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

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# ELEKTROFĪLU INDUCĒTAS CIKLOPROPĀNU REAKCIJAS AR NUKLEOFĪLIEM

# ELECTROPHILE-INDUCED CYCLOPROPANE REACTIONS WITH NUCLEOPHILES

**Promocijas darbs**
**Doctoral Thesis**

Zinātniskais vadītājs
Scientific supervisor

Profesors *Dr. chem.* A. JIRGENSONS
Professor *Dr. chem.* A. JIRGENSONS

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Promocijas darbs sagatavots kā tematiski vienota zinātnisko publikāciju kopa. Tajā ir kopsavilkums, piecas publikācijas un viens manuskripts. Publikācijas uzrakstītas angļu valodā, to kopējais apjoms, ieskaitot elektroniski pieejamo informāciju, ir 715 lpp.

# SATURS

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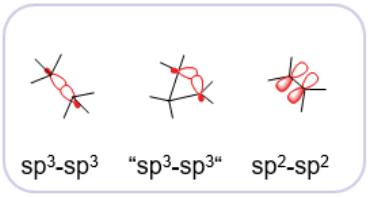
# PROMOCIJAS DARBA VISPĀRĒJS RAKSTUROJUMS

## Tēmas aktualitāte

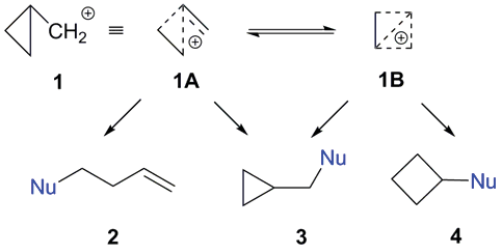
Ciklopropāns ir visvienkāršākais cikloalkāns, taču tā trīs atomos ir iekodēts augsts derivatizēšanas potenciāls. Tas izriet no *C-C* $sp^3$ hibridizēto orbitāļu nepilnīgās pārklāšanās, kas molekulāro orbitāli padara līdzīgāku olefīna $\pi$-saitei (1. att.).[1, 2]




1. att. Ciklopropāna *C-C* saites molekulāro orbitāļu salīdzinājums ar alkāna un olefīna orbitālēm.

*Neklasiskā ciklopropilmetilkatjona aminēšana*

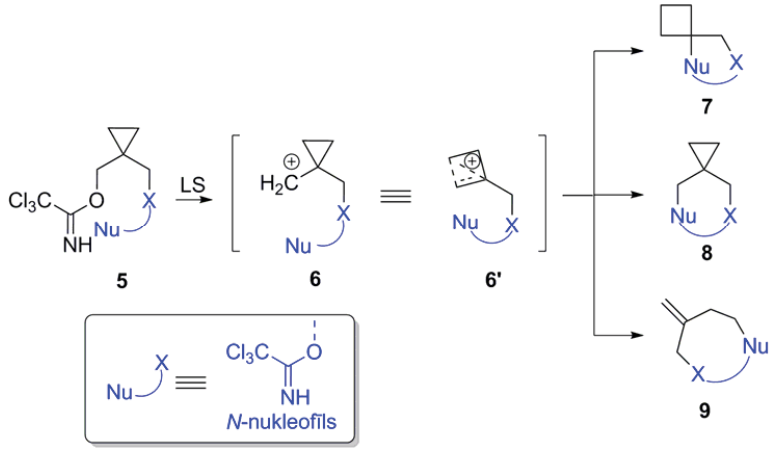
Ciklopropāna *C-C* saites molekulārās orbitāles pārklāšanās ar blakus esošo kabkatjona vakanto orbitāli nosaka ciklopropilmetilkatjona neklasisko dabu. Olā (*G. A. Olah*) veiktajos pētījumos (*NMR*, *DFT* aprēķini) parādīts, ka ciklopropilmetilkatjons visticamāk pastāv kā $\pi\sigma$-delokalizēts ciklopropilkarbinilkatjons **1A** līdzsvarā ar neklasisko biciklobutonija jonu **1B** (2. att.).[3, 4]




2. att. Neklasiskais ciklopropilmetilkatjons un tā reakcijas ar nukleofīliem.

Ciklopropilmetilkatjona **1** neklasiskā daba izskaidro tā spēju reakcijā ar nukleofīlu veidot strukturāli atšķirīgus homoalil-, ciklopropilmetil- un ciklobutilatvasinājumus **2-4**. Lai ciklopropilmetilkatjona reakcijas būtu sintētiski lietderīgas, nepieciešams kontrolēt nukleofīla pievienošanas reģioselektivitāti. Literatūrā ir zināmi vairāki piemēri gan selektīvai, gan neselektīvai produktu **2-4** iegūšanai katjona **1** reakcijā ar skābekļa nukleofīliem un halogenīdiem, savukārt tā aminēšanas reakcijas ir pētītas ļoti maz.[5–7] Līdz ar to, mēs savā darbā pievērsāmies neklasiskā katjona **1** ģenerēšanai un tā reģioselektīvas aminēšanas izpētei. Šim nolūkam kā substrātu izvēlējāmies *bis*-trihloracetimidātu **5**, kas satur gan labu aizejošo grupu (imidāta funkcija,

ko var aktivēt, kompleksējot ar Luisa skābi), lai veidotu katjonu **6**, gan iekšmolekulāro trihloracetimidāta funkciju kā *N*-nukleofīlu (3. att.). Atkarībā no nukleofīla uzbrukuma virziena neklasiskajam ciklopropilmetilkatjonam **6'** var veidoties trīs strukturāli atšķirīgi produkti **7–9**.



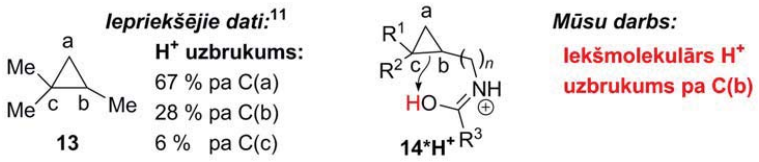

3. att. Ciklopropilmetilkatjona reakcija ar iekšmolekulāro *N*-nukleofīlu.

*Protolītiska ciklopropānu C-C saites uzšķelšana*

Otrais pētījuma virziens ietvēra protolītisku ciklopropāna *C-C* saites šķelšanas izpēti. Cikla sprieguma dēļ relatīvi vājā *C-C* saite ciklopropānā pakļaujas šķelšanai ar elektrofīliem, veidojot funkcionalizētus savienojumus **11** un **12** (4. att.).[8–10] Ciklopropānu uzšķelšanas galvenā problēma ir panākt reģioselektīvu elektrofīla uzbrukumu.[11]


4. att. Elektrofīlu inducēta ciklopropāna *C-C* saites uzšķelšana.

Ciklopropānu protolīzes reģioselektivitāte pakļaujas modificētam Markovņikova likumam, kas nosaka, ka cikla uzšķelšana pamatā notiks starp oglekļa atomiem, kas satur vislielāko un vismazāko aizvietotāju skaitu. Tomēr protolīzes selektivitāte ir samērā zema, kā tas tika nodemonstrēts *Wiberg* un *Kass* pētījumā (5. att.).[11]




5. att. Ciklopropānu protolīzes reģioselektivitāte.

Mēs savā darbā pievērsāmies reģioselektīvas ciklopropāna *C-C* saites uzšķelšanas reakcijas pētījumiem, balstoties uz iekšmolekulāru protona pārnesi no protonēta amīda **14*H**$^+$.

## Pētījuma mērķis un uzdevumi

Promocijas darba mērķis ir jaunu sintēzes metožu izveidošana, balstoties uz neklasiskā ciklopropilmetilkatjona unikālo reaģētspēju un ciklopropāna *C-C* saites reģioselektīvu protolītisku uzšķelšanu.

Darba mērķa īstenošanai izvirzīti šādi uzdevumi:

1) izpētīt ciklopropilmetilkatjona aminēšanas virzienu atkarībā no aizvietotāja dabas un atrašanās vietas izejvielā;

2) demonstrēt ciklopropilmetilkatjonu aminēšanas produktu izmantošanas iespējas, tos transformējot par būvblokiem ar augstu derivatizēšanas potenciālu;

3) izpētīt ciklopropānu protolīzi, izmantojot protonētu amīdu kā iekšmolekulāru protona donoru;

4) nodemonstrēt ciklopropānu protolīzē ģenerēto karbkatjonu iekšmolekulāru un starpmolekulāru aminēšanu.

## Zinātniskā novitāte un galvenie rezultāti

Pētījumu rezultātā izstrādātas metodes homoalilamīna, 1-amino-1-ciklobutilkarbinolu un 1-amino-1-ciklobutānkarbonskābju atvasinājumu sintēzei, kas balstītas uz neklasiskā ciklopropilmetilkatjona iekšmolekulāru aminēšanas reakciju, ģenerējot katjonu *in situ* no *bis*-trihloracetimidātiem. Demonstrēta ciklopropilgrupu saturošu heterociklu sintēze, selektīvā ciklopropil-ciklopropil- pārgrupēšanās reakcijā no 1,2-diaizvietotiem ciklopropāniem. Izstrādāta reģioselektīva ciklopropāna *C-C* saites protolītiska uzšķelšanas metode, izmantojot protonētu amīdu kā iekšmolekulāro protona donoru. Atrastas arī vairākas citas funkcionālās grupas, kas spēj veikt reģioselektīvu iekšmolekulāru protona pārnesi uz ciklopropāna *C-C* saiti, tādas kā ketoni, esteri, diimīdi, urīnvielas, karboksamīdi un karbamāti. Demonstrēta ciklopropāna uzšķelšanā ģenerētā karbkatjona iekšmolekulāra un starpmolekulāra aminēšana, veidojot strukturāli atšķirīgus produktus.

## Darba struktūra un apjoms

Promocijas darbs sagatavots kā tematiski vienota zinātnisko publikāciju kopa par neklasiskā ciklopropilmetilkatjona aminēšanas reakcijām, iegūto produktu atvasināšanas iespējām un ciklopropānu reģioselektīvo protolīzi ar tai sekojošu karbkatjona aminēšanu.

## Darba aprobācija un publikācijas

Promocijas darba galvenie rezultāti apkopoti četrās zinātniskajās oriģinālpublikācijās, vienā oriģinālpublikācijas manuskriptā, kā arī ir sagatavots viens apskatraksts. Pētījuma rezultāti prezentēti septiņās konferencēs.

Zinātniskās publikācijas

1. **Skvorcova, M.**; Grigorjeva, L.; Jirgensons, A. Tetrahydro-1,3-oxazepines *via* Intramolecular Amination of Cyclopropylmethyl Cation. *Org. Lett.* **2015**, *17* (12), 2902–2904.
2. **Skvorcova, M.**; Jirgensons, A. Allylic Amination *via* Acid Catalyzed Leaving Group Activation. *Current Green Chemistry* **2016**, *3* (2), 145–159.
3. **Skvorcova, M.**; Jirgensons, A. Amide group directed protonolysis of cyclopropane. An approach to 2,2-disubstituted pyrrolidines. *Org. Lett.* **2017**, *19* (10), 2478–2481.
4. **Skvorcova, M.**; Jirgensons, A. Intramolecular cyclopropylmethylation *via* non-classical carbenium ion. *Org. Biomol. Chem.* **2017**, *15*, 6909–6912.
5. **Skvorcova, M.**; Grigorjeva, L.; Jirgensons, A. 1-Amino-1-hydroxymethyl cyclobutane derivatives *via* intramolecular amination of nonclassical cyclopropylmethyl cation. *Chem. Heterocycl. Compd.* **2017**, *53*, 989–996.
6. **Skvorcova, M.**; Lukasevics, L.; Jirgensons, A. Ritter-type Amination of Carbenium Ions Generated by Directed Protonolysis of Cyclopropane. *Manuskripts.*

Darba rezultāti prezentēti šādās konferencēs

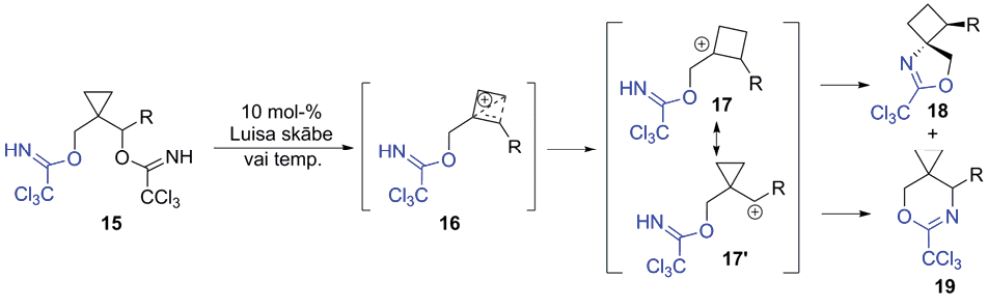
1. **Skvorcova, M.**; Jirgensons A. Amination of cyclopropylmethyl cation. *Paul Walden 9$^{th}$ Symposium on Organic Chemistry*, Riga, Latvia, May 21–22, **2015**.
2. **Skvorcova, M.**; Jirgensons A. Amide Directed Protolytic Cleavage of Cyclopropane C-C Bond. *Proceedings of 9$^{th}$ Biennial Balticum Organicum Syntheticum conference (BOS 2016)*, Riga, Latvia, July 3–6, **2016**.
3. **Skvorcova, M.**; Jirgensons A. Pyrrolidine Derivatives *via* Protolytic Cleavage of Cyclopropane C-C bond. *Proceedings of 15$^{th}$ Belgian Organic Synthesis Symposium (BOSS 2016)*, Antwerp, Belgium, July 10–15, **2016**.

4. **Skvorcova, M.**; Jirgensons A. Amide group directed protonolysis of cyclopropane. *En route* to 2,2-disubstituted pyrrolidines. *Latvijas Universitātes 75. zinātniskā konference*; *Ķīmijas sekcija*, Rīga, Latvija, **2017**. gada 10. februāris, 24. lpp.
5. **Skvorcova, M.**; Jirgensons A. Intramolecular Cyclopropylmethylation via Non-Classical Carbenium Ion. *10th Paul Walden Symposium on Organic Chemistry*. Riga, Latvia, June 15–16, **2017**.
6. **Skvorcova, M.**; Jirgensons A. Amide group directed protonolysis of cyclopropane. An approach to 2,2-disubstituted pyrrolidines. *Blue Danube Symposium on Heterocyclic Chemistry*. Austria, Linz, August 28–September 2, **2017**.
7. Lukašēvics, L. T.; **Skvorcova, M.**; Jirgensons A. Ritter-type Amination of Carbenium Ions Generated by Directed Protonolysis of Cyclopropane. *Balticum Organicum Syntheticum (BOS 2018)*, Tallinn, Estonia, July 1–4, **2018**.

# PROMOCIJAS DARBA GALVENIE REZULTĀTI

## Neklasiskā ciklopropilmetilkatjona aminēšana

Pakļaujot *bis*-trihloracetimidātus **15** Luisa skābes iniciētai neklasiskā karbkatjona **16** ģenerēšanai, var iegūt spirocikliskus oksazolīnus **18** kā ciklobutilkatjona **17** aminēšanas produktus (6. att.). Neaizvietota imidāta **15a** (R = H) gadījumā reģioselektīvi tika iegūts oksazolīns **18a** ar labu iznākumu (1. tabula). Ievadot substrāta oksimetilķēdē alifātiskus aizvietotājus (*bis*-trihloracetimidāti **15b-g**), reakcijas selektivitāte samazinājās – novērojām ciklobutil- un ciklopropilmetilkatjonu aminēšanas produktu – oksazolīnu **18** un oksazīnu **19** veidošanos. Produktu attiecība bija atkarīga no aizvietotāju lieluma – telpiski lielāku aizvietotāju gadījumā produktu attiecība ievērojami uzlabojās par labu oksazolīnam **18** (ja R = *n*-Pr, tad **18**/**19** attiecība bija 2:1, savukārt, ja R = *neo*-pentil, tad **18**/**19** – 11:1). Interesanti atzīmēt, ka aromātiska aizvietotāja gadījumā (R = Ph) reakcijas reģioselektivitāti varēja pilnībā apvērst – no *bis*-trihloracetimidāta **15h** selektīvi ieguvām oksazīnu **19h**, ko var skaidrot ar fenilgrupas spēju stabilizēt karbkatjonu **17'**.




6. att. Oksazolīnu un oksazīnu veidošanās ciklopropilmetilkatjona aminēšanā.

1. tabula

Luisa skābes katalizēta *bis*-imidātu **15** iekšmolekulāra aminēšana

| Savienojumi | R | LS | Šķīdinātājs | Produkti **18/19**[b] | Iznākums[c], % |
|---|---|---|---|---|---|
| **15-19a** | **H** | **$AlCl_3$** | **$Et_2O$** | **> 99:1** | **75** |
| **15-19b** | *n*-Pr | $AlCl_3$ | Dioksāns | 2:1 | 75 |
| **15-19c** | *i*-Pr | | | 4:1 | 70 |
| **15-19d** | *c*-Hex | | | 3:1 | 70[a] |
| **15-19e** | ***neo*-Pent** | **$BF_3 \cdot OEt_2$** | **Toluols** | **11:1** | **86**[a] |
| **15-19f** | $CH_2OMe$ | | | 4:1 | 55[a] |
| **15-19g** | $CH_2OBn$ | | | 3:1 | 49[a] |
| **15-19h** | Ph | $BF_3 \cdot OEt_2$ | DCM | 1:>99 | 75 |

[a] KMR iznākums noteikts, izmantojot 1,4-*bis*(trihlormetil)benzolu kā iekšējo standartu; [b] produktu attiecība **18/19** noteikta, reakcijas maisījumam izmantojot GC-MS; [c] produktu maisījuma **18**+**19** izdalītais iznākums.

Mēs parādījām, ka šo reakciju var iniciēt arī termiski, karsējot imidātus **15** toluolā bez Luisa skābes klātbūtnes (2. tabula). Arī šajā gadījumā veidojās abi aminēšanas produkti **18** un **19**. Tomēr jāatzīmē, ka metoksimetil- un benziloksimetilaizvietotāju gadījumā (substrāti **15f** un **15g**) termiski iniciētā reakcijā produktu attiecība ievērojami uzlabojās, ļaujot iegūt vēlamos oksazolīnus **18f,g** ar labu iznākumu.

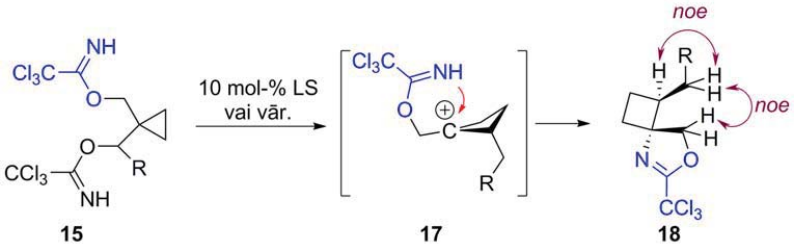
2. tabula

Termiski iniciēta *bis*-imidātu **15** iekšmolekulāra aminēšana

| Savienojums | R | Produkti **18/19**[b] | Iznākums[c], % |
|---|---|---|---|
| **15-19b** | *n*-Pr | 2:1 | 64[a] |
| **15-19c** | *i*-Pr | 4:1 | 88 |
| **15-19d** | *c*-Hex | 3:1 | 70[a] |
| **15-19e** | *neo*-Pent | 1:1 | 60[a] |
| **15-19f** | **$CH_2OMe$** | **9:1** | **80** |
| **15-19g** | **$CH_2OBn$** | **7:1** | **85** |

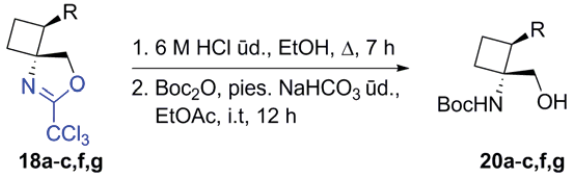
[a] KMR iznākums noteikts, izmantojot 1,4-*bis*(trihlormetil)benzolu kā iekšējo standartu; [b] produktu attiecība **18/19** noteikta, reakcijas maisījumam izmantojot GC-MS; [c] produktu maisījuma **18**+**19** izdalītais iznākums.

Vērts pieminēt, ka *bis*-trihloracetimidātu **15** transformācija par ciklobutāna atvasinājumiem notiek ar augstu diastereoselektivitāti – veidojas tikai *trans*-diastereomērs **18** (7. att.). Šādu stereoķīmisko iznākumu var skaidrot ar to, ka ciklobutilkarbkatjona **17** aminēšana notiek no stēriski mazāk traucētās puses.




7. att. *Trans*-aizvietota ciklobutāna atvasinājuma veidošanās stereoindukcijas modelis.

Lai demonstrētu metodes izmantošanas iespējas, oksazolīni **18** tika transformēti par ciklobutānu saturošiem *N*-aizsargātiem aminospirtiem **20**, tos hidrolizējot un secīgi pakļaujot reakcijai ar $Boc_2O$ (8. att., 3. tabula).



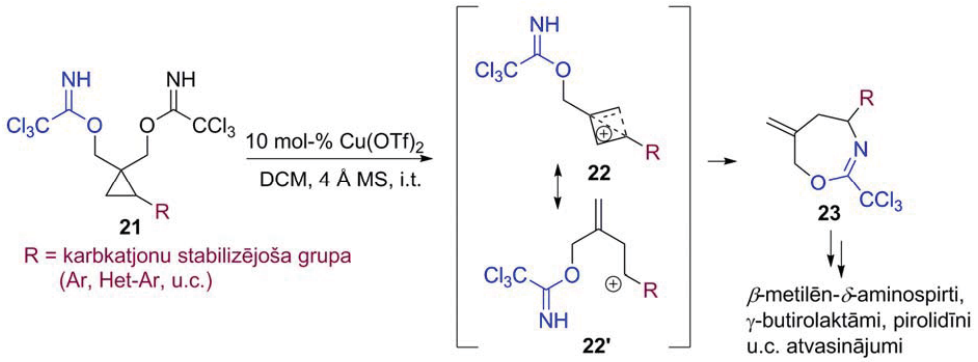

8. att. 1-Aminociklobutāna karbinolu iegūšana.

3. tabula

1-Aminociklobutilkarbinolu iegūšanas iznākumi

| Nr. p. k. | R | **20**, iznākums, % |
|---|---|---|
| 1. | H | **20a**, 59 |
| 2. | *n*-Pr | **20b**, 89 |
| 3. | *i*-Pr | **20c**, 70 |
| 4. | $CH_2OMe$ | **20f**, 73 |
| 5. | $CH_2OBn$ | **20g**, 69 |

Ievietojot ciklopropāna ciklā karbkatjonu stabilizējošu aizvietotāju, *bis*-trihloracetimidāts **21** Luisa skābes $Cu(OTf)_2$ klātbūtnē reģioselektīvi veidoja tetrahidro-1,3-oksazepīnu **23** kā ciklopropilmetilkatjona **22** homoalil-reakcijas produktu. (9. att., 4. tabula). Šādu reakcijas virzienu var skaidrot ar karbkatjonu stabilizējošas grupas ietekmi uz elektronu blīvumu sadalījumu, novirzot to tuvāk homoalilkatjona mezomērajai struktūrai **22'**.




9. att. Oksazepīnu **23** iegūšana no *bis*-trihloracetimidātiem **21**.

4. tabula

*Bis*-imidāta **21** aizvietotāji un oksazepīnu **23** iznākumi

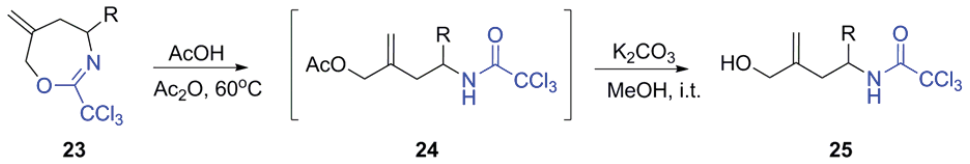
| Nr. p. k. | R | **23**, iznākums (%) |
|---|---|---|
| 1. | $C_6H_5$ | **23a**, 85 |
| 2. | 4-$MeOC_6H_4$ | **23b**, 96 |
| 3. | 4-$Me_2NC_6H_4$ | **23c**, 87 |
| 4. | 4-$FC_6H_4$ | **23d**, 83 |
| 5. | 1-Naftil | **23e**, 90 |
| 6. | 3-(*N*-Tozil)indolil | **23f**, 94 |
| 7. | (*E*)-$C_6H_5CH$=CH | **23g**, 96 |
| 8. | Vinil | **23h**, 91 |
| 9. | 2-Tienil | **23i**, 89 |
| 10. | 2-(*N*-Metil)pirolil | **23j**, 64[a] |
| 11. | 3-Furil | **23k**, 79[b] |
| 12. | $Ph(Me)_2SiCH_2$ | **23l**, 81 |
| 13. | Et | -[c] |
| 14. | $C_6H_5C$≡C | -[c] |
| 15. | 3,5-(di-Cl)-$C_6H_3$ | -[c] |

[a] 1 mol-% $Cu(OTf)_2$; [b] 10 mol-% $(CuOTf)_2 \cdot C_6H_6$; [c] produktu maisījums.

*Bis*-trihloracetimidāti **21a-k**, kas saturēja tādas karbkatjonu stabilizējošus aizvietotājus kā arilgrupas (4. tabula, 1.–5. aile), heteroarilgrupas (6., 9.–11. aile), vinilgrupas (7. un 8. aile), veidoja oksazepīnus **23a-k** ar augstiem iznākumiem (64–96 %). Arī sililmetilgrupu saturošs aizvietotājs – kā *β*-karbkatjonu stabilizējoša grupa substrātā **21l** – sekmēja oksazepīna **23l** veidošanos ar ļoti labu iznākumu – 81 % (12. aile). Savukārt *bis*-trihloracetimidāti **21m-o**, kas saturēja alifātiskos un alkinilaizvietotājus vai elektroniem nabadzīgas aromātiskās sistēmas (13.–15. aile), ciklizēšanas

reakcijā veidoja produktu maisījumu, kas visticamāk ir saistīts ar šādu aizvietotāju nepietiekamu spēju stabilizēt karbkatjonu**.**

Tetrahidro-1,3-oksazepīni **23** ir potenciāli izmantojami kā multifunkcionāli būvbloki kompleksu savienojumu sintēzē. Lai demonstrētu to sintētisko pielietojumu, tika izstrādāta ērta vienas kolbas divu stadiju procedūra nepiesātinātu aminospirtu **25** iegūšanai (10. att., 5. tabula). Tā ietvēra oksazepīna **23** cikla uzšķelšanu ar etiķskābi un sekojošu estera **24** metanolīzi.




**23** **24** **25**

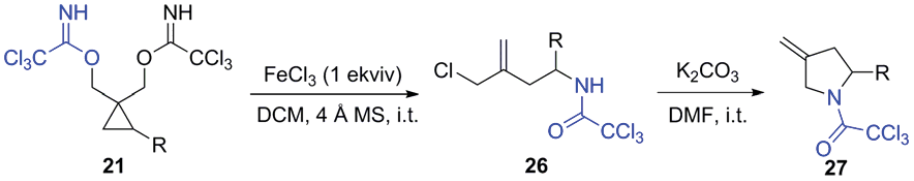
10. att. *N*-Aizsargātu aminospirtu **25** iegūšana no oksazepīniem **23**.

5. tabula

Aminospirtu **25** iznākumi no oksazepīniem **23**

| Nr. p. k. | R | **25**, iznākums, % |
|---|---|---|
| 1. | $C_6H_5$ | **25a**, 94 |
| 2. | 4-$MeOC_6H_4$ | **25b**, 96 |
| 3. | 2-Tienil | **25i**, 91 |
| 4. | Vinil | **25h**, 89 |
| 5. | $CH_2SiMe_2Ph$ | **25l**, 89 |

Mēs arī parādījām, ka no *bis*-trihloracetimidātiem **21g-i**, izmantojot ekvimolāru daudzumu $FeCl_3$, ar ļoti labiem iznākumiem var iegūt alilhlorīdus **26**, kurus var ciklizēt par 4-*exo*-metilēnpirolidīniem **27** (11. att., 6. tabula).




**21** **26** **27**

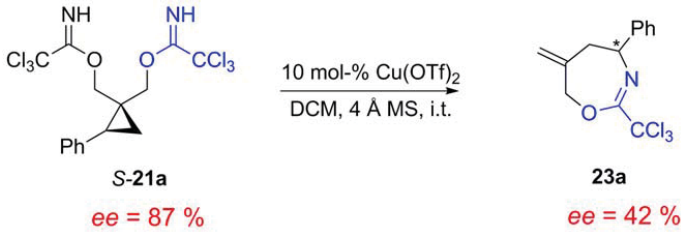
11. att. 4-*exo*-Metilēnpirolidīnu **27** iegūšana.

6. tabula

Alilhlorīdu **26** un pirolidīnu **27** iznākumi

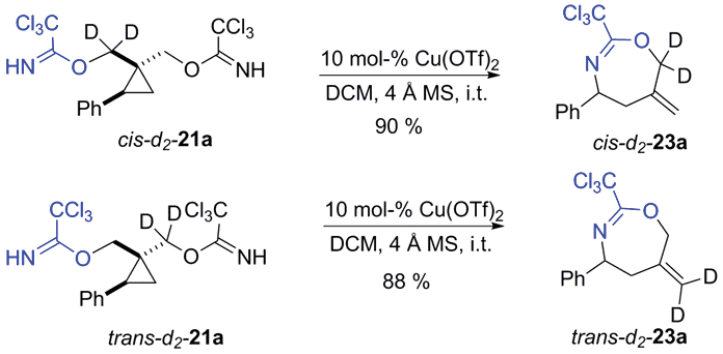
| Nr. p. k. | R | **26**, iznākums (%) | **27**, iznākums (%) |
|---|---|---|---|
| 1. | (*E*)-$C_6H_5CH$=CH | **26g**, 87 | **27g**, 89 |
| 2. | Vinil | **26h**, 77 | **27h**, 90 |
| 3. | 2-Tienil | **26i**, 86 | **27i**, 93 |

Hiralitātes pārneses pētījumos tika noskaidrots, ka enantiobagātināta *bis*-trihloracetimidāta *S*-**21a** ciklizēšanā par oksazepīnu **23a** lielā mērā (bet ne pilnībā) notiek hirālā centra racemizācija (12. att.).



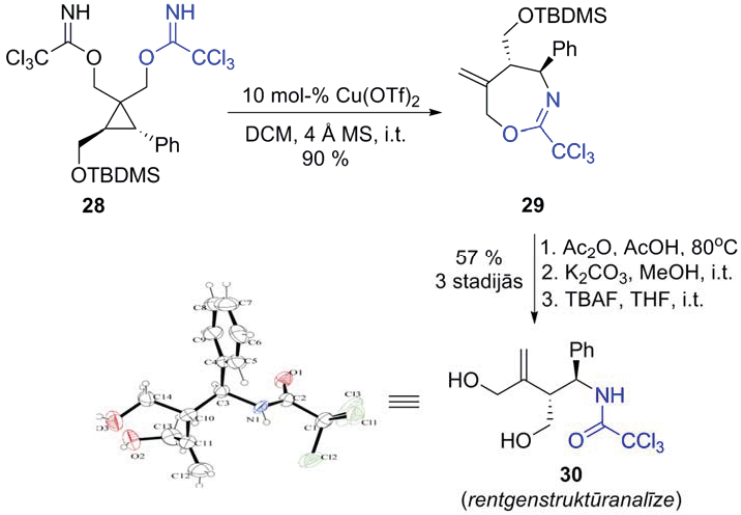

12. att. Hiralitātes pārnese no enantiobagātināta *bis*-imidāta *S*-**21a** uz oksazepīnu **23a**.

Pakļaujot deitērija iezīmes saturošus *cis*- un *trans*-imidātus $d_2$-**21a** Luisa skābes iedarbībai, novērojām selektīvu imidāta grupas eliminēšanos, kas atrodas *trans* pret Ph grupu (13. att.). Tas nozīmē, ka zema hiralitātes pārnese no substrāta *S*-**21a** uz produktu **23a** nav saistīta ar neselektīvu imidāta funkciju eliminēšanos. Savukārt daļēju hiralitātes saglabāšanos ciklizēšanas reakcijā var izskaidrot ar neklasisko karbkatjonu **22** kā starpproduktu un tā nepilnīgu racemizēšanos, jo planāra homoalilkatjona **22'** veidošanās radītu pilnīgi racēmisku produktu **23a**.




13. att. Selektīva *trans*-imidāta funkcijas eliminēšana *bis*-imidātā **21a**.

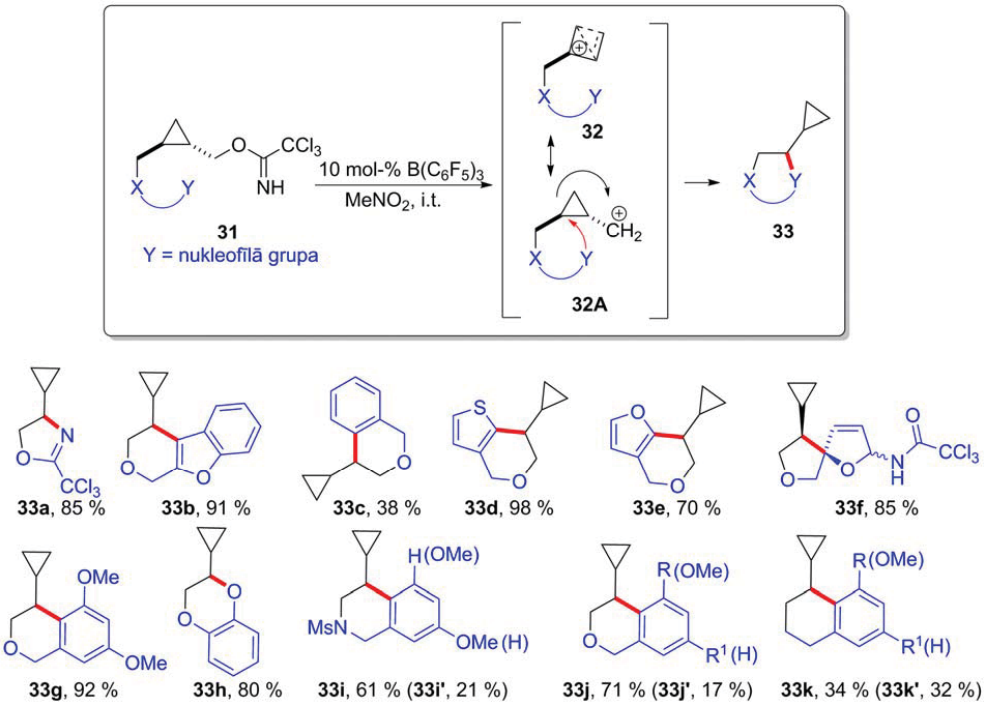
Ievadot papildu aizvietotāju ciklopropāna ciklā **28**, mēs parādījām, ka ciklopropilmetilkatjona **22/22'** aminēšana noris ar augstu diastereoselektivitāti – tika selektīvi iegūts *trans*-aizvietots oksazepīns **29** (14. att.).




14. att. Diastereoselektīva *bis*-imidāta **28** ciklizēšana un oksazepīnu **29** uzšķelšana.

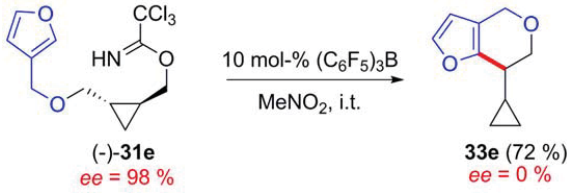
Produkta **29** konfigurācija tika pierādīta, atvasinot to trīs stadijās par diolu **30** un veicot tā rentgenstruktūras analīzi.

No *bis*-trihloracetimidāta **31a**, kas veidots uz 1,2-diaizvietota ciklopropāna bāzes, Luisa skābes ($B(C_6F_5)_3$) klātbūtnē realizējās selektīva ciklopropil-ciklopropil- pārgrupēšanās, veidojot oksazolīnu **33a** ar augstu iznākumu. Lai paplašinātu reakcijas izmantošanas iespējas, viena no imidāta funkcijām ciklopropāna atvasinājumā **31** tika aizstāta ar citiem iekšmolekulāriem nukleofīliem (fenols, aromātiskā vai heteroaromātiskā funkcija u. tml.) (15. att.). Šādā veidā no 1,2-diaizvietotiem ciklopropāna substrātiem **31** tika iegūta virkne ciklopropilgrupu saturošu produktu **33a-k**.



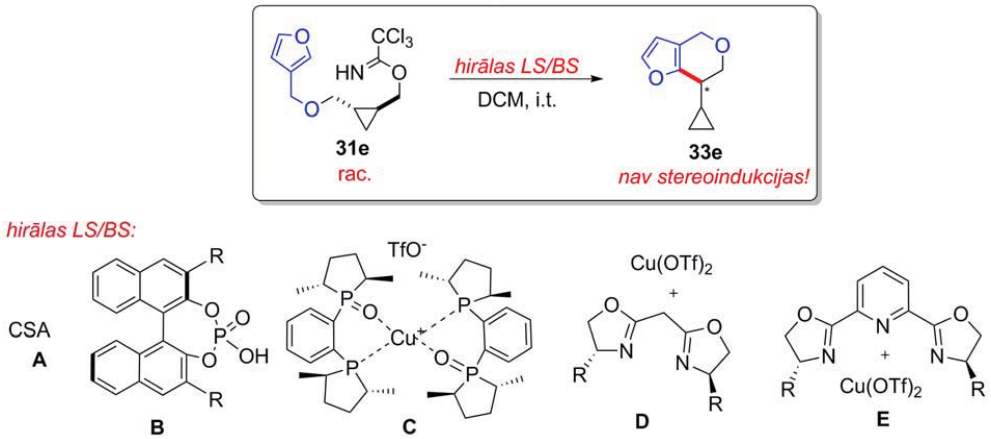

15. att. Iekšmolekulārā nukleofīla ciklopropilmetilēšana ciklopropil-ciklopropil- pārgrupēšanās reakcijā.

Lai pārbaudītu, vai reakcija notiek ar hiralitātes pārnesi vai racemizēšanos, tika izmantots enantiobagātināts substrāts (-)-**31e**, kas atrastajos reakcijas apstākļos deva racēmisku produktu **33e** (16. att.).




16. att. Ciklopropil-ciklopropil-pārgrupēšanās hiralitātes pārneses pētījums.

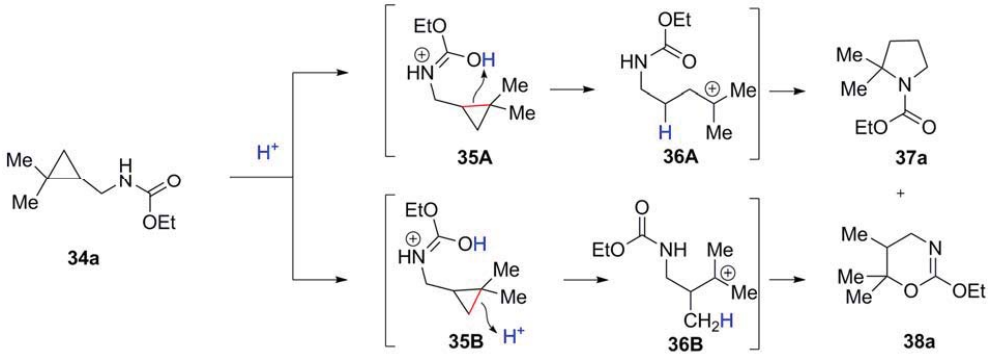
Šie pētījumi parādīja, ka ciklopropilmetilēšanas reakcija nav stereospecifiska, kas rosināja izpētīt katalizatora kontrolētas stereoindukcijas iespējas. Savienojuma **33e** iegūšanai no racēmiska substrāta **31e** tika izmēģinātas vairākas hirālās Brensteda (**A**,**B**) un Luisa skābes (**C**-**E**) (17. att.), diemžēl stereoindukciju panākt mums neizdevās.




17. att. Ciklopropil-ciklopropil-pārgrupēšanās stereoselektivitātes inducēšana ar hirālu katalizatoru.

## Protolītiska ciklopropānu *C-C* saites uzšķelšana

Amīdgrupu saturoša ciklopropāna **34a** iekšmolekulārai *C-C* saites protolīzei izmēģinājām vairākas Luisa un Brensteda skābes. Tika atklāts, ka TFA ļauj selektīvi iegūt pirolīdīnu **37a**, kas ir rezultāts *anti*-Markovņikova $H^+$ uzbrukumam (**35A**) un sekojošai katjona **36A** aminēšanai (18. att., 7. tabula). Stiprākas skābes, tādas kā MsOH un TfOH, uzrādīja samazinātu selektivitāti, veidojot arī oksazīnu **38a**. Tas, visticamāk, veidojas no katjona **36B**, kas savukārt rodas konkurējošā starpmolekulāras *C-C* saites protonolīzes reakcijā (**35B**). Vājākas skābes, tādas kā $BF_3{\cdot}Et_2O$ un $(CuOTf)_2{\cdot}C_6H_6$, nespēja iniciēt reakciju.




18. att. Ciklopropāna **34a** *C-C* saites protolīze un sekojoša katjona ciklizēšana.

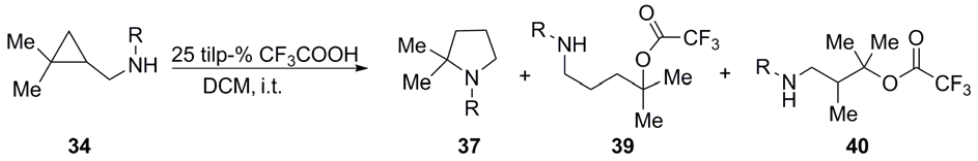
7. tabula

Skābes veicināta ciklopropānu uzšķelšana

| Nr. p. k. | Skābe (šķīdinātājs) | Produkts (iznākums %)[a] |
|---|---|---|
| 1. | TFA (neatšķ.) | **37a** (98) |
| 2. | MsOH 1 vol% (DCM) | **37a** (70), **38a** (17) |
| 3. | TfOH 1 vol% (DCM) | **37a** (47), **38a** (25) |
| 4. | $Fe(OTf)_3$ 1.0 ekviv (DCM) | **37a** (61), **38a** (17) |
| 5. | $BF_3{\cdot}OEt_2$ 1.0 ekviv (DCM) | nereaģē |
| 6. | $(CuOTf)_2{\cdot}C_6H_6$ 1.0 ekviv (DCM) | nereaģē |

[a] KMR iznākums noteikts, izmantojot 1,4-bis(trihlormetil)benzolu kā iekšējo standartu.

Pētījuma gaitā tika atklāts, ka nozīmīga loma ir arī aizvietotājam, kas substrātā **34** atrodas pie *N*-atoma. Šai funkcijai ir jābūt pietiekami bāziskai, lai veiksmīgi virzītu ciklopropāna *C*-*C* saites reģioselektīvu protonolīzi un pietiekami nukleofīlai, lai reaģētu ar protolīzē izveidoto katjonu. Karbamāta **34a**, urīnvielas **34b** un vairāki karboksiamīda atvasinājumi **34c-e** veidoja pirolidīnus **37a-e** ar augstiem iznākumiem (19. att., 8. tabula). Trihloracetamīds **34f** veidoja pirolidīna **37f** un acikliska produkta **39f** maisījumu, ko var skaidrot ar samazinātu *N*-atoma nukleofilitāti trihloracetamīdā. Tioamīda **34g**, trifluoracetāta **34i** un sulfonamīda **34j** grupu saturošie substrāti veidoja vairāku produktu maisījumu. Tas, visticamāk, ir saistīts ar šo grupu samazinātu protonēšanās spēju, kā rezultātā tiek veicinātas dažādas blakus reakcijas.




**34** **37** **39** **40**

19. att. *N*-Aizvietotāja ietekme uz ciklopropāna protolīzi.

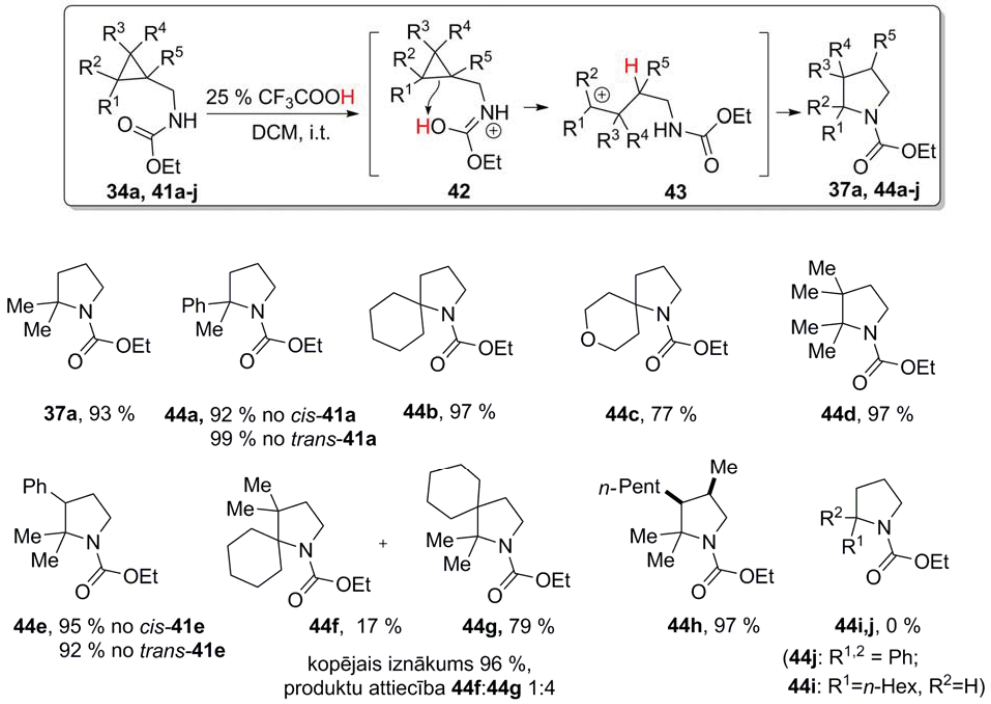
8. tabula

Aizvietotāji un iznākumi

| Nr. p. k. | **34**, R | Produkts (iznākums, %) |
|---|---|---|
| 1 | **34a**, EtOCO | **37a** (92) |
| 2 | **34b**, PhNHCO | **37b** (99) |
| 3 | **34c**, PhCO | **37c** (99) |
| 4 | **34d**, MeCO | **37d** (74)[a,b] |
| 5 | **34e**,$ClCH_2CO$ | **37e** (99)[a] |
| 6 | **34f**, $Cl_3CCO$ | **37f** : **39f** attiecībā 1:1 (97)[c, d] |
| 7 | **34g**, MeCS | **37g** (17)[e] un neidentificēti piemaisījumi |
| 8 | **34h**, 4-$NO_2C_6H_4$ | **34h**[c] nereaģē |
| 9 | **34i**, $CF_3CO$ | produktu **37i**, **39i** un **40i** maisījums |
| 10 | **34j**, $PhSO_2$ | produktu **37j**, **40j** un $PhSO_2NH_2$ maisījums |

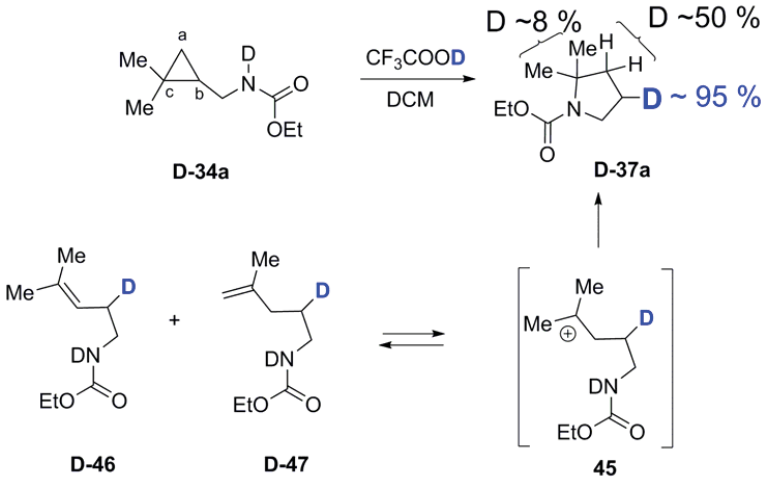
[a] 50 tilp-% TFA dihlormetānā, i. t.; [b] gaistošs produkts; [c] neatšķ. TFA; [d] KMR iznākums noteikts, izmantojot 1,4-*bis*(trihlormetil)benzolu kā iekšējo standartu.

Substrāta klāsta pētījumos tika parādīts, ka no aizvietotiem *N*-etoksikarbonilaminometilciklopropāniem **34a**,**41a-h** var selektīvi iegūt pirolidīna atvasinājumus **37a**,**44a-h** ar labiem iznākumiem (20. att.). Monoalkilaizvietots ciklopropāns **41i** ($R^1$ = *n*-Hex, $R^{2-5}$ = H) nereaģēja pat skarbākos reakcijas apstākļos (neatšķ. TFA, vārot ar atteci). Pārsteidzoši, ka difenilaizvietots ciklopropāns **41j** ($R^{1,2}$ = Ph, $R^{3-5}$ = H) arī nedeva vēlamo produktu. Šī substrāta zemā reaģētspēja liecina, ka karbkatjona stabilitāte ir tikai viens no faktoriem, kas veicina ciklopropāna *C*-*C* saites protolīzi, jo šajā gadījumā vajadzētu veidoties ļoti stabilam difenilkarbēnija jonam. Visticamāk, *C*-*C* saites protolīzi spēcīgi ietekmē arī elektronu blīvums šajā saitē.



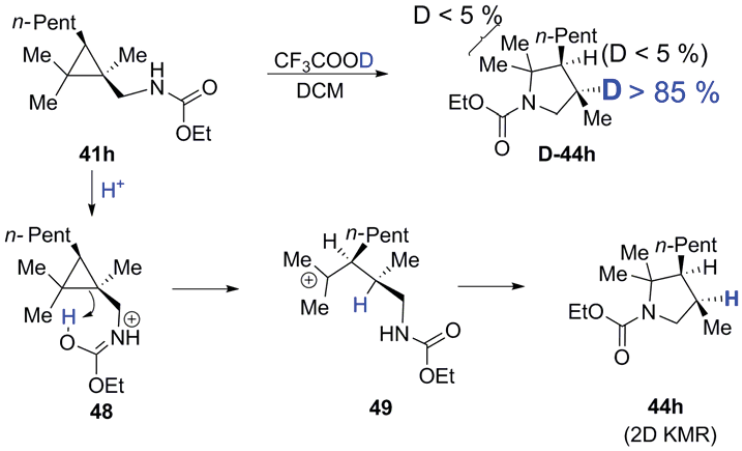

20. att. Pirolidīnu iegūšana ciklopropāna iekšmolekulāras protolīzes reakcijā.

Pakļaujot deitērija iezīmi saturošu substrātu **D-34a** deiterētas trifluoretiķskābes iedarbībai, tika novērtēta gandrīz pilnīgu deitērija ievietošanos pirolidīna 3-CH-pozīcijā, kas atbilst protona uzbrukumam pa C(b) (21. att.). Tika novērots arī neliels deitērija saturs pirolidīna 2-CH-pozīcijā un abās metilgrupās. Tas liecina, ka karbkatjona **45** starpprodukts protonēšanas/deprotonēšanas rezultātā pastāv līdzsvarā ar alkēniem **D-46** un **D-47**.




21. att. Deitērija iezīmi saturošā ciklopropāna **D-34a** protolīze.

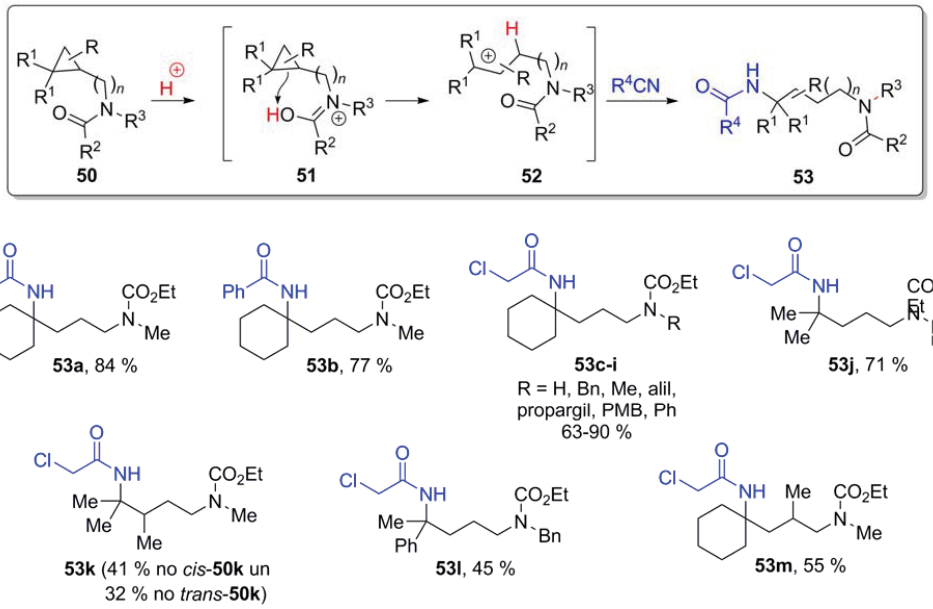
Interesanti atzīmēt, ka substrāta **41h** gadījumā tika novērots relatīvi mazs deitērija saturs pirolidīna **D-44h** 2-CH-pozīcijā un abās metilgrupās, pie tam novērojām arī konfigurācijas saglabāšanos ogleklim, pa kuru notiek protona uzbrukums (22. att.). Šis rezultāts liecina, ka protona pārnese protonētā amīdā **48** notiek pa saites (*edge*) trajektoriju.




22. att. Protona pārneses stereoķīmija ciklopropānā **41h**.

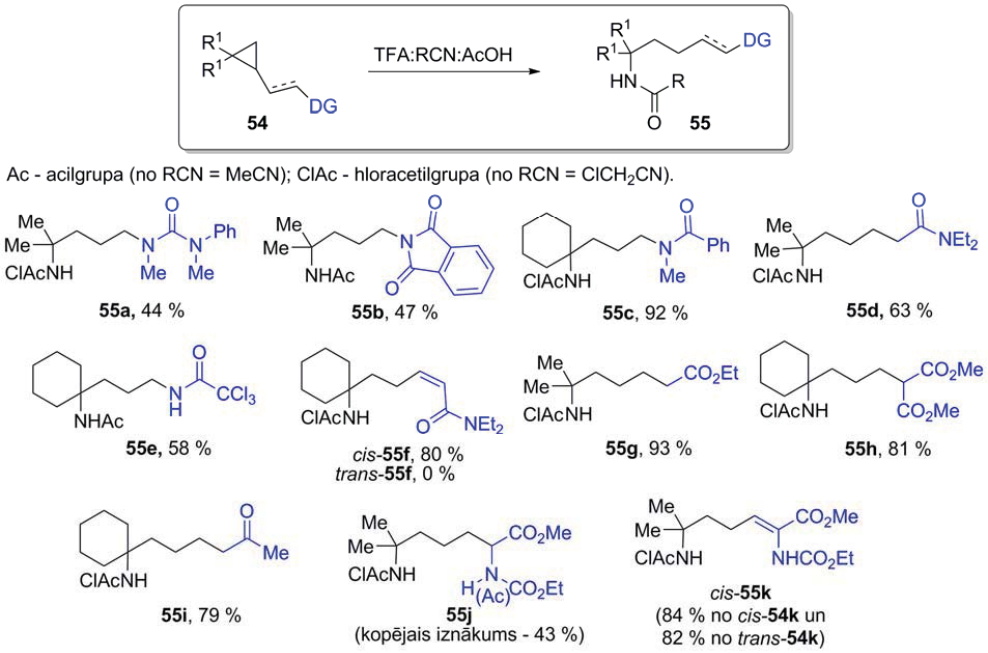
Turpinot pētījumu, nolēmām parādīt metodes iespējas arī starpmolekulārai karbkatjona aminēšanai. Šim nolūkam kā substrātus izmantojām trešējos amīdus **50**, kuros slāpekļa nukleofilitāte ir bloķēta, tādējādi novēršot cikliskā produkta veidošanos. Ciklopropānu **50a-m**

protolīzē ģenerētos karbkatjonus **52** sekmīgi aminējām Ritera reakcijas apstākļos, veidojot diamīna atvasinājumus **53a-m** (23. att.).




23. att. Ciklopropāna *C-C* saites protolīzē ģenerēta karbkatjona aminēšana Ritera reakcijas apstākļos.

Pētījuma gaitā demonstrējām arī virkni citu virzošo grupu kā ketona, estera, diimīda, urīnvielas, karboksamīdu atvasinājumus, kas spēj nodrošināt augstu ciklopropāna *C-C* saites šķelšanas selektivitāti Ritera reakcijas apstākļos (24. att.). Rezultātā tika iegūta virkne amīna atvasinājumu **55a-k**.




24. att. Virzošu grupu klāsts ciklopropāna protolīzei un sekojošai karbkatjona aminēšanai Ritera reakcijā.

Interesanti atzīmēt, ka slāpekli saturoša funkcija selektīvai protona pārnesei nav obligāti nepieciešama, kā liecina Ritera reakcija ar esteru un ketonu atvasinājumiem **54g-i**, kas ļāva iegūt vēlamos aminēšanas produktus **55g-i** ar augstu iznākumu.

# SECINĀJUMI

1. Veidojot neklasisko ciklopropilmetilkatjonu no *bis*-trihloracetimidātiem, atkarībā no aizvietotāja dabas un atrašanās vietas izejvielā, ar augstu selektivitāti var iegūt trīs strukturāli atšķirīgus aminēšanas produktus – ciklopropil-, ciklobutil- vai homoalilavasinājumus.
2. Neklasiskā ciklopropilmetilkatjona aminēšanas produktus – spirocikliskus oksazolīnus un tetrahidro-1,3-oksazepīnus – var ērti transformēt par atbilstošiem aminospirtiem, kas ir potenciāli būvbloki dažādu farmaceitiski nozīmīgu savienojumu sintēzē.
3. 1, 2–Diaizvietotu ciklopropānu gadījumā var veiksmīgi realizēt ciklopropil-ciklopropil-pārgrupēšanos selektīvā ciklopropilmetilkatjona reakcijā ar iekšmolekulāro nukleofīlu. Šāda pieeja ļauj aizstāt klasiskās ciklopropilgrupas ievadīšanas metodes, kas bieži vien nav savietojamas ar funkcionālajām grupām kompleksās molekulās.
4. Ciklopropānu *C*-*C* saiti var selektīvi uzšķelt, izmantojot protonētu amīdu kā iekšmolekulāru protona donoru. Protolīzē izveidotais karbkatjons reaģē ar amīdu kā iekšmolekulāru nukleofīlu, veidojot pirolidīna atvasinājumus. Protona uzbrukuma trajektorija noris no ciklopropāna saites (*edge*) puses, ko pierāda konfigurācijas saglabāšanās ogleklim, pa kuru notiek protona uzbrukums.
5. Ciklopropānu protolīzē ģenerēto karbkatjonu aminēšanu var realizēt arī starpmolekulāri Ritera reakcijas apstākļos, kā virzošās grupas protolīzei izmantojot ketonu, esteru, diimīdu, urīnvielu, karboksamīdu un karbamāta atvasinājumus.

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**DOCTORAL THESIS PROPOSED TO RIGA TECHNICAL UNIVERSITY FOR THE PROMOTION TO THE SCIENTIFIC DEGREE OF DOCTOR OF CHEMICAL SCIENCES**

To be granted the scientific degree of Doctor of Chemical Sciences, the present Doctoral Thesis has been submitted for the defence at the open meeting of RTU Promotion Council on 27 September 2018 at the Faculty of Materials Science and Applied Chemistry of Riga Technical University, 3 Paula Valdena Street, Room 272.

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DECLARATION OF ACADEMIC INTEGRITY

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

Marija Skvorcova ……. (signature)

Date…….

The Doctoral Thesis has been prepared as a thematically united collection of scientific publications. It consists of a summary, five scientific publications and a manuscript of a scientific publication. Publications have been written in English. The total number of pages is 715, including electronically available data.

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# GENERAL OVERVIEW OF THE THESIS

## Introduction

Cyclopropane is the simplest cyclic hydrocarbon. All three cyclopropane carbon atoms have a high derivatization potential. In cyclopropane the overlap of *C*-*C* bond forming electrons is less efficient which makes the character of the molecular orbital more similar to π-bond (Fig. 1).[1, 2]

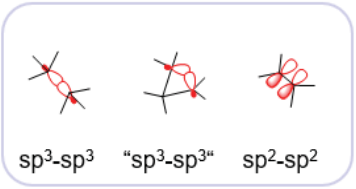



Fig. 1. Molecular orbital of cyclopropane *C*-*C* bond *vs* orbitals of alkane and alkene.

*Nonclassical cyclopropylmethyl cation amination*

Overlapping of molecular orbital of cyclopropane *C*-*C* bond with the neighbouring vacant orbital of cation determines the non-classical nature of cyclopropylmethyl cation. Studies by Olah (NMR, DFT calculations) have shown that cyclopropylmethyl cation most likely exists as a *πσ*-delocalized cyclopropyl carbinyl cation **1A** in equilibrium with non-classical bicyclobutonium ion **1B** (Fig. 2).[3, 4]

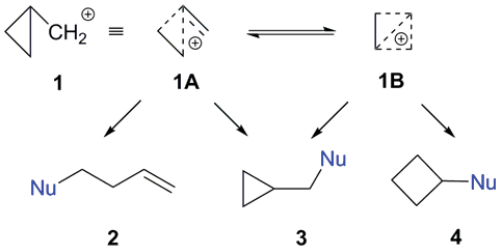



Fig. 2. Nonclassical cyclopropylmethyl cation nature and reactivity with nucleophiles.

Non-classical nature of cyclopropylmethyl cation **1** explains its ability to form structurally different homoallyl-, cyclopropylmethyl- and cyclobutyl derivatives **2**–**4** in reaction with nucleophile. Several examples in literature are known for selective, as well as non-selective formation of **2**–**4** in cation **1** reaction with *O*-nucleophiles and halogenides. Although, only few amination reactions have been studied.[5-7] It encouraged us to examine regioselective generation and subsequent amination of non-classical cation **1**. For this purpose, *bis*-trichloroacetimidate **5** was used. In substrate **5**, imidate function can act as a leaving group when activated with Lewis

acid. This would generate carbenium ion **6**, which will be trapped with other imidate as *N*-nucleophile (Fig. 3). In this reaction three structurally different products **7**–**9** can be formed, depending on the regioselectivity of intramolecular imidate attack to the carbenium ion **6'**.

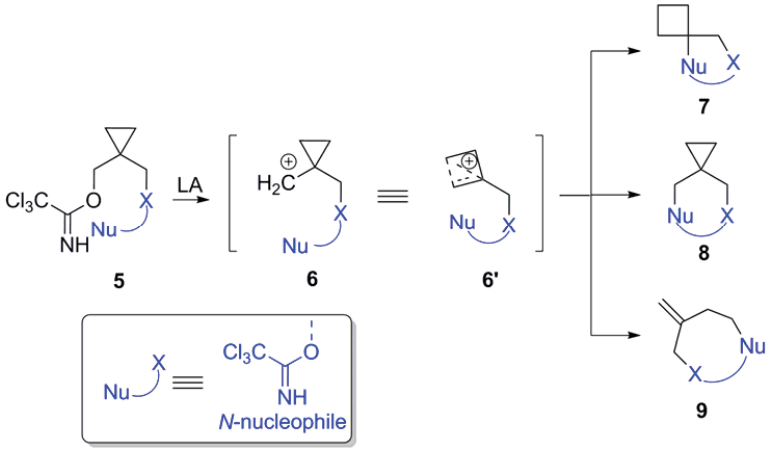



Fig. 3. Reaction of cyclopropyl methyl cation with intramolecular *N*-nucleophile.

*Protolytic cleavage of cyclopropane C-C bond*

The second part of the research includes protolytic cleavage studies of cyclopropane *C-C* bond. Due to the ring strain, bonds between the carbon atoms are considerably weaker than in typical alkane and can undergo *C-C* bond cleavage leading to functionalized compounds **11** and **12** when exposed to strong electrophilic reagents (Fig. 4).[8-10] The challenge is to achieve regioselective electrophilic attack to cyclopropane.

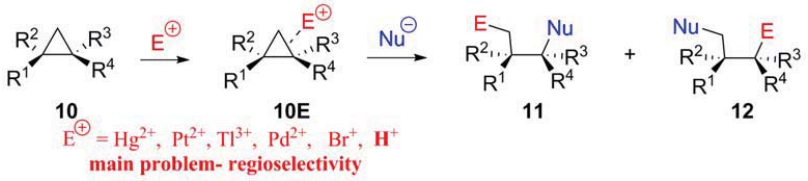



Fig. 4. Electrophilic cleavage of cyclopropane *C-C* bond.

Regioselectivity in the cyclopropane protonolysis tends to follow modified Markovnikov's rule, which predicts that preferential ring opening will occur between carbons bearing the largest and the smallest number of substituents. However, typically the selectivity is modest, as demonstrated by Wiberg and Kass systematic studies (Fig. 5).[11]

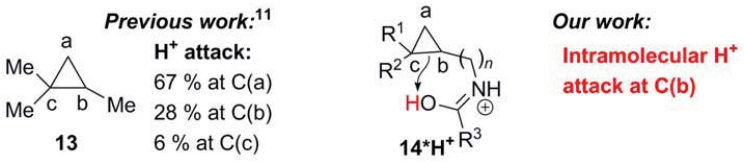



Fig. 5. Regioselectivity in protonolysis of cyclopropanes.

In our work, we focused attention on regioselective cleavage of cyclopropane *C*-*C* bond using protonated amide **14*H**$^+$ as intramolecular proton donor.

## Aims and objectives

The aim of the Thesis is to develop new synthetic methods based on unique reactivity of cyclopropylmethyl cation and regioselective cleavage of cyclopropane *C*-*C* bond.

The following tasks were set:

1) to investigate cyclopropylmethyl cation amination reaction depending on the nature of substituents and their position in the substrate;

2) to demonstrate the utility of cyclopropylmethyl cation amination products by transforming them into building blocks with high derivatization potential;

3) to investigate protonolysis of cyclopropanes using protonated amide as internal proton donor;

4) to demonstrate the intramolecular and intermolecular amination of carbenium ions generated by protonolysis of cyclopropane.

## Scientific novelty and main results

As the result of the Thesis, several methods based on intramolecular amination of nonclassical cyclopropylmethyl cation for synthesis of homoallylamine, 1-amino-1-cyclobutylcarbinol and 1-amino-1-cyclobutane carboxylic acid derivatives were developed. Synthesis of cyclopropyl-containing heterocycles from 1,2-disubstituted cyclopropanes was demonstrated based on selective cyclopropyl-cyclopropyl rearrangement. Regioselective protonolysis of cyclopropane *C*-*C* bond using protonated amide as internal proton donor was developed. Directing groups such as carbamate, carboxamide, urea, ester and ketone were found efficient for regioselective *anti*-Markovnikov cleavage of cyclopropane. An intramolecular and an intermolecular amination of carbenium ions generated by directed regioselective protonolysis of cyclopropane were demonstrated.

## Structure of the Thesis

The thesis is a collection of scientific publications focused on the amination of nonclassical cyclopropylmethyl cation, derivatization of obtained products and regioselective protonolysis of cyclopropane with subsequent amination of formed carbenium ion.

## Publications and approbation of the Thesis

Main results of the thesis were summarized in four scientific publications, a manuscript of a scientific publication, and a review article. Results of the research were presented at seven conferences.

Scientific publications:

1. **Skvorcova, M.,** Grigorjeva, L., Jirgensons, A. Tetrahydro-1,3-oxazepines *via* Intramolecular Amination of Cyclopropylmethyl Cation. *Org. Lett.* **2015**, *17* (12), 2902–2904.
2. **Skvorcova, M.**, Jirgensons, A. Allylic Amination *via* Acid Catalyzed Leaving Group Activation. *Current Green Chemistry*. **2016**, *3* (2), 145−159.
3. **Skvorcova, M.**, Jirgensons, A. Amide group directed protonolysis of cyclopropane. An approach to 2,2-disubstituted pyrrolidines. *Org. Lett.* **2017**, *19* (10), 2478–2481.
4. **Skvorcova, M.**, Jirgensons, A. Intramolecular cyclopropylmethylation *via* non-classical carbenium ion. *Org. Biomol. Chem.* **2017**, *15*, 6909−6912.
5. **Skvorcova, M.**, Grigorjeva, L., Jirgensons, A. 1-Amino-1-hydroxymethyl cyclobutane derivatives *via* intramolecular amination of nonclassical cyclopropylmethyl cation. *Chem. Heterocycl. Compd.* **2017**, *53*, 989−996.
6. **Skvorcova, M.**, Lukasevics, L., Jirgensons, A. Ritter-type Amination of Carbenium Ions Generated by Directed Protonolysis of Cyclopropane. *Manuscript.*

Results of the thesis were presented at the following conferences:

1. **Skvorcova, M.**, Jirgensons, A. Amination of cyclopropylmethyl cation. *Paul Walden 9$^{th}$ Symposium on Organic Chemistry*, Riga, 21−22 May **2015**.
2. **Skvorcova, M.**, Jirgensons, A. Amide Directed Protolytic Cleavage of Cyclopropane C-C Bond. *Proceedings of 9$^{th}$ Biennial Balticum Organicum Syntheticum conference (BOS 2016)*, Riga, Latvia, 3−6 July **2016**.
3. **Skvorcova, M.**, Jirgensons, A. Pyrrolidine Derivatives *via* Protolytic Cleavage of Cyclopropane C-C bond. *Proceedings of 15$^{th}$ Belgian Organic Synthesis Symposium (BOSS 2016)*, Antwerp, Belgium, 10−15 July **2016**.

4. **Skvorcova, M.**, Jirgensons, A. Amide group directed protonolysis of cyclopropane. *En route* to 2,2-disubstituted pyrrolidines. *Latvian University 75th International Scientific Conference: Section: Chemistry.* Riga, Latvia, 10 February **2017**.
5. **Skvorcova, M.**, Jirgensons, A. Intramolecular Cyclopropylmethylation via Non-Classical Carbenium Ion. *10th Paul Walden Symposium on Organic Chemistry*. Riga, Latvia, 15−16 June **2017**.
6. **Skvorcova, M.**, Jirgensons, A. Amide group directed protonolysis of cyclopropane. An approach to 2,2-disubstituted pyrrolidines. *Blue Danube Symposium on Heterocyclic Chemistry*. Austria, Linz, 28 August – 2 September **2017**.
7. Lukasevics, L. T., **Skvorcova, M.**, Jirgensons, A. Ritter-type Amination of Carbenium Ions Generated by Directed Protonolysis of Cyclopropane. *Balticum Organicum Syntheticum (BOS 2018)*, Tallinn, Estonia, 1−4 July **2018**.

# MAIN RESULTS OF THE THESIS

## Amination of non-classical cyclopropylmethyl cation

*Bis*-trichloroacetimidates **15** provided spirocyclic oxazolines **18** as intramolecular amination products of intermediate cyclobutyl carbenium ion **17** when exposed to Lewis acid catalyst (Fig. 6). Using unsubstituted imidate **15a** (R = H) (Table 1) regioselectively oxazoline **18a** was obtained. Using substrate bearing aliphatic substituent in the oxymethyl group (*bis*-imidates **15b-g**) selectivity of the reaction decreased. Formation of cyclobutyl carbenium ion and cyclopropylmethyl carbenium ion amination products were observed. Ratio of both amination products depended primarily on the size of the substrate substituent in alkoxymethyl group. In the case of bulky substituents (if R = *n*-Pr, ratio of **18**/**19** was 2:1; if R = *neo*-pentyl, ratio of **18**/**19** was 11:1) oxazoline **18** formed as a major product. It is interesting that using substrate bearing aromatic substituent (R = Ph) regioselectivity of the reaction was reversed − selectively oxazine **19h** was obtained. It could be explained by stabilizing effect of phenyl group on the carbenium ion that induced electron distribution in the favour to cyclopropylmethyl carbenium ion **17'**.

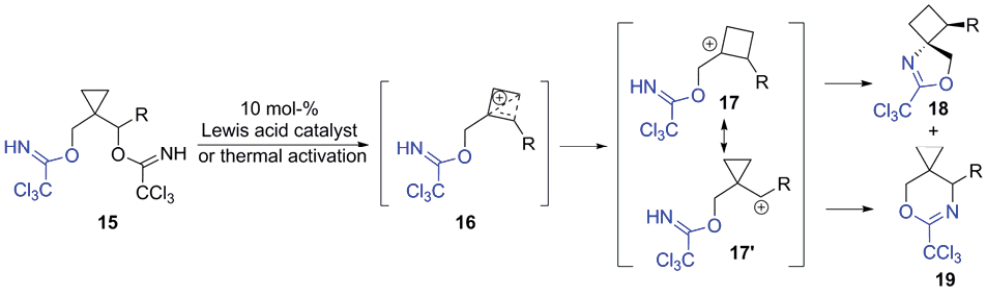



Fig. 6. Oxazoline *vs* oxazine formation *via* amination of cyclopropylmethyl cation.

Table 1

Lewis Acid Catalysed Intramolecular Amination of *Bis*-imidate **15**

| Compound | R | LA | Solvent | Ratio of **18/19**[b] | Yield[c], % |
|---|---|---|---|---|---|
| **15–19a** | **H** | **$AlCl_3$** | **$Et_2O$** | **>99:1** | **75** |
| **15–19b** | *n*-Pr | $AlCl_3$ | Dioxane | 2:1 | 75 |
| **15–19c** | *i*-Pr | | | 4:1 | 70 |
| **15–19d** | *c*-Hex | | | 3:1 | 70[a] |
| **15–19e** | ***neo*-Pent** | **$BF_3 \cdot OEt_2$** | **PhMe** | **11:1** | **86**[a] |
| **15–19f** | $CH_2OMe$ | | | 4:1 | 55[a] |
| **15–19g** | $CH_2OBn$ | | | 3:1 | 49[a] |
| **15–19h** | Ph | $BF_3 \cdot OEt_2$ | DCM | 1:>99 | 75 |

[a] NMR yield, determined using 1,4-bis(trichloromethyl)benzene as an internal standard; [b] ratio of **18/19**, determined using GC-MS; [c] Isolated yield for mixture of products **18** and **19**.

It was demonstrated that the reaction can be initiated in thermal ionization conditions by refluxing imidates **15** in toluene without Lewis acid catalyst (Table 2). In this case, both amination products **18** and **19** were formed. However, it should be noted that using methoxymethyl- and benzyloxymethyl substituents (substrates **15f** and **15g**), the thermal activation significantly improved the yield of desired oxazoline **18f, g**.

Table 2

Thermal Ionization of *Bis*-imidate **15**

| Compound | R | Ratio of **18/19**[b] | Yield[c], % |
|---|---|---|---|
| **15–19b** | *n*-Pr | 2:1 | 64[a] |
| **15–19c** | *i*-Pr | 4:1 | 88 |
| **15–19d** | *c*-Hex | 3:1 | 70[a] |
| **15–19e** | *neo*-Pent | 1:1 | 60[a] |
| **15–19f** | **$CH_2OMe$** | **9:1** | **80** |
| **15–19g** | **$CH_2OBn$** | **7:1** | **85** |

[a] NMR yield, determined using 1,4-*bis*(trichloromethyl)benzene as an internal standard; [b] ratio of **18/19**, determined using GC-MS; [c] isolated yield for mixture of products **18** and **19**.

It is noteworthy that *bis*-imidates **15** provided oxazolines **18** as a single diastereomers with *trans* configuration. Such a stereochemical outcome could be explained by stereoinduction model where the amination takes place from the sterically less hindered face of close-to-planar cyclobutyl carbenium ion **17** (Fig. 7).

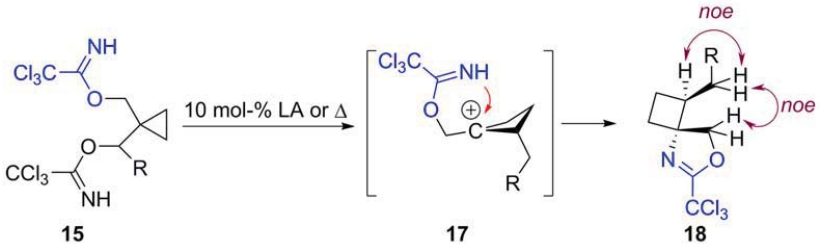



Fig. 7. Stereoinduction model for the formation of oxazolines **18** as *trans*-isomers.

In order to demonstrate the utility of oxazolines **18**, products were transformed to *Boc*-protected cyclobutane-based amino alcohols **20** in moderate to good yields (Fig. 8), (Table 3). For this purpose, oxazolines **18** were hydrolysed in acidic conditions and the resulting amino alcohols were treated with $Boc_2O$ under basic conditions.

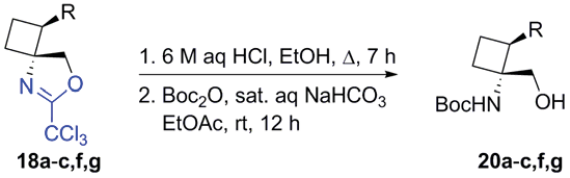



Fig. 8. Synthesis of 1-aminocyclobutylcarbinols.

Table 3

Yields of 1-aminocyclobutylcarbinols

| Entry | R | **20**, yield, % |
|---|---|---|
| 1 | H | **20a**, 59 |
| 2 | *n*-Pr | **20b**, 89 |
| 3 | *i*-Pr | **20c**, 70 |
| 4 | $CH_2OMe$ | **20f**, 73 |
| 5 | $CH_2OBn$ | **20g**, 69 |

*Bis*-trihloracetimidate **21** bearing carbocation stabilizing group efficiently provided tetrahydro-1,3-oxazepine **23** as homoallyl amination product of cyclopropylmethyl cation **22** when exposed to Lewis acid catalyst (Fig. 9), (Table 4). Such a direction of the reaction can be explained by the effect of carbocation-stabilizing group inducing electron distribution in favour of the classical homoallylcation **22'**.

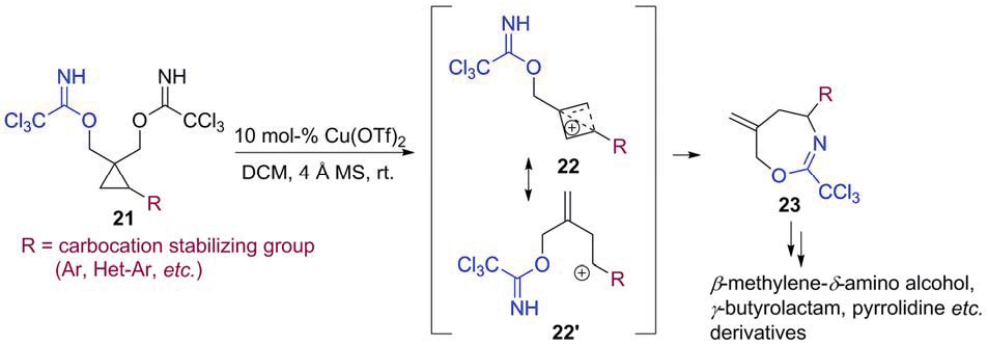



Fig. 9. The cyclization of *bis*-imidates **21** to tetrahydro-1,3-oxazepines **23**.

Table 4

Substrate Scope for the Cyclization of *Bis*-imidates **21** to Tetrahydro-1,3-oxazepines **23**

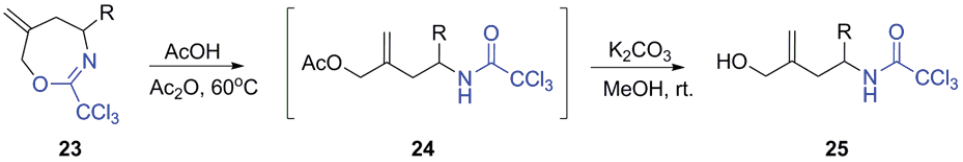
| Entry | R | **23**, yield (%) |
|---|---|---|
| 1 | $C_6H_5$ | **23a**, 85 |
| 2 | 4-$MeOC_6H_4$ | **23b**, 96 |
| 3 | 4-$Me_2NC_6H_4$ | **23c**, 87 |
| 4 | 4-$FC_6H_4$ | **23d**, 83 |
| 5 | 1-Naphthyl | **23e**, 90 |
| 6 | 3-(*N*-Tosyl)indolyl | **23f**, 94 |
| 7 | (*E*)-$C_6H_5CH$=CH | **23g**, 96 |
| 8 | Vinyl | **23h**, 91 |
| 9 | 2-Thienyl | **23i**, 89 |
| 10 | 2-(*N*-Methyl)pyrrolyl | **23j**, 64[a] |
| 11 | 3-Furyl | **23k**, 79[b] |
| 12 | $Ph(Me)_2SiCH_2$ | **23l**, 81 |
| 13 | Et | -[c] |
| 14 | $C_6H_5C$≡C | -[c] |
| 15 | 3,5-(di-Cl)-$C_6H_3$ | -[c] |

[a] 1 mol-% $Cu(OTf)_2$; [b] 10 mol-% $(CuOTf)_2 \cdot C_6H_6$; [c] mixture of products.

*Bis*-trihloracetimidates **21a-k** bearing carbocation stabilizing groups as aryl (Table 4, *Entry 1−5*), electron-rich heteroaryl (Table 4, *Entry 6, 9−11*) and vinyl substituents (Table 4, *Entry 7, 8*) selectively formed oxazepines **23a-k** with high yields (64–96 %). Substrate **21l** containing silyl group as a *β*-cation-stabilizing substituent afforded oxazepine **23l** in very good yield – 81 % (Table 4, *Entry 12*). Notably, substrates **21m-o** containing groups with lower carbenium ion stabilizing

ability such as ethyl-, alkynyl- or electron poor aryl group led to the formation of product mixture (Table 4, *Entry 13−15*).

Tetrahydro-1,3-oxazepines **23** are potentially used as multifunctional building blocks for the synthesis of complex compounds. In order to demonstrate the synthetic utility of oxazepines **23**, these were transformed to unsaturated amino alcohol derivatives **25** *via* one pot two step procedure, which involves cleavage of cyclic imidate function with acetic acid followed by methanolysis of the intermediate **24** (Fig. 10), (Table 5).




**23** **24** **25**

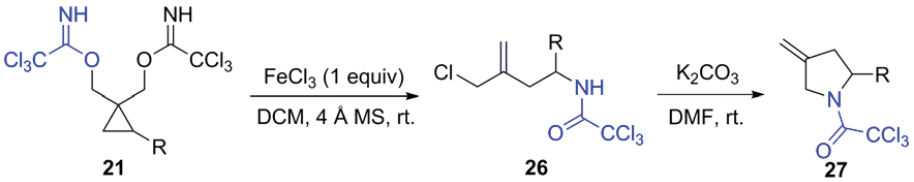
Fig. 10. Transformation of tetrahydro-1,3-oxazepines **23** to amino alcohols **25**.

Table 5

Reaction Yields

| Entry | R | **25**, yield, % |
|---|---|---|
| 1 | $C_6H_5$ | **25a**, 94 |
| 2 | 4-$MeOC_6H_4$ | **25b**, 96 |
| 3 | 2-Thienyl | **25i**, 91 |
| 4 | Vinyl | **25h**, 89 |
| 5 | $CH_2SiMe_2Ph$ | **25l**, 89 |

It can be seen that allylchlorides **26** can be easily obtained from *bis*-trichloracetimidates **21g-i** when exposed to stoichiometric amount of $FeCl_3$ (Fig. 11), (Table 6). Further, these can be cyclized to 4-*exo*-methylene-pyrrolidines 27.




**21** **26** **27**

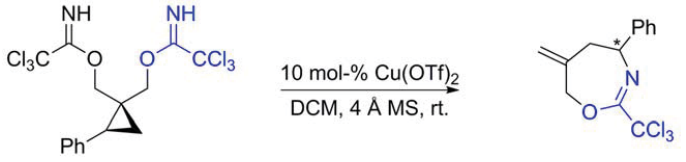
Fig. 11. Synthesis of allylchlorides **26** and 4-*exo*-methylene-pyrrolidines **27**.

Table 6

Yields of Allylchlorides **26** and 4-*exo*-methylene-pyrrolidines **27**

| Entry | R | **26**, yield (%) | **27**, yield (%) |
|---|---|---|---|
| 1 | (*E*)-$C_6H_5CH$=CH | **26g**, 87 | **27g**, 89 |
| 2 | Vinyl | **26h**, 77 | **27h**, 90 |
| 3 | 2-Thienyl | **26i**, 86 | **27i**, 93 |

The cyclization studies using enantioenriched *bis*-imidate *S*-**21a** showed that formation of tetrahydro-1,3-oxazepine **23a** proceeds with considerable degree of racemization (Fig. 12).




*S*-**21a** *ee* = 87 %

**23a** *ee* = 42 %

Fig. 12. Chirality transfer in cyclization of enantioenriched *bis*-imidate *S*-**21a** to oxazepine **23a**.

To investigate if the racemization is associated with unselective abstraction of imidate group in *bis*-imidate, substrates *cis*-$d_2$-**21a** and *trans*-$d_2$-**21a** with deuterium labelling at methylene groups were prepared (Fig. 13). In both substrates, the imidate group situated *trans* to the phenyl group was abstracted selectively to give the corresponding deuterium labeled regioisomers *cis*-$d_2$-**23** and *trans*-$d_2$-**23**, respectively. Having established that abstraction of the imidate is selective, the partial loss of enantioselectivity in the product **23a** formation could be linked to partial nature of non-classical carbenium ion intermediate **22** as the planar homoallyl carbenium ion **22'** would lead to completely racemic product **23a**.

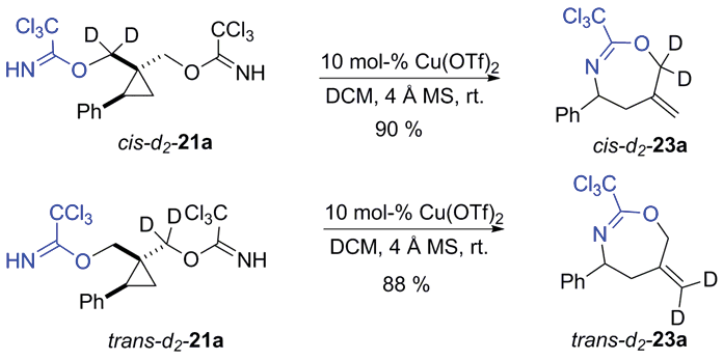



Fig. 13. Selective abstraction of *trans*-imidate function in deuterium-labeled *bis*-imidate **21a**.

Diastereoselective amination of carbenium ion **22**/**22'** bearing additional substituent next to the reaction centre was explored. Exposure of *bis*-imidate **28** to Lewis acid catalyst provided *trans*-substituted tetrahydrooxazepine **29** as the only detectable isomer (Fig. 14). To prove the configuration, the reaction product **129** was transformed to diol **30** that could be analysed by X-ray spectroscopy.

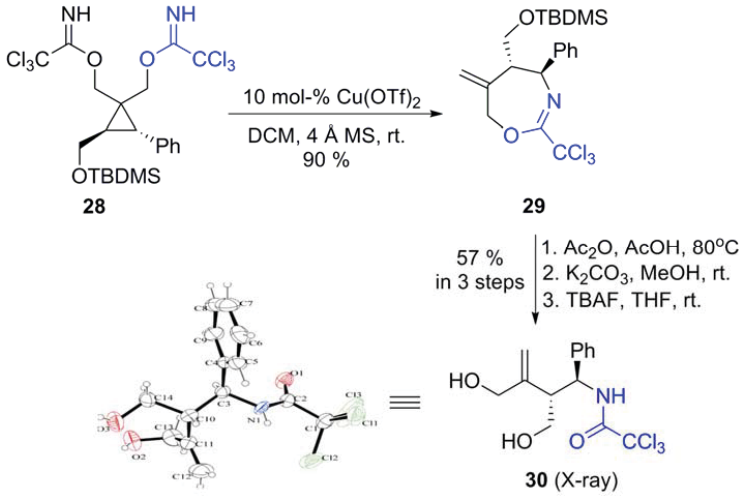



Fig. 14. Diastereoselective cyclization of *bis*-imidate **28** and cleavage of oxazepine **29**.

The cyclopropyl-cyclopropyl rearrangement selectively can be achieved from the *bis*-trichloroacetimidate **31a**, based on the 1,2-disubstituted cyclopropane base. Catalytic amount of the Lewis acid ($B(C_6F_5)_3$) promoted amination of CPM ions and provided oxazoline **33a** in high yield. In order to extend the application of the reaction, one of the imidate functions in the cyclopropane derivative **31** was replaced by other intramolecular nucleophiles (phenol, aromatic

or heteroaromatic function, etc.) (Fig. 15). This way, a series of cyclopropyl-containing products **33a-k** were obtained from 1,2-disubstituted cyclopropane derivatives **31**.

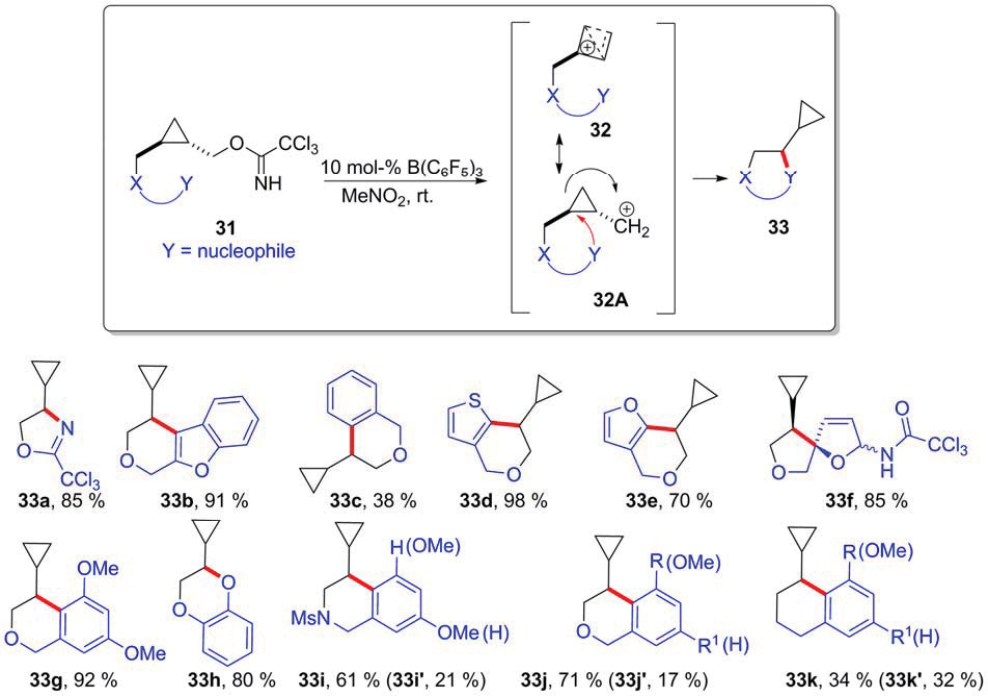



Fig. 15. Substrate scope for intramolecular cyclopropylmethylation.

In order to find whether the reaction proceeds with chirality transfer or racemization, the enantioenriched substrate (-)-**31e** was used. Under the given reaction conditions, racemic product **33e** was formed (Fig. 16).

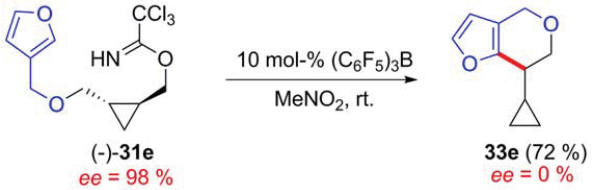



Fig. 16. Investigation of chirality transfer from enantioenriched substrate (-)-**31e**.

This investigation has shown that cyclopropylmethylation is not a stereospecific transformation. It lead to exploring catalyst-controlled stereoinduction capabilities. Unfortunately, it was not possible to obtain chiral compound **33e** from racemic **31e** using several chiral Lewis (Fig. 17, **C**−**E**) or Brønsted acids (Fig. 17, **A, B**).

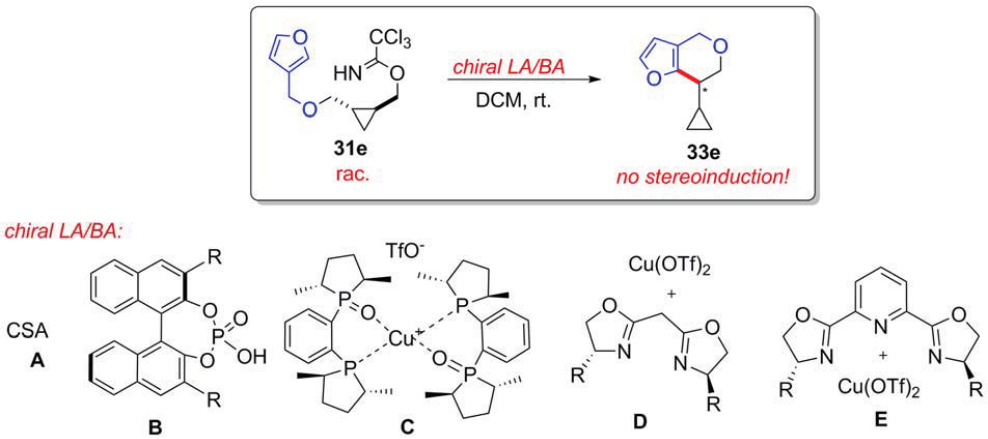



Fig. 17. Induction of stereoselectivity in cyclopropyl-cyclopropyl rearrangement reaction using chiral catalysts.

## Protolytic cleavage of cyclopropane *C-C* bond

Amide group-containing substrate **34a** was subjected to the range of Brønsted and Lewis acids. It was found that trifluoroacetic acid (TFA) was superior for selective and high yielding formation of the pyrrolidine **37a** (Fig. 17), (Table 7). This product obviously results from an *anti*-Markovnikov $H^+$ attack (**35A**) of cyclopropane 3**4a** and subsequent amination of the intermediate carbenium ion **36A**. Stronger acids such as MsOH and TfOH proved to be less selective and provided considerable amount of oxazine **38a.** The formation of oxazine **38a** could be explained by the competitive intermolecular protonolysis of the cyclopropane *C-C* bond (**35B**) followed by trapping of the carbenium ion **36B** with amide oxygen. Weaker Lewis acids such as $BF_3{\cdot}Et_2O$ and $(CuOTf)_2{\cdot}C_6H_6$ were unreactive.

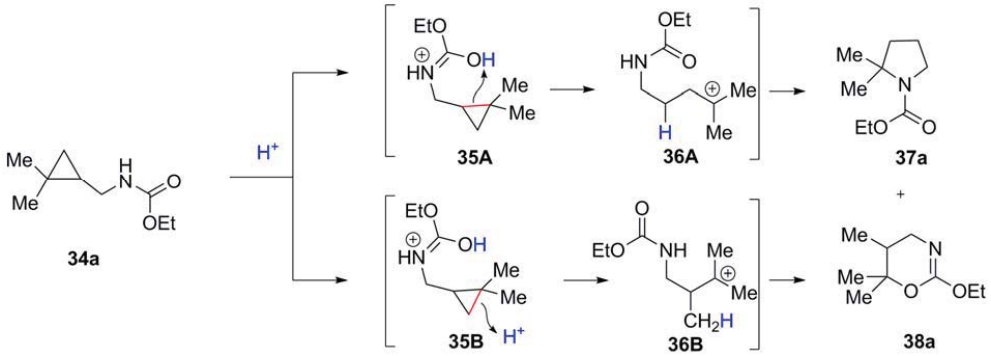



Fig. 18. Acid promoted cleavage of cyclopropane and subsequent amination of the intermediate carbenium ion.

Table 7

Acid Promoted Cleavage of Cyclopropane

| Entry | Acid (solvent) | Product (yield, %)[a] |
|---|---|---|
| 1 | TFA (neat) | **37a** (98) |
| 2 | MsOH 1 vol% (DCM) | **37a** (70), **38a** (17) |
| 3 | TfOH 1 vol% (DCM) | **37a** (47), **38a** (25) |
| 4 | $Fe(OTf)_3$ 1.0 equiv (DCM) | **37a** (61), **38a** (17) |
| 5 | $BF_3{\cdot}OEt_2$ 1.0 equiv (DCM) | no reaction |
| 6 | $(CuOTf)_2{\cdot}C_6H_6$ 1.0 equiv (DCM) | no reaction |

[a] NMR yield using 1,4-*bis*(trichloromethyl)benzene as an internal standard.

During the investigation, it was discovered that nitrogen substituent in substrate **34** plays an important role. This function should be both, enough basic to successfully direct regioselective protonolysis of cyclopropane *C-C* bond and enough nucleophile to react with the intermediate carbenium ion. Ethoxycarbonyl derivative **34a**, also urea **34b** and several carboxamides **34c-e** proved to be suitable substrates for the formation of pyrrolidine derivatives **37a-e** in good to excellent yields (Fig. 19), (Table 8). Trichloroacetamide **34f** gave mixture of pyrrolidine **37f** and the ring-opening product **39f,** which could be explained by reduced nucleophilicity of the carboxamide **34f**. Thioamide **34g**, trifluoroacetamide **34i,** and sulfonamide **34j** were reactive under protonolytic conditions, however formed mixture of products with low content of expected pyrrolidine **37**. In these substrates, protonation of carboxamide and sulfonamide function is minimized which could prevent them to act as directing groups for intramolecular proton delivery.

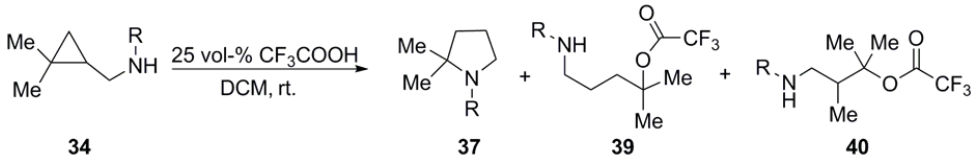



Fig. 19. Scope of the cyclopropane *N*-substituent.

Table 8

Substituents and Yields

| Entry | **34**, R | Product (yield, %) |
|---|---|---|
| 1 | **34a**, EtOCO | **37a** (92) |
| 2 | **34b**, PhNHCO | **37b** (99) |
| 3 | **34c**, PhCO | **37c** (99) |
| 4 | **34d**, MeCO | **37d** (74)[a,b] |
| 5 | **34e**,$ClCH_2CO$ | **37e** (99)[a] |
| 6 | **34f**, $Cl_3CCO$ | **37f** : **39f** in ratio 1:1 (97)[c, d] |
| 7 | **34g**, MeCS | **37g** (17)[e] and unidentified by-products |
| 8 | **34h**, 4-$NO_2C_6H_4$ | no conversion of **34h**[c] |
| 9 | **34i**, $CF_3CO$ | mixture of **37i**, **39i** and **40i** |
| 10 | **34j**, $PhSO_2$ | mixture of **37j**, **40j** and $PhSO_2NH_2$ |

[a] 50 vol% TFA in $CH_2Cl_2$, rt; [b] volatile compound; [c] neat TFA; [d] NMR yield using 1,4-*bis*(trichloromethyl)benzene as an internal standard.

Range of substituted *N*-ethoxycarbonyl aminomethyl cyclopropanes **34a**, **41a-h** gave pyrrolidines **37a**, **44a-h** in good yields (Fig. 20). Monoalkyl-substituted cyclopropane **41i** ($R^1$=*n*-Hex, $R^{2-5}$=H) was unreactive even in neat TFA under reflux. Surprisingly, diphenyl-substituted cyclopropane **41j** ($R^{1,2}$=Ph, $R^{3-5}$=H) failed to give the expected product. Low reactivity of substrate **41j** implies that the stability of intermediate carbenium ion is not the only factor that enables cyclopropane *C*-*C* bond protonolysis, as in this case very stable diphenyl carbenium ion should form. Apparently, electron density in the scissile *C*-*C* bond may also play an important role.

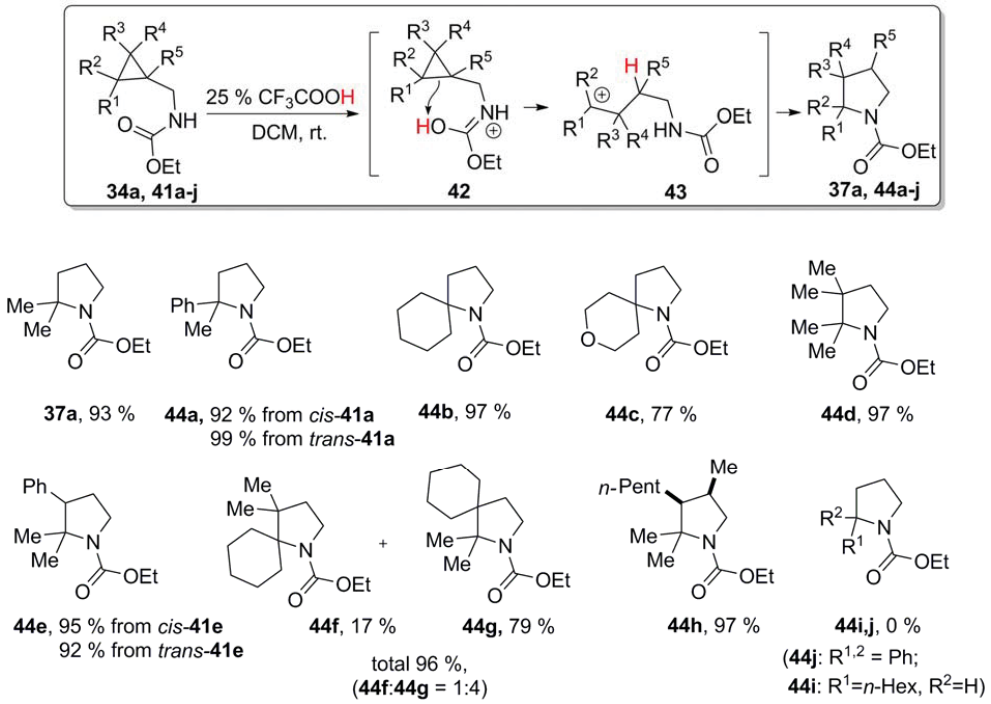



Fig. 20. Substrate scope for the synthesis of pyrrolidines.

When deuterium labeled substrate **D-34a** was subjected to the deuterated TFA, almost complete deuterium incorporation at the 3-CH position of pyrrolidine was observed (Fig. 21). As expected, such result is relevant to the proton attack at C(b) of cyclopropane. Deuterium incorporation was observed in both methyl groups and in 2-$CH_2$ position of product **D-37a** as well. This indicates that certain portion of intermediate carbenium ion **45** undergoes equilibration with alkenes **D-46** and **D-47** *via* deprotonation/protonation.

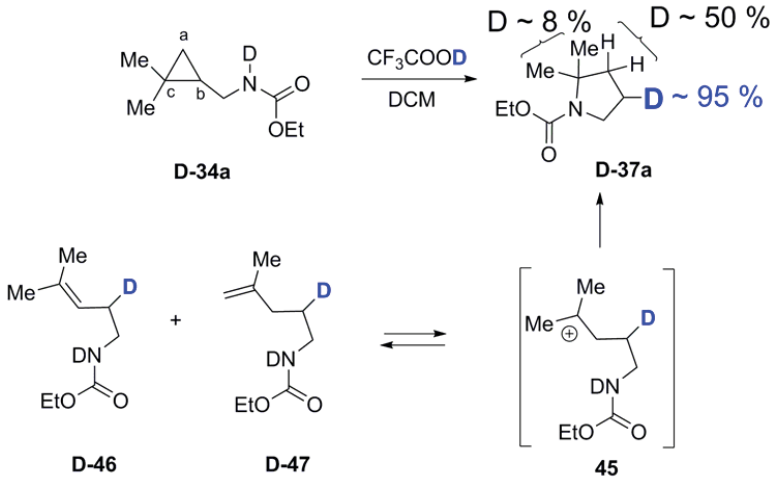



Fig. 21. Mechanism of cyclopropane **D-34a** protonolysis based on deuterium incorporation into the product **D-37a**.

Interestingly, when substrate **41h**, was subjected to deuterated TFA, a relatively small amount of deuterium incorporation was observed in the methyl groups and in 2-CH position of product **D-44h** (Fig. 22). At the same time, the retention of configuration for the carbon that is undergoing a proton attack was observed. This result is consistent with the "edge" trajectory of the proton transfer from the protonated amide **48**.

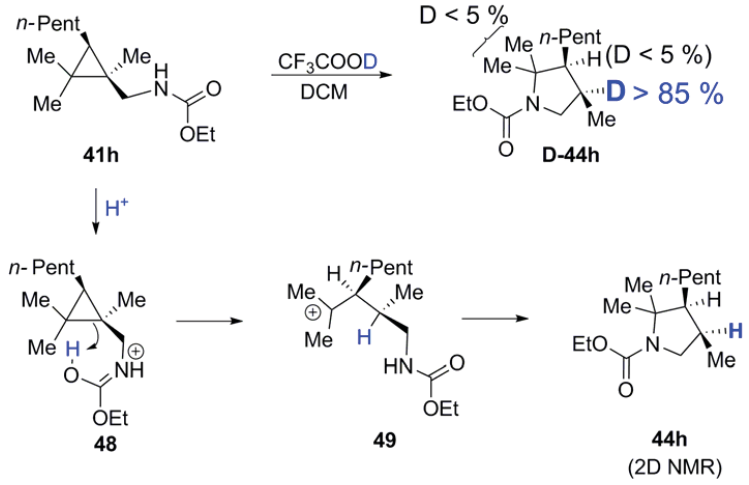



Fig. 22. Stereochemistry of proton transfer in cyclopropane **41h**.

To extend the application of carbenium ions generated by cyclopropane cleavage, the Ritter-type intermolecular amination was explored. For this purpose, tertiary amides **50** were used. To suppress the cyclization reaction, the carbamate nitrogen was blocked by introduction of additional substituent on it ($R^3 \neq H$). Carbenium ions **52** generated by protonolysis of cyclopropanes **50a-m** were successfully aminated under Ritter-type reaction conditions to form diamine derivatives **53a-m** (Fig. 23).

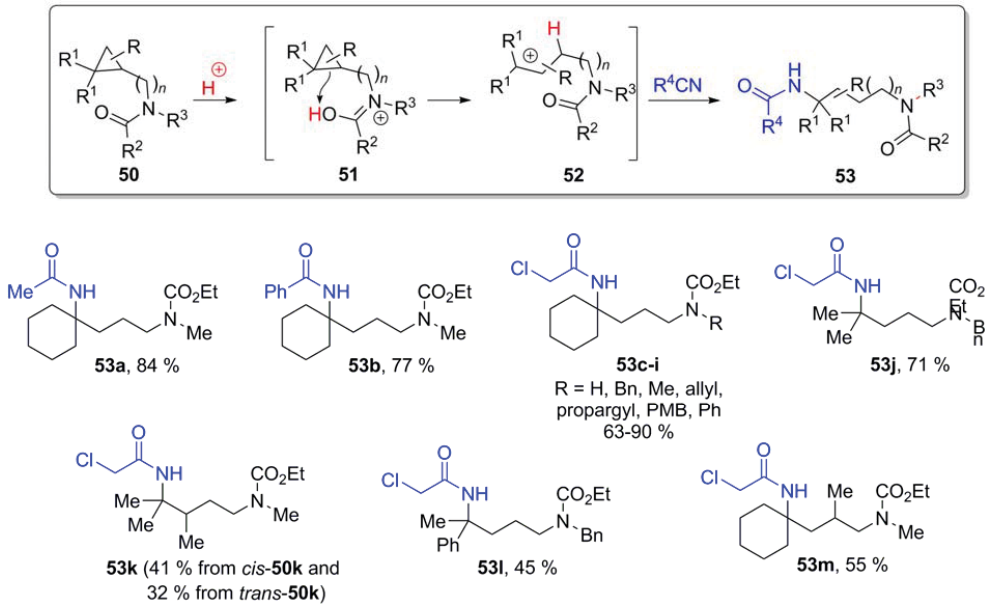



Fig. 23. Ritter-type amination of carbenium ions generated by protonolysis of cyclopropane.

In addition, it was demonstrated that several other functional groups such as carbamate carboxamide, urea, ester and ketone can efficiently direct regioselective protonolytic cleavage of cyclopropane *C-C* bond to generate the carbenium ion (Fig. 24). As a result, a series of amine derivatives **55a-k** was obtained.

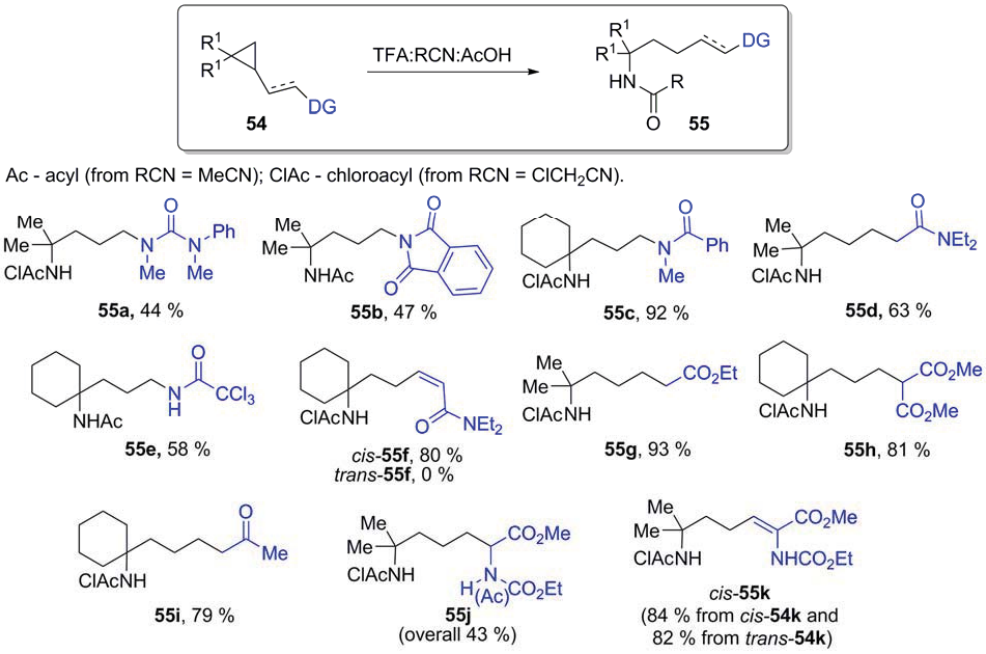



Fig. 24. Scope of directing groups.

The results with amides **54d**, *cis*-**54f**, esters **54g, h,** and ketone **54i** strongly indicates that oxygen rather than nitrogen in the amide function is involved in the intramolecular proton transfer to cyclopropane.

# CONCLUSIONS

1. Amination of the non-classical cyclopropylmethyl cation depending on cyclopropane substitution pattern in *bis*(trichloroacetimidate) system can selectively provide one of three structurally different products (cyclopropyl-, cyclobutyl or homoallylderivatives).
2. Amination products of non-classical cyclopropylmethyl cation − spirocyclic oxazolines and tetrahydro-1,3-oxazepines can be efficiently transformed into corresponding amino acids, which are potential building blocks for the synthesis of various pharmaceutically significant compounds.
3. In the case of 1,2-disubstituted-cyclopropanes, the cyclopropyl-cyclopropyl-rearrangement can be selectively achieved by intramolecular trapping of cyclopropylmethyl cation with an internal nucleophile.
4. The regioselective protonolytic *C*-*C* bond cleavage of acylated aminomethyl cyclopropanes can be achieved. The intermediate tertiary carbenium ion undergoes intramolecular amination to give 2,2-substituted pyrrolidines. The cyclopropane cleavage proceeds with the retention of configuration at the carbon to which the proton is attached. This observation is consistent with the “edge” protonation trajectory of the *C*-*C* bond.
5. Carbenium ions generated by directed protonolysis of cyclopropane can be intermoleculary aminated under Ritter-type reaction conditions using such functional groups as carbamate carboxamide, urea, ester and ketone.

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# PIELIKUMI / PUBLICATIONS

**Skvorcova, M.**; Grigorjeva, L.; Jirgensons, A. **Tetrahydro-1,3-oxazepines *via* Intramolecular Amination of Cyclopropylmethyl Cation.** *Org. Lett.* **2015**, *17*(12), 2902–2904.



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Organic LETTERS

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# Tetrahydro-1,3-oxazepines via Intramolecular Amination of Cyclopropylmethyl Cation

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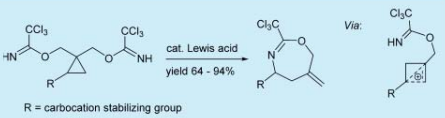
Supporting Information

**ABSTRACT:** An efficient synthesis of tetrahydro-1,3-oxazepines was developed involving the regioselective intramolecular amination of cyclopropylmethyl cation. The cation was generated by the abstraction of one imidate group in bis-imidate bearing a carbocation-stabilizing substituent. Using 1,1,2,3-tetrasubstituted cyclopropane substrates, highly diastereoselective intramolecular amination to *trans*-tetrahydro-1,3-oxazepines was achieved. The resulting tetrahydro-1,3-oxazepines were transformed to the homoallylamine derivatives in high yields.




Structural investigations of cyclopropylmethyl cation **1** have shown that it exists as an equilibrating mixture of $\pi\sigma$-delocalized bisected cyclopropylmethyl cation **1A** and non-classical bicyclobutonium ion **1B** (Figure 1).[1,2] The carbocation

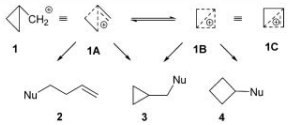



**Figure 1.** Regioselectivity in cyclopropylmethyl cation reaction with nucleophiles.

**1** is often represented as **1C** which is a hybrid of the proposed discrete structures **1A** and **1B**. The reaction of cyclopropylmethyl cation **1C** with nucleophiles can occur at any of the three possible sites bearing partial positive charge leading to homoallyl,[3] cyclopropylmethyl,[2a,3a,j,4] or cyclobutyl[4,5] derivatives **2**−**4**. Several regioselective reactions of cyclopropylmethyl cation **1** with nucleophiles have been reported as a useful approach to products based on structures **2**−**4**.[3−5]

Although not systematically studied, the available experimental data suggest that regioselectivity of intramolecular cyclization is mainly controlled by the geometric constraints and/or effects of cyclopropane substituents. A carbocation stabilizing group can be used to direct the addition of nucleophile to cyclopropylmethyl cation **1C** presumably via inducing electron distribution in favor of the classical carbocation.

Few studies have been reported for amination reactions of cyclopropylmethylcarbocation.[3j,l,5e] The reason for that could be the limited range of amine nucleophiles compatible with acidic conditions typically used to initiate the reaction. Previously, we[6] as well as others[7] have demonstrated that bis-imidates are convenient systems for amination of carbocations. In bis-imidates, one of the imidates serves as the leaving group when activated with an acid catalyst while the other acts as an *N*-nucleophile. Following this approach, it was explored whether carbenium ion **6C** derived from readily available bis-imidate **5** can be regioselectively aminated depending on the cyclopropane substituent (Table 1).

Initial studies showed that substrate **5a** containing phenyl substituent selectively forms homoallyl carbocation amination product **7a** when exposed to Lewis acid catalyst (Table 1, entry 1). Screening of catalysts revealed that relatively weak Lewis acids such as $Cu(OTf)_2$ and $(CuOTf)_2{\cdot}C_6H_6$ were the optimal catalysts for the reaction. Stronger Lewis acids or acids containing nucleophilic counterions led to decomposition of product **7** (see the Supporting Information for details). Further, the substrate scope with respect to the cyclopropane substituent was explored. Bis-imidates **5** bearing aryl substituent with electron donating groups (entries 2, 3, and 5) afforded tetrahydro-1,3-oxazepines in excellent yields. Amination of bis-imidates **5** having electron-poor aryl groups (entries 4 and 15) gave satisfying results only for substrate **5d** (entry 4). Bis-imidates **5** bearing electron-rich heteroaryl substituents also provided the expected product **7** (entries 6 and 9−11). The reaction was not limited only to aryl carbocation stabilizing groups. Substrates bearing vinyl substituent (entries 7 and 8) gave high product yield. Bis-imidates **5b** containing groups with lower carbocation stabilizing ability such as ethyl (entry 13) or alkynyl (entry 14) led to the formation of a product mixture. However, if the alkyl group contained a silyl group as a $\beta$-cation-stabilizing substituent, the amination product was obtained in good yield (entry 12).

Tetrahydro-1,3-oxazepine derivatives **7** are masked unsaturated amino alcohols which are valuable multifunctional

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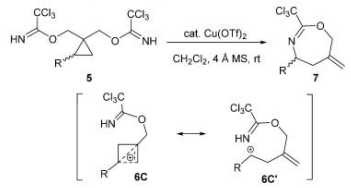
**Table 1. Substrate Scope for the Cyclization of Bis-imidates 5 to Tetrahydro-1,3-oxazepines 7[a]**



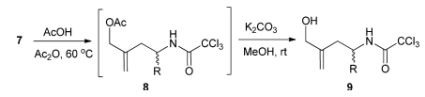

| entry | R | product, yield (%) |
|---|---|---|
| 1 | Ph | **7a**, 85 |
| 2 | 4-MeOC$_6$H$_4$ | **7b**, 96 |
| 3 | 4-Me$_2$NC$_6$H$_4$ | **7c**, 87 |
| 4 | 4-FC$_6$H$_4$ | **7d**, 83 |
| 5 | 1-naphthyl | **7e**, 90 |
| 6 | 3-(*N*-tosyl)indolyl | **7f**, 94 |
| 7 | (*E*)-C$_6$H$_5$CH═CH | **7g**, 96 |
| 8 | vinyl | **7h**, 91 |
| 9 | 2-thienyl | **7i**, 89 |
| 10[b] | 2-(*N*-methyl)pyrrolyl | **7j**, 64 |
| 11[c] | 3-furyl | **7l**, 79 |
| 12 | Ph(Me)$_2$SiCH$_2$ | **7k**, 81 |
| 13[d] | Et | |
| 14[d] | C$_6$H$_5$C≡C | |
| 15[d] | 3,5-(di-Cl)-C$_6$H$_3$ | |

[a]Bis-imidate (0.5 mmol), Cu(OTf)$_2$ (0.05 mmol), CH$_2$Cl$_2$ (5 mL). Yields are isolated yields. Please see the Supporting Information for details. [b]Cu(OTf)$_2$ (0.005 mmol). [c](CuOTf)$_2$·C$_6$H$_6$ (0.05 mmol). [d]Mixture of products.

intermediates. However, there is a limited number of methods available to access this type of amino alcohol.[8] In order to demonstrate the utility of tetrahydro-1,3-oxazepines **7**, several examples were transformed to amino alcohol derivatives **9** (Table 2). The one-pot, two-step procedure involved cleavage of cyclic imidate function with acetic acid followed by methanolysis of the intermediate **8**.

The cyclization studies with enantioenriched bis-imidate *S*-**5a** showed that tetrahydro-1,3-oxazepine **7a** forms with considerable degree of racemization (Scheme 1).

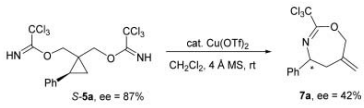
**Table 2. Transformation of Tetrahydro-1,3-oxazepines 7 to Amino Alcohols 9[a]**




| entry | R | product, yield (%) |
|---|---|---|
| 1 | Ph | **9a**, 94 |
| 2 | 4-MeOC$_6$H$_4$ | **9b**, 96 |
| 3 | 2-thienyl | **9i**, 91 |
| 4 | vinyl | **9h**, 89 |
| 5 | Ph(Me)$_2$SiCH$_2$ | **9k**, 89 |

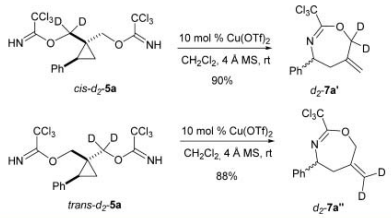
[a]Key: (1) tetrahydro-1,3-oxazepine (1.0 mmol), Ac$_2$O (1 mL), AcOH (1 mL); (2) K$_2$CO$_3$ (3.0 mmol), MeOH (2 mL). Yields are isolated yields. Please see the Supporting Information for details.

**Scheme 1. Chirality Transfer in the Cyclization of Enanatioenriched Substrate *S*-5a**




To determine if the racemization is associated with unselective abstraction of the imidate group, substrates *cis*-$d_2$-**5a** and *trans*-$d_2$-**5a** with deuterium labeling at the methylene position were prepared (Scheme 2). In both substrates, the

**Scheme 2. Selective Abstraction of *trans*-Imidate Function in Deuterium-Labeled Bis-imidate 5a**




imidate group *trans* to the phenyl group was selectively abstracted to give the corresponding deuterium labeled regioisomers $d_2$-*rac*-**7a′** and $d_2$-*rac*-**7a″**, respectively (only one isomer in each case was detected by $^1$H NMR). The exclusive *trans*-imidate elimination would be difficult to explain by the accessibility of the sterically less hindered imidate group to the catalyst. More likely, these results point to specific stereoelectronic requirement for the leaving group to facilitate the formation of cyclopropylmethyl cation/homolallyl cation.

Having established that abstraction of the imidate is selective, the partial loss of enantioselectivity in the product **7a** formation obviously stems from the availability of both faces of carbocation **6C**/**6C′**. Nevertheless, the chirality was preserved to some extent which is difficult to explain. This could be related to a partial nature of nonclassical carbocation intermediate since the planar homoallyl cation would lead to complete racemization.

Diastereoselective amination of carbocation **6C**/**6C′** bearing an additional substituent was explored (Scheme 3). Bis-imidate **11** was prepared from readily accessible stereochemically defined dicarboxylic acid derivative **10**.[9] Amination of bis-imidate **11** gave *trans*-substituted tetrahydro-1,3-oxazepine **12** as the only detectable isomer. Configuration of the reaction product **12** was determined by X-ray analysis of the derivatization product−diol **13**.

In summary, we have demonstrated that a cyclopropylmethyl cation generated by the abstraction of one imidate group in bis-imidates undergoes regioselective intramolecular amination. A homoallylamine derivative was formed selectively if cyclopropane contained a carbocation stabilizing substituent. The resulting tetrahydro-1,3-oxazepines were transformed to unsaturated amino alcohol derivatives. It was demonstrated that highly diastereoselective cyclization to *trans*-substituted tetrahydrooxazepine could be achieved starting from 1,1,2,3-tetrasubstituted cyclopropane substrates.



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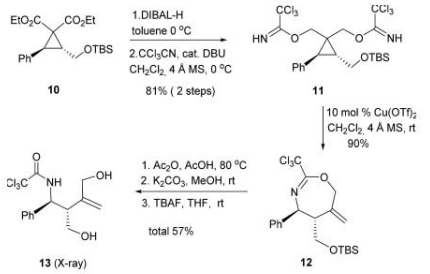
**Scheme 3. Diastereoselective Cyclization of Bis-imidate 11 to Oxazepine 12 and Derivatization to Amino Alcohol 13**




## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedures and characterization data for new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01014.

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### Notes

The authors declare no competing financial interest.

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Organic LETTERS

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# Amide-Group-Directed Protonolysis of Cyclopropane: An Approach to 2,2-Disubstituted Pyrrolidines

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Supporting Information

**ABSTRACT:** Regioselective protonolytic C−C bond cleavage of acylated aminomethyl cyclopropanes can be achieved using trifluoroacetic acid. The intermediate tertiary carbenium ion undergoes an intramolecular amination to give 2,2-substituted pyrrolidines. The strength of the acid and the amine substituent are important factors to achieve high regioselectivity, suggesting intramolecular proton transfer from the protonated amide function. Preliminary mechanistic studies revealed that cyclopropane cleavage proceeds with retention of configuration at the carbon to which the proton is attached. This observation is consistent with the "edge" protonation trajectory of the C−C bond.

Because of the ring strain, the cyclopropane C−C bonds exhibit increased reactivity compared with those of larger cycles or acyclic systems.[1] Introduction of a donor and/or acceptor group on the cyclopropane enables ring opening under relatively mild conditions with predictable regioselectivity.[2] However, unactivated cyclopropanes **1** also can undergo C−C bond cleavage leading to functionalized products **2** when exposed to strong electrophilic reagents[1b,3] such as Brønsted acids,[4] $Br_2$,[5] diborane,[6] and acetyl chloride/$AlCl_3$[7] as well as Hg(II),[8] Pd(II),[9] Pt(II),[10] Tl(III),[11] and Ti(IV)[12] salts (Figure 1).

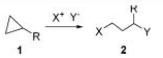


**Figure 1.** Electrophilic cleavage of cyclopropanes **1**.

Certain electrophiles induce high levels of regioselectivity by attacking the cyclopropane at the least-substituted carbon. This approach was recently demonstrated by the groups of Hennecke and Yeung, who exploited the regioselective halogenation of cyclopropane for the synthesis of lactones,[13,14] tetrahydrofurans,[13] pyrrolidines,[13] and oxazolines.[15]

The regioselectivity of the cyclopropane protonolysis tends to follow the modified Markownikoff's rule,[4j,16] which predicts the preferential ring opening to occur between the carbons bearing the largest and smallest numbers of substituents.[4a,b,h,e,k] However, typically the selectivity is modest, as demonstrated by the systematic studies of Wiberg and Kass[4k] for toluenesulfonic acid-catalyzed acetolysis of cyclopropanes with different substitution patterns (Figure 2, using cyclopropane **3** as a representative example).

We have investigated whether intramolecular proton delivery from the protonated amide function in cyclopropanes **4** (Figure 1) can direct regioselective protonolysis of the cyclopropane C−C bond. For this purpose, carbamate-

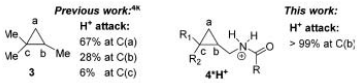
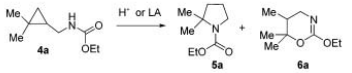



**Figure 2.** Regioselectivity of protonolysis of cyclopropanes **3** and **4**.

containing substrate **4a** was subjected to a range of Brønsted and Lewis acids (Table 1).

**Table 1. Acid-Promoted Cleavage of Cyclopropane 4a**[a]




| entry | acid/solvent | product (% yield)[b] |
|---|---|---|
| 1 | TFA (neat) | **5a** (98) |
| 2 | MsOH (1 vol %)/$CH_2Cl_2$ | **5a** (70), **6a** (17) |
| 3 | TfOH (1 vol %)/$CH_2Cl_2$ | **5a** (47), **6a** (25) |
| 4 | $Fe(OTf)_3$ (1.0 equiv)/$CH_2Cl_2$ | **5a** (61), **6a** (17) |
| 5 | $BF_3{\cdot}OEt_2$ (1.0 equiv)/$CH_2Cl_2$ | no reaction |
| 6 | $(CuOTf)_2{\cdot}C_6H_6$ (1.0 equiv)/$CH_2Cl_2$ | no reaction |

[a]Reactions were performed on a 0.1 mmol scale at rt for 24 h. [b]NMR yields using 1,4-bis(trichloromethyl)benzene as an internal standard.

According to these studies, trifluoroacetic acid (TFA) was superior for selective and high-yielding formation of pyrrolidine **5a** (Table 1, entry 1). This product obviously results from selective proton attack at C(b) of cyclopropane **4a** (Figure 2) and subsequent cyclization of the intermediate carbenium ion. Stronger acids such as MsOH or TfOH proved to be less selective, providing considerable amounts of oxazine **6a** (Table 1, entries 2 and 3). The formation of oxazine **6a** could be explained by proton attack at C(a) of the

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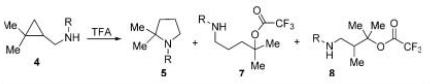
cyclopropane (Figure 2) followed by trapping of the carbenium ion with the amide oxygen. On the basis of these results, it can be proposed that TFA can induce cyclopropane C−C bond cleavage via amide protonation and intramolecular proton transfer, while in the case of stronger acids intermolecular proton transfer is a competing process. Several Lewis acids were also screened (Table 1, entries 4−6). Only $Fe(OTf)_3$ induced the cleavage of cyclopropane **4a** but did so in an unselective manner, providing both products **5a** and **6a**. Weaker Lewis acids such as $BF_3{\cdot}Et_2O$ and $(CuOTf)_2{\cdot}C_6H_6$ were unreactive.

Next, the impact of the nitrogen substituent was investigated (Table 2). In addition to ethoxycarbonyl

**Table 2. Scope of the Cyclopropane N Substituent**[a]



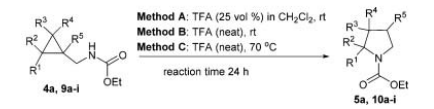

| entry | 4, R | product (% yield) |
|---|---|---|
| 1 | **4a**, EtOCO | **5a** (92) |
| 2 | **4b**, PhNHCO | **5b** (99) |
| 3 | **4c**, PhCO | **5c** (99) |
| 4 | **4d**, MeCO | **5d** (74)[b,c] |
| 5 | **4e**,$ClCH_2CO$ | **5e** (99)[b] |
| 6 | **4f**, $Cl_3CCO$ | **5f**:**7f**, 1:1 ratio (97)[d,e] |
| 7 | **4g**, MeCS | **5g** (17)[c] and unidentified byproducts |
| 8 | **4h**, 4-$NO_2C_6H_4$ | no conversion of **4h**[a,d] |
| 9 | **4i**, $CF_3CO$ | mixture of **5i**, **7i**, and **8i** |
| 10 | **4j**, $PhSO_2$ | mixture of **5j**, **8j**, and $PhSO_2NH_2$ |

[a]Reaction conditions: a solution of **4** ($c$ = 0.1 M) in TFA (25 vol %) in $CH_2Cl_2$, rt, 24 h, unless otherwise stated (see Table S2 for the impact of the TFA concentration). Isolated yields are given. [b]TFA (50 vol %) in $CH_2Cl_2$, rt. [c]Volatile compound. [d]TFA (neat). [e]NMR yield using 1,4-bis(trichloromethyl)benzene as an internal standard.

derivative **4a** (entry 1), also urea **4b** (entry 2) and several carboxamides **4c−e** (entries 3−5) proved to be suitable substrates for the formation of pyrrolidine derivatives **5a−e** in good to excellent yields. Trichloroacetamide **4f** gave a mixture of pyrrolidine **5f** and the ring-opening product **7f** (entry 6), which could be explained by the reduced nucleophilicity of **4f**. Thioamide **4g** was reactive under the protonolytic conditions but formed a mixture of products with a low content of the expected pyrrolidine **5g** (entry 7). Aniline derivative **4h** was unreactive even in neat TFA (entry 8). In the case of trifluoroacetamide **4i** (entry 9) and sulfonamide **4j** (entry 10), considerable amounts of products **8i** and **8j**, respectively, resulting from unselective proton attack at the less-substituted carbon of cyclopropane were formed. In these substrates, protonation of the carboxamide/sulfonamide function is minimized, which could prevent it from acting as a directing group for intermolecular proton delivery.

A range of substituted *N*-ethoxycarbonyl aminomethyl cyclopropanes **4a** and **9a−i** were investigated as substrates for the synthesis of pyrrolidines **5a** and **10a−i** (Table 3). Differences in reactivity were observed for diastereomeric amides *cis*- and *trans*-**9a** bearing a phenyl group. Surprisingly, while *trans*-**9a** smoothly gave the product **10a**, the conversion of *cis*-**9a** required neat TFA as a reaction medium. The formation of spirocyclic pyrrolidine **10b** from cyclopropane derivative **9b** was achieved efficiently with diluted TFA.

**Table 3. Substrate Scope for the Synthesis of Pyrrolidines**[a]




| entry | substrate | product, method (yield %) |
|---|---|---|
| 1 | **4a** | **5a**, A (92) |
| 2 | *cis*-**9a**<br>*trans*-**9a** | **10a**, B (92 from *cis*-**9a**)<br>A (99 from *trans*-**9a**) |
| 3 | **9b** | **10b**, A (97) |
| 4 | **9c** | **10c**, C (77) |
| 5 | *cis*-**9d**<br>*trans*-**9d** | **10d**, B (95 from *cis*-**9d**)<br>A (92 from *trans*-**9d**) |
| 6 | **9e** | **10e**, A (97) |
| 7 | **9f** | **10f** (17) **10f'** (79)<br>A (total 96)[b] |
| 8 | **9g** | **10g**, A (97) |
| 9 | **9h** | **10h**, B (0)[c] |
| 10 | *cis*-**9i**<br>*trans*-**9i** | **10i**, B (0)[c] |

[a]Reactions were performed on a 0.07−0.8 mmol scale, $c$ = 0.1 M. Isolated yields are given. [b]**10f**/**10f'** = 1:4, as determined by GC−MS. [c]No reaction at rt in neat TFA; mixture of products at higher temperature.

However, to achieve the ring cleavage in oxygen analogue **9c**, harsher reaction conditions were required, leading to pyrrolidine **10c** in good yield.

2,2,3-Trisubstituted pyrrolidine **10d** was prepared from both diastereomers *cis*- and *trans*-**9d**. Again a notable difference in reactivity was observed for the isomers: harsher conditions were required to achieve the cleavage of substrate



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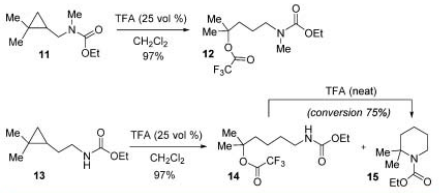
*cis*-**9d**. 2,2,3,3-Tetrasubstituted pyrrolidine **10e** was formed in high yield from the corresponding substrate **9e**.

The cleavage of the similar substrate **9f** bearing two nonequal quaternary centers provided a mixture of isomeric pyrrolidines **10f** and **10f′** with a preference for product **10f′** formation. 2,2,3,4-Tetrasubstituted pyrrolidine **10g** was obtained as a single *cis* diastereomer starting from stereodefined substrate **9g** (vide infra). Diphenyl- and hexyl-substituted cyclopropanes **9h** and **9i** failed to give the expected products **10h** and **10i**. The low reactivity of substrate **9h** implies that the stability of the intermediate carbenium ion is not the only factor that enables the protonolysis of the cyclopropane C−C bond, as in this case a very stable diphenyl carbenium ion should form. Apparently the electron density in the scissile C−C bond may also play an important role.

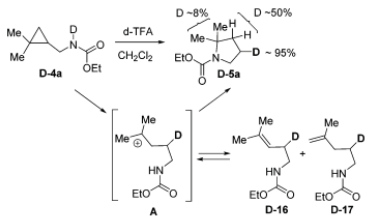
*N*-Methyl substrate **11** was also subjected to the protonolytic cleavage conditions using diluted TFA (Scheme 1). The reaction efficiently provided the corresponding trifluoroacetate **12**, indicating that N substitution does not prevent the regioselective proton attack on the cyclopropane.

**Scheme 1. Protonolytic Cleavage of Cyclopropane 11 Bearing N-Substituted Carbamate and Homologous Substrate 13**



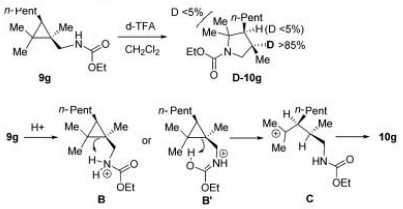

Substrate **13** with the two-carbon chain between the cyclopropane and carbamate could also be regioselectively cleaved. However, in this case a mixture of trifluoroacetatate **14** and piperidine **15** was formed. Trifluoracetate **14** could be transformed to piperidine **15** with good conversion using neat TFA as the reaction medium. To gain insight into the mechanistic details for the protonolytic cleavage of cyclopropanes **4**, deuterium-labeled substrate **D-4a** was subjected to deuterated TFA (Scheme 2). The analysis of the reaction product **D-5a** revealed almost complete deuterium incorporation at the 3-CH position of pyrrolidine, as expected for the proton attack at C(b) of cyclopropane (Figure 2). Deuterium

**Scheme 2. Mechanism of Cyclopropane D-4a Protonolysis Based on Deuterium Incorporation into the Product D-5a**




incorporation was also observed in the methyl groups and at the 2-$CH_2$ position of product **D-5a**. This indicates that a certain portion of intermediate carbenium ion **A** undergoes equilibration with alkenes **D-16** and **D-17** via deprotonation/protonation. In contrast, when substrate **9g** was subjected to deuterated TFA, a relatively small amount of deuterium incorporation was observed in the methyl groups and at the 2-CH position of product **D-10g** (Scheme 3). This confirms

**Scheme 3. Deuterium Incorporation into the Product D-10g and Stereochemistry of Proton Transfer in Cyclopropane 9g[a]**

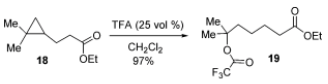



[a]See the Supporting Information for the X-ray structure determination of **9g** and NOESY structure determination of **10g**.

the high degree of stereointegrity at the chiral center of carbenium ion **C**, which allows the determination of the stereoselectivity of C−C bond protonolyis. The *cis* configuration of the starting material **9g** and the *cis* configuration of the product **10g** are consistent with the "edge" trajectory of the proton transfer from protonated amide **B** or imine tautomer **B′**.[17]

The protonolytic cleavage of ester **18** was also performed in order to investigate the role of nitrogen in amides **4** and **9** for the selective proton delivery (Scheme 4). Selective formation

**Scheme 4. Regioselective Protonolytic Cleavage of Ester 18**




of trifluoroacetate **19** was observed. This result together with the unselective cleavage of substrates **4i** and **4j** and the low reactivity of substrate **4h** indicates that oxygen rather than nitrogen in the amide function is involved in the intramolecular proton transfer to cyclopropane (tautomer **B′** in Scheme 3).

In summary, we have shown that the regioselective protonolytic C−C bond cleavage of acylated aminomethyl cyclopropanes can be achieved. The intermediate tertiary carbenium ion undergoes intramolecular amination to give 2,2-substituted pyrrolidines. The strength of the acid and the amine substituent are important factors to achieve high regioselectivity, suggesting intramolecular proton transfer from the protonated amide function. Preliminary mechanistic studies revealed that cyclopropane cleavage proceeds with retention of configuration at the carbon to which the proton is attached. This observation is consistent with the "edge" protonation trajectory of the C−C bond.



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## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00584.

Detailed experimental procedures and characterization data for new compounds (PDF)

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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(16) An exception to the modified Markownikoff's rule is the protonolysis of tricyclo[3.2.1.$0^{2,4}$]octane[4i] and tricyclo [3.2.2.$0^{2,4}$] nonane[4f] systems, in which the proton addition preferentially takes place at the most-substituted carbon of the cyclopropane.

(17) "Edge"[4i] and "corner"[4d,f,i] protonated cyclopropane transition states have been postulated to explain the retention or inversion of stereochemistry of the carbon attacked by the proton. Other hypotheses propose an "edge" trajectory of the protonation as the transition to the corner-protonated intermediate.[4c,f,g]




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# Intramolecular cyclopropylmethylation *via* non-classical carbocations†

M. Skvorcova and A. Jirgensons *

**Cyclopropyl–cyclopropyl rearrangement can be achieved selectively by intramolecular trapping of cyclopropylmethyl carbenium ions with an internal nucleophile. This can be exploited as a useful method for the introduction of a cyclopropyl group into complex molecules using readily accessible disubstituted cyclopropane intermediates.**

Cyclopropylmethyl (CPM) carbenium ion **A** can be represented as a set of resonance hybrids **B1–3** reflecting the contribution of CPM, cyclobutyl and homoallyl carbenium ions (Fig. 1).[1–8] Consequently, the selective nucleophilic attack at the non-classical ion[9,10] is a useful approach for the synthesis of cyclopropane,[1,11–13] cyclobutane[13,14–19] or homoallylic[11,12,20–28] derivatives. However, there are limited examples for the cyclopropane based product formation resulting from the rearrangement of CPM ion **A** to ion **C**. Such a cyclopropyl–cyclopropyl rearrangement has been observed in the mechanistic investigations using isotope labelled substrates.[29–31] The intermolecular reaction products of rearranged CPM ion **C** have also been isolated, typically as a mixture with other products of CPM ion reaction.[31,32] In addition, cyclopropyl–cyclopropyl rearrangement involving a CPM ion has been proposed for the biosynthesis of cyclopropane containing sterols.[2,33–35] Nevertheless, according to our literature survey, this rearrangement has not been used for the selective introduction of a cyclopropyl group into complex molecules. We explored the feasibility of this reaction type *via* generation of CPM ions from substrate **1** containing an internal nucleophile which could be assembled from readily available building blocks (Scheme 1; for the synthesis of substrates **1** see the ESI†). It was expected that, in the intramolecular version, the 5- or 6-membered ring formation would constrain the nucleophile (Y) addition to CPM ion **C** leading to products **2** (Scheme 1). This approach would constitute an alternative to commonly used cyclopropanation reactions[36–39] which often involve expensive reagents and can be incompatible with functional groups in the substrate. There is a strong motivation to develop new methods of cyclopropyl group installation as it plays an important role in drug discovery.[40] In addition, cyclopropane can serve as a precursor of an isopropyl group *via* C–C bond hydrogenolysis.[9]

Trichloroacetimidate (OTIm) in substrates **1** was found to be an appropriate leaving group for the generation of CPM ions when activated with acid catalysts.[41–46] A range of acids and solvents were tested using model substrate **1a** (see the ESI† for details). These studies revealed $B(C_6F_5)_3$ as the optimal catalyst and $CH_3NO_2$ as the reaction media at room temperature to achieve the best yield of product **1a** (Table 1).

Trichloroacetimidate can serve not only as a leaving group but also as an *N*-nucleophile. This group was used to achieve amination of CPM ions derived from bis-imidate **1b** providing oxazoline **2b**. The structure of product **2b** was proved by X-ray (see the ESI†). The phenyl group can also be used as an internal nucleophile for cyclopropylmethylation as demonstrated by the transformation of *O*-benzyl derivative **1c** to isochromane **2c** in medium yield. The introduction of a methoxy group to the aromatic system in substrate **1d** was beneficial to

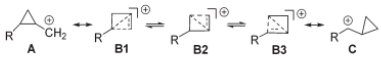
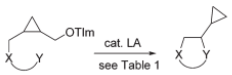



Fig. 1 Cyclopropyl–cyclopropyl rearrangement *via* non-classical CPM carbenium ions.




1, Y = nucleophilic group
TIm = C(=NH)CCl3

2

Scheme 1 Intramolecular cyclopropylmethylation *via* activation of trichloroacetimidate **1**.

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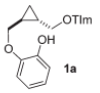
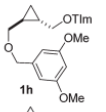
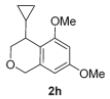
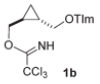
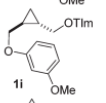
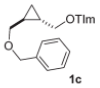
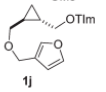
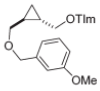
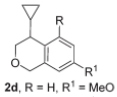
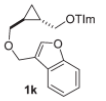
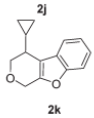
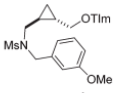
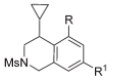
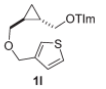
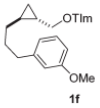
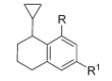
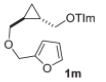
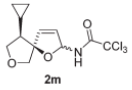
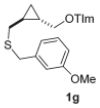
† Electronic supplementary information (ESI) available. CCDC 1562038. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ob01721a

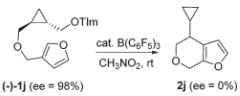
**Table 1** Substrate scope of intramolecular cyclopropylmethylation[a]

| Entry | Substrate **1** | Product **2** | Yield of **2**, % | Entry | Substrate **1** | Product **2** | Yield of **2**, % |
|---|---|---|---|---|---|---|---|
| 1 |  **1a** |  **2a** | 80 | 8 |  **1h** |  **2h** | 92 |
| 2 |  **1b** |  **2b** | 85[b] | 9 |  **1i** | Mixture of products | — |
| 3 |  **1c** |  **2c** | 32 | 10 |  **1j** |  **2j** | 76 |
| 4 |  **1d** |  **2d**, R = H, $R^1$ = MeO **2d′**, R = MeO, $R^1$ = H | 71 (**2d**) 17 (**2d′**) | 11 |  **1k** |  **2k** | 91 |
| 5 |  **1e** |  **2e**, R = H, $R^1$ = MeO **2e′**, R = MeO, $R^1$ = H | 61 (**2e**) 21 (**2e′**) | 12 |  **1l** |  **2l** | 98 |
| 6 |  **1f** |  **2f**, R = H, $R^1$ = MeO **2f′**, R = MeO, $R^1$ = H | 34 (**2f**) 22 (**2f′**) | 13 |  **1m** |  **2m** | 85 |
| 7 |  **1g** | No reaction | — | | | | |

[a] Reaction conditions: 10 mol% $B(C_6F_5)_3$, $CH_3NO_2$, r.t., 0.5 h. [b] Reaction conditions: 10 mol% $BF_3$ $OEt_2$, $CH_2Cl_2$, r.t., 2.5 h.

improve the yield of cyclopropylmethylation products which formed as a mixture of two isomers **2d** and **2d′**. Substrates **1e,f** with nitrogen and carbon atoms in the linker part provided the corresponding tetrahydroisoquinoline and tetralin derivatives **2e/e′** and **2f/f′**. Surprisingly, the sulphide analogue **1g** was unreactive – no conversion was achieved even with a stoichiometric amount of Lewis acid. The *O*-benzyl group with two methoxy substituents in substrate **1h** acted as an efficient nucleophile to give the expected product **2h** in high yield. However, substrate **1i** with the cyclopropylmethyl group linked to the phenolic oxygen provided mixture of products instead of the expected dihydrobenzofuran. Cyclopropyl-methylation of furan and thiophene in substrates **1j–l** proceeded efficiently leading to the fused dihydropyrane derivatives **2j–l**. Substrate **1m** with the linker attached to the 2nd position of furan gave the spirocyclic derivative **2m**. Interestingly, only two diastereomers of compound **2m** formed with different configurations at the carbon bearing an acetamido group. The other two stereocenters at the tetrahydrofuran ring of spirocycle **2m** have formed with high stereoselectivity – according to NOESY spectra only the isomer with the oxy group *cis*- to the cyclopropyl group could be detected.

Cyclopropyl–cyclopropyl rearrangement is expected to proceed *via* configurationally labile carbenium ion formation which should destroy the defined stereochemistry at the reaction centre. This was in agreement with the experimental results using enantioenriched substrate (−)-**1j** which led to the racemic product **2j** (Scheme 2).




Scheme 2 Investigation of chirality transfer from enantioenriched substrate (–)-**1j**.

## Conclusions

In summary we have demonstrated that cyclopropyl–cyclopropyl rearrangement can be achieved selectively by intramolecular trapping of CPM ions with an internal nucleophile. This can be exploited as a useful method for the introduction of a cyclopropyl group into complex molecules using readily accessible disubstituted cyclopropane intermediates.

## Acknowledgements

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DOI 10.1007/s10593-017-2162-1

*Chemistry of Heterocyclic Compounds* **2017**, *53*(9), 989–996

*Dedicated on the occasion of Prof. Ivars Kalvinsh 70th anniversary*

# 1-Amino-1-hydroxymethylcyclobutane derivatives *via* intramolecular amination of nonclassical cyclopropylmethyl cation

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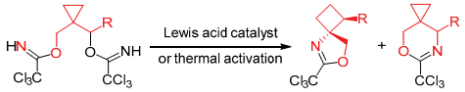


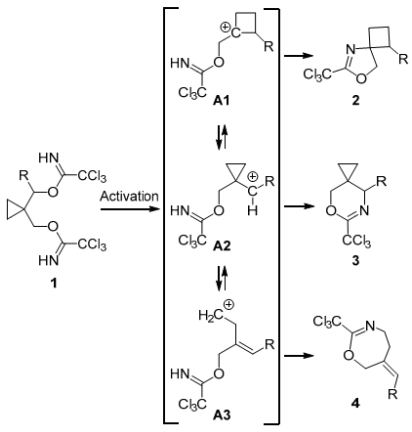

R = H, Ph, *n*-Pr, *i*-Pr, $CH_2OMe$, $CH_2OBn$

Bis(trichloroacetimidoyloxymethyl)cyclopropanes provide intramolecular amination products of intermediate cyclobutyl or cyclopropylmethyl carbenium ion when exposed to Lewis acid catalyst or thermal ionization. The ratio of the two amination products of cyclobutyl carbenium ion depends primarily on the substituent at the alkoxymethyl group of the substrate and can be altered by the solvent used and the ionization conditions. An oxazoline derivative forms as the major amination product in the case of unsubstituted bis(trichloroacetimidoyloxymethyl)cyclopropane or if the substrate contains isopropyl or alkoxymethyl substituents. The amination of cyclobutyl carbenium ion formed *in situ* proceeds with high diastereoselectivity leading to exclusive formation of *trans*-cyclobutane derivatives. The latter can be transformed to *N*-Boc-protected cyclobutane-based amino alcohols in high yields.

**Keywords**: amino alcohol, carbenium ion, cyclobutane, 5-oxa-7-azaspiro[2.5]oct-6-ene, 5-oxa-7-azaspiro[3.4]oct-5-ene, 1,3-oxazine, oxazoline, trichloroacetimidate, Lewis acid.

Cyclopropylmethyl cation, due to its nonclassical nature, can be attacked at three possible sites leading to homoallyl,[1–11] cyclopropylmethyl,[1,8,12,13] or cyclobutyl[13–20] derivatives. As a part of our ongoing interest to develop the amination reactions of carbenium ions,[21–24] we have investigated amination of the cyclopropylmethyl cation[25] depending on the cyclopropane substitution pattern in bis-(trichloroacetimidate) system **1**. Based on our previous research it could be predicted that in substrate **1**, the imidate function at the most substituted carbon will act as a leaving group when activated with Lewis acid.[21,23,26] This would generate carbenium ion which is trapped with other imidate moiety as N-nucleophile (Scheme 1). Depending on the regioselectivity of the intramolecular imidate attack on the carbenium ion the following products could be expected: [3.4]-spirocyclic oxazoline **2** if cyclobutyl carbenium ion **A1** is aminated; [2.5]-spirocyclic dihydrooxazine **3** if cyclopropylmethyl carbenium ion **A2** is aminated; tetrahydrooxazepine derivative **4** if homoallylic ion **A3** is aminated. Oxazoline derivatives **2** are precursors of cyclobutane-based β-amino alcohols and α-amino acids with potential utility in medicinal chemistry.[27] This prompted us to investigate if this type of products can be prepared from readily available bis(imidates) **1**.

**Scheme 1**

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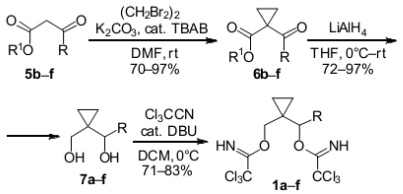
Diol **7a** for the synthesis of bis(imidate) **1a** is commercially available. The synthesis of other diols **7b**–**f** was started from β-ketoesters **5b**–**f** which were alkylated with dibromoethane to give esters of 1-acylcyclopropane carboxylic acids **6b**–**f** (Scheme 2). The latter were reduced to diols **7b**–**f** and all the diols **7a**–**f** were transformed to bis(imidates) **1a**–**f** in DBU-catalyzed reaction.

**Scheme 2**

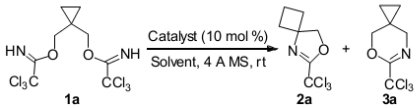



**1, 7 a** R = H;
**1, 5–7 b** R = Ph, $R^1$ = Et; **c** R = *n*-Pr, $R^1$ = Et; **d** R = *i*-Pr, $R^1$ = Me; **e** R = $CH_2OMe$, $R^1$ = Me; **f** R = $CH_2OBn$, $R^1$ = Et

Bis(trichloroacetimidate) **1a** derived from 1,1-bis(hydroxymethyl)cyclopropane (**7a**) was subjected to a range of acid catalysts to induce the carbenium ion formation (Table 1). Under these conditions, the formation of two main amination products – spirocyclic oxazoline **2a** and dihydrooxazine **3a**, was observed by NMR spectroscopy while tetrahydrooxazepine derivative **4** was no detected.

The ratio of oxazoline **2a** and dihydrooxazine **3a** varied depending on the acid catalyst and the solvent used. Brønsted acid catalyst (TsOH) provided products **2a** and **3a** in equal ratio (Table 1, entry 1). Out of the two monocoordinating Lewis acid catalysts investigated (entries 2, 3), $BF_3 \cdot Et_2O$ induced considerably improved amination product ratio in favor to compound **2a**. The efficiency of multicoordinating Lewis acids $FeCl_3$ and $AlCl_3$ was investigated in several solvents. Acetonitrile inhibited the reaction leading to incomplete conversion of starting material **1a** (entries 4, 7). In the case of $FeCl_3$ as a Lewis acid, DCM was superior to $Et_2O$ for more selective oxazoline **2a** formation (entries 5, 6) while in the case of $AlCl_3$ oxazoline **2a** formed exclusively in both solvents (entries 8, 9). From the experiment using $AlCl_3$ as catalyst in $Et_2O$, product **2a** was isolated in 75% yield.

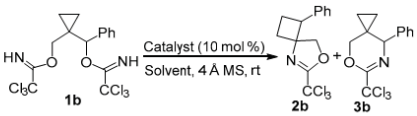
**Table 1**. Bis(imidate) **1a** rearrangement product **2a** *vs* oxazine **3a** formation depending on acid catalyst and solvent




| Entry | Catalyst | Solvent | Time, h | Conversion, %* | Ratio **2a**:**3a**** |
|---|---|---|---|---|---|
| 1 | *p*-TsOH | DCM | 24 | >99 | 1:1 |
| 2 | TMSOTf | DCM | 1.5 | >99 | 1.7:1 |
| 3 | $BF_3 \cdot OEt_2$ | DCM | 24 | >99 | 6.6:1 |
| 4 | $FeCl_3$ | MeCN | 24 | ~50 | 43:1 |
| 5 | $FeCl_3$ | $Et_2O$ | 24 | >99 | 3:1 |
| 6 | $FeCl_3$ | DCM | 24 | >99 | 5.6:1 |
| 7 | $AlCl_3$ | MeCN | 24 | 50 | 26:1 |
| 8 | $AlCl_3$ | $Et_2O$ | 24 | >99 (75**) | >99:1 |
| 9 | $AlCl_3$ | DCM | 0.1 | >99 | >99:1 |

* TLC and GC-MS data.
** Isolated yield of compound **2a**.
*** GC-MS data.

**Table 2**. Bis(imidate) **1b** rearrangement product **2b** *vs* oxazine **3b** formation depending on Lewis acid and solvent used



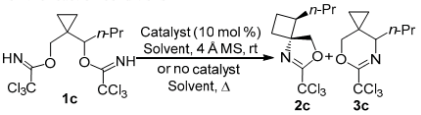

| Entry | Catalyst | Solvent | Ratio **2b**:**3b*** |
|---|---|---|---|
| 1 | $BF_3 \cdot OEt_2$ | DCM | 1:8.4 (85%**) |
| 2 | $AlCl_3$ | DCM | 1:>99 |
| 3 | $AlCl_3$ | PhMe | 1:>99 |

* GC-MS data.
** Yield of oxazine **3b**.

Next, bis(imidate) **1b** bearing phenyl substituent was subjected to the action of $BF_3 \cdot Et_2O$ and $AlCl_3$ as Lewis acid catalysts (Table 2). For this substrate, both catalysts induced preferential formation of dihydrooxazine **3b** as a product of cyclopropylmethyl carbenium ion **A2** amination. Such regioselectivity could be explained by stabilizing effect of the phenyl substituent on the carbenium ion that induced electron distribution in the favor to cyclopropylmethyl carbenium ion **A2** (Scheme 1).

When bis(imidate) **1c** bearing *n*-propyl substituent was treated with the catalysts, such as TMSOTf, $Cu(OTf)_2 \cdot C_6H_6$, the desired oxazoline **2c** formed as the minor product (Table 3, entries 1, 2). Surprisingly, in the case of $AlCl_3$ the ratio of products **2c** and **3c** was found to be highly favorable to oxazoline **2c** (entry 3). However, the isolated yield of product **2c** was low (37%) which prompted us to investigate the reaction more carefully. When the reaction was performed at lower temperature (–50°C, 2 h) in the presence of $AlCl_3$, the ratio of products **2c** and **3c** was 1:1 and NMR yield of oxazoline **2c** was 45% (using 1,4-bis(trichloromethyl)benzene as an internal standard). Increasing the temperature (rt, 3 h) led to selective formation of oxazoline **2c** (product ratio **2c**/**3c** >99:1) with the same NMR yield – 45%. This implies that dihydrooxazine **3c** slowly decomposes under the reaction conditions resulting in the increased content of oxazoline **2c**. The performance of several Lewis acid catalysts was also investigated in diethyl ether as a solvent. In the case of TMSOTf, almost exclusive formation of dihydrooxazine **3c** was observed (entry 4), while nonselective reaction took place in the case of $FeCl_3$ and $BF_3 \cdot Et_2O$ (entries 5, 6).

**Table 3**. Bis(imidate) **1c** rearrangement product **2c** *vs* oxazine **3c** formation depending on the reaction conditions




| Entry | Catalyst | Solvent | Time | Ratio **2c**:**3c*** |
|---|---|---|---|---|
| 1 | TMSOTf | DCM | 10 min | 1:3.8 |
| 2 | $Cu(OTf)_2 \cdot C_6H_6$ | DCM | 10 min | 1:5.7 |
| 3 | $AlCl_3$ | DCM | 1.5 h | 40:1** (37%***) |
| 4 | TMSOTf | $Et_2O$ | 1.5 h | 1:>99 |
| 5 | $FeCl_3$ | $Et_2O$ | 5.5 h | 1.4:1 |
| 6 | $BF_3 \cdot OEt_2$ | $Et_2O$ | 3 min | 1.4:1 |
| 7 | –*[4] | $Et_2O$ | 3 days | 1.7:1 (59%*[5]) |
| 8 | –*[4] | THF | 20 h | 1:2 (26%*[5]) |
| 9 | –*[4] | PhMe | 30 min | 2:1 (64%*[5]) |

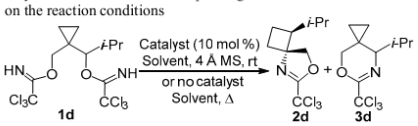
* GC-MS data.
** Dihydrooxazine **3c** decomposes during the reaction.
*** Isolated yield of oxazoline **2c**.
*[4] Refluxing.
*[5] NMR yield determined using 1,4-bis(trichloromethyl)benzene as an internal standard.

Bis(imidate) **1c** was also subjected to thermal ionization conditions by refluxing in the selected solvents (entries 7–9). The reactions in $Et_2O$ and THF required long reaction time to achieve full conversion of starting material **1c**, while the reaction proceeded in acceptable time in toluene. Thermal reaction conditions induced the formation of both oxazoline **2c** and dihydrooxazine **3c** with little preference for the rearrangement product **2c** in $Et_2O$ and toluene as the solvents. The NMR yields of oxazoline **2c** were determined in crude reaction mixtures which were in accordance with the ratio of compounds **2c** and **3c**.

Bis(imidate) **1d** bearing bulky isopropyl substituent gave the mixture of products **2d** and **3d** with preference for oxazoline **2d** formation in Lewis acid-catalyzed (TMSOTf, $BF_3 \cdot Et_2O$, $AlCl_3$) reaction (Table 4). The NMR yields of product **2d** were determined in the crude reaction mixture. These were similar for all the reaction conditions investigated, however the ratio of products **2d** and **3d** was different. This indicates the difference in stability of dihydrooxazine **3d** depending on Lewis acid, as it was observed in the case of analog **3c**. Using $BF_3 \cdot Et_2O$ as a catalyst, the best ratio of products **2d** and **3d** was obtained and in this case, the product **2d** was isolated in the yield which matched the NMR yield (entry 2). Thermal bis-(imidate) **1d** cyclization in two solvents was also performed (entries 7, 8). The reaction in toluene provided products **2d** and **3d** with high preference for the desired oxazoline **2d** which was isolated in high yield.

Oxymethyl group-containing imidates **1e**,**f** were subjected to both Lewis acid-catalyzed ($BF_3 \cdot Et_2O$) (Table 5, entries 1 and 3) and thermally induced (toluene at reflux)

**Table 4**. Bis(imidate) **1d** rearrangement product **2d** *vs* dihydroxazine **3d** formation depending on the reaction conditions

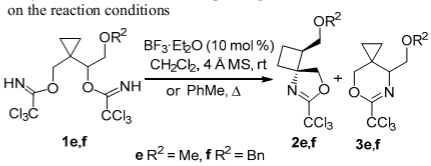



| Entry | Catalyst | Solvent | Time | Ratio **2d**:**3d*** | NMR yield of compound **2d****, % |
|---|---|---|---|---|---|
| 1 | TMSOTf | PhMe | 3 min | 2.9:1 | 66 |
| 2 | $BF_3 \cdot OEt_2$ | PhMe | 3 min | 9.1:1 | 67 (70***) |
| 3 | $AlCl_3$ | PhMe | 3 min | 4.6:1 | 70 |
| 4 | TMSOTf | DCM | 3 min | 1.9:1 | 67 |
| 5 | $BF_3 \cdot Et_2O$ | DCM | 4 min | 2.3:1 | 73 |
| 6 | $AlCl_3$ | DCM | 2 min | 3.0:1 | 76 |
| 7 | –*[4] | PhMe | 3 h | 7:1 | 89 (88***) |
| 8 | –*[4] | Dioxane | 3.5 h | 2:1 | 60 |

* GC-MS data.
** Determined using 1,4-bis(trichloromethyl)benzene as an internal standard.
*** Isolated yield of compound **2d**.
*[4] Refluxing.

cyclization (entries 2 and 4). Comparing both the ratio of cyclization products **2e**,**f** and **3e**,**f** and the NMR yields, it was observed that thermally induced reaction leads to higher yields of oxazolines **2e**,**f**. This was confirmed by high isolated yields of these compounds. It is an interesting to note that oxymethyl group-containing bis(imidates) **1e**,**f** give higher yield of oxazolines **2e**,**f** compared to propyl-substituted bis(imidate) **2c**. This could be explained by destabilizing (–I) effect of oxygen on carbenium ion which shifts the electron density in favor to cyclobutyl carbenium ion **A1**.

**Table 5**. Bis(imidate) **1e**,**f** rearrangement product **2e**,**f** *vs* dihydroxazine **3e**,**f** formation depending on the reaction conditions




| Entry | $R^2$ | Reaction conditions | Ratio **2e(f)**:**3e(f)*** | Yield, %** |
|---|---|---|---|---|
| 1 | Me | $BF_3 \cdot OEt_2$, rt | 3.9:1 | 55 |
| 2 | Me | PhMe, 115°C | 9:1 | 68 (80***) |
| 3 | Bn | $BF_3 \cdot OEt_2$, rt | 3.2:1 | 49 |
| 4 | Bn | PhMe, 115°C | 7.1:1 | 70 (85***) |

* GC-MS data.
** Summary yield of compounds **2** and **3** determined by NMR spectroscopy, using 1,4-bis(trichloromethyl)benzene as an internal standard.
*** Isolated yield of mixture of products **2e**,**f** and **3e**,**f**.

**Scheme 3**. Stereoinduction model for the formation of oxazolines **2c–f** as *trans*-isomers

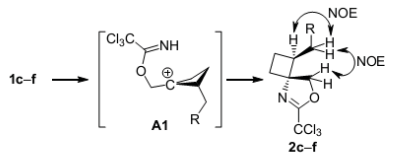
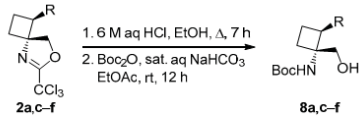



**Table 6**. Hydrolysis of oxazolines **2a**,**c–f** to 1-aminocyclobutylcarbinols **8a**,**c–f**




| Entry | Product | R | Yield, % |
|---|---|---|---|
| 1 | **8a*** | H | 59 |
| 2 | **8c** | *n*-Pr | 89 |
| 3 | **8d** | *i*-Pr | 70 |
| 4 | **8e** | $CH_2OMe$ | 73 |
| 5 | **8f** | $CH_2OBn$ | 69 |

* Commercially available.

It is noteworthy that bis(imidates) **1c–f** provided oxazolines **2c–f** as a single diastereomers with *trans* configuration. The configuration of these products was confirmed by 2D NMR NOESY experiments (see Scheme 3 for diagnostic interactions). Such a stereochemical outcome could be explained by stereoinduction model where the amination takes place from the sterically less hindered face of close-to-planar cyclobutyl carbenium ion **A1**.

In order to demonstrate the utility of oxazolines, these were transformed to Boc-protected cyclobutane-based amino alcohols **8a**,**c–f** in moderate to good yields (Table 6). For this purpose, oxazolines **2a**,**c–f** were hydrolyzed in acidic conditions and the resulting amino alcohols were treated with $Boc_2O$ in weakly basic conditions.

Bis(trichloroacetimidoyloxymethyl)cyclopropanes provide an intramolecular amination products of intermediate cyclobutyl carbenium ion or cyclopropylmethyl carbenium ion when exposed to acid catalysis or thermal ionization. The ratio of the two amination products depends primarily on the substituent at the oxymethyl group of the substrate and can be altered by the solvent and the ionization conditions. Amination product of cyclobutyl carbenium ion – oxazoline, forms as a major product in the case of unsubstituted bis(trichloroacetimidoyloxymethyl)cyclopropane or if the substrate contains isopropyl or oxymethyl substituent. The amination of *in situ* formed cyclobutyl carbenium ion proceeds with high diastereoselectivity leading to exclusive formation of *trans*-cyclobutane-containing oxazolines. These can be transformed to *N*-Boc-protected cyclobutane-based amino alcohols in high yields.

## Experimental

$^1H$ and $^{13}C$ NMR spectra were recorded on a Varian Mercury spectrometer (400 and 100 MHz, respectively) using the residual chloroform signal as internal standard. LC/ESI-MS were performed on a Waters 2695 Alliance instrument, column: Phenomenex, Gemini 5u C18 11OA, 50 × 2 mm, 5 μm; mobile phase: acetonitrile – 0.1% aq HCOOH. Flash chromatography was carried out using Merck Kieselgel (230–400 mesh). Elemental analyses were performed using a Carlo-Erba EA1108 Elemental Analyzer. Thin-layer chromatography was performed on silica gel and was visualized by staining with $KMnO_4$. All reactions were carried out under argon atmosphere. Solvents were purified and dried by standard procedures prior to use; petroleum ether of boiling range 60–80°C was used. Reagents and starting materials were obtained from commercial sources and used as received.

**Ethyl 1-benzoylcyclopropanecarboxylate (6b)**.[28] $K_2CO_3$ (6.910 g, 50.0 mmol) followed by 1,2-dibromoethane (2.25 ml, 26.0 mmol) and TBAB (0.032 g, 0.1 mmol) were added to a solution of β-oxoester **5b** (3.844 g, 20.0 mmol) in DMF (12 ml). The mixture was stirred at room temperature for 20 h till the full consumption of starting material (TLC control: eluent petroleum ether – EtOAc, 10:1). To the reaction mixture, EtOAc (25 ml) and $H_2O$ (35 ml) were added and the organic phase was separated. The aqeuous phase was washed with EtOAc (3 × 25 ml) and the combined organic phases were washed with saturated aqeuous NaCl (2×30 ml). Combined organic phase was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Yield 4.250 g (97%). Colorless oil. Compound **6b** was used for the next step without additional purification. $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 0.95 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 1.51–1.55 (2H, m, $CH_2C\underline{H}_2$); 1.59–1.62 (2H, m, $C\underline{H}_2CH_2$); 4.04 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 7.42–7.46 (2H, m, H Ph); 7.53–7.56 (1H, m, H Ph); 7.89–7.91 (2H, m, H Ph).

**Ethyl 1-butyrylcyclopropanecarboxylate (6c)** was prepared analogously to compound **6b** from β-oxoester **5c** (3.704 g, 20.0 mmol), $K_2CO_3$ (6.910 g, 50.0 mmol), $(CH_2)_2Br_2$ (2.25 ml, 26.0 mmol), TBAB (0.032 g, 0.1 mmol), DMF (15 ml). Yield 2.865 g (80%). Colorless oil. $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 0.91 (3H, t, *J* = 7.3, $CH_2CH_2C\underline{H}_3$); 1.28 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 1.42 (4H, s, $CH_2CH_2$); 1.58–1.66 (2H, m, $CH_2C\underline{H}_2CH_3$); 2.81 (2H, t, *J* = 7.3, $C\underline{H}_2CH_2CH_3$); 4.20 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$). $^{13}C$ NMR spectrum, δ, ppm: 13.9; 14.3; 17.8; 18.5; 35.0; 44.0; 61.4; 171.3; 205.5. Found, *m*/*z*: 185.1197 $[M+H]^+$. $C_{10}H_{17}O_3$. Calculated, *m*/*z*: 185.1178.

**Methyl 1-isobutyrylcyclopropanecarboxylate (6d)** was prepared analogously to compound **6b** from β-oxoester **5d** (4.040 g, 28.00 mmol), $K_2CO_3$ (9.682 g, 70.00 mmol), $(CH_2)_2Br_2$ (3.15 ml, 36.40 mmol), TBAB (0.045 g, 0.14 mmol), DMF (20 ml). Yield 3.425 g (73%). Yellow oil. $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 1.10–1.12 (6H, m, $CH(C\underline{H}_3)_2$); 1.41–1.44 (4H, m, $CH_2CH_2$); 3.38 (1H, septet, *J* = 6.8, $C\underline{H}(CH_3)_2$); 3.74 (3H, s, $OCH_3$). $^{13}C$ NMR spectrum, δ, ppm: 18.2; 19.2; 33.9; 39.3; 52.5; 171.9;

209.4. Found, *m/z*: 171.1015 $[M+H]^+$. $C_9H_{15}O$. Calculated, *m/z*: 171.1021.

**Methyl 1-(2-methoxyacetyl)cyclopropanecarboxylate (6e)** was prepared in analogy to compound **6b** from β-oxoester **5e** (1.470 g, 10.00 mmol), $K_2CO_3$ (3.470 g, 25.11 mmol), $(CH_2)_2Br_2$ (1.57 ml, 13.00 mmol), TBAB (0.016 g, 0.05 mmol), DMF (15 ml). Yield 1.198 g (75%). Colorless oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.51–1.58 (4H, m, $CH_2CH_2$); 3.41 (3H, s, $CH_2OCH_3$); 3.73 (3H, s, $OCH_3$); 4.50 (2H, s, $CH_2OCH_3$). $^{13}$C NMR spectrum, δ, ppm: 19.6; 32.9; 52.3; 59.3; 77.8; 171.0; 202.7. No ionization in HRMS or GC/MS.

**Ethyl 1-[2-(benzyloxy)acetyl]cyclopropanecarboxylate (6f)** was prepared analogously to compound **6b** from β-oxoester **5f** (1.000 g, 4.23 mmol), $K_2CO_3$ (1.46 g, 10.58 mmol), $(CH_2)_2Br_2$ (0.66 ml, 5.50 mmol), TBAB (0.01 g, 0.02 mmol), DMF (10 ml). Yield 0.776 g (70%). Colorless oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.21 (3H, t, *J* = 7.2, $OCH_2CH_3$); 1.48–1.54 (4H, m, $CH_2CH_2$); 4.14 (2H, q, *J* = 7.2, $OCH_2CH_3$); 4.57 (4H, s, $OCH_2Ph$, $OCH_2C(=O)$); 7.27–7.35 (5H, m, H Ph). $^{13}$C NMR spectrum, δ, ppm: 4.0; 19.3; 33.3; 61.3; 73.5; 75.3; 127.9 (2C); 128.5; 137.5; 170.6; 202.9. Found, *m/z*: 285.1103 $[M+Na]^+$. $C_{15}H_{18}O_4Na$. Calculated, *m/z*: 285.1103.

**[1-(Hydroxymethyl)cyclopropyl](phenyl)methanol (7b)**.[29] A solution of β-oxoester **6b** (1.000 g, 4.58 mmol) in THF (20 ml) was cooled in an ice bath, and $LiAlH_4$ (0.696 g, 18.33 mmol) was added in small portions. The reaction mixture was warmed to room temperature and stirred for ~0.5 h until full consumption of the starting material (TLC control, eluent EtOAc). The reaction mixture was cooled in an ice bath and quenched with saturated aqueous Segnet's salt (20 ml). The mixture was extracted with $Et_2O$ (3×30 ml). The combined organic phase was dried over $Na_2SO_4$ and evaporated under reduced pressure to give product **7b**. Yield 0.794 g (97%). Colorless oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.50–0.56 (1H, m), 0.63–0.69 (2H, m), and 0.70–0.75 (1H, m, $CH_2CH_2$); 2.20 (1H, t, *J* = 4.9, $CH_2OH$); 3.06 (1H, d, *J* = 4.4, CHOH); 3.23 (1H, dd, *J* = 11.4, *J* = 4.4) and 3.76 (1H, dd, *J* = 11.4, *J* = 4.4, $CH_2OH$); 4.50 (1H, d, *J* = 3.8, CHOH); 7.27–7.42 (5H, m, H Ph).

**1-[1-(Hydroxymethyl)cyclopropyl]butan-1-ol (7c)** was prepared analogously to compound **7b** from β-oxoester **6c** (2.86 g, 15.5 mmol), $LiAlH_4$ (1.76 g, 46.5 mmol), THF (40 ml). Yield 2.030 g (92%). Yellowish oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.33–0.39 (2H, m, $CH_2CH_2$); 0.52–0.59 (2H, m, $CH_2CH_2$); 0.90 (3H, t, *J* = 7.2, $CH_2CH_3$); 1.28–1.68 (4H, m, $CH_2CH_2CH_3$); 3.02 (2H, dd, *J* = 11.6, *J* = 5.1, $CH_2OH$ ); 3.33–3.56 (2H, br. s, 2OH); 4.06 (1H, d, *J* = 12.0, CHOH). $^{13}$C NMR spectrum, δ, ppm: 8.1; 10.5; 14.2; 19.6; 26.1; 36.8; 67.7; 78.8. Found, *m/z*: 167.1090 $[M+Na]^+$. $C_{10}H_{17}O_3$. Calculated, *m/z*: 167.1048.

**1-[1-(Hydroxymethyl)cyclopropyl]-2-methylpropan-1-ol (7d)**[30] was prepared analogously to compound **7b** from β-oxoester **6d** (1.300 g, 7.64 mmol), $LiAlH_4$ (1.159 g, 30.55 mmol), THF (20 ml). Yield 0.722 g (72%). Colorless oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.47–0.61 (4H, m, $CH_2CH_2$); 0.94 (3H, d, *J* = 6.9) and 1.06 (3H, d, *J* = 6.4, $CH(CH_3)_2$); 1.60 (1H, br. s, OH); 2.00–2.09 (1H, m, $CH(CH_3)_2$); 2.44 (1H, br. s, OH); 2.50 (1H, d, *J* = 9.6, CHOH); 2.95 (1H, d, *J* =11.4) and 4.26 (1H, d, *J* = 11.4, $CH_2OH$).

**1-[1-(Hydroxymethyl)cyclopropyl]-2-methoxyethanol (7e)** was prepared analogously to compound **7b** from β-oxoester **6e** (1.07 g, 6.21 mmol), $LiAlH_4$ (0.94 g, 2.49 mmol), THF (35 ml). Yield 0.69 g (74%). Colorless oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.45–0.52 (2H, m, $CH_2CH_2$); 0.59–0.66 (2H, m, $CH_2CH_2$); 2.68 (1H, d, *J* = 3.6, OH); 2.84 (1H, dd, *J* = 6.3, *J* = 5.0, OH); 3.25 (1H, dt, *J* = 7.2, *J* = 3.5, $CH_AOCH_3$); 3.37–3.43 (4H, m, $CH_BOCH_3$); 3.53–3.67 (3H, m, $CH_2OH$, $CHCH_2OCH_3$). $^{13}$C NMR spectrum, δ, ppm: 7.7; 10.7; 24.5; 59.2; 67.1; 75.2; 76.6. Found, *m/z*: 169.0875 $[M+Na]^+$. $C_7H_{14}NaO_3$. Calculated, *m/z*: 169.0841.

**2-(Benzyloxy)-1-[1-(hydroxymethyl)cyclopropyl]ethanol (7f)** was prepared analogously to compound **7b** from β-oxoester **6f** (0.430 g, 1.64 mmol), $LiAlH_4$ (0.249 g, 6.56 mmol, 4 equiv), THF (15 ml). Yield 0.340 g (93%). Crystaline white solid. Mp 69–70°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.42–0.49 (2H, m, $CH_2CH_2$); 0.56–0.63 (2H, m, $CH_2CH_2$); 3.06 (2H, s, $CH_2OH$); 3.30 (2H, br. s, 2OH); 3.62–3.70 (3H, m, $OCH_2CHOH$); 4.58 (2H, d, *J* = 2.0, $OCH_2Ph$); 7.27–7.37 (5H, m, H Ph). $^{13}$C NMR spectrum, δ, ppm: 7.7; 10.7; 24.3; 67.3; 72.8; 73.7; 76.7; 127.9; 128.0; 128.6; 137.7. Found, %: C 70.29; H 8.20. $C_{13}H_{18}O_3$. Calculated, %: C 70.24, H 8.16.

**Cyclopropane-1,1-diyldimethanediyl bis(2,2,2-trichloroethanimidoate) (1a)**. Molecular sieves (4 Å) and DBU (25 ml, 0.17 mmol) were added to a solution of diol **7a** (0.086 g, 0.84 mmol) in DCM (5 ml). The resulting mixture was cooled in an ice bath and trichloracetonitrile (0.34 ml, 3.36 mmol) was added. The reaction was stirred while cooling in an ice bath for 4 h until complete consumtion of the starting material (TLC control, eluent EtOAc–hexane, 1:10). The reaction mixture was filtered through a short pad of Celite and the filtrate was evaporated. The residue was purified by flash chromatography on silica gel column (eluent EtOAc – petroleum ether, 1:20) to give product **1a**. Yield 0.270 g (82%). Colorless oil. $^1$H NMR spectrum, δ, ppm: 0.76 (4H, s, $CH_2CH_2$); 4.27 (4H, s, $2CH_2OC(=NH)$); 8.25 (2H, s, 2NH). $^{13}$C NMR spectrum, δ, ppm: 9.2; 19.7; 72.5; 91.6; 163.1. The product is unstable in the HRMS conditions.

**[Phenyl(1-{[(2,2,2-trichloroethanimidoyl)oxy]methyl}-cyclopropyl)methyl 2,2,2-trichloroethanimidoate (1b)** was prepared analogously to compound **1a** from diol **7b** (0.190 g, 1.07 mmol), DBU (32 ml, 0.213 mmol), $CCl_3CN$ (0.33 ml, 3.20 mol), DCM (7 ml). Yield 0.354 g (71%). Yellow oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.67–0.81 (3H, m) and 0.92–0.96 (1H, m, $CH_2CH_2$); 4.02 (1H, d, *J* = 11.6) and 4.34 (1H, d, *J* = 11.6, $CH_2OC(=NH)$); 6.11 (1H, s, CHPh); 7.27–7.42 (5H, m, H Ph); 8.21 (1H, s, NH); 8.27 (1H, s, NH). $^{13}$C NMR spectrum, δ, ppm: 7.6; 8.4; 24.1; 73.2; 80.8; 91.6; 91.8; 126.9; 128.3; 128.4; 137.3; 161.4; 163.0. The product is unstable in the HRMS conditions.

**(1-{1-[(2,2,2-Trichloroethanimidoyl)oxy]butyl}cyclopropyl)methyl 2,2,2-trichloroethanimidoate (1c)** was prepared analogously to compound **1a** from diol **7c** (1.72 g,

11.91 mmol), DBU (0.36 ml, 2.38 mmol), $CCl_3CN$ (4.81 ml, 47.64 mmol), DCM (35 ml). Yield 4.20 g (82%). Yellowish oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.62–0.67 (1H, m), 0.71–0.76 (1H, m), and 0.77–0.82 (1H, m, $CH_2CH_2$); 0.88–0.95 (4H, m, $CH_2CH_3$, $CH_2CH_2$); 1.40–1.52 (2H, m, $CH_2CH_2CH_3$); 1.80–1.98 (2H, m, $CH_2CHOC(=NH)$); 3.96 (1H, d, *J* = 12.0) and 4.65 (1H, d, *J* = 12.0, $CH_2OC(=NH)$); 4.74 (1H, dd, *J* = 8.5, *J* = 5.0, $CH_2CHOC(=NH)$); 8.24 (2H, s, 2NH). $^{13}$C NMR spectrum, δ, ppm: 8.7; 10.7 14.1; 19.3; 22.9; 35.1; 72.9; 83.3; 91.6; 92.1; 162.9; 163.1. The product is unstable under the HRMS conditions.

**2-Methyl-1-(1-{[(2,2,2-trichloroethanimidoyl)oxy]methyl}cyclopropyl)propyl 2,2,2-trichloroethanimidoate (1d)** was prepared analogously to compound **1a** from diol **7d** (2.04 g, 14.1 mmol), DBU (2.10 ml, 14.1 mmol), $CCl_3CN$ (2.84 ml, 28.3 mmol), DCM (30 ml). Yield 4.34 g (71%). Colorless oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.52–0.57 (1H, m), 0.76–0.82 (1H, m), 0.83–0.88 (1H, m), and 0.90–0.97 (1H, m, $CH_2CH_2$); 0.99 (3H, d, *J* = 7.2, $CHCH_3$); 1.10 (3H, d, *J* = 7.2, $CHCH_3$); 2.24–2.39 (1H, m, $CH(CH_3)_2$); 3.84 (1H, d, *J* = 12.1, $CH_AOC(=NH)$); 4.47 (1H, d, *J* = 9.8, $CHOC(=NH)$); 4.71 (1H, dd, *J* = 12.1, *J* = 1.2, $CH_BOC(=NH)$); 8.23 (2H, s, 2NH). $^{13}$C NMR spectrum, δ, ppm: 9.8; 9.9; 19.6; 20.0; 21.8; 32.3; 73.1; 88.7; 91.6; 92.2; 163.1; 163.3. The product is unstable under the HRMS conditions.

**(1-{2-Methoxy-1-[(2,2,2-trichloroethanimidoyl)oxy]-ethyl}cyclopropyl)methyl 2,2,2-trichloroethanimidoate (1e)** was prepared analogously to compound **1a** from diol **7e** (0.400 g, 2.74 mmol), DBU (82 ml, 0.55 mmol), $CCl_3CN$ (0.82 ml, 8.21 mmol), DCM (10 ml). Yield 0.952 g (80%). Colorless oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.64–0.69 (1H, m), 0.77–0.84 (2H, m) and 0.97–1.02 (1H, m, $CH_2CH_2$); 3.35 (3H, s, $OCH_3$); 3.80–3.82 (2H, m), 3.89 (1H, d, *J* = 12.1), and 4.65 (1H, dd, *J* = 11.9, *J* = 1.0, $2CH_2$); 4.97 (1H, dd, *J* = 4.2, *J* = 7.0, $CHOC(=NH)$); 8.26 (1H, s, NH); 8.34 (1H, s, NH). $^{13}$C NMR spectrum, δ, ppm: 8.7; 10.6; 21.4; 59.3; 72.9; 73.8; 81.7; 91.5; 92.0; 162.9 (2C). Found, *m*/*z*: 454.9072 $[M+Na]^+$. $C_{11}H_{14}Cl_6N_2NaO_3$. Calculated, *m*/*z*: 454.9033.

**(1-{2-(Benzyloxy)-1-[(2,2,2-trichloroethanimidoyl)oxy]-ethyl}cyclopropyl)methyl 2,2,2-trichloroethanimidoate (1f)** was prepared analogously to compound **1a** from diol **7f** (0.291 g, 1.31 mmol), DBU (39 ml, 0.26 mmol), $CCl_3CN$ (0.4 ml, 3.93 mmol), DCM (10 ml). Yield 0.550 g (83%). Yellowish oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.64–0.69 (1H, m), 0.76–0.84 (2H, m), and 1.02–1.07 (1H, m, $CH_2CH_2$); 3.85 (1H, d, *J* = 11.3), 3.89–3.94 (2H, m), 4.54–4.61 (2H, m), and 4.66 (1H, dd, *J* = 11.3, *J* = 0.9, $3CH_2$); 5.04 (1H, dd, *J* = 7.4, *J* = 4.4, $OCH_2CHOC(=NH)$); 7.23–7.33 (5H, m, H Ph); 8.23 (1H, s, NH); 8.38 (1H, s, NH). $^{13}$C NMR spectrum, δ, ppm: 8.6; 10.8; 21.4; 71.3; 72.9; 73.3; 82.1; 91.4; 92.0; 127.6; 127.7; 128.4; 138.3; 162.8 (2C). Found, *m*/*z*: 530.9393 $[M+Na]^+$. $C_{17}H_{18}N_2NaO_3$. Calculated, *m*/*z*: 530.9346.

**Cyclization of bis(imidate) 1** (General method A). Bis(imidate) **1** (1.00 mmol) was dissolved in the selected solvent (10 ml) under argon atmosphere. To this solution, 4 Å molecular sieves were added followed by Lewis acid (0.10 mmol, 10 mol %). The mixture was stirred at room temperature until full consumption of the starting material. (TLC control, eluent EtOAc–hexane, 1:8). The reaction mixture was filtered through the short Celite column, and the filtrate was evaporated. The residue was purified by flash chromatography on silica gel column (eluent EtOAc – petroleum ether, 1:8) to give products **2** and/or **3**.

(General method B). Bis(imidate) **1** (1.00 mmol) was dissolved in the selected solvent (10 ml) under argon atmosphere; 4 Å molecular sieves were added to this solution. The reaction mixture was set to reflux until complete consumption of the starting material (TLC control, eluent EtOAc–hexane, 1:8). The reaction mixture was filtered through the short Celite column, and the filtrate was evaporated. The residue was purified by flash chromatography on silica gel column (eluent EtOAc – petroleum ether, 1:8) to give products **2** and/or **3**.

**6-(Trichloromethyl)-7-oxa-5-azaspiro[3.4]oct-5-ene (2a)** was prepared using general method A from bis(imidate) **1a** (See Table 1). Colorless oil. $^1$H NMR spectrum, δ, ppm: 1.74–1.86 (1H, m) and 2.06–2.22 (3H, m, $CH_2CH_2CH_2$); 2.47–2.55 (2H, m, $CH_2CH_2CH_2$); 4.56 (2H, s, $CH_2O$). $^{13}$C NMR spectrum, δ, ppm: 14.9; 34.9; 72.8; 82.1; 86.9; 161.5. Found, *m*/*z*: 227.9747 $[M+H]^+$. $C_7H_9Cl_3NO$. Calculated, *m*/*z*: 227.9750.

**6-(Trichloromethyl)-5-oxa-7-azaspiro[2.5]oct-6-ene (3a)** was isolated as by-product using general method A from bis(imidate) **1a** (see Table 1). Colorless oil. $^1$H NMR spectrum, δ, ppm: 0.67–0.68 (4H, m, $CH_2CH_2$); 3.46 (2H, s, $CH_2O$); 4.10 (2H, s, $CH_2N$).

**8-Phenyl-6-(trichloromethyl)-5-oxa-7-azaspiro[2.5]oct-6-ene (3b)** was prepared using general method A from bis(imidate) **1b**. Yield 0.062 g (85%) (see Table 2). Yellow oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.48–0.53 (1H, m) and 0.63–0.73 (3H, m, $CH_2CH_2$); 4.00 (1H, dd, *J* = 10.9, *J* = 1.0) and 4.22 (1H, d, *J* = 10.9, $CH_2O$); 4.49 (1H, s, CHPh); 7.15–7.38 (5H, m, H Ph). $^{13}$C NMR spectrum, δ, ppm: 6.8; 10.2; 19.5; 62.3; 72.8; 92.6; 127.7 (2C); 128.4; 139.6; 155.0. Found, *m*/*z*: 304.0102 $[M+H]^+$. $C_{13}H_{13}Cl_3NO$. Calculated, *m*/*z*: 304.0063.

**1-Propyl-6-(trichloromethyl)-7-oxa-5-azaspiro[3.4]oct-5-ene (2c)** was prepared using general method A from bis(imidate) **1c** (see Table 3). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.90 (3H, t, *J* = 7.2, $CH_3$); 1.18–1.48 (5H, m, $CHCH_2CH_2CH_3$); 1.95–2.01 (1H, m) and 2.05–2.13 (1H, m, $CH_2CH_2CH$); 2.50–2.57 (1H, m) and 2.67–2.75 (1H, m, $CH_2CH_2CH$); 4.36 (1H, d, *J* = 9.0) and 4.85 (1H, d, *J* = 9.0, $CH_2O$). $^{13}$C NMR spectrum, δ, ppm: 14.2; 20.0; 22.5; 32.4; 33.0; 44.0; 75.0; 76.9; 86.8; 161.1. Found, *m*/*z*: 270.0259 $[M+H]^+$. $C_{10}H_{15}Cl_3NO$. Calculated, *m*/*z*: 270.0219.

**8-Propyl-6-(trichloromethyl)-5-oxa-7-azaspiro[2.5]oct-6-ene (3c)** was isolated as by-product using general method A from bis(imidate) **1c** (see Table 3). Colorless oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.56–0.72 (3H, m) and 0.68–0.75 (1H, m, $CH_2CH_2$); 0.93–0.97 (3H, m, $CH_2CH_2CH_3$); 1.44–1.68 (4H, m, $CH_2CH_2CH_3$); 3.03–3.06 (1H, m, CHN); 3.67 (1H, dd, *J* = 10.8, *J* = 1.7) and 4.43 (1H, dd, *J* = 10.8, *J* = 1.2, $CH_2O$). $^{13}$C NMR spectrum, δ, ppm: 6.4; 11.6; 14.4; 18.1; 19.8; 37.0; 59.5; 72.3; 152.7. Found, *m*/*z*: 270.0259 $[M+H]^+$. $C_{10}H_{15}Cl_3NO$. Calculated, *m*/*z*: 270.0219.

**1-Isopropyl-6-(trichloromethyl)-7-oxa-5-azaspiro[3.4]oct-5-ene (2d)** was prepared using general method A or B from bis(imidate) **1d** (see Table 4). Colorless oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.79 (3H, d, *J* = 6.5, CHC$\underline{H}_3$); 0.84 (3H, d, *J* = 6.5, CHC$\underline{H}_3$); 1.22–1.32 (1H, m, $CH_2CH_2C\underline{H}$); 1.54–1.64 (1H, m, $C\underline{H}(CH_3)_2$); 1.87–1.92 (1H, m) and 1.97–2.04 (1H, m, $CH_2C\underline{H}_2CH$); 2.30–2.38 (1H, m) and 2.51–2.59 (1H, m, $C\underline{H}_2CH_2CH$); 4.37 (1H, d, *J* = 9.0) and 4.91 (1H, d, *J* = 9.0, $CH_2O$). $^{13}$C NMR spectrum, δ, ppm: 19.5; 19.7; 21.6; 29.9; 32.2; 51.9; 74.7; 86.8; 160.9. Found, *m/z*: 270.0253 $[M+H]^+$. $C_{10}H_{15}Cl_3NO$. Calculated, *m/z*: 270.0219.

**8-Isopropyl-6-(trichloromethyl)-5-oxa-7-azaspiro[2.5]-oct-6-ene (3d)** was isolated as by-product using general method A or B from bis(imidate) **1d** (see Table 4). Colorless oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.46–0.51 (1H, m) and 0.55–0.60 (1H, m, $C\underline{H}_2CH_2$); 0.68–0.73 (1H, m) and 0.85–0.91 (1H, m, $CH_2C\underline{H}_2$); 1.05–1.09 (6H, d, *J* = 7.0, $CH(C\underline{H}_3)_2$); 1.81–1.89 (1H, m, $C\underline{H}(CH_3)_2$); 2.65 (1H, dd, *J* = 8.0, *J* = 2.2, CHN); 3.51 (1H, dd, *J* = 10.7, *J* = 2.2), and 4.61 (1H, dd, *J* = 10.7, *J* = 2.2, $CH_2O$). $^{13}$C NMR spectrum, δ, ppm: 7.5; 11.8; 17.1; 20.1; 20.6; 34.3; 65.7; 72.6; 77.4; 152.4. Found, *m/z*: 270.0240 $[M+H]^+$. $C_{10}H_{15}Cl_3NO$. Calculated, *m/z*: 270.0219.

**1-Methoxymethyl-6-(trichloromethyl)-7-oxa-5-azaspiro-[3.4]oct-5-ene (2e)** was prepared using general method B from bis(imidate) **1e** (see Table 5). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.61–1.70 (1H, m), 2.07–2.20 (2H, m), and 2.40–2.49 (1H, m, $C\underline{H}_2CH_2CH$); 2.85–2.92 (1H, m, $CH_2CH_2C\underline{H}$); 3.33 (3H, s, $OCH_3$); 3.42–3.50 (2H, m, $C\underline{H}_2OMe$); 4.37 (1H, d, *J* = 9.2) and 4.82 (1H, d, *J* = 9.2, $C\underline{H}_2OC(=N)$). $^{13}$C NMR spectrum, δ, ppm: 18.2; 33.3; 43.6; 59.0; 71.9; 74.4; 77.9; 86.9; 161.3. Product **2e** is unstable in the HRMS conditions.

**1-Benzyloxymethyl-6-(trichloromethyl)-7-oxa-5-aza-spiro[3.4]oct-5-ene (2f)** was prepared using general method B from bis(imidate) **1f** (see Table 5). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.68–1.72 (1H, m), 2.13–2.19 (2H, m), and 2.42–2.50 (1H, m, $C\underline{H}_2CH_2CH$); 2.91–2.98 (1H, m, $CH_2CH_2C\underline{H}$); 3.50–3.60 (2H, m, $CHC\underline{H}_2OCH_2$); 4.37 (1H, d, *J* = 9.4, $CH_AOC(=N)$); 4.46–4.56 (2H, m, $OC\underline{H}_2Ph$); 4.84 (1H, d, *J* = 9.4, $CH_BOC(=N)$); 7.27–7.37 (5H, m, H Ph). $^{13}$C NMR spectrum, δ, ppm: 18.1; 33.2; 43.5; 69.2; 73.2; 74.3; 77.9; 86.9; 127.5; 127.8; 128.5; 138.1; 161.4. Found, *m/z*: 348.0325 $[M+H]^+$. $C_{10}H_{17}O_3$. Calculated, *m/z*: 348.0346.

***tert*-Butyl-1-(hydroxymethyl)-2-propylcyclobutyl carbamate (8c)**. 6 M aqueous HCl (2 ml) was added to a solution of oxazoline **2c** (0.158 g, 0.58 mmol) in EtOH (2 ml), and the mixture was stirred for 1 h at room temperature, then it was refluxed for 7 h. The solvents were removed *in vacuo*, and saturated aq $NaHCO_3$ solution (10 ml) was added to the residue followed by di-*tert*-butyl dicarbonate (0.275 g, 2.00 mmol) solution in EtOAc (10 ml). The reaction mixture was stirred for 12 h at room temprature. The organic phase was separated, and the aquoeus phase was extracted with EtOAc (3 × 10 ml). The combined, organic phases were washed with saturated aq NaCl (10 ml) and dried over $Na_2SO_4$. The extract was evaporated and the residue was purified by flash chromatography on silica gel (eluent EtOAc – light petroleum ether, gradient from 1:4 to 1:1). Yield 0.130 g (89%). Colorless solid, mp 58–61°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.87 (3H, t, *J* = 7.2, $CH_2CH_2C\underline{H}_3$); 1.12–1.30 (3H, m, $C\underline{H}_2C\underline{H}_2CH_3$); 1.35–1.48 (10H, m, $C(CH_3)_3$, $C\underline{H}_2CH_2CH_2$); 1.51–1.58 (1H, m, $C\underline{H}CH_2CH_2$); 1.88–2.03 (2H, m, $CHC\underline{H}_2CH_2$); 2.14–2.19 (1H, m) and 2.29–2.37 (1H, m, $CHCH_2C\underline{H}_2$); 3.53–3.65 (1H, br. s, OH); 3.77–3.85 (2H, m, $C\underline{H}_2OH$); 4.87–4.95 (1H, br. s, NH). $^{13}$C NMR spectrum, δ, ppm: 14.3; 20.9; 21.6; 28.5; 28.6; 32.2; 45.3; 59.4; 65.1; 80.1; 156.2. Found, %: N 5.80; C 64.20; H 10.40. $C_{13}H_{25}NO_3$. Calculated, %: N 5.76; C 64.16; H 10.36.

***tert*-Butyl-[1-(hydroxymethyl)cyclobutyl] carbamate (8a)** was prepared in analogy to compound **8c** from oxazoline **2a** (0.228 g, 1.00 mmol), EtOH (2 ml), 6 M HCl aqueous solution (2 ml), di-*tert*-butyl dicarbonate (0.437 g, 2.00 mmol), and EtOAc (10 ml). Yield 0.119 g (59%). Compound physical and chemical data are consistent with commercially available sample.

***tert*-Butyl-1-(hydroxymethyl)-2-isopropylcyclobutyl carbamate (8d)** was prepared in analogy to compound **8c** from oxazoline **2d** (0.100 g, 0.41 mmol), EtOH (2 ml), 6 M HCl aqueous solution (2 ml), di-*tert*-butyl dicarbonate (0.179 g, 2.00 mmol), and EtOAc (10 ml). Yield 0.063 g (70%). Colorless solid, mp 61–63°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.72 (3H, d, *J* = 6.4) and 0.86 (3H, d, *J* = 6.4, $CH(C\underline{H}_3)_2$); 1.34–1.45 (10H, m, $OC(CH_3)_3$, $C\underline{H}(CH_3)_3$); 1.51–1.61 (1H, m) and 1.83–1.97 (3H, m, $C\underline{H}_2C\underline{H}_2CH$); 2.20–2.34 (1H, m, $CH_2CH_2C\underline{H}$); 3.82 (2H, s, $C\underline{H}_2OH$); 4.12 (1H, br. s, OH); 4.95 (1H, br. s, NH). $^{13}$C NMR spectrum, δ, ppm: 20.0; 20.5; 22.1; 27.8; 28.5; 28.7; 53.4; 59.5; 64.8; 80.1; 156.4. Found, %: N 5.79; C 64.19; H 10.39. $C_{13}H_{25}NO_3$. Calculated, %: N 5.76; C 64.16; H 10.36.

***tert*-Butyl-1-(hydroxymethyl)-2-(methoxymethyl)cyclobutyl carbamate (8e)** was prepared in analogy to compound **8c** from oxazoline **2e** (0.198 g, 0.73 mmol), EtOH (2 ml), 6 M HCl aqueous solution (2 ml), di-*tert*-butyl dicarbonate (0.319 g, 1.46 mmol), and EtOAc (10 ml). Yield 0.130 g (73%). Colorless solid, mp 70–73°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.37–1.45 (11H, m, $C(CH_3)_3$, $CH_2C\underline{H}_2CH$); 1.77–1.83 (1H, m) and 1.88–1.97 (1H, m, $C\underline{H}_2CH_2CH$); 2.36–2.50 (1H, m, $CH_2CH_2C\underline{H}$); 2.95 (1H, br. s, OH); 3.32 (3H, s, $OCH_3$); 3.41–3.50 (2H, m, $C\underline{H}_2OMe$); 3.54–3.59 (1H, m) and 3.81 (1H, d, *J* = 10.2, $C\underline{H}_2OH$); 5.14 (1H, br. s, NH). $^{13}$C NMR spectrum, δ, ppm: 17.3; 27.1; 28.5; 42.1; 58.9 (2C); 64.5; 72.9; 79.4; 155.3. Found, %: N 5.76; C 58.75; H 9.49. $C_{12}H_{23}NO_4$. Calculated, %: N 5.71; C 58.75; H 9.45.

***tert*-Butyl-2-(benzyloxymethyl)-1-(hydroxymethyl)cyclobutyl carbamate (8f)** was prepared in analogy to compound **8c** from oxazoline **2f** (0.172 g, 0.49 mmol), EtOH (2 ml), 6 M HCl aqueous solution (2 ml), di-*tert*-butyl dicarbonate (0.214 g, 0.98 mmol), and EtOAc (10 ml). Yield 0.110 g (69%). Colorless solid, mp 96–97°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.41–1.51 (10H, m, $C(CH_3)_3$, $CH_2C\underline{H}_2CH$); 1.81–1.87 (2H, m, $C\underline{H}_2CH_2CH$); 1.91–1.99 (1H, m, $CH_2C\underline{H}_2CH$); 2.41–2.50 (1H, m, $CH_2CH_2C\underline{H}$); 3.00 (1H, br. s, OH); 3.56–3.61 (3H, m,

$CH_2OCH_2$, $CH_AOH$); 3.86 (1H, d, $J$ = 8.8, $CH_BOH$); 4.52 (2H, s, $OCH_2Ph$); 5.12 (1H, br. s, NH); 7.26–7.38 (5H, m, H Ph). $^{13}C$ NMR spectrum, δ, ppm: 17.3; 27.1; 28.5; 42.2; 59.0; 64.6; 70.3; 73.4; 79.5; 128.0; 128.1; 128.7; 137.5; 155.4. Found, %: N 4.40; C 67.29; H 8.51. $C_{18}H_{27}NO_4$. Calculated, %: N 4.36; C 67.26; H 8.47.

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REVIEW ARTICLE

# Allylic Amination via Acid Catalyzed Leaving Group Activation

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**Abstract:** ***Background:*** Allylic amination *via* acid catalyzed activation of a leaving group is promoted by non-expensive and low toxicity Lewis acid and Bronsted acid catalysts to give valuable allyl amine derivatives. In many cases, non-toxic by-products such as water or acetic acid are generated. Moreover catalysts that perform the reactions in water as a solvent and the use of recyclable catalysts have been developed.

***Methods:*** Peer-reviewed research literature methods on allylic amination *via* acid catalyzed activation were compiled using data bases such as *Sci-Finder* and *Scopus*.

***Results:*** The mini-review summarizes the most important methods for allylic amination *via* acid catalyzed activation of a leaving group in the recent decade. These are divide in two main groups - Lewis acid and Bronsted acid catalysed reactions.

***Conclusion:*** Allylic amination *via* acid catalyzed activation of a leaving group meet criteria of the green chemistry paradigm which has motivated method development for this type of reaction in recent years.

**Keywords:** Allylic substitution, allylic amination, lewis acids, bronsted acids, green chemistry, allylic alcohols, carbenium ion.

## INTRODUCTION

Allylic substitution in substrates **1** bearing an allylic leaving group is a useful transformation to generate allyl amine derivatives **2** which possess high synthetic utility (Scheme **1**) [1-6]. There are four principal approaches to achieve the allylic substitution with amine nucleophiles: Pathway A involves oxidative addition of a substrate **1** to a transition metal, ligand exchange and reductive elimination to give $S_N$ or $S_N'$ products **2** or **2'**; Pathway B relies on the activation of a double bond in the substrate **1** by coordination with $\pi$–acidic metals followed by attack of a nitrogen nucleophile to the double bond. Subsequent de-metalation *via* $\beta$–heteroatom elimination gives $S_N'$ product **2'**; Pathway C involves nucleophilic displacement of a good leaving group in substrate **1** with strong nitrogen nucleophiles and can proceed *via* $S_N$ or $S_N'$ mechanism to give product **2** or **2'**; Pathway D involves activation of a leaving group in substrate **1** with an acid followed by the substitution with a non-basic nitrogen nucleophile to give product **2** or **2'**.

The green chemistry initiatives aim to develop more *eco*-friendly and economic alternatives to the current methods. In this regard, allylic amination *via* pathways C and D are more attractive as these avoid the use of toxic and expensive transition metals. Pathway D has additional benefits from the green chemistry perspective because it requires only a catalytic amount of Lewis or Bronsted acid to promote the reaction. Moreover substrates that participate in this reaction often bear a poor leaving group such as alcohol or acetate which makes them more stable and less toxic than allyl halides or pseudo halides. These features have motivated the development of number of methods for this type of allylic amination in the recent years. Several examples of this reaction type have been included in the review articles covering specific areas in organic synthesis [7-12]. However, to the best of our knowledge, there is no review article focused on the allylic amination reactions *via* an acid catalyzed leaving group activation. In this mini-review we have compiled the most important contributions on this topic in the recent decade. The methods are divided in two main groups - Lewis acid and Bronsted acid catalysed allylic amination reactions.

### 1. Lewis Acid Catalysed Allylic Amination

*Bismuth Lewis acid catalysis*. The groups of Matsunaga and Shibasaki have developed $Bi(OTf)_3$ catalyzed substitution of the hydroxy group in allylic alcohols **3**,**8**-**11** with non-basic nitrogen nucleophiles [13]. Allylic alcohol **3** was used as the model substrate to investigate the amination reaction with sulfonamides **4**, carbamates **5**, and carboxamides **6** (Scheme **2**). The addition of $KPF_6$ in the catalytic amounts significantly reduced the reaction time and improved the yield of product **7**. The addition of drierite™ as a water scavenger enabled a reduction in the amount of catalyst and co-catalyst. In this reaction, sulfonamides **4** and carbamates **5** were found to be considerably more reactive then carboxamides **6**. Allylic amination of enantioenriched allylic alcohol **3** with tosylamide **4a** and carbamate **5b** led to racemic product **7**. This indicated that the reaction proceeds *via* car-

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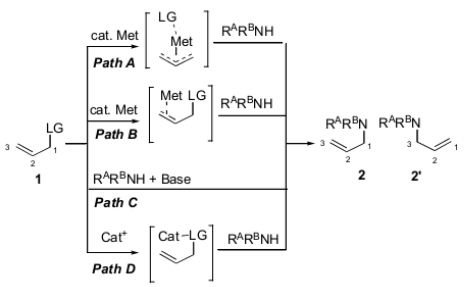
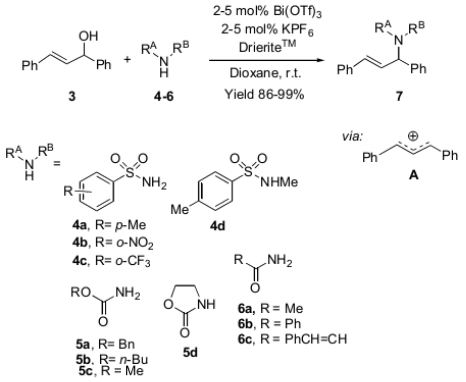
benium ion **A** which is formed by abstraction of hydroxy group in substrate **3** after coordination with a catalyst.




(Scheme **1**). Types of allylic substitution with amine nucleophiles.




(Scheme **2**). $Bi(OTf)_3$ catalysed amination of allylic alcohol **3**.

A wide range of allylic alcohols including the cyclic alcohols **8** as well as primary, secondary and tertiary alcohols **9-11** were investigated as substrates for the allylic amination with sulfonamide **4a,d** and carbamate **5b** (Scheme **3**). The yields of the amination products **12** were good to excellent. In the case of unsymmetrically substituted substrates, the formation of both $S_N2$ and/or $S_N2'$ products **12** and **12′** was observed. The regioselectivity was in the favour to the less substituted product or to the product with double bond conjugated to aryl group.

Uenishi's group has reported the Lewis acid catalysed intramolecular substitution of enantioenriched allylic alcohols **13** with Boc-amine to give products **14** with high chirality transfer (Scheme **4**) [14-16]. A range of metal salts were screened for this transformation in addition to $Bi(OTf)_3$. From these, $SnCl_4$ and $FeCl_3$ also gave high yield of the product **14**. However, $Bi(OTf)_3$ gave the best yield and importantly, almost quantitative chirality transfer. Addition of molecular sieves was crucial to obtain the high yield of product **14**. Dichloromethane as the solvent was important to achieve high chirality transfer while considerable erosion of both yield and chirality transfer was observed performing the reaction in toluene or nitromethane. From several *N*-substituents explored, *N*-Boc derivatives provided the highest chirality transfer. Substitution on the aromatic ring also had significant impact on chirality transfer. Electron donating groups such as methoxy and hydroxy in the *para* position to alkenyl substituent or *ortho*-methyl groups significantly decreased the enantioselectivity.

The observed stereochemical results for the formation of enantioenriched products **14** were explained by the concerted *syn*-$S_N2'$ reaction mechanism (Scheme **5**). According to this, $Bi(OTf)_3$ activates hydroxy leaving group by forming bismuth alkoxide **15** in which bismuth directs the incoming nucleophile by coordination with Boc group. Electron donating group enables ionization of intermediate **15** to allyl carbenium ion which leads to non-stereoselective $S_N1$ pathway.

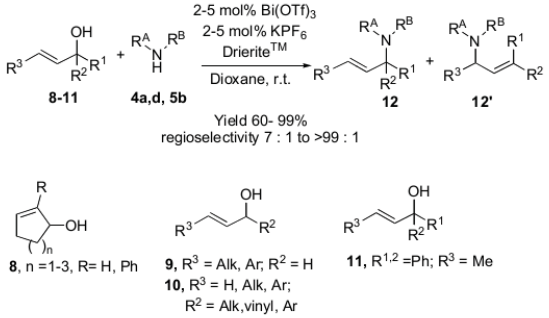
The above described $Bi(OTf)_3$ catalyzed allylic amination was applied for the stereoselective synthesis of tetrahydroisoquinoline alkaloids: (−)-trolline (**18**), (+)-crispin A (**19**), (+)-oleracein E (**20**), (+)-dysoxyline (**21**), (+)-colchiethanamine (**22**), and (+)-colchiethine (**23**) (Scheme **6**) [17, 18]. For this purpose, the *S* - and *R*- enantiomers of resorcine derivative **16** were subjected to $Bi(OTf)_3$ catalyst resulting in tetrahydroisoquinoline enanatiomers **17** with high chirality transfer. The cyclization products were used as key intermediates for the synthesis of natural products **18-23**.

Acid catalysed allylic amination of enantioenriched allylic alcohol **24** to tetrahidroisoquinoline **25** was the key step for synthesis of (-)-schulzeine B (**26**) (Scheme **7**) [19]. The use of $Bi(OTf)_3$ as catalyst for the cyclization at $0^oC$ gave high chirality transfer, but a poor yield of the product **25**. Increasing the temperature improved the yield of product **25**, but slightly decreased the chirality transfer. Using $HClO_4$ as catalyst, good yield and high chirality transfer for key intermediate **25** was obtained.

The successful performance of $HClO_4$ is not consistent with the chelation controlled $S_N2'$ mechanism proposed for $Bi(OTf)_3$ induced chirality transfer (Scheme **5**). Obviously, chirality transfer in these reactions would require another explanation.

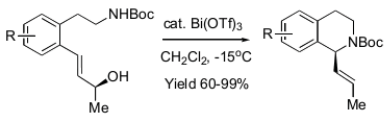
*Iron catalysts.* Jana *et al.* have shown several examples for intermolecular allylic amination with tosylamide (**4a**) and primary carboxamides **6a,b,d** promoted by substoichiometric amount of $FeCl_3$ (Scheme **8**) [20]. Allylic alcohols **10** possessing at least one phenyl substituent were used as the substrates. In the case of methyl group as substituent in the substrate **10** (R = Me, $R^1$ = Ph), regioselective formation of products **12** with conjugated double bond were formed.

Najera's group have performed comparative studies of $FeCl_3 \cdot 6H_2O$ and TfOH as catalysts for allylic amination of alcohols (Scheme **9**) [21]. Using alcohol **3** as model substrate the efficiency of various nitrogen nucleophiles such as sulfonamides **4**, carbamates **5**, carboxamides **6**, anilines **27** and benzotriazole (**28**) were investigated. Both catalysts $FeCl_3 \cdot 6H_2O$ and TfOH were suitable for this transformation, however in the case of TfOH lower catalyst loadings and milder reactions conditions could be applied compared to the




(Scheme **3**). $Bi(OTf)_3$ catalysed amination of structurally different allylic alcohols **8-11**.

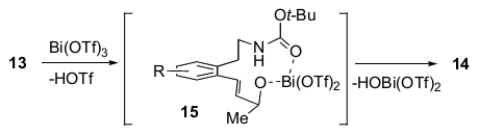
$FeCl_3{\cdot}6H_2O$ catalyzed reactions. On the other hand, for certain amino components **4d**, **5d**, **27b**, **28** better yields were achieved with $FeCl_3{\cdot}6H_2O$ as a catalyst.




**13**, *ee* >98%

**14,** *ee* >84%;
if R = H, 6-Me, 6-Cl, 7-Me, 7-Cl;
*ee* <54%;
if R = 6-MeO; 6-OH 8-Me, 2-MeI

(Scheme **4**). $Bi(OTf)_3$ catalysed intramolecular amination of allylic alcohols **13** with chirality transfer.

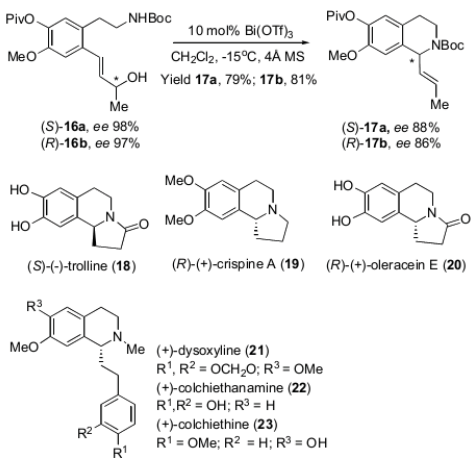



(Scheme **5**). Proposed mechanism for chirality transfer in $Bi(OTf)_3$ catalysed allylic amination.

Structurally diverse allylic alcohols **8-10** were subjected to the reaction with tosylamide (**4a**) using either $FeCl_3{\cdot}6H_2O$ or TfOH as catalysts (Scheme **10**). For these substrates, TfOH appeared to be the more efficient catalyst. In the case of regioisomers of alcohols **9**,**10** (R = Ph, $R^1$ = H, Me or R = H, Me; $R^1$ = Ph) the isomer **12** with the conjugated double bond formed (R = Ph) exclusively. In the case of allyl alcohol **9a** (R = Me, $R^1$= H), the mixture of both isomers **12** and **12′** formed.

The lack of chirality transfer from enantioenriched alcohol **10** (R= Ph, $R^1$ = Et) and the single regioisomer **12** formation from isomeric allylic alcohols **9** and **10** led to conclusion that the reaction proceeds *via* a carbenium ion intermediate.

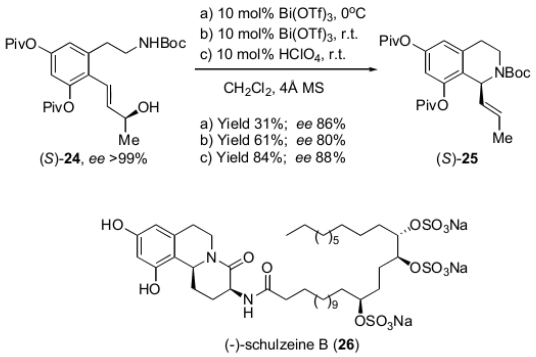
Najera's group has also reported the allylic amination of allylic alcohols **3** catalyzed by $FeCl_3{\cdot}6H_2O$ in water as the solvent (Scheme **11**) [22]. These conditions allows the allylic substitution of alcohol **3** with a wide range of *N*-nucleophiles such as sulfonamides **4**, carbamate **5a**, amide **6b**, anilines **27**, benzotriazole (**28**) and trimethylsilyl azide **29**, to give amides **7** and azide **30**.




(Scheme **6**). $Bi(OTf)_3$ catalyzed allylic amination as a key step for the stereoselective synthesis of alkaloids **18**-**23**.

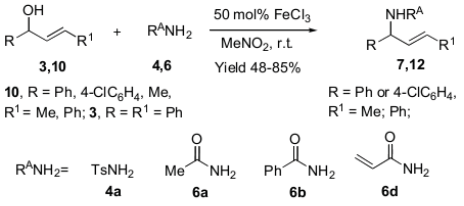
The allylic amination reaction of alcohol **3** in water proceeded efficiently, but required higher temperature and gave slightly lower yields than the $FeCl_3{\cdot}6H_2O$ catalyzed processes in organic solvents (Scheme **9**). This could be explained by formation of less Lewis acidic species in water – $[Fe(H_2O)_{6-n}(OH)_n]^{+3-n}Cl_{3-n}$ and also by the limited solubility of organic compounds in aqueous media.

Under the optimized reaction conditions $FeCl_3{\cdot}6H_2O$ catalyzed amination of regioisomeric alcohols **10a**, *E*-**10b** and *Z*-**10b** with tosylamide (**4a**) in water afforded sulfonamide **12b** as a single regioisomer (Scheme **12**). This indicates a carbocation intermediate which can isomerize to




(Scheme **7**). $Bi(OTf)_3$ catalyzed allylic amination as a key step for the stereoselective synthesis of alkaloid **26**.

thermodynamically more stable *trans*-allyl carbenium ion which preferentially gives the product **12b** with the conjugated double bond.




(Scheme **8**). $FeCl_3$ catalysed amination of allylic alcohols **3** and **10**.

Cossy's group has developed $FeCl_3$ catalyzed diastereoselective synthesis of substituted piperidines **32** which involved intramolecular allylic substitution of a hydroxyl group or acetate by the carbamate or tozylamide in substrates **31** [23]. The simplest substrate **31** (R, $R^1$, X = H) gave very poor yield of the cyclization product even with high catalyst loading. However, introduction of a substituent on the allylic chain enabled the substitution of both acetate and hydroxyl groups. If the substrate **31** contained an amine function at the secondary carbon, the reaction gave the disubstituted piperidine **32** with very high diastereoselectivity. It was proved that the diastereoselectivity is thermodynamically controlled by exposing the mixture of both *trans*- and *cis*-isomers of the cyclization product **32** to the reaction conditions. Equilibration of the mixture to give *cis*-isomer was observed implying that the reversible reaction takes place *via* zwiterionic intermediate **B**.

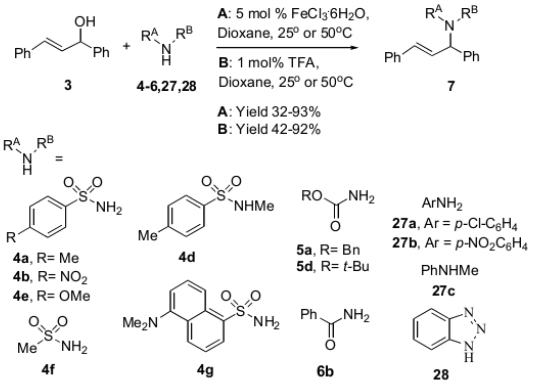
Wang *et al.* have developed the synthesis of dihydroquinolines **34** and quinolones **35** based on $FeCl_3 6H_2O$ catalyzed intramolecular allylic amination (Scheme **14**) [24]. Both secondary and tertiary alcohols **33a**,**33b** could be used as the substrates to give dihydroquinolines **34** in good to excellent yields. In the case of secondary alcohols **33a** all the examples contained carbenium ion stabilizing aryl or vinyl substituents at the double bond. If the reaction mixture, after the cyclization, was treated in strongly basic conditions, elimination of tosyl- or mesyl group was achieved leading to quinolones **35**.

Enantionriched enantiomers of secondary alcohol **33a** (R = Ph, $R^{1,2}$ = H, Pg =Ts) gave no chirality transfer leading to racemic product **34**. This indicated $S_N1$ type reaction mechanism *via* allyl carbenium ion intermediate.

The group of Kim has performed $FeCl_3$ catalysed allylic amination of Baylis-Hillman adducts **36** with tosyl and mesyl amides **4a** and **4f** to give allylamines **37** (Scheme **15**) [25]. The aryl group adjacent to the reaction center in substrates **36** was crucial for the successful allylic amination as in the case of pentyl substituent the reaction failed.

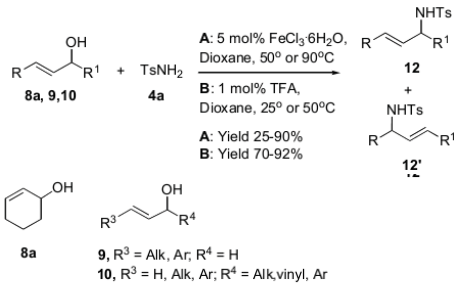
*Aluminium Lewis acid catalysis.* Ohshima *et al.* reported $Al(OTf)_3$ as a powerful catalyst for the amination of allylic alcohols **3**,**10** with tosylamide (**4a**), carbamates **5**, carboxamides **6** and aniline **27b** (Scheme **16**) [26]. For most of the amine components, the reaction took place at room temperature, while for less reactive carboxamides **6a,d,e** microwave heating was required to promote the reaction. In the case of isomeric methyl, phenyl substituted substrates **10a** and **10b** the amination product **12** with conjugated double bond was obtained which was explained by cationic intermediate formation.

*Magnesium Lewis acid catalysis*. Jia's group has reported $Mg(ClO_4)_2$ as a mild Lewis acid catalyst for intramolecular allylic amination of allylic alcohols 38,40,42 [27] (Scheme **17**). Tertiary alcohol 38a was more reactive then secondary alcohol 38b while the reaction of primary alcohol 38c was sluggish even using equimolar amount of $Mg(ClO_4)_2$. The allylic acetates 38 were more reactive than the free alcohols. *N*-Tosyl derivatives, exhibited better reactivity than *N*-Boc-analogues. The reaction could also be used to form the seven membered ring 41 from amide 40. Acyclic *N*-Ts-*N* Boc protected substrates 42a,b could also be subjected to intramolecular allylic amination leading to pyrrolidine and piperidine derivatives 43a,b as mixtures of diastereomers. In

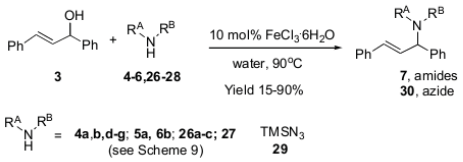



(Scheme **9**). $FeCl_3{\cdot}6H_2O$ catalysed amination of allylic alcohol **3**.

this case *in situ* Boc cleavage took place generating *N*-Ts amine as the nucleophile for the intramolecular allylic substitution.

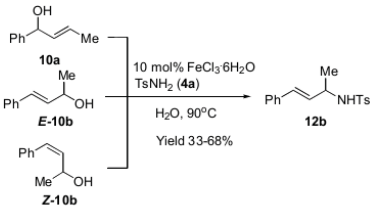



(Scheme **10**). $FeCl_3{\cdot}6H_2O$ catalysed amination of structurally different allylic alcohols **8a, 9, 10**.

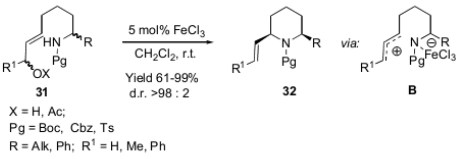



(Scheme **11**). $FeCl_3{\cdot}6H_2O$ catalysed allylic amination in water.

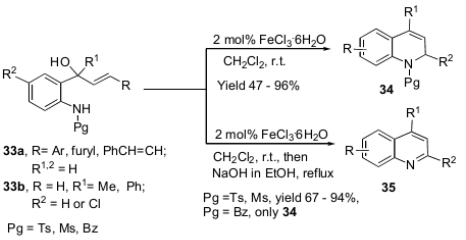
The method was applied to the total synthesis of demethoxyfumitremorgin C (**46**) which involved intramolecular allylic amination of *bis*-Boc substrate **44** as a key step (Scheme **18**). When subjected to $Mg(ClO_4)_2$ catalyst, monodeprotection and subsequent cyclization gave product **45** as a mixture of diastereomers. The *cis*-diastereomer was isolated by flash chromatography and transformed to demethoxyfumitremorgin C (**46**).



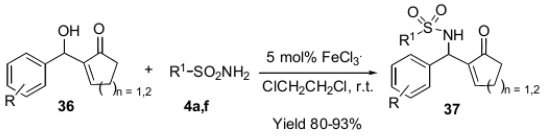

(Scheme **12**). Formation of single amination product **12b** from different alcohol isomers **10a**, ***E*-10b**, **Z-10b**.




(Scheme **13**). Diastereoselective synthesis of piperidines **32** *via* $FeCl_3$ catalysed intramolecular allylic amination.



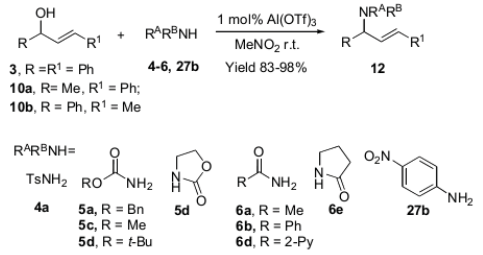

(Scheme **14**). Synthesis of dihydroquinolines **34** and quinolones **35** *via* $FeCl_3{\cdot}6H_2O$ catalyzed intramolecular allylic amination.



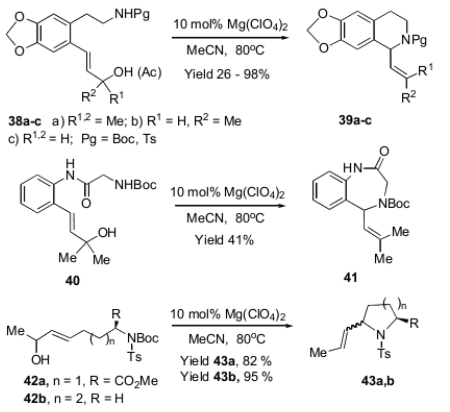

**36**, R = H, *p*-Cl, *p*-MeO, *o*-OMe, *p*-Me

**4a**, $R^1$ = $MeC_6H_4$; **4f**, $R^1$ = Me

(Scheme **15**). $FeCl_3$ catalyzed allylic amination of Baylis-Hillman adducts **36**.

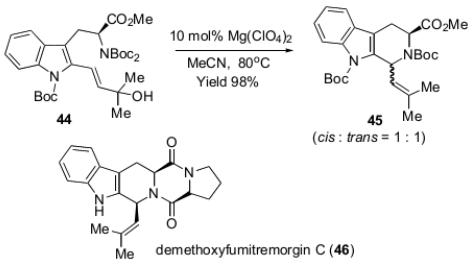



(Scheme **16**). $Al(OTf)_3$ catalyzed amination of allylic alcohols **3**,**10a**,**b**.

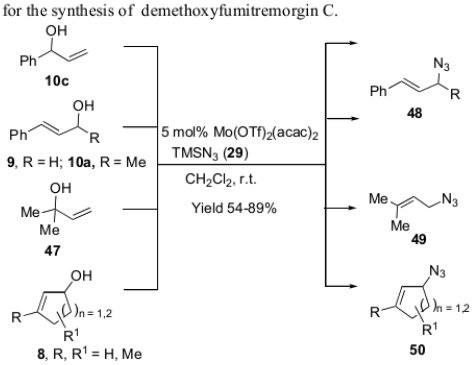



(Scheme **17**). $Mg(ClO_4)_2$ catalyzed intramolecular amination of allylic alcohols **38**,**40**,**42**.

*Molybdenum Lewis acid catalysis*. The seminal work by the group of Kocovsky demonstrated $Mo(OTf)_2(acac)_2$ as an efficient Lewis acid catalyst for azidation of allylic alcohols **8**-**10**,**47** to form azides **48**-**50** (Scheme **19**) [28]. Isomeric alcohols **10c** and **9** (R = H) and unsymmetrically substituted alcohol **10a** (R = Me) gave single azide regioisomer **48** with conjugated double bond. Tertiary alcohol **47** gave azide **49** as $S_N'$ product, while cyclic alcohols **8** provided azides **50** as $S_N$ products. These results suggest that the azide attack occurs at the less substituted carbon in putative carbenium ion intermediate.




(Scheme **18**). $Mg(ClO_4)_2$ catalyzed allylic amination as the key step for the synthesis of demethoxyfumitremorgin C.

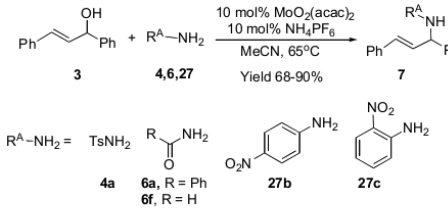



(Scheme **19**). $Mo(OTf)_2(acac)_2$ catalysed azidation of structurally diverse allylic alcohols.

The group of Zhu has reported $MoO_2(acac)_2$ catalyzed allylic substitution in alcohol **3** with various non-basic amine nucleophiles **4**,**6**,**27** (Scheme **20**) [29]. The model reaction with formamide (**6f**) showed that acetonitrile is the solvent of choice and the activity of the catalyst can be increased with $NH_4PF_6$ as an additive.

*Silver Lewis acid catalysis*. Rueping's group has demonstrated direct azidation of primary, secondary and tertiary allylic alcohols in the presence of catalytic amount AgOTf and $TMSN_3$ (**29**) as the azide source (Scheme **21**) [30]. Primary alcohols **9** gave primary azides **51** with high regioselectivity. Secondary alcohols **10** gave azide isomer **48** with conjugated double bond irrespective whether isomer **10a** or **10b** was used as a staring material. Cyclic substrate **10d** gave a mixture of regioisomers. Tertiary alcohols **11** ($R^{1,2}$= Alk)

gave tertiary azide **52** as the major isomer. However if one of the substituents at the tertiary carbon was phenyl group ($R^1$= Ph, $R^2$= Me), mixtures or regioisomers were formed.




(Scheme **20**). $Mo(OTf)_2(acac)_2$ catalysed amination of allylic alcohol **3**.

Chirality transfer was investigated with enantiomerically pure allylic alcohol **10b** ($R^1$=Ph, $R^{2,4}$=H, $R^3$=Me), however racemic azide **48** was obtained This observation is consistent with $S_N1$ type reaction mechanism *via* carbenium ion intermediate.

*Copper Lewis acid catalysis.* Mild and efficient synthesis of azides **48,51** directly from the corresponding allylic alcohols **9,10** could be achieved in the presence of $Cu(ClO_4)_2{\cdot}6H_2O$ as catalyst and $TMSN_3$ (**29**) as a nitrogen source (Scheme **22**) [31].

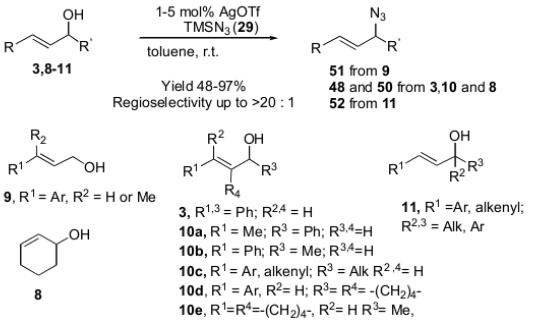
Isomeric alcohols ***E,Z*-9a** and **10c** were subjected to the optimal reaction conditions to give the primary azide **51a** as the sole product (Scheme **23**). These results suggest an involvement of a carbocation intermediate in the azidation of alcohols **9**,**10**.

Another interesting example provided by the authors was the azidation of Baylis-Hillman adduct **53** using $Cu(ClO_4)_2{\cdot}6H_2O$ as catalyst (Scheme **24**). In contrast to the amination of ketone derivatives **36** (Scheme **15**), azidation of the ester gave primary azide **54** as the major product. It was observed by *in situ* NMR reaction monitoring that the mixture of regioisomeric azides **54** and **55** is formed first. Regioisomer **55** undergoes slow rearrangement to the thermodynamically more stable isomer **54**.

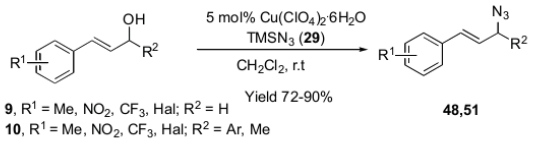
Rana *et al.* reported an efficient one-pot process for direct azidation of allylic alcohols **56** or their methyl ethers **57** followed by a click reaction to give substituted 1,2,3-triazoles **58** [32]. They described two methods involving the sequential reactions (Scheme **25**). Method A involved magnetically separable nano $Fe_3O_4$ catalyzed azidation of allylic alcohols with $TMSN_3$ (**29**) as the first step followed by $CuSO_4{\cdot}H_2O$ catalyzed click reaction of azides with alkynes. In the method B, $Cu(OTf)_2$ served as a single catalyst for both reaction steps.

Powell and Pelletier have reported several examples of the amination of allylic acetates **59-61** with sulfonamides **4** promoted by the catalytic system consisting of $Cu(OTf)_2$ and *t*-BuOOAc (Scheme **26**) [33]. Although detailed mechanistic studies were not performed, it was hypothesized that the reaction proceeds *via* formation of carbenium ion species by abstraction of the acetate by the catalyst.

*Boron Lewis acid catalysis.* Srihari's group presented facile approach for the synthesis of allylic azides **66** from readily available aryl vinyl carbinols **65** (Scheme **27**) [34]. These substrates were subjected to nucleophilic substitution reaction with $TMSN_3$ (**29**) in the presence of catalytic amount of $BF_3{\cdot}OEt_2$ to leading to regioselective formation of

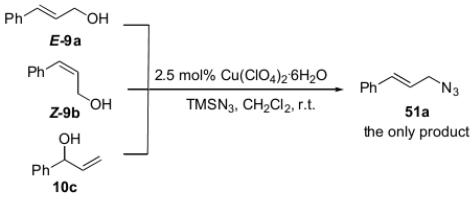



(Scheme **21**). AgOTf catalysed azidation of structurally different allylic alcohols.

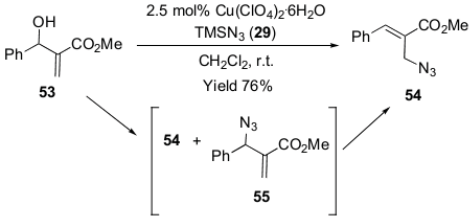



(Scheme **22**). $Cu(ClO_4)_2{\cdot}6H_2O$ catalysed azidation of allylic alcohols **9** and **10**.

primary allylic azides **66**. The formation of intramolecular allylic substitution product **67** was not observed. Authors propose that first both hydroxyl groups in substrates **65a** are silylated with $TMSN_3$ leading to intermediate **68** (Scheme **28**). Next, $BF_3$ activates the silyloxy group in allylic position which is substituted by the attack of azide ion.




(Scheme **23**). Formation of single azidation product **51a** from different alcohol isomers **9a**, ***Z*-9b**, ***E*-10c**.




(Scheme **24**). $Cu(ClO_4)_2{\cdot}6H_2O$ catalysed azidation of Baylis-Hillman adduct **53**.

The scope of the method was demonstrated also for the azidation of several allylic alcohols **10** lacking the phenolic hydroxyl group.

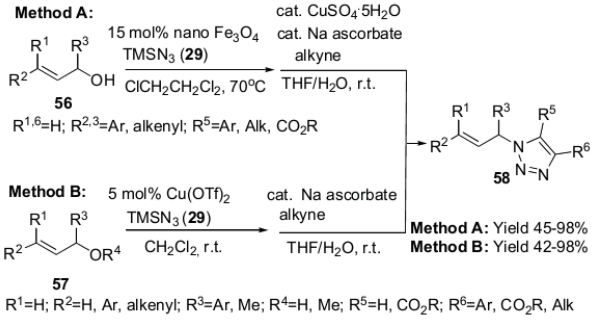
*Calcium Lewis acid catalysis.* Haubenreisser and Niggemann have reported a $Ca(NTf_2)_2/Bu_4NPF_6$ catalytic system for the amination of allylic alcohols [35]. Addition of $Bu_4NPF_6$ as co-catalyst was crucial for the catalytic activity which was presumably due to formation of active $CaNTf_2PF_6$ species *via* anion exchange. The model substrate **8a** reacted with a wide range of non-basic nitrogen nulceohiles such as sulfonamides **4**, carbamates **5**, carboxamides **6** and anilines **27** forming allylamine derivatives **12** (Scheme **29**). The scope of the method was demonstrated for the amination of three different allylic alcohols **8b**, ***E*-10b** and **69** with both carbamate **5h** and aniline **27b** to give allylamine derivatives **12** (Scheme **30**). Substrates **8b**, ***E*-10b** gave $S_N$ prooducts **12d** and **12b**, while in the case of alcohol **69** an $S_N'$ product **12e'** was obtained.

Equilibration of carbamate **12e** with tosyl amide (**4a** under the reaction conditions produced the mixture of products **12e** and **12f** (~1 : 1, after 48 h) indicating that the allylic substitution is reversible (Scheme **31**).

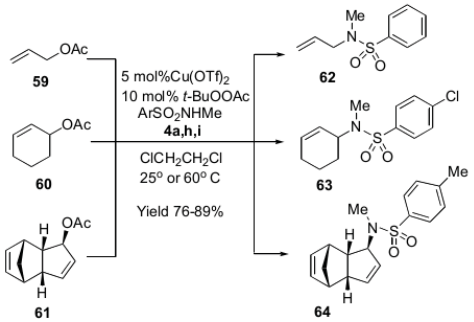
Investigation of the influence of water content revealed that the reaction does not proceed under strictly anhydrous conditions. This observation was not well explained, but may be linked to the reversible formation of ether ROR as an inactive species in the reaction mixture. The presence of water may shift this equilibrium to the more reactive alcohol ROH. The addition of 1, 2 and 5 equivalents of water required heating to facilitate the reaction, which might be associated to the coordination of water to the calcium ion.

*Lewis acid catalysed allylic bis-imidate cyclization.* Jirgensons's group have developed the Lewis acid catalyzed cyclization of *bis*-imidates **70** to give oxazolines and oxazines **71** which are precursors of unsaturated amino alcohols (Scheme **32**) [36-38]. The reaction was proposed to proceed *via* generation of the most stable carbenium ion **C** by abstraction of one imidate group followed by the trapping with another imidate as *N*-nucleophile. This group of reactions was reviewed previously [39].

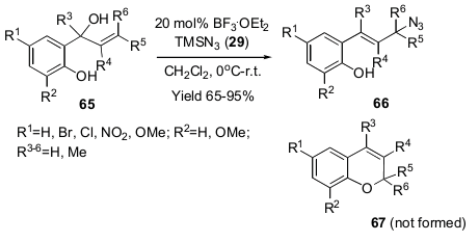
Recent work by Jirgensons's group has demonstrated the synthesis of stereodefined disubstituted oxazolines *cis*-**73** and *trans*-**73** (Scheme **33**) [40]. The stereochemistry of the product formation was defined mainly by the configuration of the double bond in the substrate **72**: *E*-configuration imidate *E*-**72** gave preferentially *cis*-oxazoline *cis*-**73**, while *Z*-configuration imidate *E*-**72** gave preferentially *trans*-oxazoline *trans*-**73**.



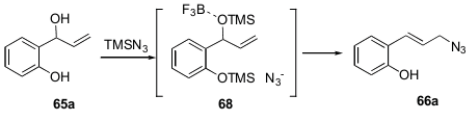

(Scheme **25**). Nano $Fe_3O_4$ and $Cu(OTf)_2$ catalyzed azidation of allylic alcohols.



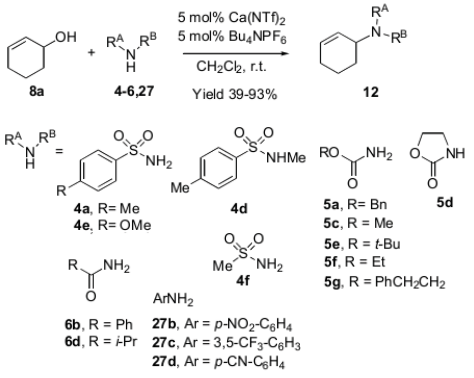

(Scheme **26**). $Cu(OTf)_2$ catalyzed amination of allylic acetates.



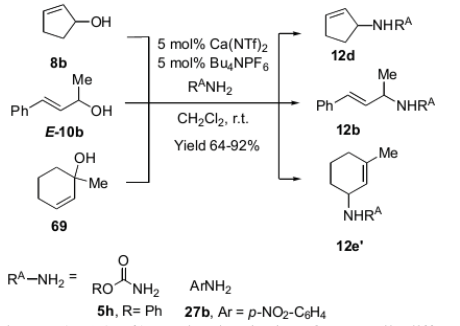

(Scheme **27**). $BF_3OEt_2$ catalysed azidation of allylic alcohols **65**.



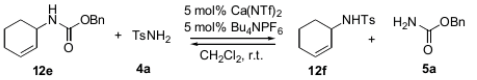

(Scheme **28**). The proposed intermediate **68** in azidation of alcohols **65**.



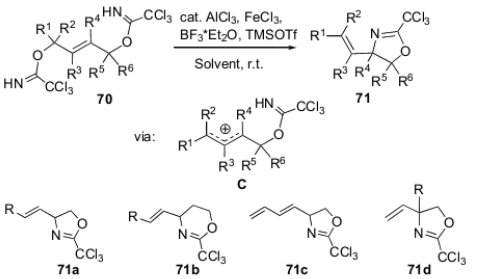

(Scheme **29**). $Ca(NTf_2)_2$ catalysed amination of allylic alcohol **8a**.




(Scheme **30**). $Ca(NTf_2)_2$ catalysed amination of structurally different allylic alcohols **8b**, ***E*-10b**, **69**.




(Scheme **31**). The proof of reversibility in $Ca(NTf_2)_2$ catalysed allylic amination.

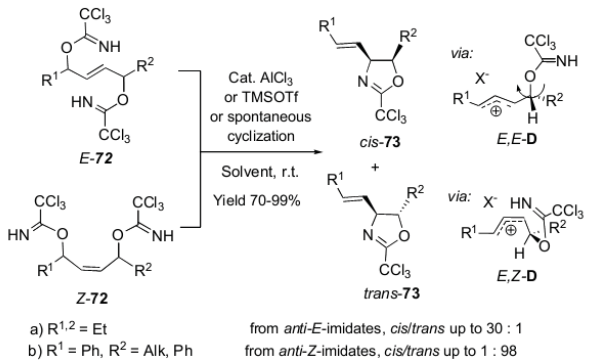



(Scheme **32**). Lewis acid catalysed cyclization of allylic bisimidates **70**.

DFT calculations indicated that the cyclization of carbenium ion **D** has very low activation energy which is comparable to the energy of bond rotations. Based on this the stereoselectivity trends were explained by the formation of the most stable carbenium ion conformations *E,E*-**D** or *E,Z*-**D** followed by the cyclization *via* the energetically most favourable bond rotations.

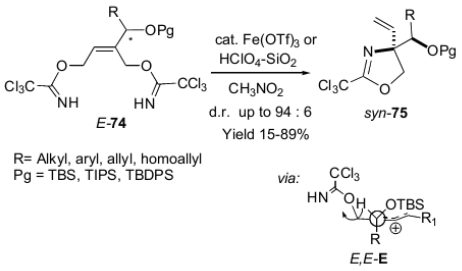
The intramolecular allylic amination of *bis*-imidates was applied to the stereoselective syntheses of oxazolines **75** which are precursors of threoninol derivatives (Scheme **34**) [41].

In analogy to the cyclization of bis-imidates **72** (Scheme **33**), the diasteroeselective cyclization of substrates *E*-**74** to syn-oxazoline *syn*-**75** was explained by the formation of the most stable carbenium ion conformation *E,E*-**E** followed by cyclization *via* most favourable bond rotations (Scheme **34**). The most stable conformation of carbenium ion *E,E*-**E** was proposed where R group is perpendicular to the plane of carbenium ion to minimize the steric interactions while the posi-




(Scheme **33**). Synthesis of stereodefined disubstituted oxazolines *cis*-**73** and *trans*-**73**.

tion of TBSO group is determined by minimized dipole-dipole interaction with imidate and/or repulsive interaction of C-O σ* orbital with carbenium ion. It could be assumed that at the cyclization stage, imidate C-O bond rotation in carbenium ion *E,E*-**E** is energetically most favorable leading to syn-oxazoline *syn*-**75**. This hypothesis was further supported by comparing the cyclization selectivity of double bond isomers *E*-**74a** and *Z*-**74a** (Scheme **35**). In carbenium ion *E,E*-**E** generated from bis-imidate *E*-**74a**, rotation around C-C bond is restricted preventing to form oxazoline *anti*-**75a**. In carbenium ion *E,Z*-**E** generated from the bis-imidate ***E*-74a**, rotation around C-C bond is facilitated which may explain the lack of selectivity in oxazoline **75a** formation for this substrate.




(Scheme **34**). Diastereoselective synthesis of threoninol derivatives *syn*-**75** *via* acid catalysed cyclization of bis-imidates ***E*-74**.

## 2. Bronsted Acid Catalysed Allylic Amination

For several of the Lewis acid catalyzed transformations described above, Bronsted acids such as TfOH [21] and $HClO_4$ [19, 41] were also shown to be effective catalysts. Bronsted acid catalyses may provide additional options such as enantioselective reactions, and design of recyclable catalysts including heterogeneous catalysts as discussed below.

*Homogeneous Bronsted acid catalysis.* The first enantioselective intermolecular amination of allylic alcohols by a chiral phosphoramides was reported by Du and Zhuang (Scheme **36**) [42]. Screening of catalysts for the amination of model substrate **3** with tosylamide (**4a**) revealed **76** as the optimal catalyst for the enatioselective synthesis of allylamine **7** in *ee* 65%. Using catalyst **76**, a range of alcohols **10** were explored as substrates for the synthesis of enantioenriched allylamines **12**. Generally good enantioselectivity was achieved, which dropped in the case of bulky aryl substituents.

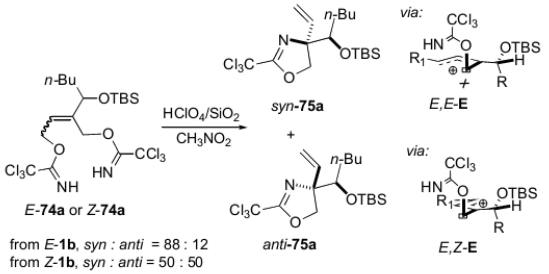
This method is based on the concept of chiral ion-pair directed catalysis, which assumes the formation of chiral contact ion pair **F** between the carbenium ion and chiral Bronsted acid anion (Scheme **37**).

The regioselectivity of amination on carbenium ion **F** is mainly determined by the electronic effect of the substituents. The reaction occurred preferentially at the carbon adjacent to the electron rich aryl group.

The group of Chisholm demonstrated two examples of allylic amination of electron poor dichloroaniline (**27e**) with trichloracetimidates **77** and **78** catalysed by racemic camphorsulfonic acid (CSA) (Scheme **38**) [43]. The proposed reaction mechanism involves generation of carbenium ion intermediate by the protonation of imidate group in substrates **77**,**78** with aniline CSA salt.

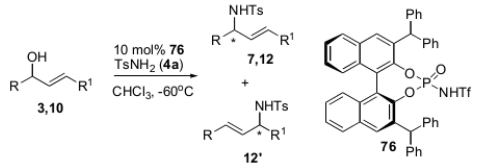
The group of Xia has introduced the sulfonic acid containing ionic liquid [BsTdim][OTf] as an efficient catalyst for amination of allylic alcohol **3** with sulfonamides **4**, carbamates **5**, carboxamides **6** and azoles **81** (Scheme **39**) [44]. It was demonstrated that the catalyst **82** can be recovered and re-used.

A protocol for *C-N* bond formation in water using a water-soluble calyx[4]resorcinarene sulfonic acid **83** was reported by Shimizu *et al*. (Scheme **40**) [45]. Catalyst screening with alcohol **3** as a model substrate revealed that acids such as TfOH, MsOH and TsOH are not effective, while catalyst **83** gave high yields of amination products **7** with tosylamide (**4a**) benzyl carbamate (**5b**) and benzamide (**6a**). Two additional substrates *E*-**10b** and **8a** were also successfully subjected to allylic amination with tosylamide (**4a**) us-



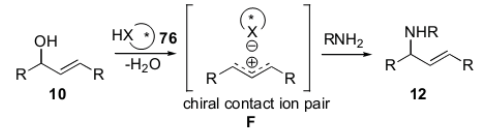

(Scheme **35**). The proposed stereoinduction model for the diastereoselective formation of oxazolines *syn*-**75**.

ing sulfonic acid **83** as a catalyst. Recycling of the catalyst **83** was demonstrated and no decrease in product **7** yield was observed after several repeated uses for alcohol **3** amination.

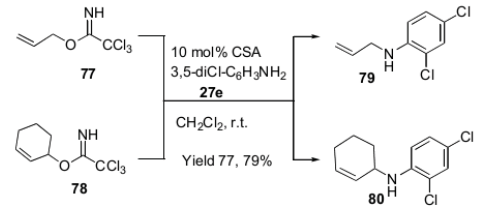



R = $R^1$ = Ar, yield 60-88%, *ee* 18-85%
R =Ar, $R^1$= Ar', yield 16-87%, *ee* 13-94%, regioselectivity 3/1-20/1

(Scheme **36**). Enantioselective amination of allylic alcohols promoted by chiral Bronsted acid catalyst **76**.

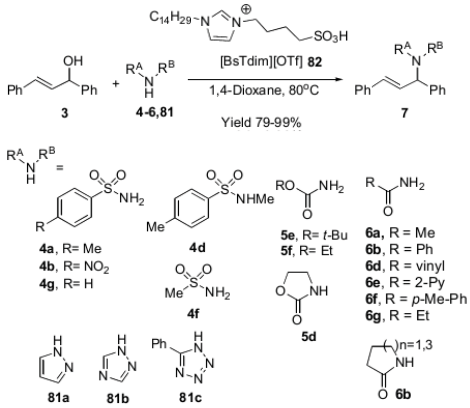



(Scheme **37**). The proposed intermediate chiral contact ion pair **F** in enantioselective allylic substitution.




(Scheme **38**). Camphorsulfonic acid catalysed amination of allylic imidates.

The efficiency of the sulfonic acid **83** was ascribed to its dual-function as a Bronsted acid catalyst and a phase-transfer catalyst according to the plausible mechanism shown in (Scheme **41**). The water-soluble catalyst **83** forms host-guest complexes with alcohols in the organic-aqueous interfacial layer. The dehydration reaction of alcohol is promoted by the sulfonic acid moieties of catalyst **83** resulting in allylic cation which is trapped by the amide to give the amination product.

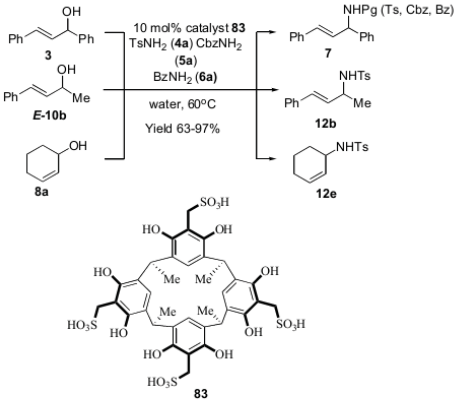



(Scheme **39**). Sulfonic acid containing ionic liquid **82** catalysed amination of allylic alcohol **3**.

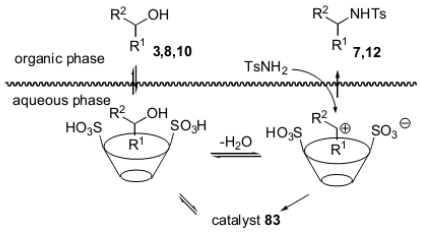
The group of Ren has reported dodecylbenzene sulfonic acid (DBSA) as a surfactant-type catalyst for the intramolecular allylic amination of triazenylaryl allylic alcohols **84** in water as the reaction medium. (Scheme **42**) [46]. This provided 2-pyrorlidine 2-*H* indazoles **85** which can be transformed to indazoles by reduction of the *N-N* bond with Zn.

The same transformation could be achieved with $Bi(OTf)_3$ as a catalyst in $CH_2Cl_2$ as a solvent, which in the case of certain substrates **84** provided better yields of product **85** compared to the DBSA catalyzed reaction [47].

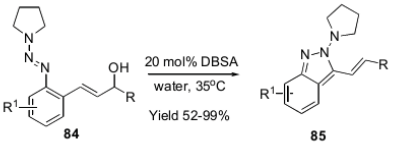
*Heterogenous Bronsted acid catalysis*. Sanz *et al.* demonstrated an example of allylic alcohol **3** amination with *p*-nitroaniline **26a** using polymer-supported *p*-toluenesulfonic acid as catalyst (Scheme **43**) [48].



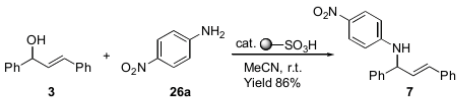

(Scheme **40**). Calyx[4]resorcinarene sulfonic acid **83** catalysed amination of allylic alcohols **3**, ***E*-10b**, **8a**.




(Scheme **41**). The proposed mechanism of sulfonic acid **83** catalysed allylic amination.

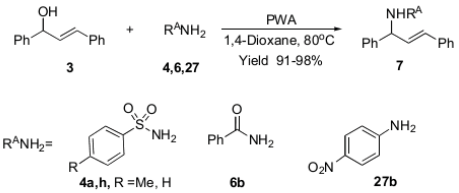



(Scheme **42**). Dodecylbenzene sulfonic acid catalysed intramolecular allylic amination.



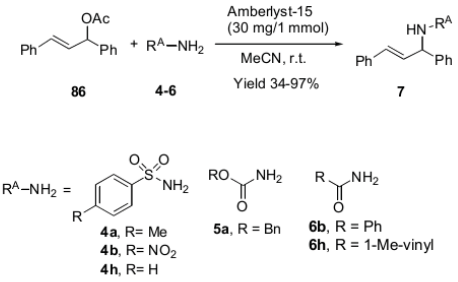

(Scheme **43**). Polymer-supported *p*-toluenesulfonic acid catalysed amination of allylic alcohol **3**.

Wang *et al.* reported an amination of allylic alcohol **3** with benzenesulfonamides **4a,h**, carboxamide **6b** and aniline **27b** by using an insoluble phosphotungstic acid (PWA) catalyst (Scheme **44**) [49]. Carbenium ion species were proposed as intermediates for this reaction.



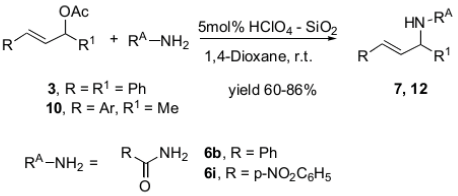

(Scheme **44**). Phosphotungstic acid catalysed amination of allylic alcohol **3**.

Liu *at al* developed the allylation of sulfonamide **4a**,**b**,**h**, carbamate **5a** and carboxamides **6b**,**h** with allylacetate **86** using Amberlyst-15 as a recyclable heterogeneous catalyst (Scheme **45**) [50].



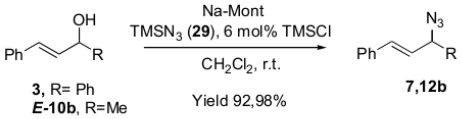

(Scheme **45**). Amberslyst-15 as catalysed amination of allylic acetate **86**.

Song *et al.* have demonstrated $HClO_4$ impregnated $SiO_2$ as another type of heterogeneous catalyst for the allylic amination of allylic alcohols **3**,**10** with carboxamides **6b**,**i** (Scheme **46**) [51].



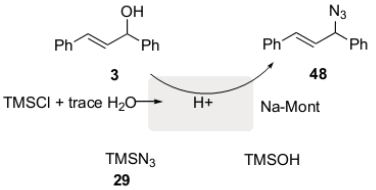

(Scheme **46**). $HClO_4$ impregnated $SiO_2$ catalysed amination of allylic alcohols **3**,**10**.

A combination of TMSCl and natural montmorillonite clay was shown as an efficient solid acid catalyst for the azidation of allylic alcohols **3**,**10b** with trimethylsilyl azide (**29**) (Scheme **47**) [52].



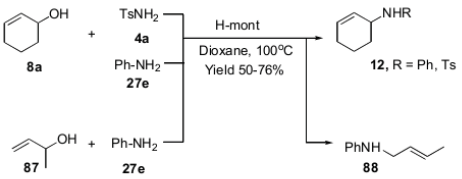

(Scheme **47**). Montmorillonite clay catalysed azidation of allylic alcohols **3**,**10**.

A plausible reaction mechanism is shown in (Scheme **48**). Trace of water in the solvent or Na-Mont catalyst most likely initiated generation of HCl from hydrolysis of TMSCl. The absorbed HCl inside the Na-Mont catalyst promotes the generation of a carbenium ion, which then reacts with $TMSN_3$ (**29**) forming the corresponding azide **48** and trimethylsilanol.



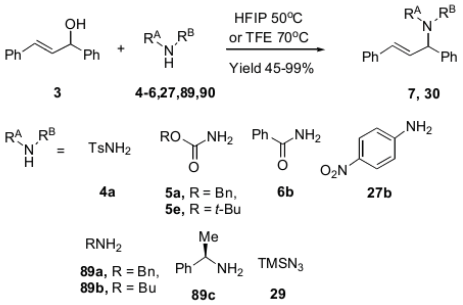

(Scheme **48**). The proposed mechanism for montmorillonite clay catalysed allylic azidation.

The proton exchanged montmorillonite (H-mont) can efficiently catalyze allylic substitution of allylic alcohols **8a**,**87** with electron deficient *N*-nucleophiles such as aniline (**27e**) and *p*-toluenesulfonamide (**4a**). This afforded the corresponding allylic amines **12**,**88** in good yields (Scheme **49**) [53].

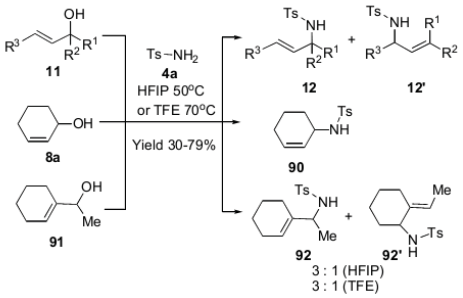



(Scheme **49**). Acidic montmorillonite catalysed amination of allylic alcohols **8a**, **87**.

*Acidic solvents.* Najera's group has demonstrated that Bronsted acidic fluorinated alcohol solvents such as 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and 2,2,2-trifluoroethanol (TFE) induce the reaction of allylic alcohols with nitrogen nucleophiles (Schemes **50**, **51**) [54]. The developed procedure is simple, works under mild conditions (r.t., 50 and 70 °C) providing high yields, especially when HFIP is used as a solvent and aryl group containing allylic alcohols are used the substrates. Using allylic alcohol **3** as a model substrate, it was shown that sulfonamide **4a**, carbamates **5a**,**e**, carboxamide **6b**, and amines **27b**,**89a-c** can be successfully utilized as nitrogen nucleophiles. Trimethylsilylazide **29** was also a suitable nucleophile to make allylic azide **30**.



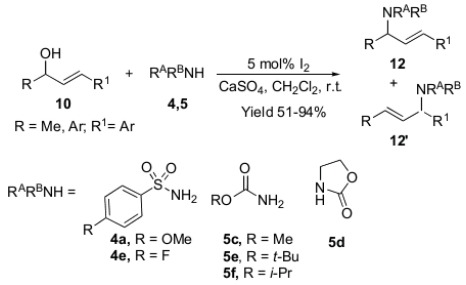

(Scheme **50**). Amination of allylic alcohol **3** in fluorinated alcohol solvents.




(Scheme **51**). Amination of structurally different allylic alcohols in fluorinated alcohol solvents.

The scope of the reaction was demonstrated for the allylic amination of structurally diverse substrates **8a**, **11, 91** with tosylamide (**4a**) (Scheme **51**). The regioselectivity for aryl group containing substrates **11** was in favour to the isomer **12** with conjugated double bond ($R^3$ = Ar). In the case substrate **11** with aliphatic substituents ($R^{1,2}$= Me, $R^3$ = H) poor regioselectivity in the amination was observed, while in the case ($R^{1-3}$= Me) only the formation of allylamine derivative **12′** was reported in low yield. Regioselectivity was poor also in the case of cyclic substrate **91**.

*Iodine as catalyst.* The group of Chan reported iodine-catalyzed allylic alkylation of sulfonamides **4** and carbamates **5** with allylic alcohols **10** (Scheme **52**) [55]. The formation of an allylic carbenium ion intermediate was proposed resulting from the reaction of the allylic alcohol **10** with *in situ* generated HI. In the case of the unsymmetrically substituted substrates **10** (R = Me; $R^1$ = Ar), regioselective formation of products **12** with conjugated double bond formed; while in the case of substrates **10** (R = Ar; $R^1$ = Ar′) mixtures of isomers formed.




(Scheme **52**). Iodine catalysed amination of allylic alcohols **10**.

Iodine as catalyst for allylic amination transformations was demonstrated by Wang *et al.* and Liu *et al*. in acetonitrile as a solvent [56-58].

## CONCLUSION

Allylic amination *via* acid catalyzed activation of a leaving group involves non-expensive and low toxic Lewis acid and Bronsted acid catalysts and in many cases non-toxic by-products such as water or acetic acid are generated. Moreover the design of catalysts to perform the reactions in water as a solvent and the use of recyclable catalysts has been advanced in recent years. Consequently, this reaction type meets many criteria of the green chemistry paradigm. Less developed are asymmetric transformations for this type of allylic amination which are currently limited to few examples of chirality transfer, substrate controlled diastereoselectivity and enantioselective catalysis. It is expected that the next decade will bring achievements in asymmetric allylic amination *via* acid catalyzed activation of a leaving group to broaden the scope of this method for the synthesis of allyl amine derivatives.

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

## ACKNOWLEDGEMENTS

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**Skvorcova, M.**; Lukasevics, L.; Jirgensons, A. **Ritter-type Amination of Carbenium Ions Generated by Directed Protonolysis of Cyclopropane.** *Manuscript.*

# Ritter-type Amination of Carbenium Ions Generated by Directed Protonolysis of Cyclopropane

Marija Skvorcova, Lukass T. Lukasevics, and Aigars Jirgensons*

A directed intramolecular protonolyis of cyclopropane C-C bond is demonstrated as a strategy to generate carbenium ion for the amination with nitriles under Ritter reaction conditions. Directing groups such as carbamate, carboxamide, urea, ester and ketone were found efficient for regioselective anti-Markovnikov cleavage of cyclopropane. Depending on the directing group, the Ritter-type amination provided orthogonally protected 1,4-diamine, ε–amino carboxylic, and ε-amino ketone derivatives.

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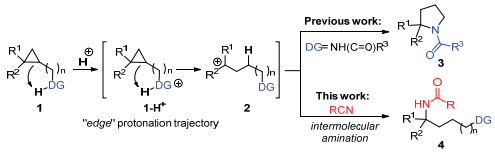
## Introduction

Functionalization of *C-C* bond can provide an acess to useful compounds from readlily availble starting materials and as such has received an increased attention in recent years.[1-5] However, development of such a transformation is a very challanging task due to the relative inertness of this sigma bond. In cyclopropane, due to the ring strain, the overalp of *C-C* bond forming electrons is less efficient which makes the character of the molecular orbital more similar to π-bond.[6-10] The reactivity of cyclopropane has been demonstrated in the metal promoted reactions[3,11-16] and at the exposure to electrophiles such as halogenes, hypervalent iodine, Lewis and Brensted acids.[17-23] The regioselectivity of electrophilic cyclopropane cleavage typically is high except for protonolysis. Modified, anti-Markovnikov rule has been proposed to predict the protolytic *C-C* bond cleavage between the most substituted and least subsituted carbons of cyclopropane, however with few exceptions the selectivity is moderate.[18] Recently, we reported that the *C-C* bond of acylated aminomethyl cyclopropanes can be regioselectively cleaved in anti-Markovnikov fassion between the two most substituted carbons. In this transformation, protonated amide **1-H⁺** (DG = NH(C=O)R³) served as a directing group for intramolecular proton transfer to C-C bond *via* "edge" trajectory leading to carbenium ion **2** formation (Scheme 1).[24] Intramolecular amination of the carbenium ion **2** with amide provided pyrrolidines **3** in good yields.



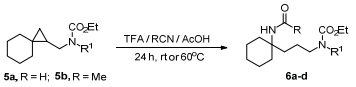

Scheme 1.

To extend the application of carbenium ions **2** generated by cyclopropane **1** cleavage, we explored the Ritter-type intermolecular amination.[25,26] In the context of this reaction, we also investigated the scope of directing groups for selective cyclopropane C-C bond protolysis.

## Results and discussion

To examine the intermolecular amination of carbenium ion **2**, cyclopropane derivatives **5a,b** were subjected to the reaction with nitriles using TFA as a proton source (Table 1). The reaction of carbamate **5a** with acetonitrile provided the desired product **6a**, although in low yield (*Table 1,* entry 1). Not unexpectedly, significant amount of pyrrolidine **3** (Scheme 1) was produced from the substrate **5a**. To suppress the cyclization reaction, the carbamate *nitrogen* was *blocked* by introduction of a methyl group. Consequently, the reaction of *N*-methylated analogue **5b** with acetonitrile provided *diamine derivative 6b in medium yield (Table 1, entry 2).* The *a*ddition of AcOH to the reaction mixture and increased temperature was beneficial to improve the yield of *product* **6b** *(Table 1, entry 3). Chloroacetonitrile[27] and benzonitrile were also found as suitable amino components for the transformation of substrate 5b to diamine derivatives 6c and 6d (Table 1, entries 4 and 5).*

**Table 1. Optimization of the Ritter-type Amination[a]**




**5a**, R = H; **5b**, R = Me — **6a-d**

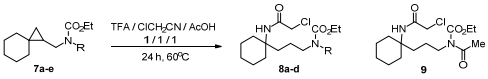
| entry | $R^1$ | RCN | temp. | ratio of TFA / RCN / AcOH | Product, yield (%) |
|---|---|---|---|---|---|
| 1 | H | MeCN | rt | 4 / 1 / 0 | **6a**, 9 |
| 2 | Me | MeCN | rt | 4 / 1 / 0 | **6b**, 62 |
| 3 | Me | MeCN | 60 | 1 / 1 / 1 | **6b**, 84 |
| 4 | Me | $ClCH_2CN$ | 60 | 1 / 1 / 1 | **6c**, 84 |
| 5 | Me | PhCN | 60 | 1 / 1 / 1 | **6d**, 77 |

[a]Reactions were performed on a 0.22 - 0.47 mmol scale, *c* = 0.1 M. Isolated yields are given.

With the efficient amination conditions in hand, the scope of the carbamate *N*-substituents was examined (Table 2). In the reaction with chloroacetonitrile, substrates **7a-d** bearing different types of *N*-substituents gave the desired amination products **8a-d** in good yields (Table 2, entries 1-4). Interestingly, *N*-PMB substituted carbamate **7e** gave *N*-acetylated product **9**. Such a product formation can be explained by the formation of acylium ion from acetic acid which presumably attacks the carbamate function after the cleavage of PMB group in acidic conditions (Table 2, entry 5).

The scope of cyclopropane substitution was investigated for substrates **10a-e** in the Ritter reaction with chloroacetonitrile (Table 3). 2-Me,2-Ph-substituted substrate **10a** gave product **11a** in lower yield (Table 3, entry 1) compared to 2,2-dialkyl substituted cyclopropanes **5b** and **7a-e** (Tables 1, 2). The introduction of an additional substituent at the 2,2-dialkyl cyclopropane ring (substrates **10b,c**) led to drop in the yields of products **11b,c** (Table 3, entries 2,3). 2,2,3,3-Tetrasubstituted cyclopropane **10d** failed to give amide **11d**, instead significant amount of *C-N* bond ionization product was isolated (Table 3, entry 4). With cyclopropane **10e** bearing only Ph group in the 2-position, the reaction did not occur at all (Table 3, entry 5).

**Table 2. Scope of the Carbamate *N*-Substituent**[a]

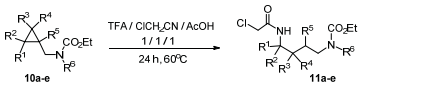



**7a-e** **8a-d** **9**

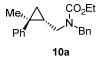
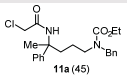
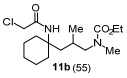
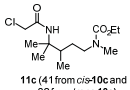
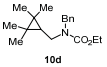
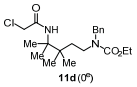
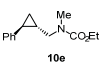
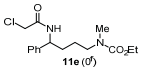
| entry | Substrate, R | Product, yield (%) |
|---|---|---|
| 1 | **7a**, Bn | **8a**, 63 |
| 2 | **7b**, allyl | **8b**,90 |
| 3 | **7c**, propargyl | **8c**,88 |
| 4 | **7d**, Ph | **8d**,74 |
| 5 | **7e**, PMB | **9**, 87 |

[a]Reactions were performed on a 0.15 – 0.48 mmol scale, *c* = 0.1 M. Isolated yields are given.

**Table 3. Scope of cyclopropane substitution**[a]



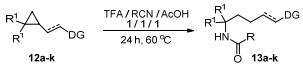

**10a-e** **11a-e**

| entry | substrate | product (yield %) |
|---|---|---|
| 1 |  **10a** |  **11a** (45) |
| 2 |  **10b** |  **11b** (55) |
| 3 |  *cis*-**10c** *trans*-**10c** |  **11c** (41 from *cis*-**10c** and 32 from *trans*-**10c**) |
| 4 |  **10d** |  **11d** (0[d]) |
| 5 |  **10e** |  **11e** (0[f]) |

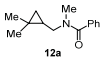
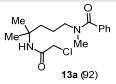
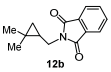
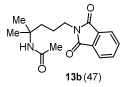
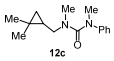
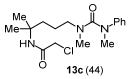
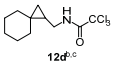
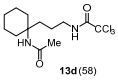
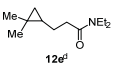
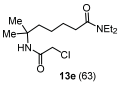
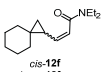
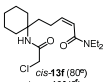
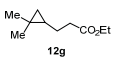
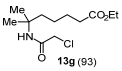
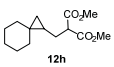
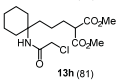
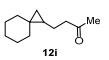
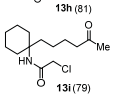
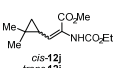
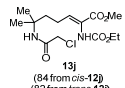
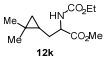
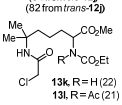
[a]Reactions were performed on a 0.12 - 0.25 mmol scale, *c* = 0.1 M. Isolated yields are given.[e]mixture of products. Ionization of substrate **10d** was observed leading to ethyl acetyl(benzyl)carbamate as main product; [f]no reaction of susbtrate **10e**.

Next, the scope of directing groups for intermolecular proton transfer in substrates **12a-k** were explored to generate carbenium ions for the Ritter-type amination (Table 4). The reaction of chloroacetonitrile with *N*-methylbenzamide **12a** provided the desired diamine derivative **13a** in high yield (Table 4, entry 1). Phtalimide and urea in substrates **12b,c** were less efficient directing groups leading to lower yield of products **13b,d** due to the side product formation (Table 4, entries 2,3). The reaction of acetonitrile with substrate **12d** containing trichloroacetamido group gave considerably improved yield of diamine **13d** (Table 4, entry 4) compared to analogues ethoxycarbamate **5a** (Table 1). This can be attributed to weaker nucleophilicity of trichloroacetamide preventing the intramolecular amination.

**Table 4. Scope of the Directing Groups**[a]




**12a-k** **13a-k**

| entry | substrate | product (yield %) |
|---|---|---|
| 1 |  **12a** |  **13a** (92) |
| 2 |  **12b** |  **13b** (47) |
| 3 |  **12c** |  **13c** (44) |
| 4 |  **12d**[b,c] |  **13d** (58) |
| 5 |  **12e**[d] |  **13e** (63) |
| 6 |  *cis*-**12f** *trans*-**12f** |  *cis*-**13f** (80[e]) *trans*-**13f** (0[f]) |
| 7 |  **12g** |  **13g** (93) |
| 8 |  **12h** |  **13h** (81) |
| 9 |  **12i** |  **13i** (79) |
| 10 |  *cis*-**12j** *trans*-**12j** |  **13j** (84 from *cis*-**12j**) (82 from *trans*-**12j**) |
| 11 |  **12k** |  **13k**, R = H (22) **13l**, R = Ac (21) |

[a]Reactions were performed on 0.08 – 0.47 mmol scale, *c* = 0.1 M. Isolated yields are given. [b]*reaction conditions: 25% TFA in MeCN, rt;* [c]*addition of AcOH reduce the yield;* [d]reaction was performed at rt - mixture of products at higher temperature. [e]NMR yield determined by using 1,3-*bis*(*trichloromethyl*)*benzene;* [f]*no reaction.*

Carboxamide **12e** also proved to be competent substrate providing the product **13e** in medium yield (Table 4, entry 5).

Notable difference in the reactivity was observed for *α,β*-unsaturated amide isomers *cis*-**12f** and *trans*-**12f** (Table 4, entry 6). Isomer *cis*-**12f** gave the desired product *cis*-**13f** smoothly, while the other isomer *trans*-**12f** was unreactive. Such a result is in accordance with intramolecular proton transfer to *C-C* bond of cyclopropane in isomer *cis*-**12f** which is not possible for isomer *trans*-**12f**. Ester and keto groups in substrates **12g-i** were found as very efficient directing groups for the protolysis of cyclopropane leading to amination products **13g-i** in the reaction with chloroacetonitrile (Table 4, entries 7-9). The results with amides **12e**,***cis*-12f**, esters **12g,h** and ketone **12i** strongly indicates that the oxygen atom is involved in intramolecular proton transfer to cyclopropane. Both isomers of unsaturated amino acid *cis*-**12j** and *trans*-**12j** were transformed to chloroacetamide **13j** in good yields. (Table 4, entry 10). The product **13j** formation as a single isomer can be explained by the acid promoted isomerization of the double bond either in substrate or in the product to form the thermodynamically more stable *cis*-isomer. Saturated analogue **12k** bearing more nucleophilic carbamate function gave the expected product **13k** with significantly reduced yield together with *N*-acylated by-product **13l**.

## Conclusions

Carbenium ions generated by directed protonolysis of cyclopropane can be intermoleculary aminated under Ritter-type reaction conditions. Several functional groups such as carbamate carboxamide, urea, ester and ketone efficiently direct regioselective protonolytic cleavage of cyclopropane C-C bond to generate the carbenium ion.

### Conflicts of interest

There are no conflicts to declare.

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