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

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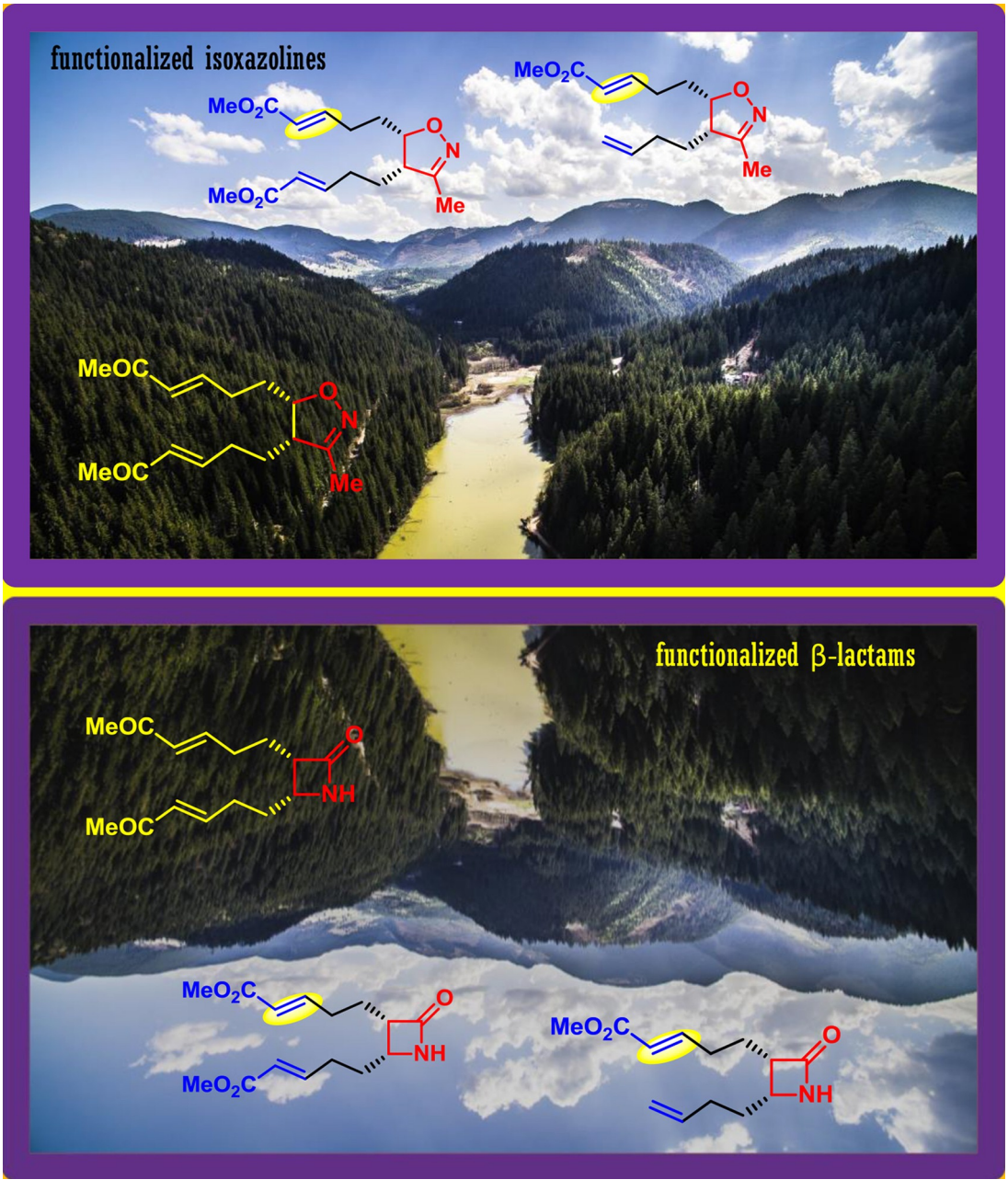

Abstract: This article presents selective transformations of some readily available cyclodienes through simple chemical procedures into novel functionalized small-molecular entities. The syntheses hereby described involved selective cycloadditions, followed by ring-opening metathesis of the resulting β-lactam or isoxazoline derivatives and selective cross-metathesis by differentiation of the olefin bonds on the alkenylated heterocycles. The cross-metathesis transformations have been detailed, which were performed under various experimental conditions with the aim of exploring chemodiscrimination of the olefin bonds and delivering the corresponding functionalized β-lactam or isoxazoline derivatives.

Keywords: cross-metathesis, selective coupling, β-lactam, isoxazoline, functionalization

1. Introduction

Highly functionalized small-molecular entities are considered to be promising scaffolds in drug design. Some terms such as "conformational restriction"[1] "escape from flatland"[2] or "scaffold hopping"[3] have received high relevance in medicinal chemistry over the past decade. Due to their special stereochemical structure, highly-functionalized three-dimensional small molecules with multiple stereogenic centers and versatile chemical diversity represent interesting scaffolds in drug development. Biological properties of a certain molecule are in strong connection with its three-dimensional arrangement. The introduction of a three-dimensional shape into a compound library leads to architectural complexity and increased structural diversity. Accordingly, selective and controlled synthetic approaches with regard to cost, generalization, and applicability towards such moieties containing sp^3 hybridized carbon atoms are of relevant significance in synthetic organic and medicinal chemistry.[4]

Diversity-oriented synthesis (DOS) with the aim to create structurally diverse, three-dimensional small-molecular elements has been applied as a well-known approach to generate molecular libraries. Several strategies used in DOS regarding selectivity and stereocontrol of various methods were reported in the literature. The main characteristics of these strategies are the application of readily available and easily accessible starting materials towards the formation of complex elements with high chemical and sterical diversity.[5]

Since the ring C–C double bond affords a large number of possible chemical transformations, cyclic dienes with nearly planar shape of different ring sizes are regarded to be readily attainable starting substances to the access of structurally diverse molecular structures. Among a large number of chemical transformations, the ring C=C bond of cyclic dienes may provide valuable β-lactams[1a,b,6] or γ-lactams,[7] which are known to be interesting precursors for the synthesis of versatile compounds. These are amino esters, oxo esters, amino acids, amino alcohols, amino ketones, azido esters, hydroxylated amino esters, and fluorinated amino esters, possessing various functional elements displaying stereostructural and chemical diversity.[1a,b,6] Furthermore, cyclic amino acids, as conformationally rigid structures, are interesting monomers as building elements in the synthesis of various types of oligopeptides[1,8] and cyclic amino acid structures with pharmaceutical importance.[1a,b,9]

Thanks to the commercial availability of a large number of relatively robust Ru-based metathesis catalysts, olefin metathesis transformations have exerted a high impact on synthetic chemistry and become a common and useful methodology for the creation of molecular entities containing olefin bond over the last twenty years. Various types of metathesis reactions have become powerful tools for the formation of one or more C–C double bonds in organic molecules. By using metathesis synthetic approaches, a number of sophisticated organic molecules, natural products, biologically active substances, and various pharmaceuticals have been synthesized.[10,12a–f]

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2. Functionalization of Cyclodienes Through β-lactam Formation/ROM/CM Protocols

[2 + 2] Cycloaddition of chlorosulfonyl isocyanate (CSI) to the C=C bond is considered to be a highly useful synthetic procedure for the construction of a β-lactam skeleton. This cycloaddition strategy to cycloalkadienes of different ring sizes (cyclopentadiene, cyclohexadienes, cyclooctadienes, norbornadiene) was earlier applied efficiently in our group to create versatile molecular entities, varied small-molecular libraries with high chemical and structural diversity, such as amino

esters, azido esters, hydroxylated amino acids, fluorinated amino esters, orthogonally protected amino esters, alkenylated amino esters, various heterocycles or aryl-substituted amino esters.[1a,b,11] The strategy involved further selective transformations of the cycloalkene-fused β-lactams through their ring C=C bond.

Due to ring strain, unsaturated β-lactam **(±)-2**, synthetized by CSI cycloaddition to norbornadiene across its ring C–C double bond, easily suffered ring cleavage under the condition of ring-opening metathesis (ROM) in the presence of Grubbs-1 catalyst (G-1), and provided divinyl-substituted lactam **(±)-3**. Next, azetidinone derivative **(±)-3** afforded the corresponding dicoupled derivatives **(±)-4** and **(±)-5** in the reaction with methyl vinyl ketone or methyl acrylate, respectively, through cross-metathesis (CM) in the presence of Hoveyda-Grubbs 2 catalyst (HG-2) in refluxing CH_2Cl_2 (Scheme 1).[12b]

A similar behavior was observed in the case of larger ring systems of lactam derivatives. Cyclooctene-fused β-lactam regioisomers **(±)-7** and **(±)-11**, derived from cyclooctadienes **6** and **10** through CSI cycloaddition, could also be converted across ROM followed by CM to the corresponding functionalized azetidinone isomers **(±)-8**, **(±)-9**, **(±)-12**, and **(±)-13** (Scheme 2).[12b]

It should be noted that dialkenylated β-lactam derivatives described above were easily transformed into the corresponding functionalized β-amino acid derivatives.[12b]

The ROM/CM protocol was effectively applied to the access of some dialkenylated cyclopentane β-amino ester isomers as well. An illustrative example is depicted in

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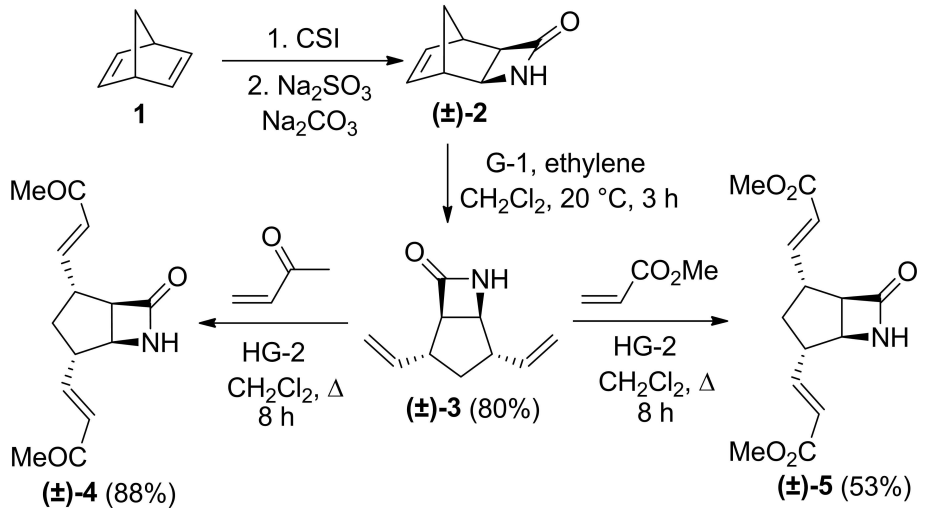
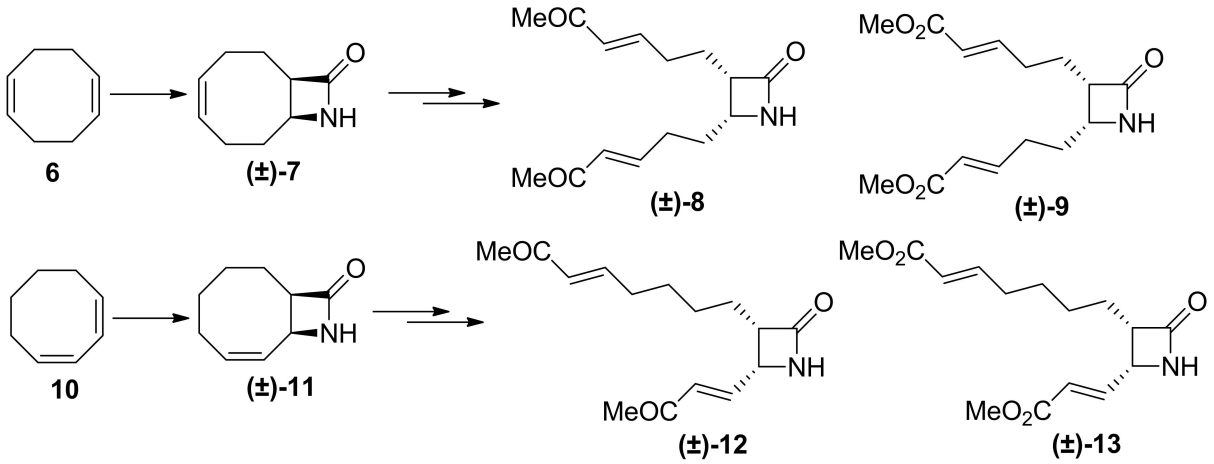
Ferenc Fülöp was born in Szank, Hungary in 1952. He received his MSc degree in Chemistry in 1975 and his Ph.D. in 1979 from József Attila University, Szeged, Hungary. At the beginning of his carrier he worked in Chinoin Pharmaceuticals, Budapest for six years. In 1991, he was appointed as a full professor at the Institute of Pharmaceutical Chemistry, University of Szeged, and between 1998 and 2017 was the head of the Institute. He is a member of the Hungarian Academy of Sciences and has a wide range of research interests in synthetic organic chemistry. His recent activities have focused on the use of amino alcohols and β-amino acids in enzymatic transformations, various asymmetric syntheses, foldamer construction, and flow chemistry, in view of the development of pharmacologically active derivatives.

Attila M. Remete graduated as chemist in 2014 from University of Szeged (Hungary). He has been working at the Institute of Pharmaceutical Chemistry, University of Szeged since 2010. In 2014 he started his Ph.D. under the supervision of Loránd Kiss and received his degree in 2019. He is currently assistant lecturer and his recent topic focuses on the preparation of highly substituted fluorinated building elements from β-amino acid derivatives.

Zsanett Benke graduated as chemist in 2017 from University of Szeged, Faculty of Science and Informatics (Hungary). In 2017 she started her Ph.D. at the Institute of Pharmaceutical Chemistry, University of Szeged (Hungary) under the supervision of Loránd Kiss. Her Ph.D. topic focuses on the selective transformations of cycloalkadienes into highly functionalized three-dimensional molecules.



Scheme 1. Cycloaddition of CSI to norbornadiene (**1**) and ROM/CM of the resulting bicyclic lactam **(±)-2**.



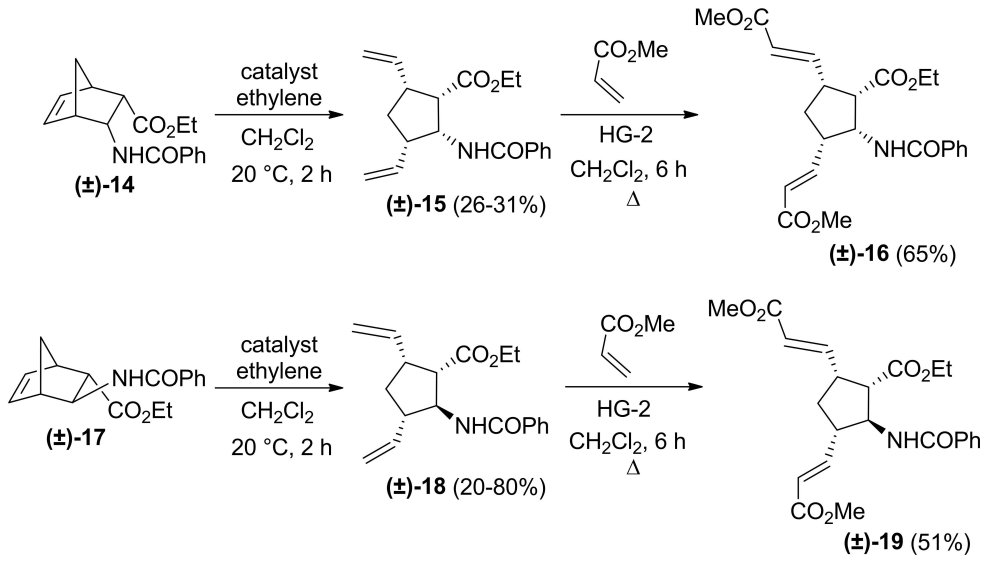
Scheme 2. Cycloaddition of CSI to 1,5- (**6**) and 1,3-cyclooctadiene (**10**) and ROM/CM of formed bicyclic lactams **(±)-7** and **(±)-11** (yields: 48–74%).

Scheme 3. Norbornene β-amino ester diastereoisomers **(±)-14** (prepared by ammonolysis of *cis*-5-Norbornene-*endo*-2,3-dicarboxylic anhydride, followed by Hofmann degradation)[12g] and **(±)-17** (prepared by base mediated isomerization of **(±)-14**)[12a] were subjected to ROM in the presence of four Ru-based catalysts furnishing divinyl-substituted amino esters **(±)-15** and **(±)-18** (see Scheme 3). Then the products reacted further under CM conditions in the presence of HG-2 catalyst in refluxing CH_2Cl_2 to deliver the corresponding highly functionalized cyclopentanes **(±)-16** and **(±)-19** (Scheme 3).[12a]

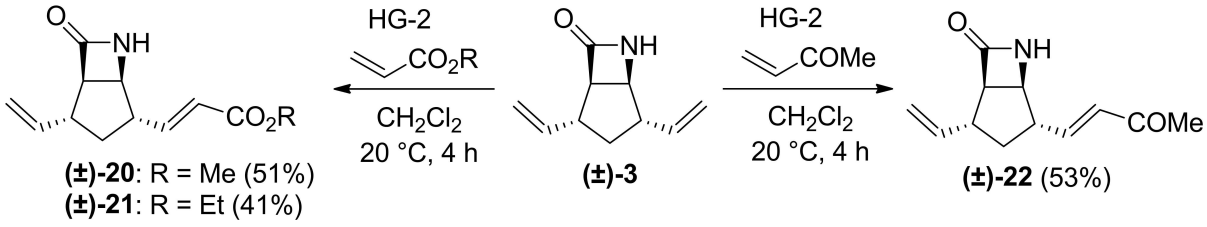
2.1. Functionalization of Cyclodienes Through β-lactam Formation/ROM and Selective CM Protocols

All CM transformations presented above, performed in the presence of various commercial Ru-based catalysts in refluxing CH_2Cl_2, proceeded smoothly yielding the corresponding expected dimetathesized products. However, it was observed that, after a careful selection of CM reaction conditions regarding the catalyst, temperature, time, and catalyst loading, a distinct behavior of the apparently similar C=C was observed. For example, divinyl-substituted lactam **(±)-3**, after some experimental investigations in the reaction with acrylates or methyl vinyl ketone, gave monocoupled products **(±)-20**, **(±)-21**, and **(±)-22** (Scheme 4).[12c]

The observed chemodiscrimination in the chemical comportment of the olefin bonds in **(±)-3** was explained on the



Scheme 3. Transformation of unsaturated bicyclic amino esters **(±)-14** and **(±)-17** through ROM/CM protocol. Note: catalysts G-1, G-2, HG-1, HG-2 were used in ROM; the highest yields were attained with HG-2 for **(±)-14** and with HG-1 for **(±)-17**.



Scheme 4. Selective transformation of lactam **(±)-3** under CM conditions.

basis of a hydrogen-bonding directing effect in the transition state of the CM reaction, which arises between the N–H (as hydrogen bond donor) and Ru–Cl (as hydrogen bond acceptor) moieties. Thus, the H-bonding structure accelerates the CM of the vinyl group closest to the lactam nitrogen atom (Figure 1).

The above hypothesis was corroborated by analyzing the CM transformation of *N*-Boc-protected lactam **(±)-24**, which cannot function as a H-donor scaffold. In this case the reaction was found not to be selective and, under similar experimental conditions, afforded two monometathesized products **(±)-25** and **(±)-26** in a ratio of 2 : 1 (Scheme 5).[12c]

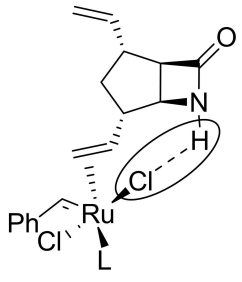
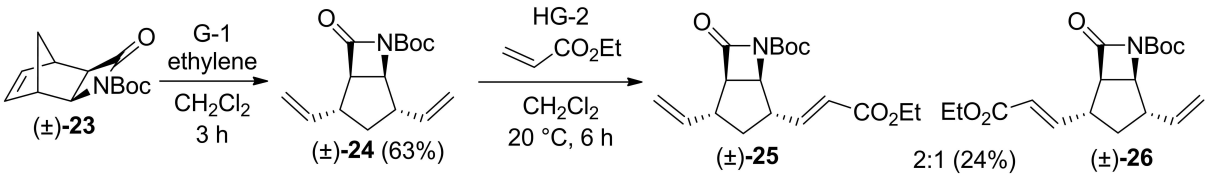


Figure 1. Hydrogen-bonding directing effect in the CM reaction.

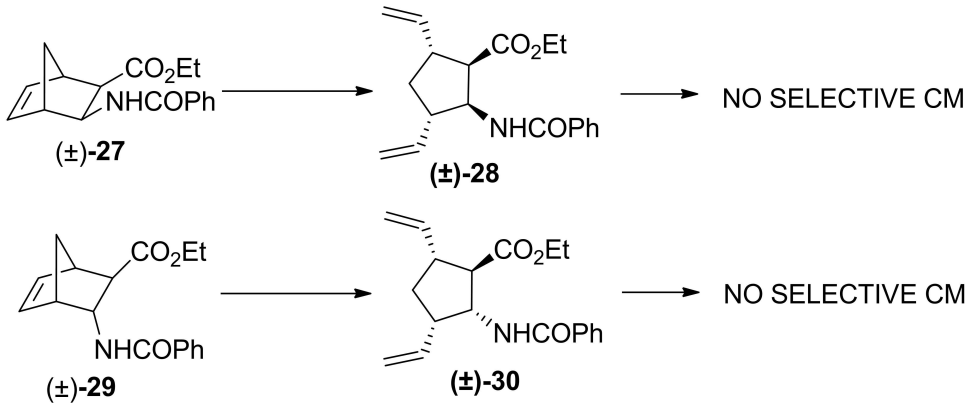
Further investigations in view of the chemodiscrimination of the olefin bonds were executed by using some divinyl-substituted β-amino ester diastereoisomers with a cyclopentane skeleton.

In the case of divinyl-substituted amino esters **(±)-28** and **(±)-30** after some experimental investigations, CM reactions proceeded non-selectively (Scheme 6) giving mixtures of monometathesized products in 4 : 1 and 2 : 1 ratio. In contrast, isomer **(±)-18** under similar conditions afforded monometathesized compounds **(±)-31**, **32**, and **(±)-33** (Scheme 7) in a completely chemoselective manner.[12c]

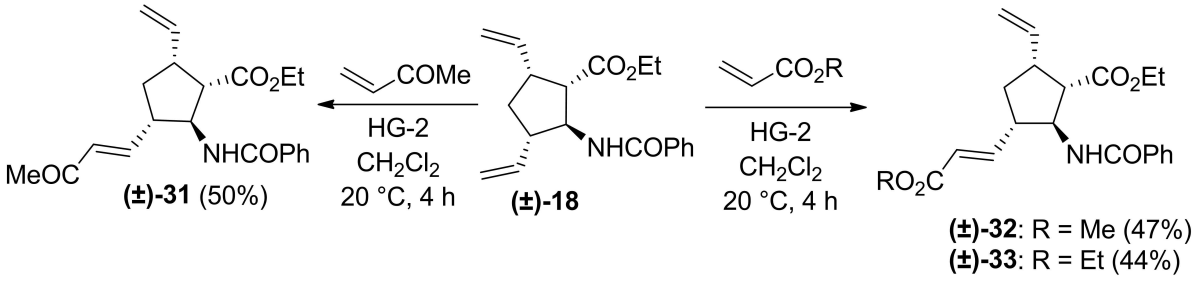
The phenomena described above can presumably be explained by a preferred coordinating transition state in the CM reaction. Compound **(±)-18** gives a more stable six-membered, *cis*-fused chelate ring across a metallacyclobutane intermediate, while the transformation of **(±)-28** and **(±)-30**



Scheme 5. Non-selective transformation of lactam **(±)-24** under CM conditions.



Scheme 6. Non-selective transformation of amino esters **(±)-28** and **(±)-30** under CM conditions.



Scheme 7. Selective transformation of amino ester **(±)-18** under CM conditions.

involved intermediates with less stable structure (Figure 2).[12c] Thus, formation of a stable chelate ring system disfavors CM of the vinyl group closer to the ester function, whereas the C=C bond next to the NHCOH moiety will react smoothly.

Returning to strained fused azetidinones with higher ring systems, non-selective CM was described for the transformation of lactam **(±)-34** derived from 1,5-cyclooctadiene, which furnished two monometathesized compounds **(±)-35** and **(±)-36** in 4 : 1 and 2 : 1 ratio, respectively (Scheme 8).[12e]

In contrast to lactam **(±)-34**, CM of its isomer **(±)-37** with ethyl and methyl acrylates and methyl vinyl ketone took place with chemodifferentiation of the C=C bonds and, presumably due to steric factors, provided a single monometathesized product each [**(±)-38**, **(±)-39**, and **(±)-40**] (Scheme 9).[12e]

3. Functionalization of Cyclodienes Through Isoxazoline Formation/ROM/CM Protocols

The nitrile oxide cycloaddition protocol to access a series of interesting β-amino acid derivatives containing an isoxazoline framework bearing functionalized cycloalkenes was efficiently applied.[1a,b,13]

In a recent work some readily available commercial cyclodienes were selectively transformed through nitrile oxide 1,3-dipolar cycloaddition into the corresponding cycloalkene-fused isoxazolines (Scheme 10).[14a]

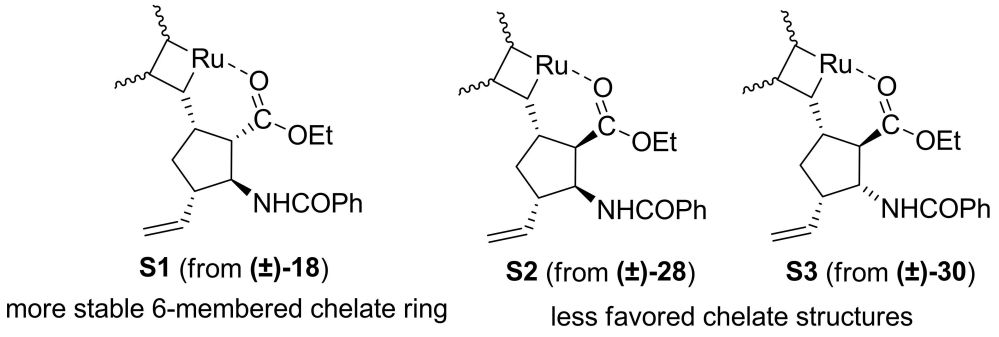
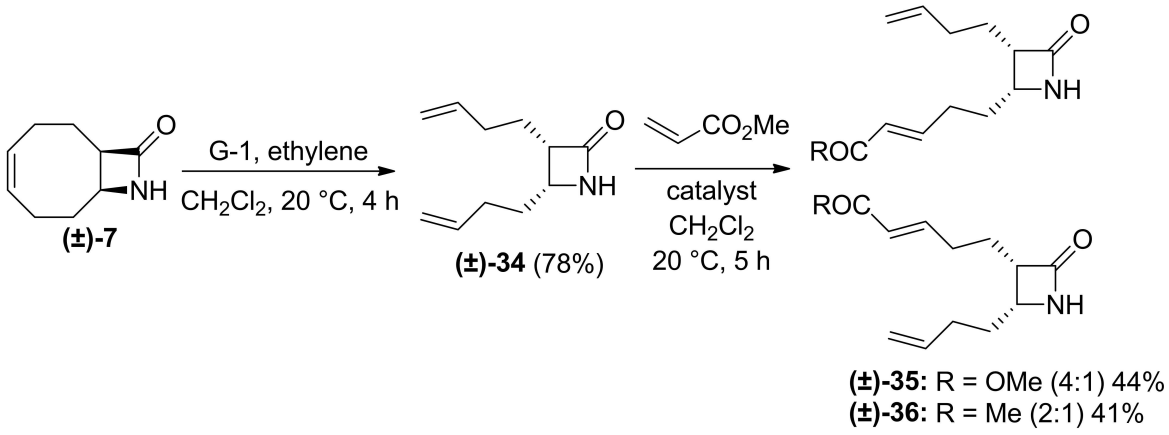
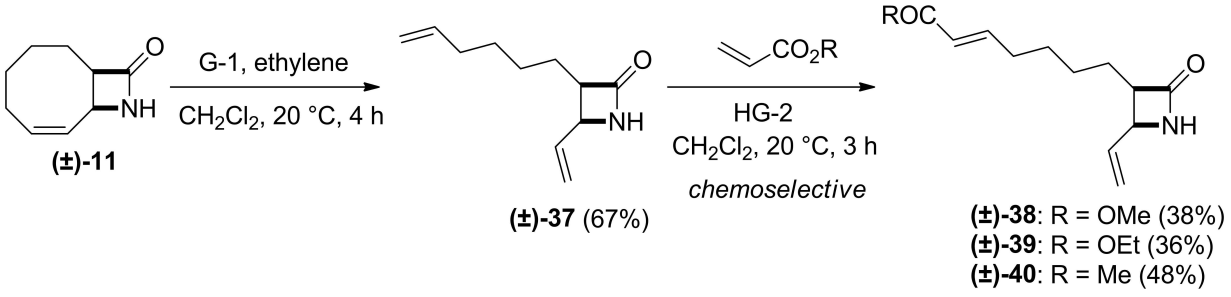


Figure 2. Structures of chelate ring intermediates.



Scheme 8. Non-selective transformation of lactam **(±)-34** under CM conditions. Note: catalyst = G-1, G-2, HG-1, or HG-2.



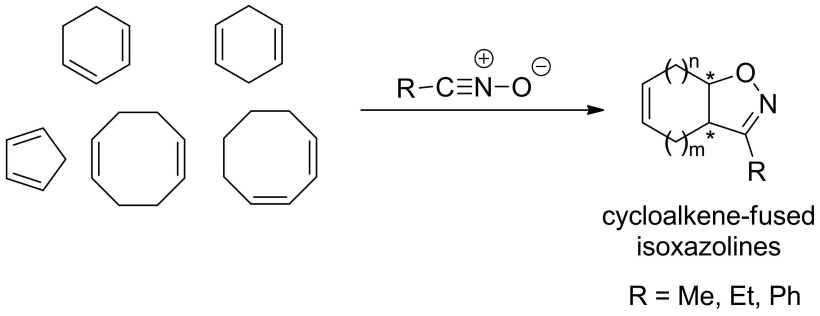
Scheme 9. Selective transformation of lactam **(±)-37** under CM conditions.

3.1. Functionalizations by ROM/CM of Cycloalkene-fused Isoxazolines With Non-fluorinated Olefins

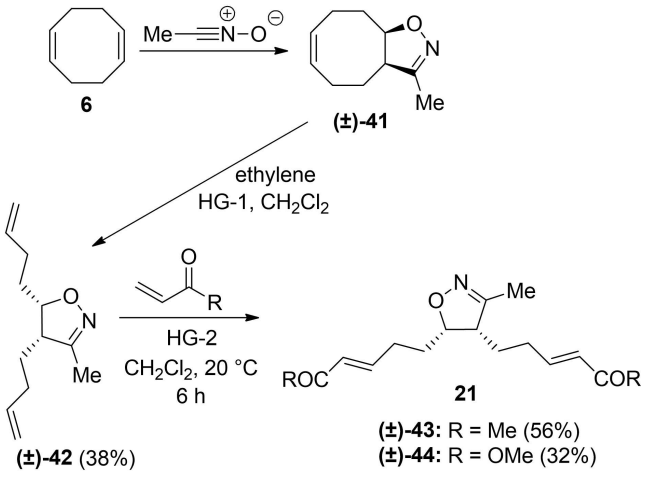
Similar to cycloalkane-anellated azetidinones, cycloalkene-fused isoxazolines as ring-strained systems are regarded as potential model compounds for ROM. An illustrative example is shown in Scheme 11. Cyclooctene-fused isoxazoline **(±)-41** easily underwent ring opening in the presence of HG-1 catalyst furnishing the corresponding dialkenylated isoxazoline **(±)-42**. Compound **(±)-42**, when reacted with methyl vinyl ketone or methyl acrylate in the presence of HG-2, led to dicoupled derivatives **(±)-43** and **(±)-44** in a CM reaction (Scheme 11).[14]

3.2. Functionalizations by ROM/CM of Cycloalkene-fused Isoxazolines With Fluorine-containing Olefins

In earlier studies we acquired useful findings with respect to selective functionalization strategies based on the formation of



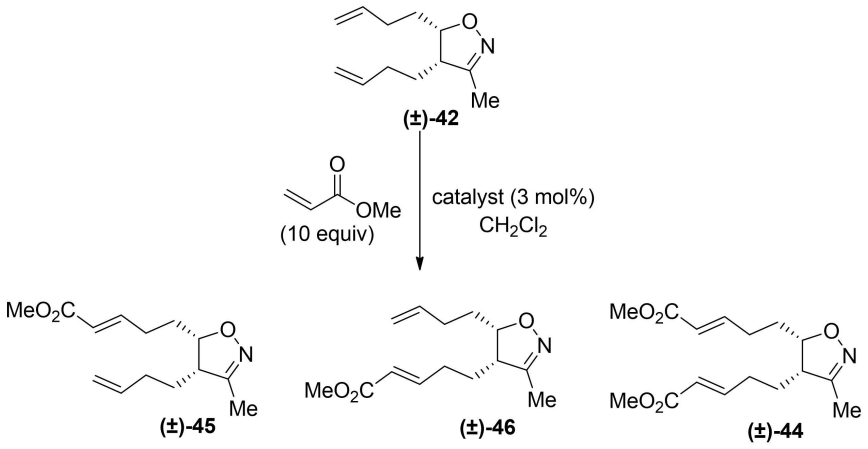
Scheme 10. Selective synthesis of several cycloalkene-fused isoxazolines.



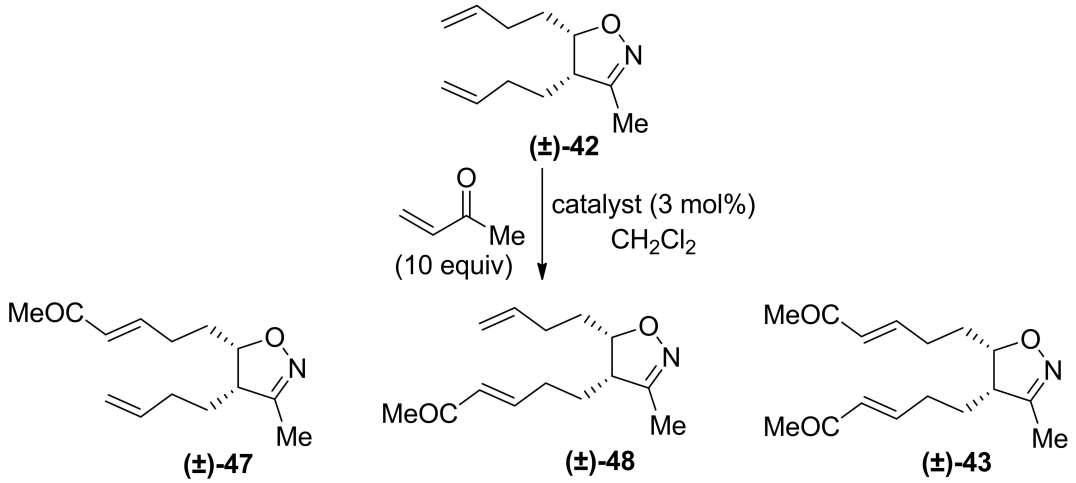
Scheme 11. Transformation of isoxazoline **(±)-41** derived form 1,5-cyclooctadiene through ROM/CM.

cycloalkene-fused β-lactams and isoxazolines through cycloadditions, followed by various metathesis strategies. Similar functionalization studies were further applied in view of the creation of novel small molecular entities. For this reason, 1,5-cyclooctadiene the selected starting model compound was converted through selective nitrile oxide cycloaddition into cyclooctene-fused isoxazoline **(±)-41** which, in turn, afforded dialkenylated izoxazoline **(±)-42** by ring-opening metathesis (ROM).[14] Our aim was to convert compound **(±)-42** into novel functionalized scaffolds and to study the chemical behavior of practically equivalent olefin bonds in **(±)-42** under CM transformations. Hereby, in this section some preliminary results will be briefly presented.

First, methyl acrylate was applied as CM partner in the reaction with dialkenylated isoxazoline **(±)-42**. The CM reaction was systematically studied in the presence of readily available commercial catalysts, namely Grubbs 1 (G-1), Grubbs-2 (G-2), Hoveyda-Grubbs-1 (HG-1), and Hoveyda-Grubbs-2 (HG-2). After several test reactions by varying experimental conditions [temperature (0 °C, room temperature, reflux), solvent (CH_2Cl_2/THF), reaction time], conversion of **(±)-42** was detected only in the case of HG-2 catalyst (Scheme 12). Note, that in the case of G-1, G-2, and



Scheme 12. Transformation of **(±)-42** with methyl acrylate through CM reaction.



Scheme 13. Transformation of **(±)-42** with methyl vinyl ketone through CM reaction.

HG-1 under reflux conditions at prolonged reaction time, the formation of unidentified polymeric materials was observed.

Compound **(±)-42** was subjected to CM with methyl acrylate by varying the amount of the ester and the catalyst. The best conversion in CM was attained by using the ester in high excess (10 equiv). However, the amount of catalyst (HG-2, 3 mol%, 5 mol% or 10 mol%) did not significantly affect the outcome regarding the conversion of the metathesis reaction. The reaction of **(±)-42** with methyl acrylate at reflux for 2 h afforded three products: monometathesized compounds **(±)-45** and **(±)-46** and dicoupled derivative **(±)-44**. The products, after concentration of the reaction mixture, could be separated by means of column chromatography and characterized on the basis of 2D NMR spectroscopic data providing CM products in 4%, 2%, and 62% isolated yields (Scheme 12, Table 1). Note, that a prolonged heating resulted in a decrease of the yield of CM products, accompanied by the formation of polymeric substances. Efforts have been performed in view of the modification of the ratio of the three products to access monocoupled products. Unfortunately, all attempts to significantly affect the ratio of the substances failed.

Table 1.

Entry	Temperature	Reaction time	Catalyst	Yield of (±)-45	Yield of (±)-46	Yield of (±)-44
1*	reflux	2 h	HG-2	4%	2%	62%
2**	reflux	2 h	HG-2	4%	10%	42%
3**	RT	2 h	traces of CM products			
4**	RT	6 h	HG-2	22%	15%	32%

*workup without addition of H_2O – **workup with the addition of 2 drops of H_2O

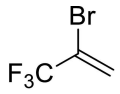
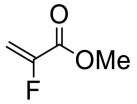
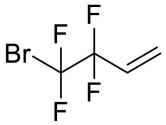
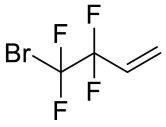
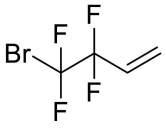
Since prolonged heating resulted in certain polymerization, an obvious conclusion was to decompose the activity of the catalyst thereby avoiding polymerization taking place in the concentrated reaction mixture. Consequently, we modified the reaction workup by the addition of 2 drops of water. Thus, when the reaction was carried out under reflux for 2 h, a decrease of the dimetathesized product yield was observed [**(±)-44**, 42%]. In contrast, the isolated yield of monocoupled product **(±)-46** increased to 10%, while the yield of the other monocoupled product **(±)-45** was practically unchanged. When the same reaction was performed at room temperature for 2 h, only trace amounts of the CM products could be detected. However, when this CM was repeated at room temperature for a prolonged time (6 h), the yield of monometathesized products **(±)-45** and **(±)-46** increased significantly (Table 1, entry 4). Note, that the two monocoupled products [**(±)-45**, **(±)-46**] and dicoupled product **(±)-44** could be separated and isolated by chromatography, and their structures were certified by means of 2D NMR spectroscopy (COSY, HSQC, HMBC).

We continued our experimental investigations in view of the formation of novel Michael acceptor scaffolds, by using methyl vinyl ketone, another CM partner, containing a C–C double bond. In a few preliminary studies performed at reflux temperature, we found only unidentifiable polymeric materials. At room temperature after 6 h, in contrast, both expected monocoupled derivatives **(±)-47** and **(±)-48** as well as dicoupled CM product **(±)-43** were formed. After successful separation, the desired product materials were isolated in moderate yields (Scheme 13, Table 2).

Table 2.

Entry	Temperature	Reaction time	Catalyst	Yield of **(±)-47**	Yield of **(±)-48**	Yield of **(±)-43**
1	RT	6 h	HG-2	25%	41%	26%
2	reflux	2 h	HG-2	unidentifiable polymeric materials		

Table 3. Reactions of isoxazoline **(±)-42**

Entry	Olefin	Temp.	Time	Catalyst	Yield of metathesis product
1		RT or Δ	2 to 24 h	(*)	0%
2		RT or Δ	2 to 24 h	(*)	0%
3		RT	6 h	HG-2	5% (**)
4		RT	24 h	HG-2	4% (**)
5		Δ	4 h	HG-2	9% (**)

(*) catalyst: G-1, G-2, HG-1, HG-2 – (**) mixtures of monocoupled products **(±)-49** and **(±)-50** was detected (approximately in an 1 : 1 ratio)

Table 4.

Entry	Temperature	Reaction time	Catalyst	Yield of **(±)-52**	Yield of **(±)-53**	Yield of **(±)-54**
1	reflux	6 h	HG-2	14%	12%	0%
2	RT	6 h	HG-2	traces of metathesis products		

Table 5.

Entry	Temperature	Reaction time	Catalyst	Yield of **(±)-55**	Yield of **(±)-55**	Yield of **(±)-57**
1	reflux	7 h	G-2	22%	16%	0%
2	RT	7 h	G-2	traces of metathesis products		

Organofluorine chemistry is considered to be a rapidly expanding hot topic area during the last two decades. Because of the high impact of fluorine-containing molecules in drug design (approximately 25% of the drugs introduced to the market contain one or more fluorine atoms) and agriculture, the synthesis of fluorinated organic derivatives has been recognized to be an increasing research area in synthetic organic chemistry.[15] Moreover, the availability of a range of fluorine-containing substrates as well as the discovery of metathesis catalysts, tolerant to various functional groups, have broadened the utility of metathesis strategies for the construction of versatile fluorinated scaffolds.[15f]

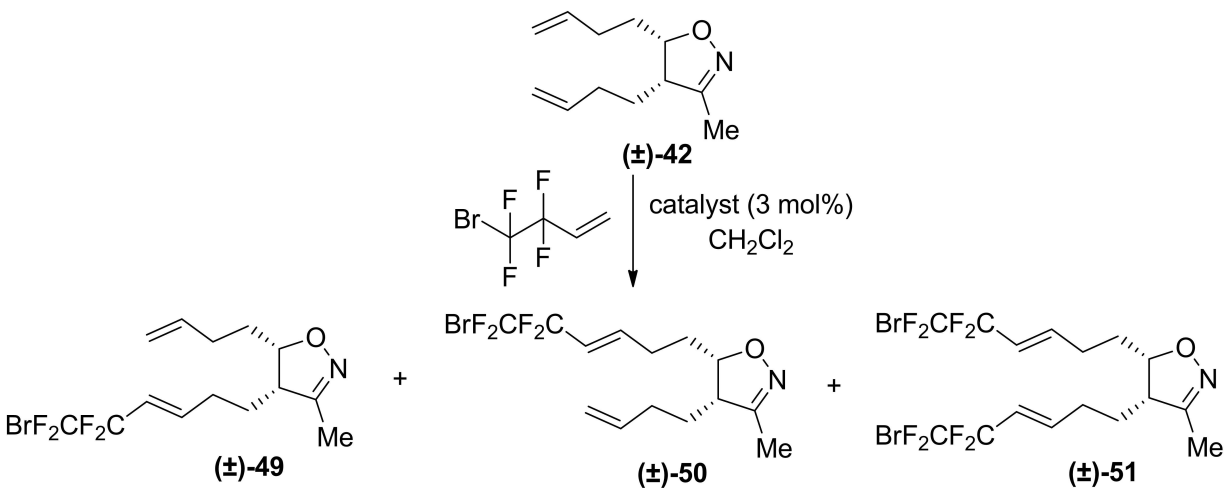
Taking into consideration the above-mentioned relevance of fluorine-containing organic molecules, we planned to continue our experimental investigations with the application of some readily available commercial fluorinated olefins as CM partner derivatives. These included 2-bromo-3,3,3-trifluoroprop-1-ene, methyl 2-fluoroacrylate, 4-bromo-3,3,4,4-tetrafluorobut-1-ene, allyl 2,2,2-trifluoroacetate, and 2,2,2-trifluoroethyl acrylate. Note, that although we performed some preliminary CM metathesis experiments using lactams derived from cyclooctadiene or norbornadiene with fluorine-containing metathesis partners, these gave only very limited results.[12f]

CM experiments with the above-mentioned fluorine-containing olefins have been systematically accomplished in CH_2Cl_2 by variation of reaction temperature, time or type of catalyst, and catalyst loading. It was observed that CM product (s) were not formed with 2-bromo-3,3,3-trifluoroprop-1-ene and methyl 2-fluoroacrylate. At reflux temperature at a longer reaction time, again, only unidentifiable polymeric substances could be detected (Table 3).

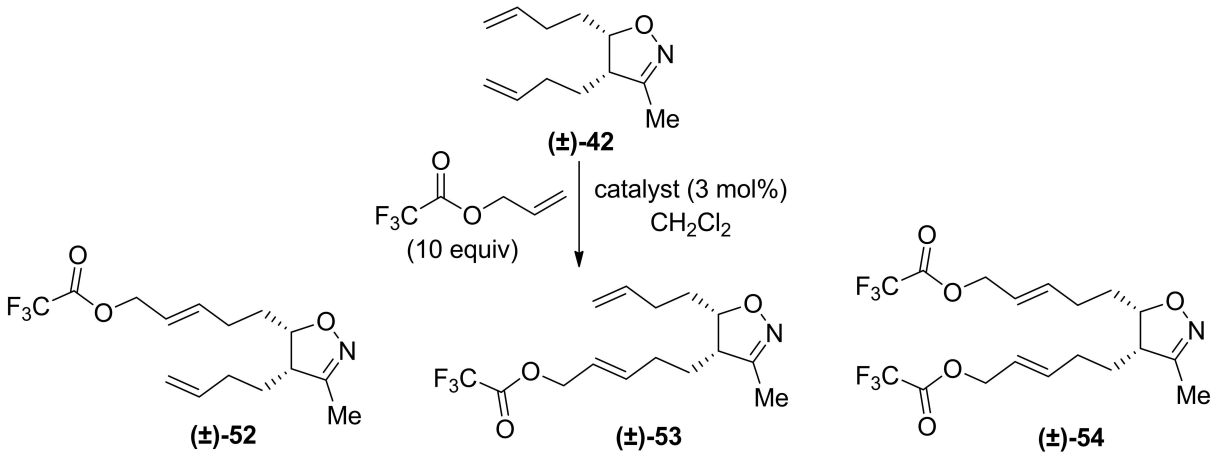
Unfortunately, the reaction with 4-bromo-3,3,4,4-tetrafluorobut-1-ene also proved to be unsuccessful. Although a conversion to CM products occurred in the presence of HG-2 catalyst, only an inseparable mixture of mono- and dimetathesized products **(±)-49**, **(±)-50**, and **(±)-51** was formed in very low yields (Table 3, Scheme 14).

In continuation, two fluorine-containing esters were submitted to CM with **(±)-42**. In several attempts allyl 2,2,2-trifluoroacetate provided no CM products at room temperature. At reflux temperature, somewhat surprisingly, only monometathesized compounds **(±)-52** and **(±)-53** were detected, and the formation of the expected dicoupled product was not observed. Although the monocoupled substances were formed in modest yields, they could be separated and isolated by means of column chromatography (Scheme 15, Table 4).

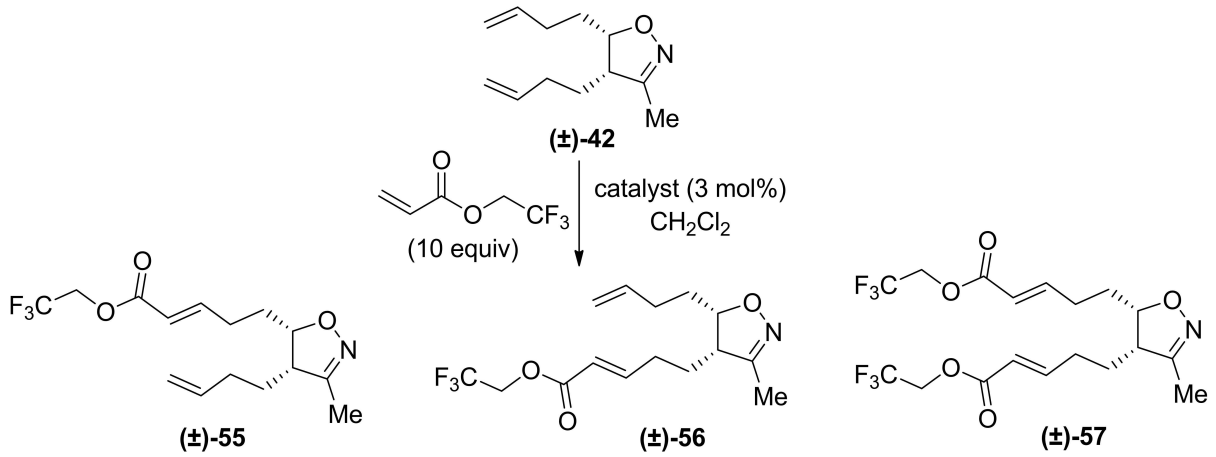
Interestingly, a somewhat similar outcome of the CM reaction of **(±)-42** with 2,2,2-trifluoroethyl acrylate could be found. Again, the dimetathesized product was not formed at reflux temperature. Instead, the reaction resulted in both monocoupled derivatives **(±)-55** and **(±)-56**, which were separated, isolated, and characterized (Scheme 16, Table 5).



Scheme 14. Transformation of **(±)-42** with 4-bromo-3,3,4,4-tetrafluorobut-1-ene through CM reaction.



Scheme 15. Transformation of **(±)-42** with allyl 2,2,2-trifluoroacetate through CM reaction.



Scheme 16. Transformation of **(±)-42** with 2,2,2-trifluoroethyl acrylate through CM reaction.

4. Conclusions

In the current paper diversity-oriented synthetic procedures have been described for the access of versatile functionalized, three-dimensional small molecules. Chemical transformations were based on the functionalization of cyclodienes across cycloadditions performed with chlorosulfonyl isocyanate or nitrile oxides. The obtained cycloalkene-fused β-lactams or isoxazolines were converted via their ring olefin bond involving ring-opening metathesis to the corresponding dialkenylated β-lactams or isoxazolines. Then the products were subjected to cross-metathesis, affording novel functionalized molecular entities under *stereocontrol*. The chemical behavior of the olefin bonds was also studied under varied experimental conditions with chemodifferentiation taking place in their cross-metathesis transformations. Further experiments in view of the extension of the synthetic procedures thereby described, regarding selectivity, substrate and reagent scope as well as the conversion and robustness are currently under investigation in our group.

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We are grateful to the Hungarian Research Foundation (NKFIH No K 119282) for financial support. The financial support of the GINOP-2.3.2-15-2016-00060 project is also acknowledged. This research was supported by the EU-funded Hungarian grant EFOP-3.6.1-16-2016-00008. Ministry of Human Capacities, Hungary grant 20391-3/2018/FEKUSTRAT is also acknowledged.

References

[1] a) L. Kiss, I. M. Mándity, F. Fülöp, *Amino Acids* **2017**, *49*, 1441–1455 and references cited herein; b) L. Kiss, F. Fülöp, *Chem. Rev.* **2014**, *114*, 1116–1169; c) A. Nagy, V. G. Gőz, I. Pintér, V. Farkas, A. Perczel, *Amino Acids* **2019**, *51*, 669–678; d) I. M. Mándity, E. Weber, T. A. Martinek, G. Olajos, G. K. Tóth, E. Vass, F. Fülöp, *Angew. Chem. Int. Ed.* **2009**, *48*, 2171–2175; *Angew. Chem.* **2009**, *121*, 2205–2209; e) Y. H. Shin, S. H. Gellman, *J. Am. Chem. Soc.* **2018**, *140*, 1394–1400.

[2] a) F. Lovering, *Med. Chem. Commun.* **2013**, *4*, 515–519; b) F. Lovering, J. Bikker, C. Humblet *J. Med. Chem.* **2009**, *52*, 6752–6756; c) B. Cox, K. I. Booker-Milburn, L. D. Elliott, M. Robertson-Ralph, V. Zdorichenko *ACS Med. Chem. Lett.* **2019**, *10*, 1512–1517.

[3] a) H. J. Böhm, A. Flohr, M. Stahl, *Drug Discovery Today Technol.* **2004**, *1*, 217–224; b) Y. Hu, D. Stumpfe, J. Bajorath, *J. Med. Chem.* **2017**, *60*, 1238–1246.

[4] a) M. Garcia-Castro, S. Zimmermann, M. G. Sankar, K. Kumar, *Angew. Chem. Int. Ed.* **2016**, *55*, 7586–760; *Angew. Chem.* **2016**, *128*, 7712–7732; b) A. W. Hung, A. Ramek, Y. Wang, T. Kaya, J. A. Wilson, P. A. Clemons, D. W. Young, *PNAS* **2011**, *108*, 6799–6804; c) D. J. Foley, R. G. Doveston, I. Churcher, A. Nelson, S. P. Marsden, *Chem. Commun.* **2015**, *51*, 11174–11177.

[5] a) R. J. Spandl, M. Diaz-Gavilan, J. M. G. O' Connel, G. L. Thomas, D. L. Spring, *Chem. Rec.* **2008**, *8*, 129–142; b) C. J. O'Connor, H. S. G. Beckmann, D. L. Spring, *Chem. Soc. Rev.* **2012**, *41*, 4444–4456; c) S. Sen, S. G. Prabhu, C. Bathula, S. Hati, *Synthesis* **2014**, *46*, 2099–2121; d) S. Collins, S. Bartlett, F. Nie, H. F. Sore, D. R. Spring, *Synthesis* **2016**, *48*, 1457–1473.

[6] a) L. Kiss, F. Fülöp, *Chem. Rec.* **2018**, *18*, 266–281; b) M. Nonn, Z. Benke, S. Fustero, F. Fülöp, L. Kiss, *Eur. J. Org. Chem.* **2019**, 5285–5293.

[7] a) R. Singh, R. Vince, *Chem. Rev.* **2012**, *112*, 4642–4686; b) Z. Yang, Y Fang, H. Park, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 2515–2519.

[8] a) L. Jaeyeon, J. Shim, P. Kang, M. G. Choi, S. H. Choi, *Org. Biomol. Chem.* **2018**, *16*, 433–438; b) M. Szefczyk, E. Weglarz-Tomczak, P. Fortuna, A. Krzyszton, E. Rudzinska-Szostak, Ł. Berlicki, *Angew. Chem. Int. Ed.* **2017**, *56*, 2087–2091; *Angew. Chem.* **2017**, *129*, 2119–2123; c) T. A. Martinek, F. Fülöp, *Chem. Soc. Rev.* **2012**, *41*, 687–702; d) L. K. A. Pilsl, O. Reiser, *Amino Acids* **2011**, *41*, 709–718; e) W. S. Horne, S. H. Gellman, *Acc. Chem. Res.* **2008**, *41*, 1399–1408; f) F. Sussman, V. M. Sanchez-Pedregal, J. C. Estvez, R. Balo, J. Jimnez-Barbero, A. Ard, A. Gimeno, M. Royo, M. C. Villaverde, R. J. Estvez, *Chem. Eur. J.* **2018**, *24*, 10625–10629; g) Y. H. Shin, S. H. Gellman, *J. Am. Chem. Soc.* **2018**, *14*, 1394–1400.

[9] a) H. Ju, S. Xiu, X. Ding, M. Shang, R. F. Jia, B. Huang, P. Zhan, X. Liu, *Eur. J. Med. Chem.* **2020**, *187*, 111940; b) K. Wang, Z. Lei, L. Zha, B. Chen, F. Yang, K. Liu, H. Zhu, H. Zhao, R. Cao, K. Zhang, Y. Tian, *Eur. J. Med. Chem.* **2020**, *185*, 111841; c) H. Ju, J. Zhang, Z. Sun, Z. Huang, W. Qi, B. Huang, P. Zhan, X. Liu, *Eur. J. Med. Chem.* **2018**, *146*, 220–231; d) P. C. Wang, D. C. Chiu, J. T. Jan, W. I. Huang, Y. C. Tseng, T. T. Li, T. J. Cheng, K. C. Tsai, J. M. Fang, *Eur. J. Med. Chem.* **2018**, *145*, 224–234; e) J. Zhang, N. A. Murugan, Y. Tian, C. Bertagnin, Z. Fang, D. Kang, X. Kong, H. Jia, Z. Sun, R. Jia, P. Gao, V. Poongavanam, A. Loregian, W. Xu, X. Ma, X. Ding, B. Huang, P. Zhan, X. Liu, *J. Med. Chem.* **2018**, *61*, 6379–6397; f) D. C. Chiu, T. C. Lin, W. I. Huang, T. J. Cheng, K. C. Tsaic, J. M. Fang, *Org. Biomol. Chem.* **2017**, *15*, 9910–9922; g) H. Zhang, L. Zhou, S. Amichai, K. Zandi, B. Cox, R. Schinazi, F. Amblard, *Bioorg. Med. Chem. Lett.* **2019**, *29*, 126639.

[10] a) E. J. Groso, C. S. Schindler, *Synthesis* **2019**, *51*, 1100–1114; b) C. Lecourt, S. Dhambri, L. Allievi, Y. Sanogo, N. Zeghbib, R. B. Othman, M. I. Lannou, G. Sorin, J. Ardisson, *Nat. Prod. Rep.* **2018**, *35*, 105–124; c) S. Monsaert, A. L. Vila, R. Drozdzak, P. Van Der Voort, F. Verpoort, *Chem. Soc. Rev.* **2009**, *38*, 3360; d) S. Kress, S. Blechert, *Chem. Soc. Rev.* **2012**, *41*, 4389; e) M. J. Koh, T. T. Nguyen, J. K. Lam, S. Torker, J. Hyvl, R. R. Schrock, A. H. Hoveyda, *Nature* **2017**, 542, 80; f) Y. Chauvin, *Angew. Chem. Int. Ed.* **2006**, *45*, 3741; g) B. J. Smith, G. A. Sulikowski, *Angew. Chem. Int. Ed.* **2010**, *49*,

1599; h) J. Prunet, *Eur. J. Org. Chem.* **2011**, 3634; i) P. Jakubec, D. M. Cockfield, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 16632; j) M. Rosillo, G. Domínguez, L. Casarrubios, U. Amador, J. Pérez-Castells, *J. Org. Chem.* **2004**, *69*, 2084; k) G. A. Cortez, C. A. Baxter, R. R. Schrock, A. H. Hoveyda, *Org. Lett.* **2007**, *9*, 2871; l) S. Chikkali, S. Mecking, *Angew. Chem. Int. Ed.* **2012**, *51*, 5802; m) C. S. Higman, J. A. M. Lummiss, D. E. Fogg, *Angew. Chem. Int. Ed.* **2016**, *55*, 3552.

[11] a) M. Nonn, L. Kiss, E. Forró, R. Sillanpää, F. Fülöp, *Tetrahedron* **2014**, *70*, 8511–8519; b) L. Kiss, E. Forró, F. Fülöp, *Beilstein J. Org. Chem.* **2015**, *11*, 596–603; c) M. Cherepanova, L. Kiss, E. Forró, F. Fülöp, *Eur. J. Org. Chem.* **2014**, 403–409.

[12] a) L. Kiss, M. Kardos, E. Forró, F. Fülöp, *Eur. J. Org. Chem.* **2015**, 1283–1289; b) M. Kardos, L. Kiss, F. Fülöp, *Asian J. Org. Chem.* **2015**, 1155–1159; c) M. Kardos, L. Kiss, M. Haukka, S. Fustero, F. Fülöp, *Eur. J. Org. Chem.* **2017**, 1894–1901; d) L. Kiss, M. Kardos, C. Vass, F. Fülöp, *Synthesis* **2018**, *50*, 3571–3588; e) M. Nonn, Z. Benke, S. Fustero, F. Fülöp, L. Kiss, *Eur. J. Org. Chem.* **2019**, 5285–5293; f) A. M. Remete, Z. Benke, L. Kiss, *Fluorine Notes* **2019**, *6*(127); g) G. Bernáth, G. Stájer, A. E. Szabó, F. Fülöp, P. Sohár, *Tetrahedron* **1985**, *41*, 1353–1365.

[13] a) L. Kiss, M. Nonn, F. Fülöp, *Synthesis* **2012**, *44*, 1951–1963; b) M. Nonn, L. Kiss, R. Sillanpää, F. Fülöp, *Beilstein J. Org. Chem.* **2012**, *8*, 100–106.

[14] a) Z. Benke, M. Nonn, F. Fülöp, L. Kiss, *ChemistrySelect* **2019**, *4*, 2886–2891; b) Z. Benke, M. Nonn, M. Kardos, S. Fustero, L. Kiss, *Beilstein J. Org. Chem.* **2018**, *14*, 2698–2707.

[15] a) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; b) Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications, Imperial College Press, London (**2012**). Edited by V. Gouverneur, K. Müller; c) Y. Zhou, Y. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 442–518; d) H. Mei, J. Han, K. D. Klika, K. Izawa, T. Sato, N. A. Meanwell, V. A. Soloshonok, *Eur. J. Med. Chem.* **2020**, *186*, 111826; e) L. Kiss, A. M. Remete, *Eur. J. Org. Chem.* **2019**, 5574–5602; f) S. Fustero, A. Simón-Fuentes, P. Barrio, G. Haufe, *Chem. Rev.* **2015**, *115*, 871–930.

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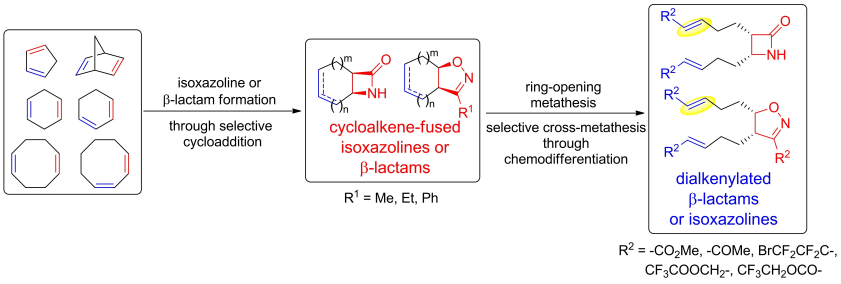

L. Kiss, Z. Benke, A. M. Remete, F. Fülöp**

The article describes selective transformations of some readily available cyclodienes through simple chemical procedures into novel functionalized small-molecular entities. The syntheses were based selective cycloadditions, followed by ring-opening metathesis of the resulting β-lactam or isoxazoline scaffolds and selective cross-metathesis by discrimination of the olefin bonds on the alkenylated heterocycles.