**Ph.D. thesis**


# Diversity-oriented synthesis of functionalized alicycles through dipolar cycloaddition/metathesis reaction protocols


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# University of Szeged

# Doctoral School of Pharmaceutical Sciences

Educational programme:   Pharmaceutical Chemistry and Drugs Research

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## 1. Introduction and aims

In the past two decades, diversity-oriented synthesis (DOS) has been recognized as a widely used procedure to generate highly functionalized three-dimensional small-molecules containing molecular libraries. During last ten years, more attention has been paid to the preparation of structurally and functionally diverse molecules than rather increasing molecular size. The metathesis reaction is an efficient, widespread method for the formation of C=C bonds, due to the mild reaction conditions and its capability to create structurally diverse molecules.

Functionalized isoxazoline skeleton containing molecules have a variety of biological properties, thus play an important role in organic and medicinal chemistry. Furthermore, the isoxazoline skeleton can be transformed into various valuable scaffolds, such as amino alcohols, amino diols, β-hydroxyketones.

In the Institute of Pharmaceutical Chemistry, isoxazoline derivatives were synthesized by starting from unsaturated cyclic β-amino acids by using regio- and stereoselective 1,3-dipolar cycloaddition of nitrile oxide. Furthermore, cyclic β-amino acids and β-lactams were modified via metathesis reactions (ROM and CM). Thus versatile substituted β-amino acids and β-lactams were prepared successfully.

The present Ph.D. work aims were the selective transformations of cyclodienes through 1,3-dipolar cycloaddition. For these transformations, various types and members of cyclodienes were used as starting materials. The free C=C bonds of the prepared isoxazoline derivatives were further transformed by metathesis reactions. Electron-deficient terminal olefins (methyl acrylate and methyl vinyl ketone), and fluorinated olefins were used as cross-partners since our additional goal was to supplement the circle of the prepared compounds with some fluorine containing derivatives.

## 2. Applied methods

The products of my reactions were separated and purified by column chromatography on silica gel. The prepared compounds were characterized by melting point measurement, NMR, and high resolution mass spectrometry (HRMS) measurements. The regio- and stereochemistry of the compounds were determined based on 2D spectra (COSY, NOESY, HSQC, and HMBC) measured with a 500 MHz NMR instrument.

## 3. Results and discussion

### 3.1. Synthesis of isoxazoline derivatives

The regio- and stereoisomers of isoxazoline derivatives condensed with an alicyclic ring were prepared by 1,3-dipolar cycloaddition of nitrile oxide (generated from $EtNO_2$, $nPrNO_2$ as well as $BnNO_2$ with $Boc_2O$ as dehydration agent and DMAP as the base) to various cyclodienes (cyclopentadiene, 1,4-cyclohexadiene, 1,3-cyclohexadiene, 1,5-cyclooctadiene, 1,3-cyclooctadiene, and 2,5-norbornadiene) as starting materials.



(i) $EtNO_2$/$nPrNO_2$/$BnNO_2$, $Boc_2O$, DMAP, MeCN, 20-80 °C, 24-48 h
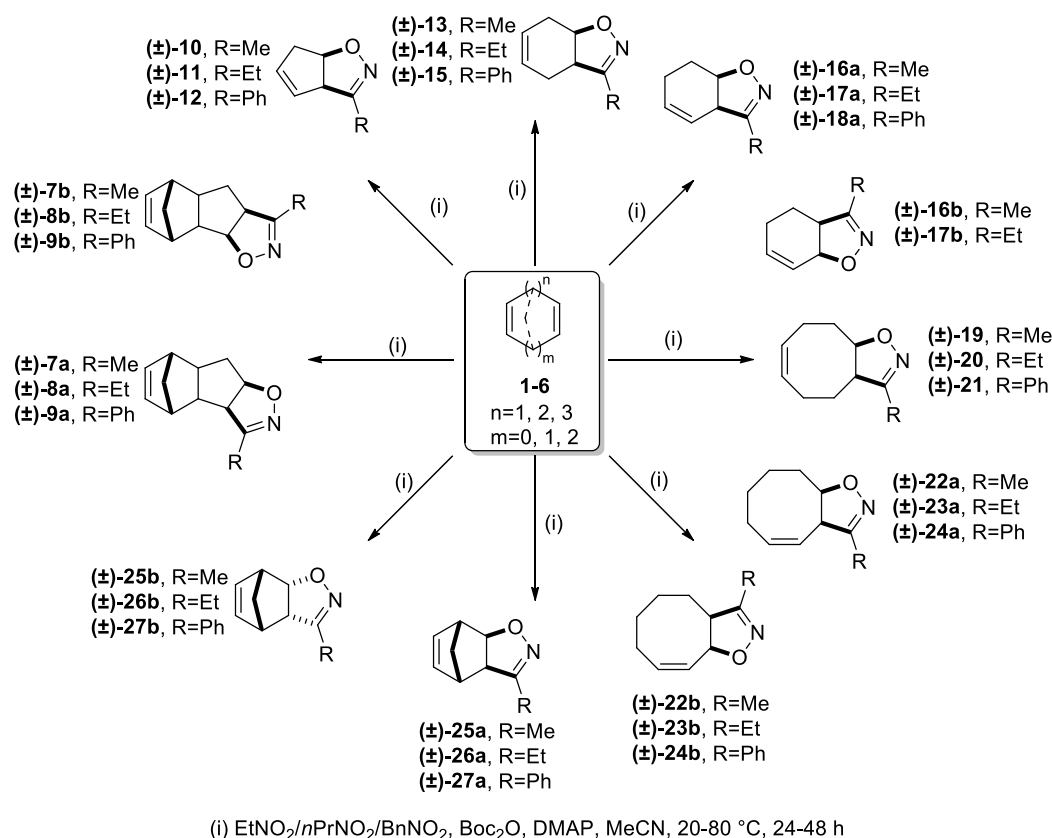
**Scheme 1:** Synthesis of isoxazoline derivatives condensed with an alicyclic ring

As long as cyclopentadiene (**1**) was used as a starting material, besides the cycloaddition adduct **(±)-10–(±)-12**, dicyclopentadiene-condensed isoxazoline regioisomers **(±)-7ab–(±)-9ab** were obtained as main products. Starting from 1,4-cyclohexadiene (**2**), only traces of the cycloaddition products were obtained, but starting from its stereoisomer 1,3-cyclohexadiene (**3**), regioisomeric products were obtained. The main products in each case were compounds **(±)-16a–(±)-18a**. When phenylnitromethane was used as the nitrile oxide source, formation of the minor cycloaddition product **(±)-18b** did not occur. In the case of 1,5-cyclooctadiene (**4**), a single product [**(±)-19–(±)-21**] was obtained in each case in moderate yield. In the case of 1,3-cyclooctadiene (**5**), a mixture of regioisomers **(±)-22ab–(±)-24ab** was also achieved, and their separation was unsuccessful. However, the ratio of their formation was successfully determined

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in each case based on 2D NMR spectra (COSY, HSQC). In the dipolar cycloaddition reaction of nitrile oxide to 2,5-norbornadiene (**6**), two products were obtained in good yield. The main product was the *exo* stereoisomer and the by-product was the *endo* stereoisomer. Their separation was successful in all cases by column chromatography. (Scheme 1)

The prepared isoxazoline derivatives [**(±)-7a/b–(±)-27a/b**] were used as starting materials in the next experiments.

### 3.2. Transformation of isoxazoline derivatives via ring-opening metathesis

Stereocontrolled ring-opening metathesis was accomplished to isoxazoline derivatives, the corresponding ring-opened products were obtained with a good to excellent yield. The ring-opening metathesis (ROM) was carried out in ethylene atmosphere, at room temperature in the presence of ruthenium based catalyst (1st generation Grubbs and Hoveyda-Grubbs, 2nd generation Grubbs and Hoveyda-Grubbs, as well as 3rd generation Grubbs catalyst) for 2 hours. (Figure 1)
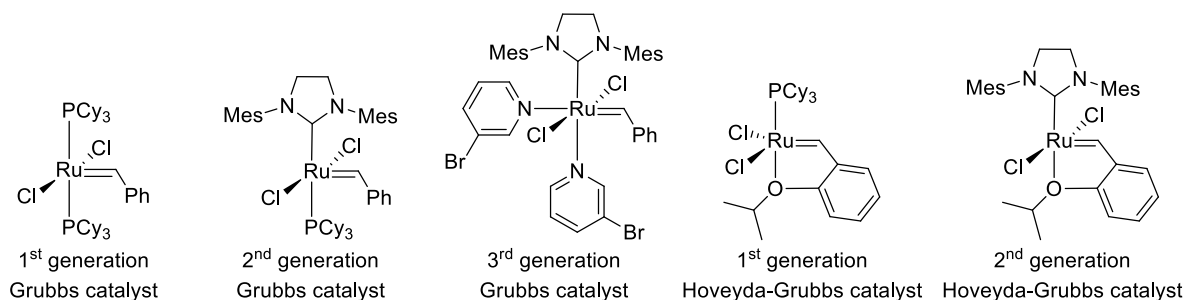


**Figure 1:** The applied Ru-based catalysts

Small amount of polymeric products were also formed besides ring-opened products. The catalyst degradation proved to be a good solution to repress the polymer formation, for this reason $NaHCO_3/H_2O$ and MeOH solution was used.

Ring-opening metathesis of 3-methyl-cyclooctene-isoxazoline **(±)-19** was performed from the prepared cyclooctene skeleton condensed isoxazoline derivatives. During the reaction, a single product was isolated after purification by column chromatography in 68% yield. (Scheme 2)
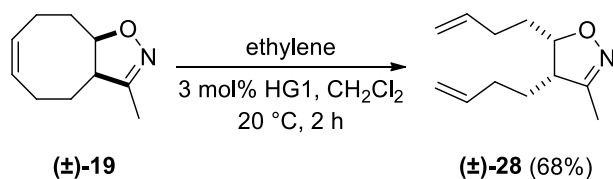


**Scheme 2:** Ring-opening metathesis of 3-methyl-cyclooctene-isoxazoline [**(±)-19**]

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In the ring-opening metathesis of isoxazoline derivatives condensed with norbornene skeleton [(±)-25a–(±)-27a], we aimed to test the performance of some commercially available catalysts. During the reactions, a single product was isolated, the (±)-29–(±)-31 ring-opened isoxazoline derivatives. (Scheme 3) We found that the HG1 catalyst resulted in the ring-opened products in good to excellent yields. In the case of the 2nd generation catalysts (G2 and HG2), better results were obtained with a reaction time of 1 h than 2 h, and the 3rd generation Grubbs catalyst required a particularly short reaction time, 10 min. The main reason for this was the formation of polymers.



**(±)-25a**, R=Me  
**(±)-26a**, R=Et  
**(±)-27a**, R=Ph  

**(±)-29**, R=Me (76%)  
**(±)-30**, R=Et (75%)  
**(±)-31**, R=Ph (87%)  
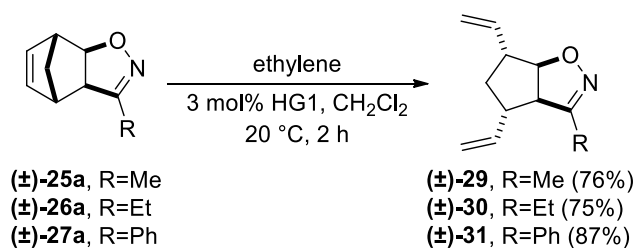
**Scheme 3:** Synthesis of isoxazoline derivatives condensed with divinyl-substituted cyclopentane skeleton

### 3.3. Transformation of isoxazoline derivatives via cross metathesis

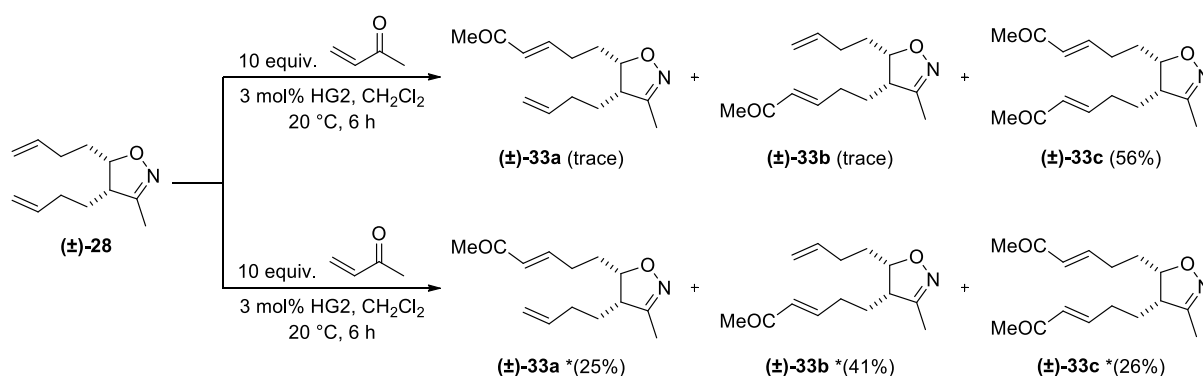#### 3.3.1. Cross metathesis with methyl acrylate and methyl vinyl ketone

The C=C bond of the dialkenyl substituted isoxazoline derivatives allows further functionalizations. The cross metathesis was carried out in $CH_2Cl_2$ in the presence of Ru-based catalysts (G2, HG2, and G3). Methyl acrylate, methyl vinyl ketone, and various fluorinated terminal olefins were used as cross-partners. The reactions took place in a stereocontrolled manner and the products have *E* geometry in all cases.

During transformation of compound **(±)-28** by using methyl acrylate as cross-partner monocoupled regioisomers **(±)-32a** and **(±)-32b** were formed in a variable ratio and yield in addition to dicoupled product **(±)-32c**. We experienced that, when the reaction was carried out at room temperature, in the presence of HG2 catalyst for 6 hours significant amount of monocoupled products **(±)-32a** and **(±)-32b** were formed. When the reaction was executed at reflux, in the presence of HG2 catalyst for 2 hours the dicoupled product **(±)-32c** was formed in a good yield. We also studied the effect of the catalyst. (Scheme 4)
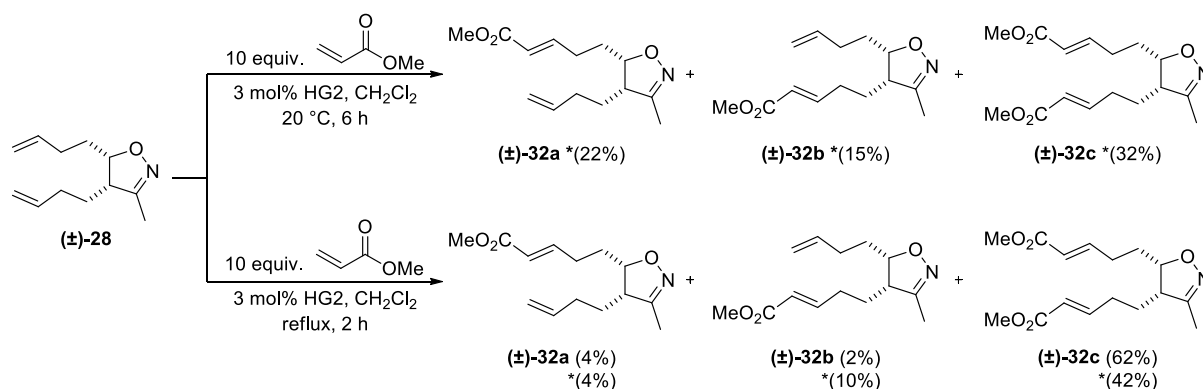
**Scheme 4:** Synthesis of cross-metathesized products with methyl acrylate; (*yields with catalyst degradation)

In that case, when methyl vinyl ketone was used as cross-partner, monocoupled regioisomers [(±)-33a and (±)-33b] and dicoupled product [(±)-33c] were obtained. The reaction was carried out at room temperature in the presence of HG2 catalyst for 6 hours. We studied the effect of the catalyst as well. (Scheme 5)



**Scheme 5:** Synthesis of cross-metathesized products with methyl vinyl ketone; (*yields with catalyst degradation)

The separation of the monocoupled regioisomers (±)-32a/b and (±)-33a/b was successful by column chromatography. The structure of the regioisomers was determined by 2D NMR (COSY, HSQC, and HMBC) data.

Expanding the cross metathesis to isoxazoline derivatives condensed with divinyl substituted cyclopentane skeleton (±)-29–(±)-31, cross metathesis with methyl acrylate and methyl vinyl ketone gave similar results. During the reactions, monocoupled regioisomers (±)-34ab–(±)-39ab and dicoupled products (±)-34c–(±)-39c were formed. The separation of the monocoupled regioisomers [(±)-34ab, (±)-35ab, (±)-38ab, and (±)-39ab] was unsuccessful, but the ratio of their formation was determined in all cases. (Scheme 6)
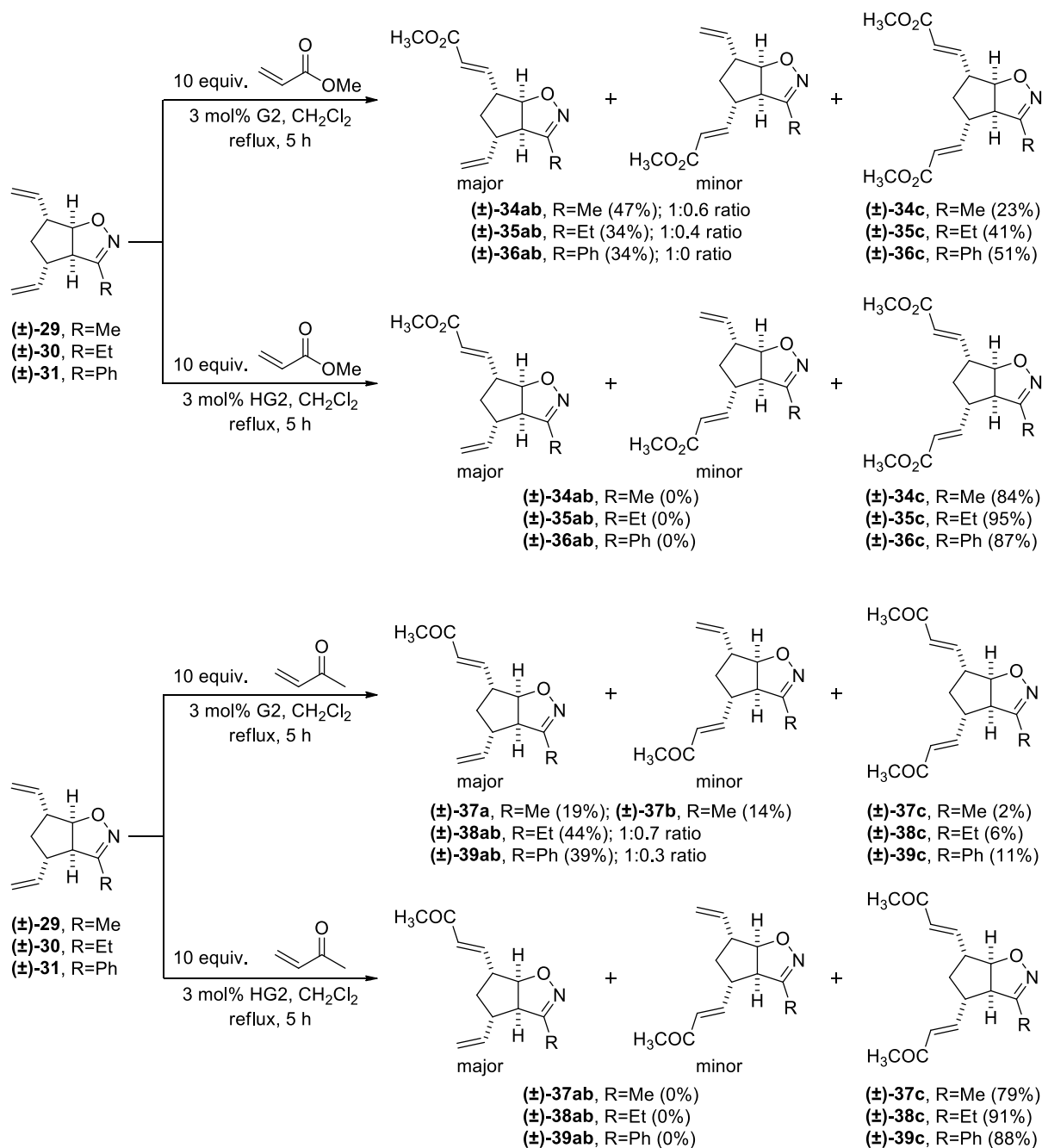
**Scheme 6:** Transformation of divinyl-cyclopenta-isoxazoline derivatives [(±)-29–(±)-31] via cross-metathesis with methyl acrylate and methyl vinyl ketone

Generally speaking, the application of the G2 and G3 catalysts resulted in monocoupled regioisomers, until the HG2 catalyst led to dicoupled product in a good yield. In the case of methyl-, ethyl- and phenyl-substituted isoxazoline derivatives it was found that the ratio of minor product [(±)-34b–(±)-39b] formation decreased in line with the increasing molecular size of the isoxazoline ring substituent. This phenomenon most probably is due to steric reasons. (Figure 2)
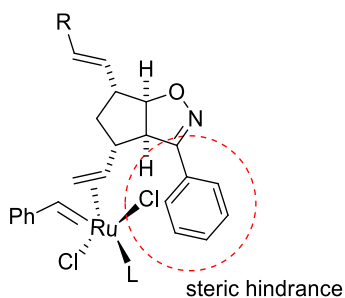
**Figure 2:** The formed steric hindrance between the ligand of the catalyst and Ph group in the intermediate

### 3.3.2. Cross metathesis with fluorinated olefins

Considering the wide biological significance of fluorine-containing compounds, we aimed to supplement the range of synthesized compounds with fluorinated derivatives. To this end, fluorine containing terminal olefins were used as cross-partners, such as 2-bromo-3,3,3-trifluoro-1-propene, 4-bromo-3,3,4,4-tetrafluoro-1-butene, allyl 1,1,2,3,3,3-hexafluoropropyl ether, methyl 2-fluoroacrylate, allyl trifluoroacetate, 1,1,1,3,3,3-hexafluoroisopropyl acrylate, 1H,1H-heptafluorobutyl acrylate, 2,2,2-trifluoroethyl acrylate, 4-fluorostyrene, 2-allylhexafluoroisopropanol or allyl-1H,1H,2H,2H-perfluorooctyl ether. The cross metathesis reaction was carried out in $CH_2Cl_2$ in the presence of Ru-based catalyst (G2, HG2, and G3) in the same manner as before.

In that case, when dialkenyl substituted β-lactam [(±)-40 and (±)-44] and its *N*-Boc protected counterpart [(±)-41] or divinyl substituted bicyclic β-lactam [(±)-46] and its *N*-Boc protected counterpart [(±)-47] were used as starting materials in the cross metathesis reaction, and allyl 1,1,2,3,3,3-hexafluoropropyl ether was used as cross-partner, the dicoupled products were formed during the reactions. (Scheme 7)

In the case of *N*-Boc protected β-lactam [(±)-50] when the reaction was carried out at reflux a monocoupled regioisomer [(±)-51a] also was formed besides the dicoupled product [(±)-51b]. Two factors can contribute to the outcome of the reaction. On the one hand, chelation of the metallacycle intermediate with the carbonyl oxygen can hinder further reactions by stabilizing the metallacycle. On the other hand, the steric hindrance of the vinyl group can minimize its reactivity. (Scheme 7)
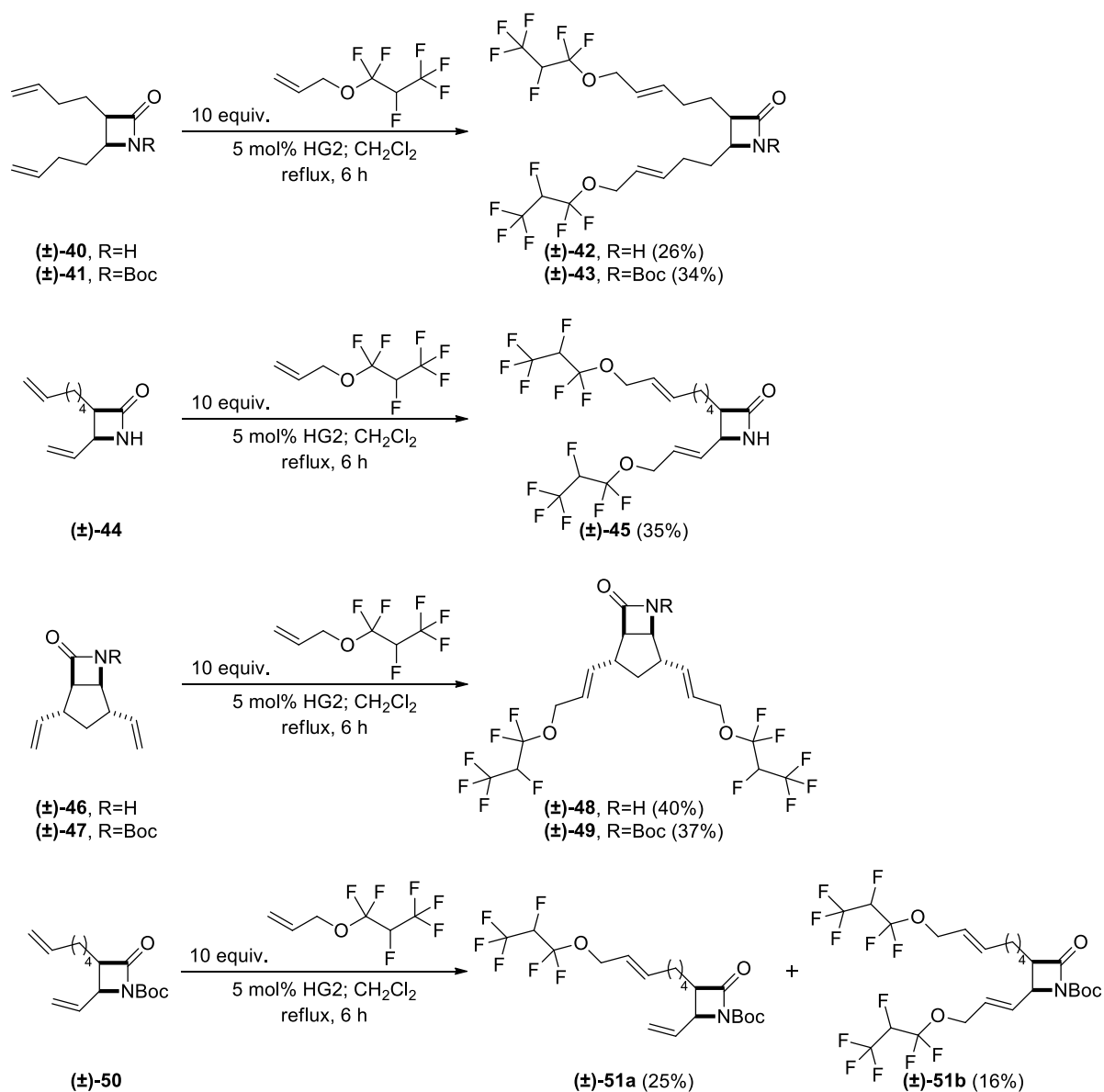
**Scheme 7:** Cross-metathesis of β-lactam with allyl 1,1,2,3,3,3-hexafluoropropyl ether

The results were found to be temperature dependent, when dialkenyl substituted bicyclic β-lactam [(±)-46] and its *N*-Boc protected counterpart [(±)-47] were used in the cross metathesis. When the reaction was executed at room temperature mixture of monocoupled regioisomers [(±)-52ab and (±)-53ab] was obtained in a ratio of 1.5:1. The separation of the regioisomers was unsuccessful. (Scheme 8)
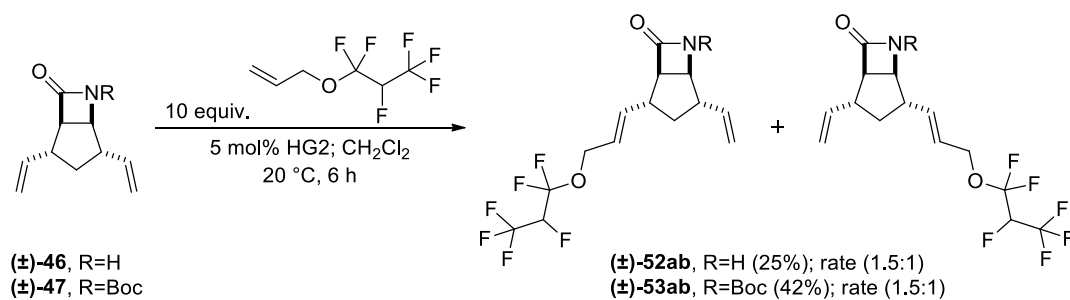
**Scheme 8:** Temperature dependent cross metathesis products

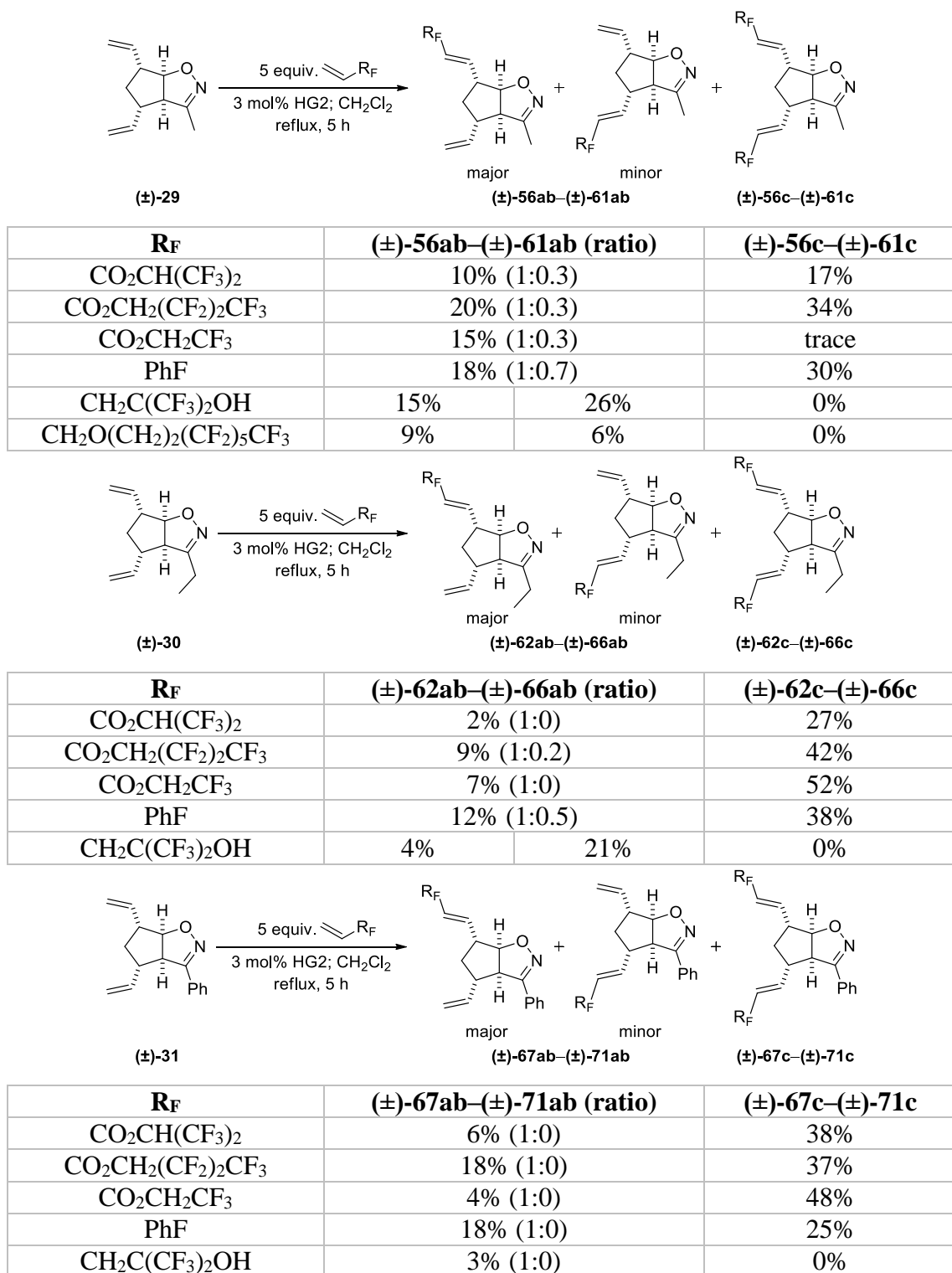When di(but-3-en-1-yl)-3-methylisoxazoline [(±)-28] as starting material, 4-bromo-3,3,4,4-tetrafluoro-1-butene, allyl trifluoroacetate or 2,2,2-trifluoroethyl acrylate as cross-partners were used in the cross-metathesis reaction, a mixture of monocoupled regioisomers [(±)-54ab, (±)-55ab and (±)-56ab] was formed. The regioisomers were separated. (Scheme 9)
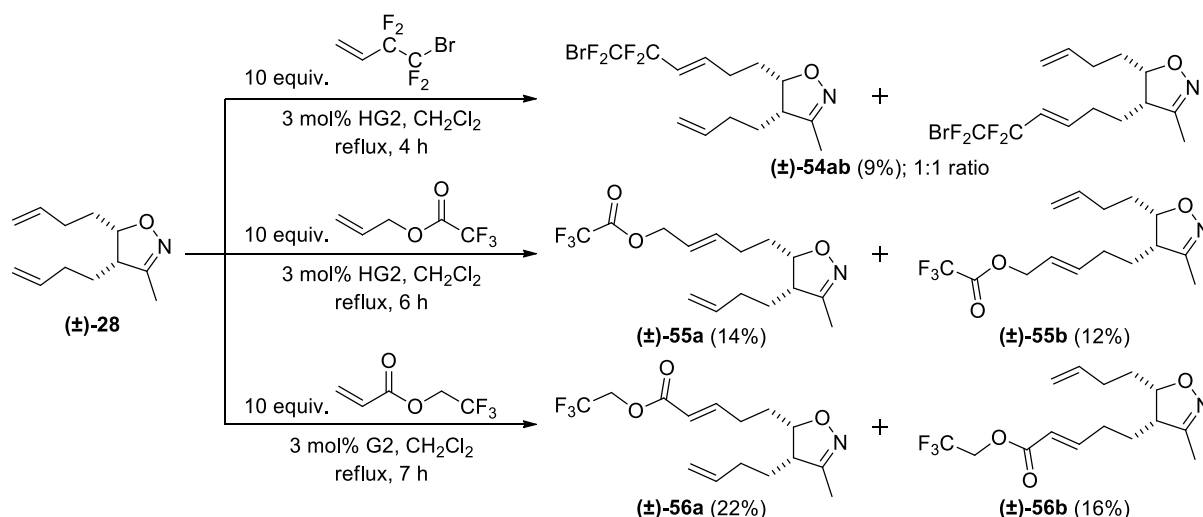


**Scheme 9:** Cross metathesis of dialkenyl substituted isoxazoline derivative with fluorinated olefins

The synthesis of fluorine containing substituted isoxazoline derivatives was expanded to divinyl-cyclopenta-isoxazoline derivatives as well. Among the commercially available Ru-based catalysts, G2, HG2, and G3 were used in the cross-metathesis reactions. We also compared the performance and selectivity of the applied catalysts. The following fluorine-containing olefins were used as cross-partners: 1,1,1,3,3,3-hexafluoroisopropyl acrylate, 1H, 1H-heptafluorobutyl acrylate, 2,2,2-trifluoroethyl acrylate, 4-fluorostyrene, 2-allyl hexafluoroisopropanol or allyl-1H,1H,2H,2H-perfluorooctyl ether. During the reactions, monocoupled regioisomers and dicoupled products were formed. In general, HG2 catalyst resulted in a significant amount of dicoupled products [(±)-56c–(±)-71c], whereas G2 and G3 catalysts favored the formation of monocoupled regioisomers [(±)-56ab–(±)-71ab]. Separation of regioisomers was unsuccessful. A similar tendency was observed

as in the case of methyl acrylate and methyl vinyl ketone. The increasing molecular size of the substituent of the isoxazoline ring (methyl, ethyl, phenyl substituent) decreased the ratio of formation of monocoupled regioisomers. Regioselectivity was achieved in the case of phenyl-substituted isoxazoline. This phenomenon could also be explained by steric reasons. (Scheme 10)



| $R_F$ | $(\pm)$-56ab–$(\pm)$-61ab (ratio) | | $(\pm)$-56c–$(\pm)$-61c |
|---|---|---|---|
| $CO_2CH(CF_3)_2$ | 10% (1:0.3) | | 17% |
| $CO_2CH_2(CF_2)_2CF_3$ | 20% (1:0.3) | | 34% |
| $CO_2CH_2CF_3$ | 15% (1:0.3) | | trace |
| PhF | 18% (1:0.7) | | 30% |
| $CH_2C(CF_3)_2OH$ | 15% | 26% | 0% |
| $CH_2O(CH_2)_2(CF_2)_5CF_3$ | 9% | 6% | 0% |



| $R_F$ | $(\pm)$-62ab–$(\pm)$-66ab (ratio) | | $(\pm)$-62c–$(\pm)$-66c |
|---|---|---|---|
| $CO_2CH(CF_3)_2$ | 2% (1:0) | | 27% |
| $CO_2CH_2(CF_2)_2CF_3$ | 9% (1:0.2) | | 42% |
| $CO_2CH_2CF_3$ | 7% (1:0) | | 52% |
| PhF | 12% (1:0.5) | | 38% |
| $CH_2C(CF_3)_2OH$ | 4% | 21% | 0% |



| $R_F$ | $(\pm)$-67ab–$(\pm)$-71ab (ratio) | $(\pm)$-67c–$(\pm)$-71c |
|---|---|---|
| $CO_2CH(CF_3)_2$ | 6% (1:0) | 38% |
| $CO_2CH_2(CF_2)_2CF_3$ | 18% (1:0) | 37% |
| $CO_2CH_2CF_3$ | 4% (1:0) | 48% |
| PhF | 18% (1:0) | 25% |
| $CH_2C(CF_3)_2OH$ | 3% (1:0) | 0% |

**Scheme 10:** Cross metathesis transformation of divinyl-3-alkyl-cyclopenta isoxazoline derivatives with fluorinated olefins

### 3.4. Synthesis of *N*-heterocycles via intramolecular aza-Michael addition

Functionalized *N*-heterocycles can be found in a variety of biologically active compounds (synthetic compounds and natural compounds). The synthesized dicoupled cross metathesis products function as Michael acceptor substrates in intramolecular aza-Michael additions.

Lactam ring-opening of (±)-72 was executed, followed by base catalyzed intramolecular aza-Michael addition in the presence of DBU base. Upon completion of the reaction, a single product was obtained, a substituted indolizidine compound [(±)-73]. (Scheme 11)
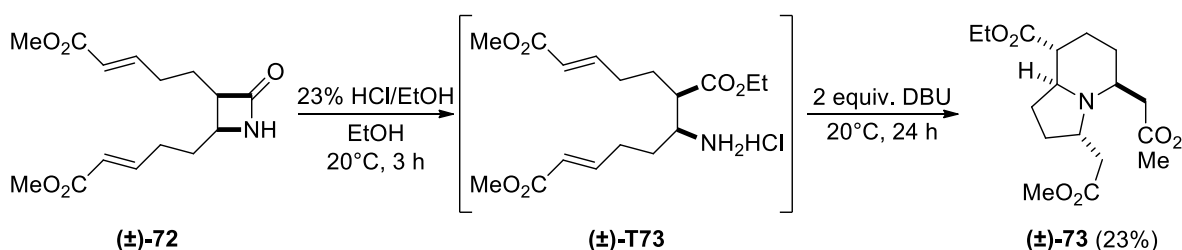


**Scheme 11:** Transformation of **(±)-72** via intramolecular aza-Michael addition

When the 2-azetidinon ring-opening with EtOH/HCl solution was performed for a longer reaction time (48 hours), in addition to the ring-opening, transesterification also took place. The intramolecular aza-Michael addition of the resulting product [(±)-T74] was executed, the formed product was the corresponding indolizidine [(±)-74] in the same way as above. (Scheme 12)
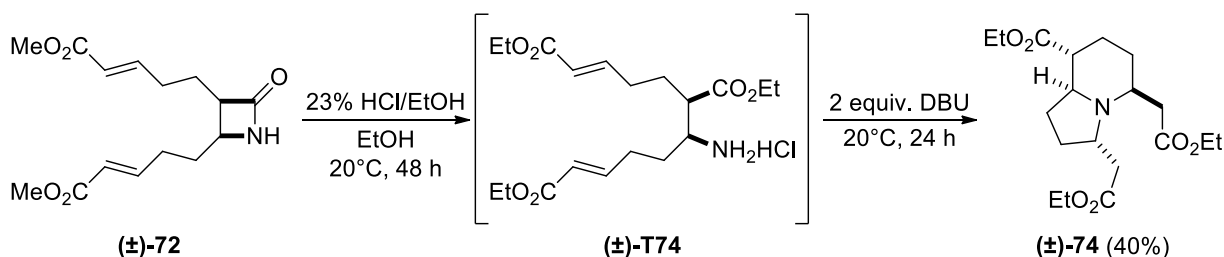


**Scheme 12:** Transformation of **(±)-72** via intramolecular aza-Michael addition

According to Baldwin's rules, the ring closing reactions proceeded in a 5-*exo*-trig and a 6-*exo*-trig manner, since both cyclizations are favored according to Baldwin's rules, thus the formed products were piperidine/pyrrolidine condensed (indolizidine) products. During the conjugate addition formed two new stereogenic centers, their configuration was determined on the basis of 2D NMR (NOESY, COSY, HSQC, and HMBC) data.

# Publication list

*Papers related to the thesis*

I. **Zsanett Benke**, Melinda Nonn, Ferenc Fülöp, Loránd Kiss

An Insight into Selective Olefin Bond Functionalization of Cyclodienes through Nitrile Oxide 1,3-Dipolar Cycloadditions

*ChemistrySelect* **2019**, *4*, 2886, IF: 1.505

II. Attila M. Remete, **Zsanett Benke**, Loránd Kiss

Stereocontrolled synthesis of fluorine-containing functionalized β-lactam derivatives through cross-metathesis reactions

*Fluorine Notes* Volume # 6 (127), November–December **2019**

III. Loránd Kiss, **Zsanett Benke**, Attila M. Remete, Ferenc Fülöp

Diversity-oriented Functionalization of Cyclodienes Through Selective Cycloaddition/Ringopening/Cross-metathesis Protocols; Transformation of a Flatland into Three-dimensional Scaffolds With Stereo- and Regiocontrol

*Chemical Record* **2020**, *20*, 1129, IF: 6.163

IV. **Zsanett Benke**, Attila M. Remete, Anas Semghouli, Loránd Kiss

Selective functionalization of norbornadiene through nitrile oxide cycloaddition/ring-opening/cross-metathesis protocols

*Asian J. Org. Chem.* **2021** (accepted article)

DOI: 10.1002/ajoc.202100147, IF 3.13

*Other publications*

V. **Zsanett Benke**, Melinda Nonn, Márton Kardos, Santos Fustero, Loránd Kiss

Ring-opening metathesis of some strained bicyclic systems; stereocontrolled access to diolefinated saturated heterocycles with multiple stereogenic centers

*Beilstein J. Org. Chem.* **2018**, *14*, 2698, IF 2.34

VI. Melinda Nonn, **Zsanett Benke**, Santos Fustero,; Ferenc Fülöp, Loránd Kiss

Chemodiscrimination of olefin bonds through cross-metathesis reactions – synthesis of functionalized β-lactam and β-amino acid derivatives

*Eur. J. Org. Chem.* **2019**, 5285, IF 2.882

*Conference lectures*

VII. **Zsanett Benke**, Melinda Nonn, Ferenc Fülöp, Loránd Kiss

Funkcionalizált, biciklusos származékok átalakításai sztereokontrollált gyűrűnyitó metatézissel

*MTA Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium '18*

Szeged, Hungary, 6–7 September, 2018, oral presentation

VIII. **Zsanett Amália Benke**

Cikloalkadiének szelektív funkcionalizálásai nitril-oxidok 1,3 dipoláros cikloaddíciójával

*XLI. Kémiai Előadói Napok*

Szeged, Hungary, 15–17 October, 2018, Abstr. p. 76, oral presentation

IX. **Zsanett Amália Benke**, Melinda Nonn, Ferenc Fülöp, Loránd Kiss

Ciklodiének szelektív funkcionalizálásai nitril-oxidok dipoláris cikloaddíciójával

*MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése*

Balatonszemes, Hungary, 3–5 July, 2019, oral presentation

X. **Zsanett Amália Benke**

2,5-Norbornadién szelektív funkcionalizálása cikloaddíciót követő metatézis transzformációkkal

*A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány 19. Tudományos Előadóülése*

Szeged, Hungary, May, 2020, virtual conference

XI. **Zsanett Amália Benke**

Fluortartalmú építőelemek szintézise metatézis reakciók alkalmazásával

*XLIII. Kémiai Előadói Napok*

Szeged, Hungary, 27–28 October, 2020, Abstr. p. 31, oral presentation