e** (R¹ = CH₂CH₂OH, Si = *t*-BuMe₂Si), **10r** (R¹ = CH₂CH₂OMs, Si = *t*-BuMe₂Si). [f] A modified solvent system was used: PhCN/DCM (4:3 v/v).

Scheme 33. Synthesis of amidines in a Ritter-type reaction.

Variation of substituents at the product C=C bond was achieved by employing different electrophilic halogenating reagents (NBS, NCS, NIS), enabling the synthesis of vinyl halide-containing products **19a-c** (Hal = Br, Cl, I). The highest yields of amidines **19** (up to 76 %) were obtained from substrates containing simple aliphatic chains **12a,b,d**. In contrast, aryl-substituted propargyl silane **12k**^[18] afforded lower amidine yields (22–30 %) under Ritter-type conditions. Additional stabilization of the carbocation intermediate by a neighboring aryl group (R¹ = Ar) likely slows down nitrile addition, as indirectly evidenced by increased reaction time. For example, alkylsilane **12b** reached full conversion after 45 minutes, whereas arylsilane **12k** required 1.5 hours.

Compatibility with various functional groups was also examined. Substrates containing a terminal aryl ether **11i**, azide **10p**, mesylate **10r**, and even a free alcohol group **10e**, underwent Ritter-type reactions to give amidine products **19** in moderate yields (30–47 %).

Among alternative secondary nucleophiles for amidine synthesis, sulfonamides (NsNH₂, TsNH₂) gave the highest amidine **19** yields (73–76 %). Nitrogen heterocycles (e.g., 2,6-dichloropurine, 1,2,4-triazole, imidazole) were also compatible, although the yields were lower (15–46 %). Stronger nucleophiles such as cyclohexanol, cyclohexanethiol, and cyclohexylamine did not afford the expected imidate/thioimidate/amidine products under standard conditions.

Nitriles with longer alkyl chains (C₃–C₄) and acrylonitrile gave lower amidine **19** yields (41–66 %) compared to acetonitrile. In the case of benzonitrile, a mixed solvent system (PhCN/DCM, 4:3 v/v) was used to avoid freezing at –45 °C. However, benzonitrile exhibited low selectivity towards Ritter-type product formation, yielding amidine **19w** in only 22 %. Instead, the reaction predominantly followed a β-H elimination pathway, forming the respective diene.^[18]

In solution, amidines can exhibit configurational isomerism ((*E*)/(*Z*) around the C=N bond), rotational isomerism (syn/anti around the C–N bond), and tautomerism, all of which complicate structural analysis.^[46] NMR studies of amidines **19a-w** showed the following: in CDCl₃, two sets of signals were typically observed, whereas in DMSO-d₆, only one isomer was detected. For amidine **19m**, the major/minor isomer ratio in CDCl₃ was 96:4. The N–H signal appeared as a doublet with a coupling constant of ³*J* = 9.6 Hz relative to the C(3)–H proton, indicating a vicinal relationship. Additionally, the geometry of amidine **19m** was determined using X-ray structure analysis, which established the (*E*)-configuration for both the C=N and C=C bonds (Fig. 1). This was further confirmed by 2D NOESY NMR correlations between the C(1)–H proton and the (*i*-Pr)₃Si group. These findings are consistent with previous observations in electrophilic halogenation of propargyl silanes, which preferentially yielded (*E*)-configured trisubstituted olefins.^[19]

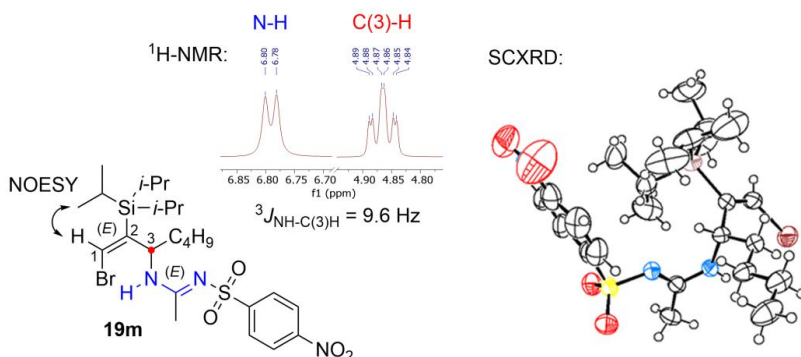
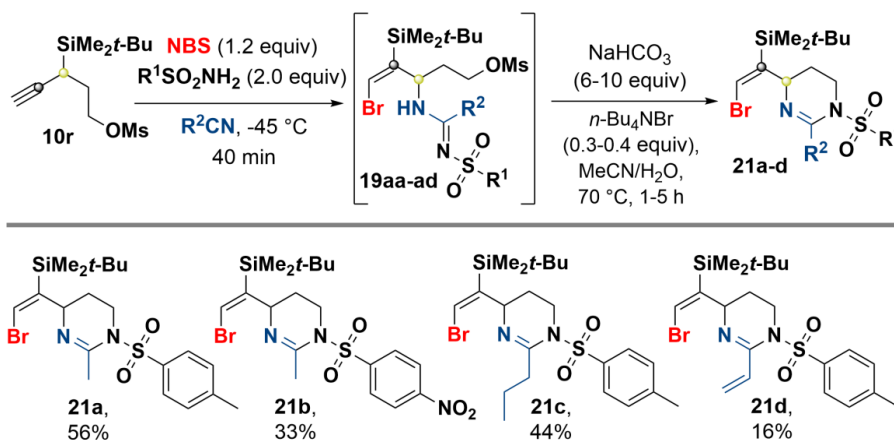


Fig. 1. Elucidation of amidine **19m** structure.

Finally, the synthetic utility of acyclic Ritter-type products was demonstrated in heterocycle synthesis (Scheme 34). Under standard Ritter-type conditions (1.2 equiv NBS, 2.0 equiv TsNH₂, nitrile solvent, T = -45 °C), mesylate **10r** afforded amidines **19aa-ad** that underwent intramolecular S_N2 cyclization in the presence of a base (NaHCO₃) to yield tetrahydropyrimidine derivatives **21a-d**.

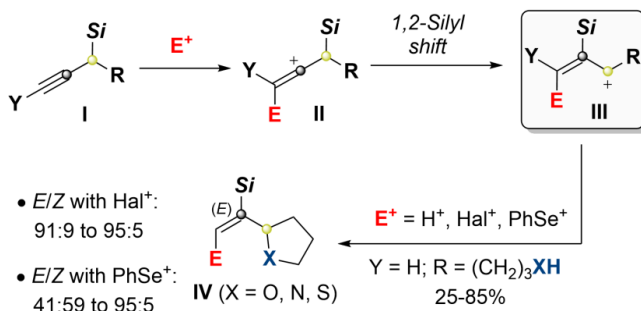


Scheme 34. Ritter-type reaction for the synthesis of tetrahydropyrimidine derivatives **21**.

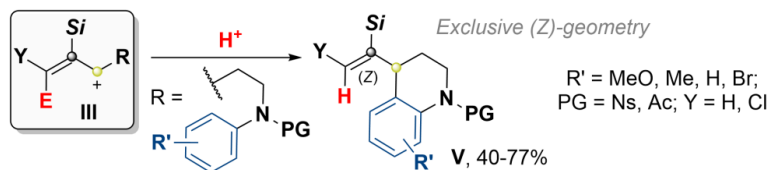
In conclusion, propargyl silane transformations under Ritter-type conditions afforded a broad spectrum of products, starting from acyclic structures – allylamides **18** and amidines **19** – to heterocycles **20-21**. By combining external electrophile attack on the propargyl silane triple bond with vinyl-allyl cation rearrangement *via* the 1,2-silyl shift, and two subsequent nucleophile attacks, the author obtained structurally complex motifs from simple starting materials. Full details of this research are described in Appendix 6: Turka, S.; Kronkalne, R.; Rogaļevs, R.; Puriņš, M.; Mishnev, A.; Turks, M. 1,2-Silyl Shift – Ritter Reaction Cascade for the Synthesis of Dihydroisoquinolines and Allylamine Derivatives (*Manuscript in preparation*).

CONCLUSIONS

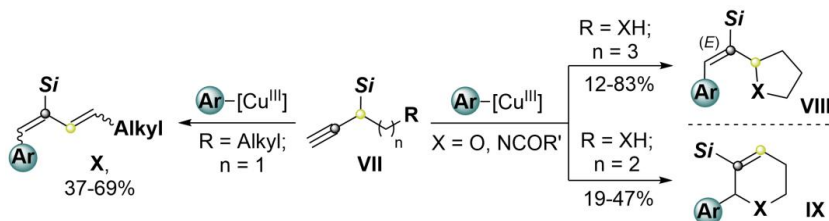
1. Electrophile-induced 1,2-silyl shift in propargyl silanes affords reactive allyl cation intermediates **III** that can be quenched by internal *O*-, *N*- and *S*-nucleophiles to form five-membered heterocycles **IV**: tetrahydrofurans (*X* = *O*), pyrrolidines (*X* = *N*-PG), and thiolanes (*X* = *S*), bearing geminally disubstituted (*E* = *H*) or stereodefined trisubstituted (*E* = Hal, PhSe) olefin side chains.



2. Quenching the β -silicon-stabilized allyl cation intermediates **III** with internal electron-rich aryl systems affords bicyclic heterocycles **V** with (*Z*)-configured olefin side chains *via* Brønsted acid-promoted Friedel-Crafts-type cyclization.

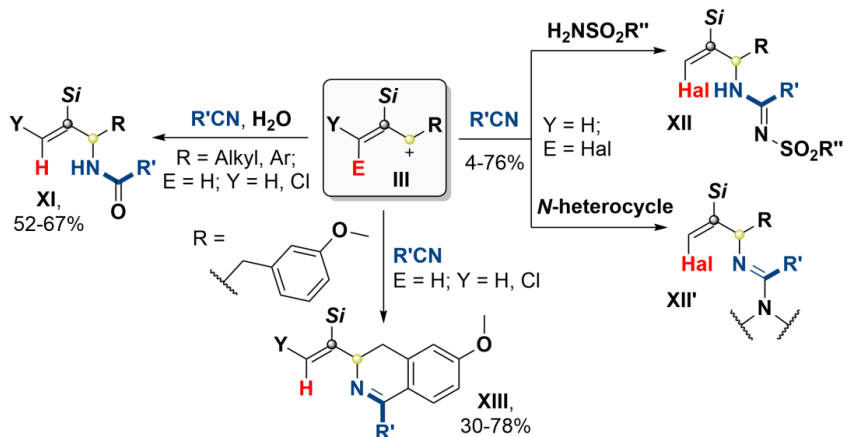


3. Combination of diaryl- λ^3 -iodanes with a Cu(I) catalyst enables in situ generation of electrophilic $Ar-Cu(III)$ reagents, which, as formal Ar^+ synthons, add to the propargyl silane triple bond to induce arylation – 1,2-silyl shift – heterocyclization sequences **VII**→**VIII** and **VII**→**IX** depending on the side chain length. In the absence of reactive internal nucleophiles, arylated silyl dienes **X** are obtained instead.

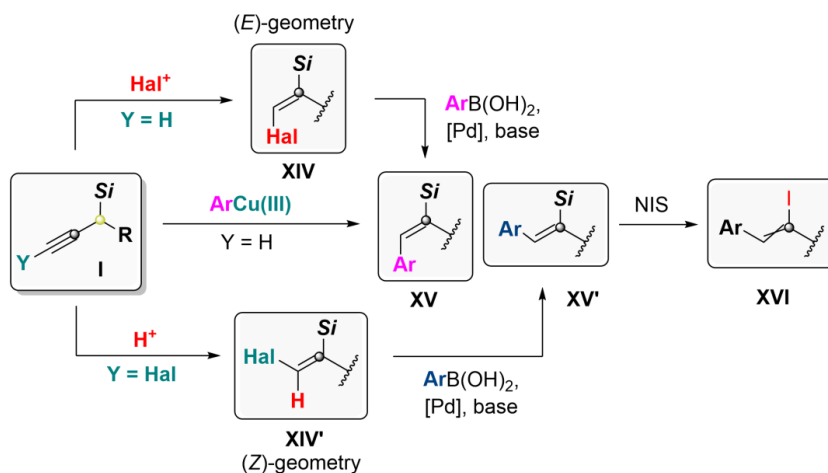


4. Under Ritter-type conditions, propargyl silanes can be combined with two incoming nucleophiles to afford allylamides **XI** (*X* = *O*) and amidines **XII** (*X* = *N*-PG) with highly

functionalized olefin fragments. Propargyl silanes bearing electron-rich aryl systems can be subjected to a Bischler-Napieralski-type reaction to yield dihydroisoquinolines **XIII**.



- Olefin geometry can be controlled by combining: (a) non-halogenated silanes **I** ($Y = H$) with electrophilic halogenation ($E^+ = Hal^+$) reagents to achieve (*E*)-geometry; or (b) halogenated silanes **I** ($Y = Hal$) with Brønsted acid activation ($E^+ = H^+$) to achieve (*Z*)-geometry. The olefin side chain can be further modified by cross-coupling reactions or electrophilic $Si \rightarrow I$ exchange with retention of the alkene configuration. By activating propargyl silane **I** with $Ar-Cu(III)$, styrene derivatives **XV** are obtained directly, omitting the Pd-catalyzed vinyl halide cross-coupling step.



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