



A study on selective transformation of norbornadiene into fluorinated cyclopentane-fused isoxazolines

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Abstract

This work presents an examination of the selective functionalization of norbornadiene through nitrile oxide 1,3-dipolar cycloaddition/ring-opening metathesis (ROM)/cross-metathesis (CM) protocols. Functionalization of commercially available norbornadiene provided novel bicyclic scaffolds with multiple stereogenic centers. The synthesis involved selective cycloadditions, with subsequent ROM of the formed cycloalkene-fused isoxazoline scaffolds and selective CM by chemodifferentiation of the olefin bonds of the resulting alkenylated derivatives. Various experimental conditions were applied for the CM transformations with the goal of exploring substrate and steric effects, catalyst influence and chemodifferentiation of the olefin bonds furnishing the corresponding functionalized, fluorine-containing isoxazoline derivatives.

Introduction

Olefin metathesis is considered to be a powerful synthetic tool for the creation of olefin bonds [1]. Several types of metathesis reactions, such as ring-opening metathesis (ROM), cross-metathesis (CM), ring-closing metathesis (RCM) or ring-opening/cross-metathesis (ROCM) have found high utility in the creation of C=C bonds and in the synthesis of a number of organic molecules, functionalized scaffolds or various building blocks. The efficient catalytic activity and remarkable functional group tolerance of commercially available versatile Ru-based olefin metathesis catalysts have allowed wide applica-

bility of these transformations [1-8]. Moreover, the robustness of many commercial Ru-based catalysts has enabled the general application of olefin metathesis in the synthesis of versatile functionalized heterocycles [9-11], a wide variety of natural products (especially macrocycles) [12], alkaloids [13], amino acids and functionalized biomolecules such as peptides [14-20] or various drugs [21]. Due to the ring strain, bicyclic systems and derivatives, such as norbornadiene derivatives can easily be converted across ROM or ROCM into a variety of alkenylated, functionalized scaffolds [22-34]. Although metathesis is a re-

versible process, it is often shifted towards a certain direction. For example, the equilibrium of the reaction of ethylene with a strained ring system and the corresponding ROM product is shifted towards ROM because ring strain disfavors reclosing of the ring system. Therefore, functionalized norbornenes, which are highly strained scaffolds, easily provide a number of functionalized cyclopentanes across the ROM/CM process.

It is well known that the structure of a certain metathesis substrate, the nature of the catalyst and all experimental conditions may highly influence metathesis reactions and determine the outcome of olefin metathesis. The accurate prediction of a specific catalyst, including its efficiency, the suitable experimental conditions such as catalyst loading, temperature, solvent, reaction time or even work-up seem to be a difficult task. It is observed that there is no single universal catalyst suitable for all types of metathesis reactions, and there is no general relationship between the structure of the substrate and the type of catalyst. These assumptions might be valid, in particular, for selective processes such as selection between the olefin bonds by chemodifferentiation or chemodiscrimination [1-8,22].

Since the nature of the substrate, catalyst as well as reaction conditions affect the outcome of metathesis, various publications were dedicated to studies describing selective CM or ROCM transformations. The accurate prediction of selectivity regarding CM reactions is still considered to be a challenging issue among synthetic organic chemists. Of numerous factors contributing to the observed selectivities in metathesis reactions, H-bonding interactions between chloride ligands as H-bond acceptors and OH or NH functions in the metathesis intermediate appear to be determining [35,36].

Selectivity derived from chelation is considered to be another important contributor. Through the formation of intermediates with stable (e.g., six-membered) chelate ring systems, the chelation ability of oxygen functionalities to ruthenium during metathesis can greatly influence the outcome of the CM reaction [36,37]. Steric factors are another important phenomenon, which will possibly contribute to the selectivity of olefin bonds during a CM reaction [38-43].

Investigations of various types of olefins in CM, such as substituted and functionalized styrenes, unsaturated tertiary alcohols, olefins with quaternary carbon centers, acrylates, allyl ethers or allyl acetates gave a general model suitable for the prediction of product selectivity and olefin bond chemodifferentiation in cross metathesis. In general, regarding the reactivity of the olefin bond in CM, alkenes can be categorized by the relative ability to undergo homodimerization via CM and the possibility of the corresponding homodimers for novel secondary me-

tathesis reactions [44]. Thus, olefins can be categorized as type I (fast homodimerization), type II (slow homodimerization), type III (no homodimerization) and type IV (unreactive olefins, spectators to CM) [44].

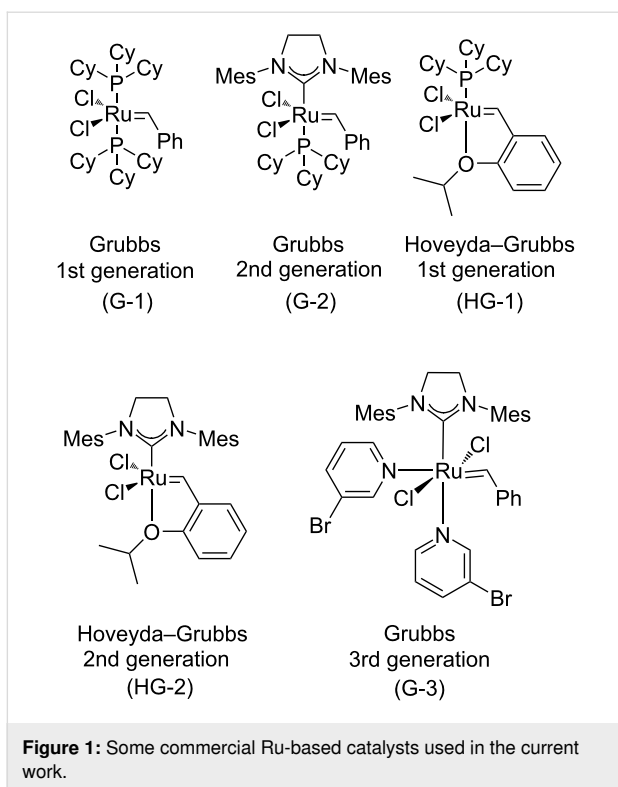
Although olefins with perfluorinated alkane moiety are considered as to be of type II, only a handful of literature data are available on the behavior of fluorine-containing olefins or perfluorinated alkenes. The incorporation of fluoroalkyl moieties (such as difluoromethyl, trifluoromethyl and perfluoroalkyl groups) into an organic molecule can often enhance the pharmacokinetic properties of lead candidates in drug research through the improvement in lipophilicity, absorption, distribution, hydrophobicity and metabolism. Considering the high importance of organofluorine chemistry and that of fluoroalkyl groups in pharmaceutical chemistry, a wide range of novel and efficient protocols for the introduction of fluorinated scaffolds or fluoroalkyl groups onto organic molecular entities represent a hot topic in synthetic organic chemistry [45-48]. In order to prepare a certain fluorinated organic molecule, two common approaches are used: i) late-stage fluorination, when the fluorine atom is incorporated in the final step of the synthetic protocol (e.g., deoxofluorinations) or ii) application of various commercial fluorine-containing scaffolds (e.g., fluorine-containing amines, fluorine-containing alkenes etc.) [49-58]. It is to be noted that a recent review has been devoted to the synthesis of various fluorine-containing derivatives through various metathesis techniques by the application of versatile fluorinated substrates [59].

Results and Discussion

The aim of the current work was to investigate the selective functionalization of readily available norbornadiene across nitrile oxide cycloaddition/ROM/CM protocols in view of the access of various fluorine-containing molecular entities as well as to explore the chemical behavior of olefin bonds in the reaction with some fluorinated alkene derivatives in view of chemodifferentiation. The reactions were performed with various olefin metathesis catalysts to find the most optimal conditions (Figure 1).

The starting divinyl-substituted bicyclic isoxazolines were synthesized according to literature methods, as shown in Figure 2, utilizing nitrile oxide cycloaddition according to the Mukaiyama method followed by ROM of the major product. All five catalysts provided the desired products to some extent, but HG-1 gave the highest yield of (±)-**4**: 76%, (±)-**5**: 75% and (±)-**6**: 87% [41].

Further functionalization of compounds (±)-**4-6** was attempted via CM with a high number of fluorine-containing alkenes



(Figure 3). Compounds **7a** and **7b** as well as **7f–h** were type I olefins, while acrylate esters **7c–e** were type II olefins. Because 1st generation metathesis catalysts usually perform poorly in CM reactions with acrylates [31,32,36,39,41], only G-2, HG-2 and G-3 were used in our CM steps.

CM reactions of compound (\pm)-**4** were investigated first. With 4-bromo-3,3,4,4-tetrafluorobut-1-ene and allyl 2,2,2-trifluoroacetate, no CM product was observed. However, CM reactions with 1,1,1,3,3,3-hexafluoropropan-2-yl acrylate (**7c**) were successful (Scheme 1 and Table 1). When catalyst HG-2 was used (Table 1, entries 1 and 2), decomposition of the catalyst with

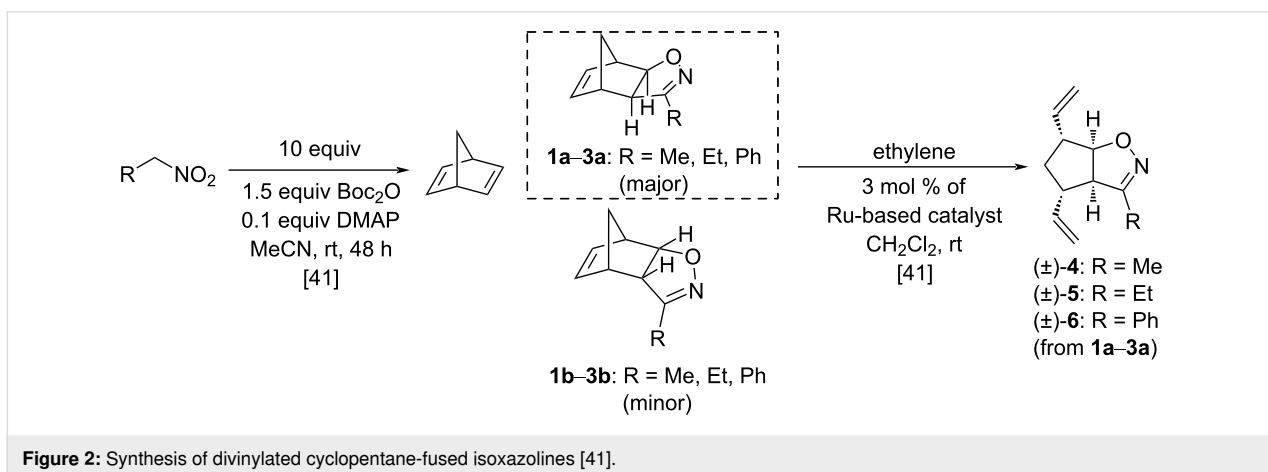
NaHCO₃ in aqueous MeOH during workup improved the yield. Therefore, catalyst decomposition was incorporated into the workup procedure of all other CM reactions.

The outcome of the reaction between (\pm)-**4** and **7c** was catalyst-dependent (Table 1). In the presence of HG-2, the main product was dicoupled (\pm)-**8c** accompanied by the unseparable mixture of monocoupled products (\pm)-**8a** and (\pm)-**8b**. Despite the partial signal overlap, 2D NMR analysis of the (\pm)-**8a** and (\pm)-**8b** mixture was possible, and the structure of both (\pm)-**8a** and (\pm)-**8b** as well as the compound ratio could be determined. When catalyst G-2 or G-3 was applied for the CM reaction, only monocoupled products were formed. Notably, G-2 or G-3 catalysts had lower selectivity towards (\pm)-**8a** (ratio of (\pm)-**8a** and (\pm)-**8b**: 3.3:1 with HG-2 and 2.5:1 with G-2 or G-3), but they, in particular G-2, provided a superior combined yield of (\pm)-**8a** and (\pm)-**8b**.

Note, that although the yield of the CM is relatively low, a full conversion of the starting isoxazoline could be detected. However, all CM transformations alongside the desired coupled compounds afforded a significant amount of unidentifiable polymeric material.

CM reactions of compound (\pm)-**4** with 2,2,3,3,4,4,4-heptafluorobutyl acrylate (**7d**) were also successful (Scheme 2 and Table 2). Again, the catalyst HG-2 provided mainly the dimetathesized product. CM in the presence of G-2 or G-3 gave mainly an inseparable mixture of monometathesized products, but some dimetathesized (\pm)-**9c** was formed too. Similar to Table 1, G-2 provided the highest combined yield of (\pm)-**9a** and (\pm)-**9b**, but it was the least regioselective (ratio of (\pm)-**9a** and (\pm)-**9b**: 3.3:1 with HG-2, 2.5:1 with G-3 and 2:1 with G-2).

We continued our investigation with CM reactions of compound (\pm)-**4** with 2,2,2-trifluoroethyl acrylate (**7e**, Scheme 3



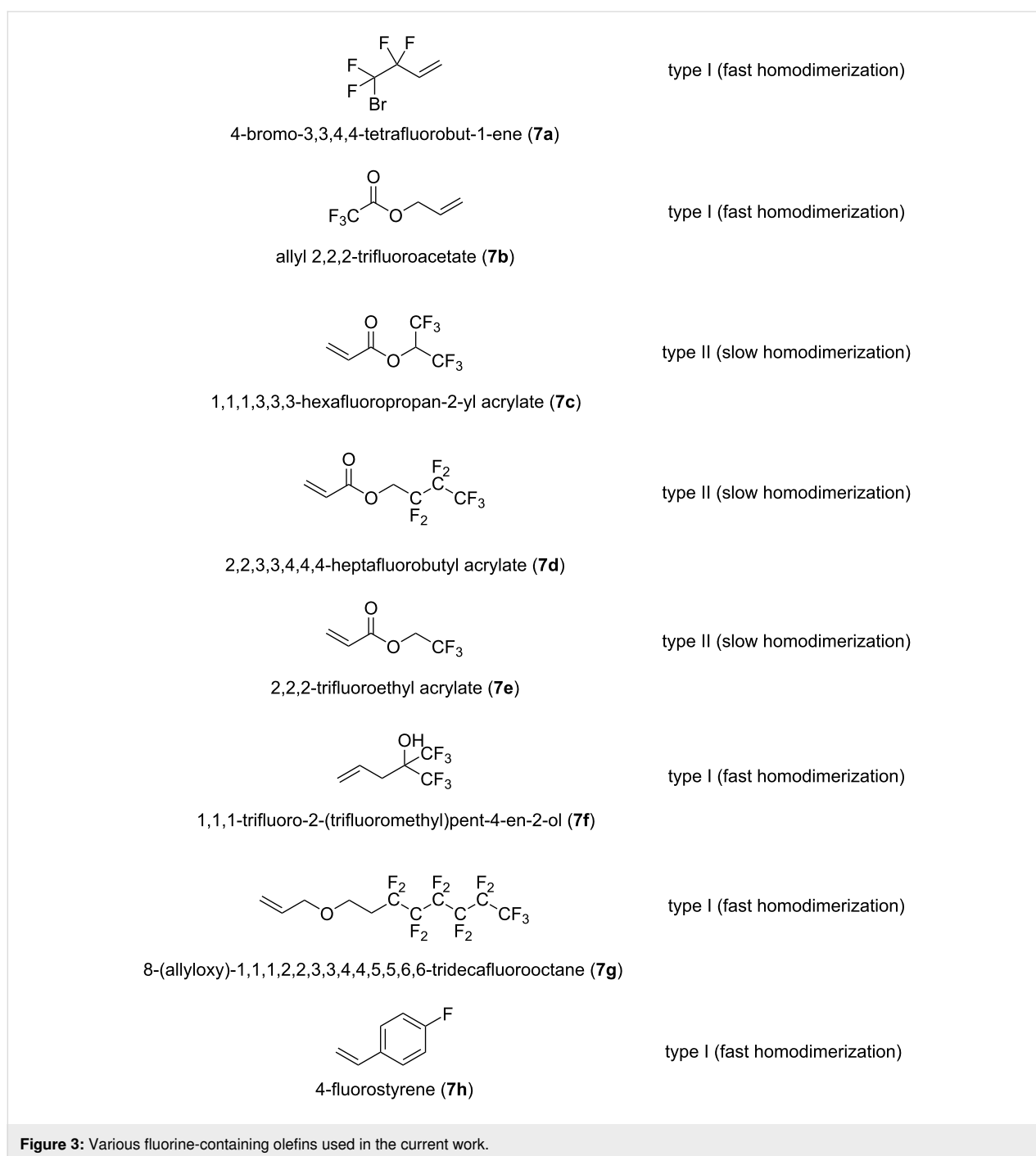
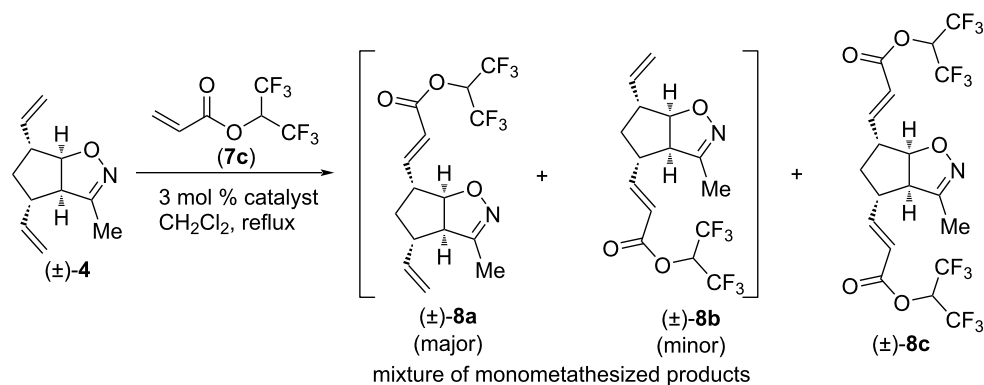


Figure 3: Various fluorine-containing olefins used in the current work.

and Table 3). Interestingly, even with HG-2 catalyst, dicoupled product (\pm)-**10c** formed only in trace amounts. With G-2 and G-3 catalysts, only monocoupled products (\pm)-**10a** and (\pm)-**10b** were formed as an inseparable mixture. Similar to Table 1, HG-2 provided the lowest combined yield of monocoupled products, but it had the highest regioselectivity (ratio of (\pm)-**10a** and (\pm)-**10b**: 3.3:1 with HG-2 and 1.66:1 with G-2 and G-3, respectively). The highest yield for the (\pm)-**10a** and (\pm)-**10b** mixture (23%) was achieved with G-2 catalyst.

Then, substrate (\pm)-**4** was subjected to CM with type I olefin **7f** utilizing HG-2 and G-2 catalysts (Scheme 4 and Table 4). As shown in Tables 1–3, G-3 gave similar or slightly inferior yield compared to G-2. To our surprise, dimetathesized product (\pm)-**11c** was not formed, and the two monometathesized products were separable. Interestingly, regioselectivity was reversed compared to those in Tables 1–3: the main product was (\pm)-**11b** (26% with HG-2, 25% with G-2), while isomeric product (\pm)-**11a** was formed in lower yield (15% with HG-2 and

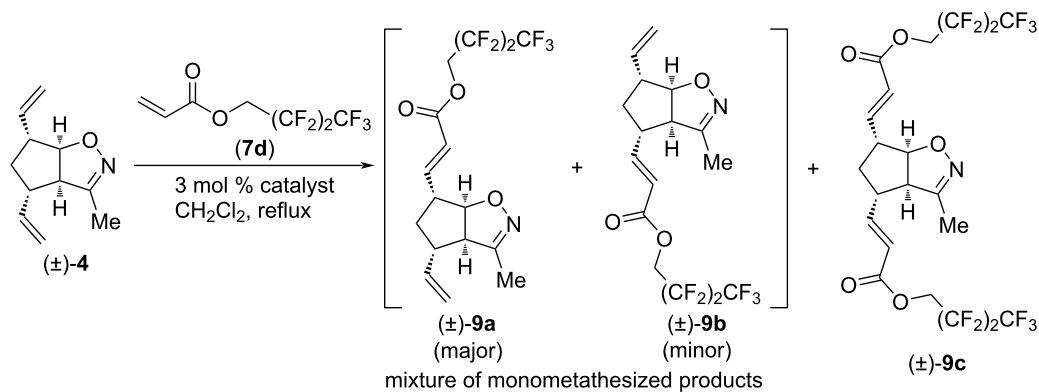


Scheme 1: Cross-metathesis of divinylated isoxazoline (\pm)-4 with 1,1,1,3,3,3-hexafluoropropan-2-yl acrylate (**7c**).

Table 1: CM of isoxazoline (\pm)-4 with 1,1,1,3,3,3-hexafluoropropan-2-yl acrylate (**7c**).

entry	catalyst	reaction time	yield and ratio of (\pm)- 8a and (\pm)- 8b	yield of (\pm)- 8c
1	HG-2	5 h	5% (3.3:1)	16% ^a
2	HG-2	5 h	10% (3.3:1)	17%
3	G-3	5 h	15% (2.5:1)	0%
4	G-2	5 h	25% (2.5:1)	0%

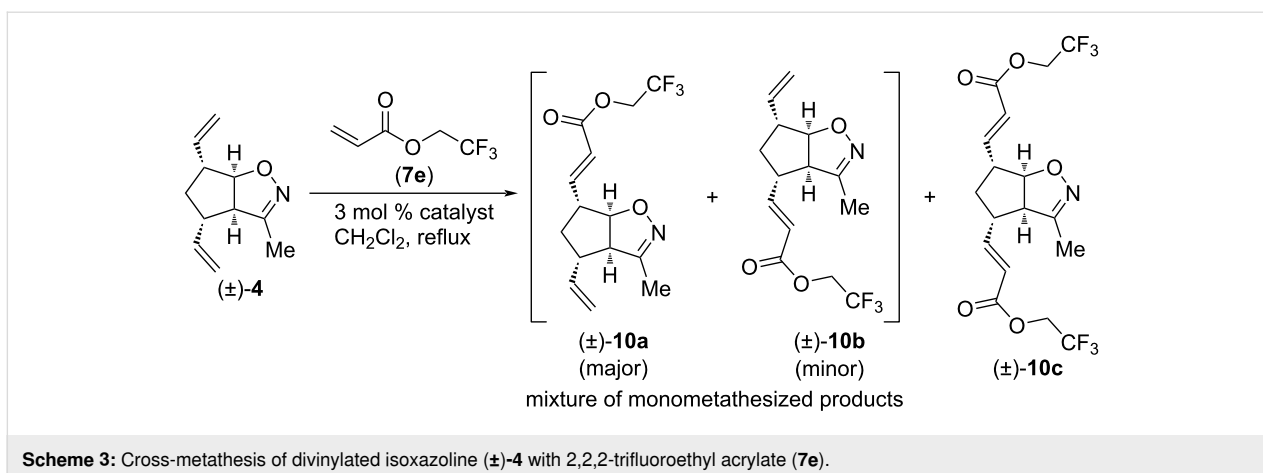
^aMeOH, $\text{H}_2\text{O}/\text{NaHCO}_3$ were not added before concentration of the mixture. Note: all yields reported in tables are isolated yield values.



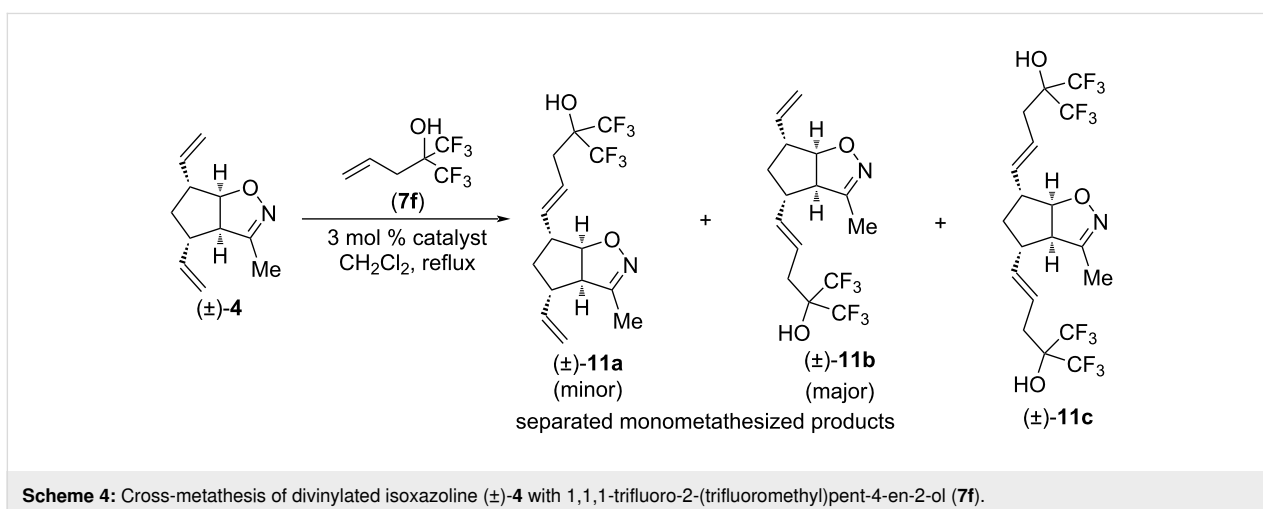
Scheme 2: Cross-metathesis of divinylated isoxazoline (\pm)-4 with 2,2,3,3,4,4,4-heptafluorobutyl acrylate (**7d**).

Table 2: CM of isoxazoline (\pm)-4 with 2,2,3,3,4,4,4-heptafluorobutyl acrylate (**7d**).

entry	catalyst	reaction time	yield and ratio of (\pm)- 9a and (\pm)- 9b	yield of (\pm)- 9c
1	HG-2	5 h	20% (3.3:1)	34%
2	G-3	5 h	11% (2.5:1)	trace
3	G-2	5 h	36% (2:1)	10%

**Table 3:** CM of isoxazoline (\pm)-4 with 2,2,2-trifluoroethyl acrylate (**7e**).

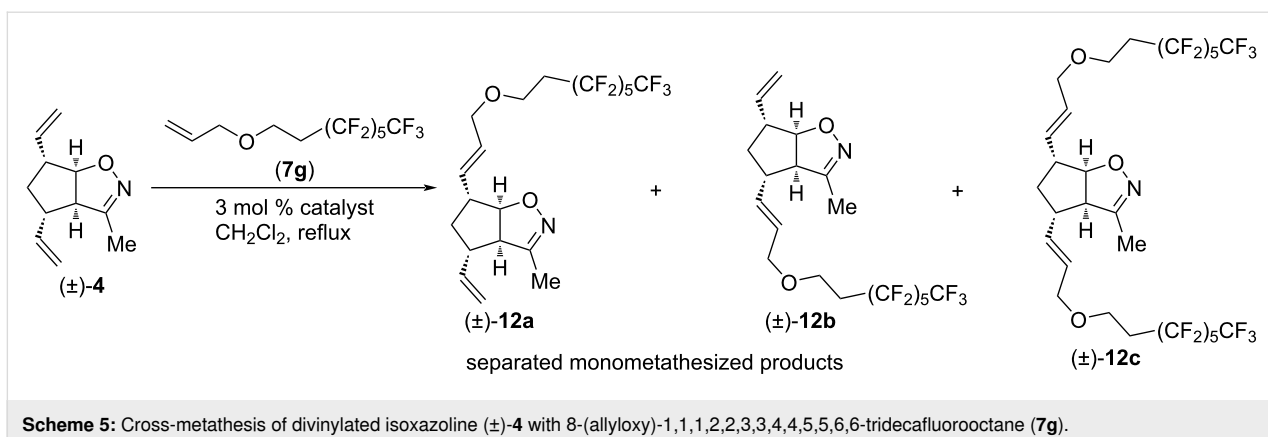
entry	catalyst	reaction time	yield and ratio of (\pm)-10a and (\pm)-10b	yield of (\pm)-10c
1	HG-2	5 h	15% (3.3:1)	trace
2	G-3	5 h	19% (1.66:1)	0%
3	G-2	5 h	23% (1.66:1)	0%

**Table 4:** CM of isoxazoline (\pm)-4 with 1,1,1-trifluoro-2-(trifluoromethyl)pent-4-en-2-ol (**7f**).

entry	catalyst	reaction time	yield of (\pm)-11a	yield of (\pm)-11b	yield of (\pm)-11c
1	HG-2	5 h	15%	26%	0%
2	G-2	5 h	10%	25%	0%

10% with G-2). G2 catalyst showed better regioselectivity (ratio of (\pm)-11a and (\pm)-11b: 1:1.73 with HG-2 and 1:2.5 with G-2).

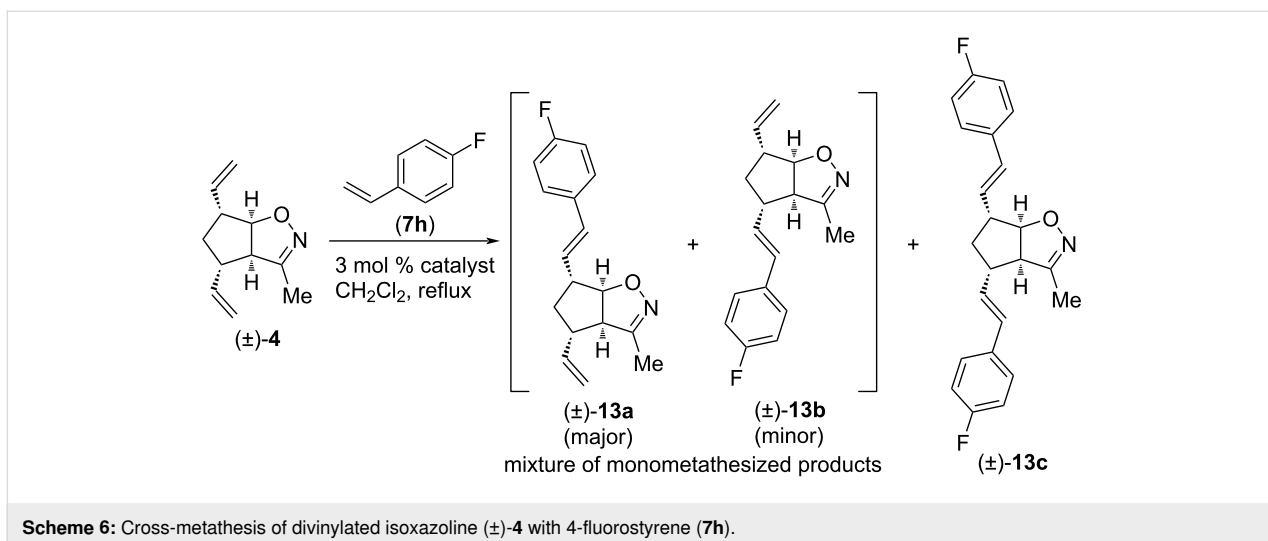
Next, CM reactions of isoxazoline (\pm)-4 with type I olefin **7g** were studied (Scheme 5 and Table 5) applying HG-2 and G-2 catalysts. Under these conditions, dicoupled product (\pm)-12c

**Table 5:** CM of isoxazoline (\pm)-**4** with 8-(allyloxy)-1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorooctane (**7g**).

entry	catalyst	reaction time	yield of (\pm)- 12a	yield of (\pm)- 12b	yield of (\pm)- 12c
1	HG-2	5 h	9%	6%	0%
2	G-2	5 h	3%	5%	0%

was not detected. The formed monocoupled products (\pm)-**12a** and (\pm)-**12b** were separable. HG-2 provided both (\pm)-**12a** and (\pm)-**12b** in better yield. Interestingly, (\pm)-**12a** was the main product with HG-2, and (\pm)-**12b** with G-2.

In the final test of compound (\pm)-**4**, it was subjected to CM with 4-fluorostyrene (**7h**), a type I olefin (Scheme 6 and Table 6). With HG-2 catalyst, the main product was dicoupled (\pm)-**13c**, while the minor product was an inseparable mixture of mono-

**Table 6:** CM of isoxazoline (\pm)-**4** with 4-fluorostyrene (**7h**).

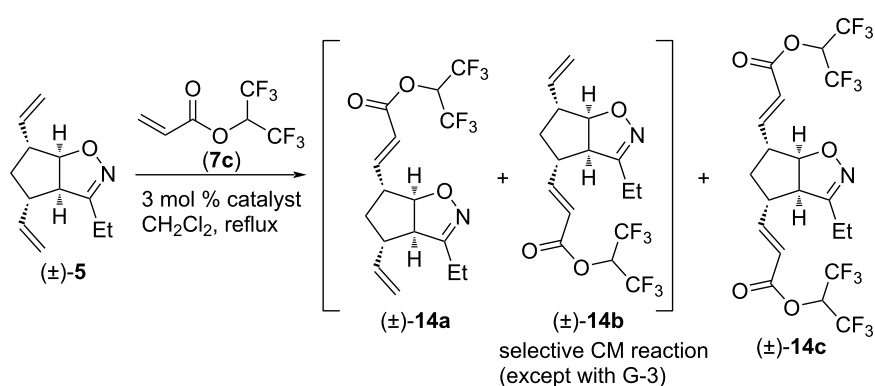
entry	catalyst	reaction time	yield and ratio of (\pm)- 13a and (\pm)- 13b	yield of (\pm)- 13c
1	HG-2	5 h	18% (1.4:1)	30%
2	G-3	5 h	28% (1.4:1)	5%
3	G-2	5 h	36% (1.4:1)	12%

coupled products (\pm)-**13a** and (\pm)-**13b**. When G-2 or G-3 catalyst, respectively, was applied for the CM reaction, the major product mixture was (\pm)-**13a** and (\pm)-**13b** (the best yield was achieved with G-2) accompanied by some (\pm)-**13c**. Interestingly, regioselectivity of all three catalysts was the same, with a 1.4:1 ratio of (\pm)-**13a** and (\pm)-**13b**.

We continued our work with the study of CM reactions of compound (\pm)-**5**, which has a slightly longer alkyl chain on the heteroring compared to that of (\pm)-**4**. Similar to (\pm)-**4**, no CM product was observed with olefins **7a** and **7b**. In contrast, CM reactions with **7c** were successful (Scheme 7 and Table 7). With

HG-2 catalyst, dimetathesized compound (\pm)-**14c** was the main product, and some monometathesized (\pm)-**14a** was also formed. With G-2 catalyst, the outcome was the opposite. Interestingly, G-3 catalyst provided only an inseparable mixture of monometathesized products (\pm)-**14a** and (\pm)-**14b** (note, that compound (\pm)-**14b** was not formed in the presence of HG-2 or G-2).

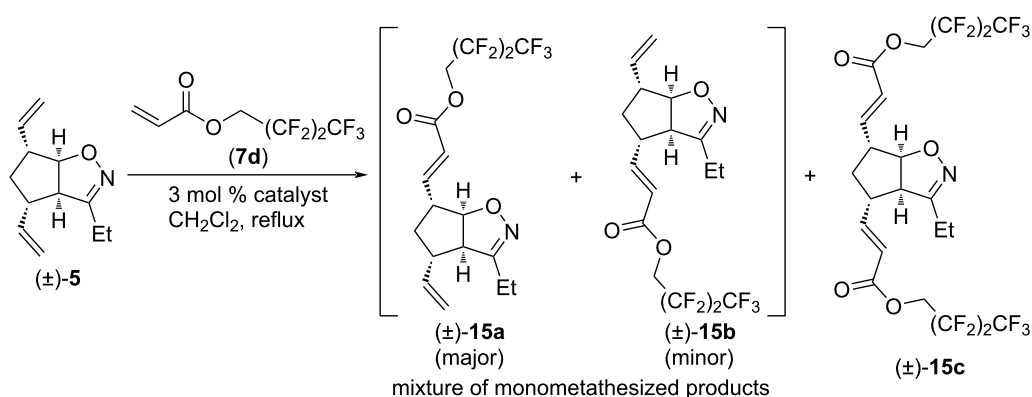
CM reactions of isoxazoline (\pm)-**5** with olefin **7d** in the presence of G-3 catalyst led to the inseparable mixture of monocoupled products (\pm)-**15a** and (\pm)-**15b** (Scheme 8 and Table 8). With G-2 catalyst, a mixture of (\pm)-**15a** and (\pm)-**15b** was formed



Scheme 7: Selective CM of divinylated isoxazoline (\pm)-**5** with 1,1,1,3,3,3-hexafluoropropan-2-yl acrylate (**7c**).

Table 7: CM of isoxazoline (\pm)-**5** with 1,1,1,3,3,3-hexafluoropropan-2-yl acrylate (**7c**).

entry	catalyst	reaction time	yield and ratio of (\pm)- 14a and (\pm)- 14b	yield of (\pm)- 14c
1	HG-2	5 h	2% (1:0)	27%
2	G-3	5 h	13% (2:1)	0%
3	G-2	5 h	16% (1:0)	7%



Scheme 8: Cross-metathesis of divinylated isoxazoline (\pm)-**5** with 2,2,3,3,4,4,4-heptafluorobutyl acrylate (**7d**).

Table 8: CM of isoxazoline (\pm)-**5** with 2,2,3,3,4,4,4-heptafluorobutyl acrylate (**7d**).

entry	catalyst	reaction time	yield and ratio of (\pm)- 15a and (\pm)- 15b	yield of (\pm)- 15c
1	HG-2	5 h	9% (5:1)	42%
2	G-3	5 h	8% (2:1)	0%
3	G-2	5 h	34% (3.3:1)	18%

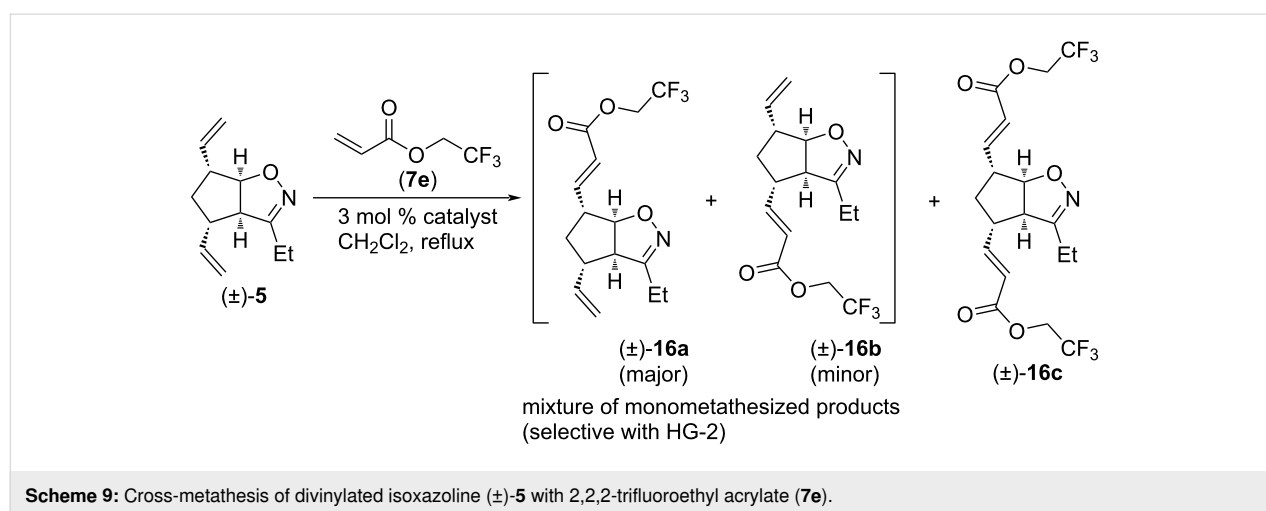
in significantly higher yield, and some dicoupled product (\pm)-**15c** was also isolated from the reaction mixture. With HG-2 catalyst, (\pm)-**15c** was the main product, but an amount of (\pm)-**15a** and (\pm)-**15b** was formed as well. Judging from the ratio of (\pm)-**15a** and (\pm)-**15b**, HG-2 catalyst was the most regioselective and G-3 was the least regioselective.

The next CM partner was 2,2,2-trifluoroethyl acrylate (**7e**, Scheme 9 and Table 9). With HG-2 catalyst, dimetathesized product (\pm)-**16c** was formed in medium yield, and some monometathesized product (\pm)-**16a** was present too. With G-2 catalyst, the inseparable mixture of monometathesized compounds (\pm)-**16a** and (\pm)-**16b** (in 2.5:1 ratio) was the main product, accompanied with some (\pm)-**16c**. Only monometathesized products formed with G-3 catalyst, but both the yield and regioselectivity were inferior compared to those found with G-2.

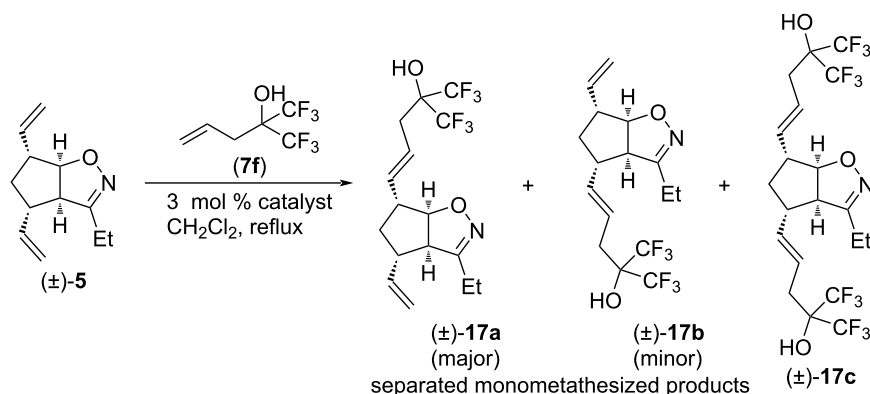
CM reactions of substrate (\pm)-**5** and type I olefin **7f** were studied only with HG-2 and G-2 catalysts, respectively (Scheme 10 and Table 10). In both cases, only a mixture of monocoupled products (\pm)-**17a** and (\pm)-**17b** was formed, which was separable. The main product was always (\pm)-**17a**. HG-2 was more regioselective (ratio of (\pm)-**17a** and (\pm)-**17b**: 5:1 with HG-2 and 3.3:1 with G2), but G-2 provided a higher yield.

We also attempted CM reactions of (\pm)-**5** with 8-(allyloxy)-1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorooctane (**7g**, Scheme 11). However, dimetathesized product (\pm)-**18c** was not formed, and isolation of monometathesized products (\pm)-**18a** and (\pm)-**18b** (or a mixture thereof) in pure form failed despite repeated attempts of chromatographic separation.

Finally, isoxazoline (\pm)-**5** was subjected to CM with 4-fluorostyrene (**7h**, Scheme 12 and Table 11). HG-2 catalyst provided

**Table 9:** CM of isoxazoline (\pm)-**5** with 2,2,2-trifluoroethyl acrylate (**7e**).

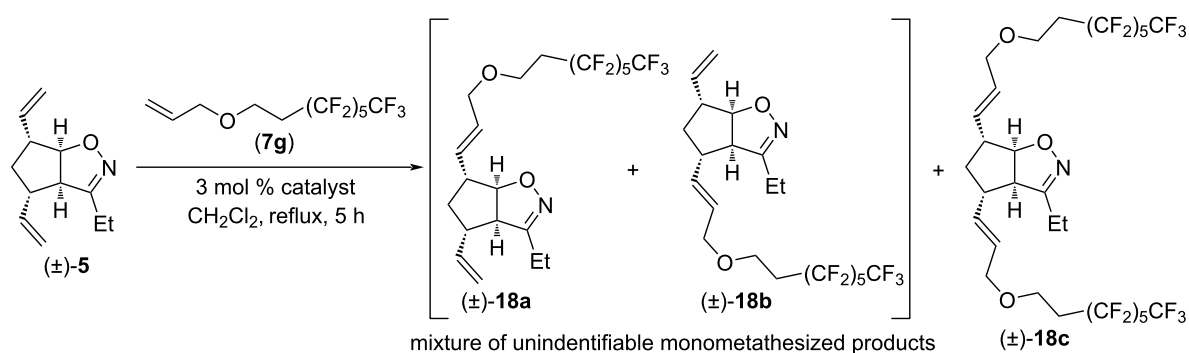
entry	catalyst	reaction time	yield and ratio of (\pm)- 16a and (\pm)- 16b	yield of (\pm)- 16c
1	HG-2	5 h	7% (1:0)	52%
2	G-3	5 h	25% (2:1)	0%
3	G-2	5 h	34% (2.5:1)	8%



Scheme 10: Cross-metathesis of divinylated isoxazoline (\pm)-5 with 1,1,1-trifluoro-2-(trifluoromethyl)pent-4-en-2-ol (**7f**).

Table 10: CM of isoxazoline (\pm)-5 with 1,1,1-trifluoro-2-(trifluoromethyl)pent-4-en-2-ol (**7f**).

entry	catalyst	reaction time	yield of (\pm)-17a	yield of (\pm)-17b	yield of (\pm)-17c
1	HG-2	5 h	21%	4%	0%
2	G-2	5 h	34%	11%	0%



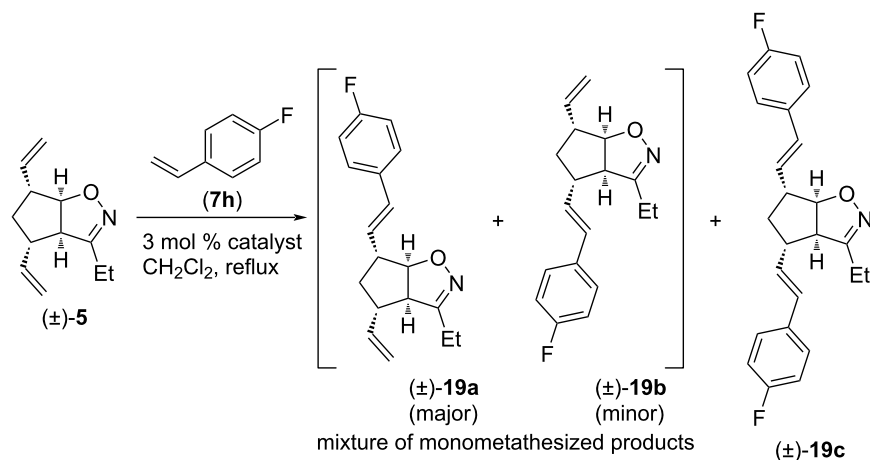
Scheme 11: Cross-metathesis of divinylated isoxazoline (\pm)-5 with 8-(allyloxy)-1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorooctane (**7g**).

mainly dicoupled product (\pm)-19c, but some amount of (\pm)-19a and (\pm)-19b mixture was isolated too. G-3 catalyst provided mainly the inseparable mixture of monocoupled products (\pm)-19a and (\pm)-19b, but some (\pm)-19c was formed as well. With G-2 catalyst, a product mixture of (\pm)-19a and (\pm)-19b was formed in slightly higher yield than with G-3, but it was accompanied with a considerable amount of (\pm)-19c. With all three catalysts, the ratio of (\pm)-19a and (\pm)-19b was 2:1.

We continued our work with the study of CM reactions of phenyl-substituted isoxazoline (\pm)-6. Similar to (\pm)-4 and (\pm)-5, no CM product was observed with olefins **7a** and **7b**. However, CM reactions with **7c** were successful (Scheme 13 and Table 12). With HG-2 catalyst, dimetathesized compound

(\pm)-20c was the main product and monometathesized compound (\pm)-20a was the minor product. With G-2 catalyst, that preference was reversed. G-3 catalyst provided product (\pm)-20a in an exclusive manner, and this was the most efficient way to synthesize this monometathesized compound. Importantly, formation of alternative monometathesized product (\pm)-20b was not observed.

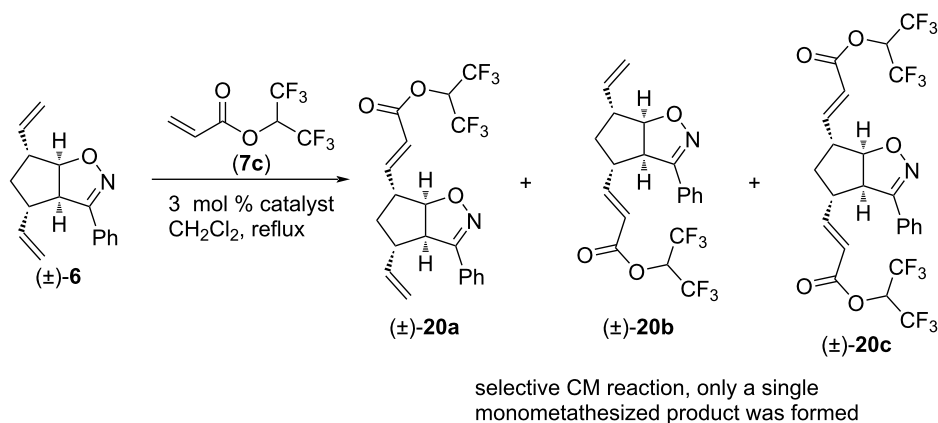
Then, CM reactions of (\pm)-6 with alkene **7d** were explored (Scheme 14 and Table 13). G-3 catalyst yielded (\pm)-21a as the sole monocoupled product, while HG-2 and G-2 catalysts gave both monocoupled (\pm)-21a and dicoupled (\pm)-21c. The best yield of (\pm)-21c was achieved with HG-2 catalyst (although G-2 catalyst also produced a surprisingly high amount



Scheme 12: Cross-metathesis of divinylated isoxazoline (±)-5 with 4-fluorostyrene (7h).

Table 11: CM of isoxazoline (±)-5 with 4-fluorostyrene (7h).

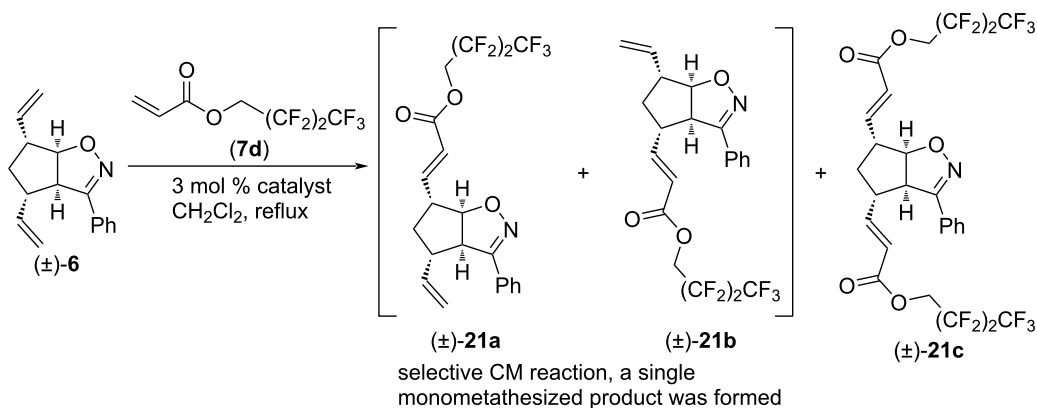
entry	catalyst	reaction time	yield and ratio of (±)-19a and (±)-19b	yield of (±)-19c
1	HG-2	5 h	12% (2:1)	38%
2	G-3	5 h	35% (2:1)	7%
3	G-2	5 h	37% (2:1)	22%



Scheme 13: Cross-metathesis of divinylated isoxazoline (±)-6 with 1,1,1,3,3,3-hexafluoropropan-2-yl acrylate (7c).

Table 12: CM of isoxazoline (±)-6 with 1,1,1,3,3,3-hexafluoropropan-2-yl acrylate (7c).

entry	catalyst	reaction time	yield and ratio of (±)-20a and (±)-20b	yield of (±)-20c
1	HG-2	5 h	6% (1:0)	38%
2	G-3	5 h	30% (1:0)	0%
3	G-2	5 h	16% (1:0)	7%



Scheme 14: Cross-metathesis of divinylated isoxazoline (±)-6 with 2,2,3,3,4,4,4-heptafluorobutyl acrylate (7d).

Table 13: CM of isoxazoline (±)-6 with 2,2,3,3,4,4,4-heptafluorobutyl acrylate (7d).

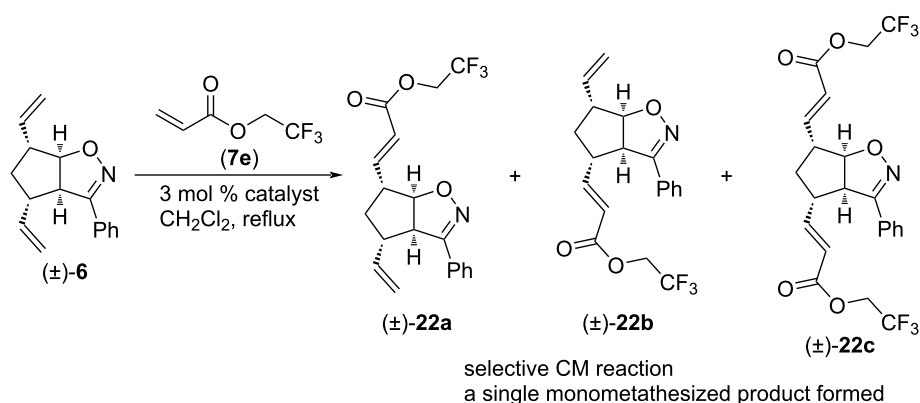
entry	catalyst	reaction time	yield and ratio of (±)-21a and (±)-21b	yield of (±)-21c
1	HG-2	5 h	18% (1:0)	37%
2	G-3	5 h	17% (1:0)	0%
3	G-2	5 h	27% (1:0)	32%

of (±)-21c, while the synthesis of (±)-21a was the most efficient with G-2 catalyst. Note, that this CM reaction was also regioselective.

CM reactions of compound (±)-6 with olefin 7e were also regioselective (Scheme 15 and Table 14). G-3 catalyst yielded only monometathesized (±)-22a as a single product, HG-2 catalyst gave mainly dimetathesized (±)-22c (together with some (±)-22a) and G-2 catalyst gave mainly monometathesized

(±)-22a (together with some (±)-22c). The best yield of (±)-22c was achieved with HG-2 catalyst, while the synthesis of (±)-22a was the most efficient with G-2 catalyst.

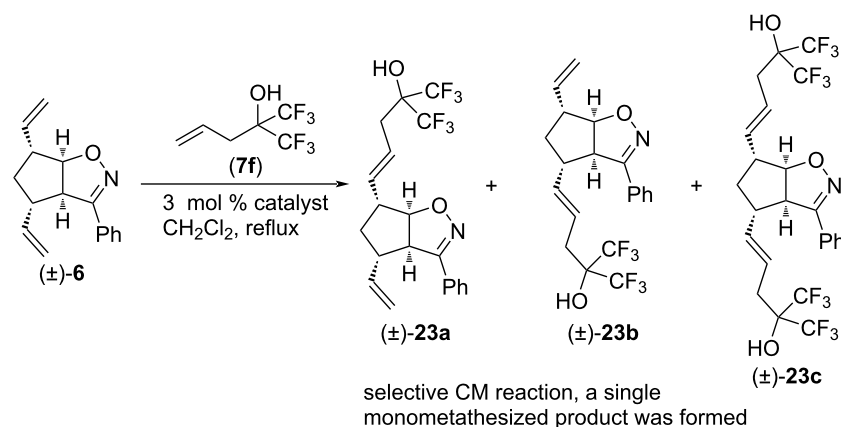
Cross metathesis of substrate (±)-6 with unsaturated alcohol 7f was also performed (Scheme 16 and Table 15). The reaction was completely regioselective with HG-2 and G-2 catalysts, and provided only a single monocoupled product, (±)-23a. The best yield was achieved with G-2 catalyst.



Scheme 15: Cross-metathesis of divinylated isoxazoline (±)-6 with 2,2,2-trifluoroethyl acrylate (7e).

Table 14: CM of isoxazoline (\pm)-**6** with 2,2,2-trifluoroethyl acrylate (**7e**).

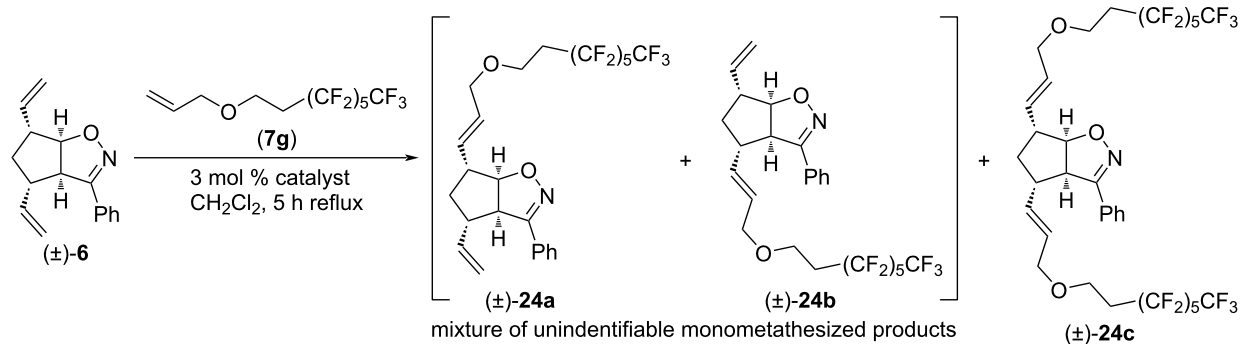
entry	catalyst	reaction time	yield and ratio of (\pm)- 22a and (\pm)- 22b	yield of (\pm)- 22c
1	HG-2	5 h	4% (1:0)	48%
2	G-3	5 h	22% (1:0)	0%
3	G-2	5 h	37% (1:0)	11%

**Scheme 16:** Cross-metathesis of divinylated isoxazoline (\pm)-**6** with 1,1,1-trifluoro-2-(trifluoromethyl)pent-4-en-2-ol (**7f**).**Table 15:** CM of isoxazoline (\pm)-**6** with 1,1,1-trifluoro-2-(trifluoromethyl)pent-4-en-2-ol (**7f**).

entry	catalyst	reaction time	yield and ratio of (\pm)- 23a and (\pm)- 23b	yield of (\pm)- 23c
1	HG-2	5 h	3% (1:0)	0%
2	G-2	5 h	54% (1:0)	0%

We also attempted CM reactions of (\pm)-**6** with 8-(allyloxy)-1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorooctane (**7g**, Scheme 17). However, dimetathesized product (\pm)-**24c** was not formed, and

isolation of monometathesized products (\pm)-**24a** and (\pm)-**24b** (or a mixture thereof) in pure form failed, despite repeated attempts of chromatographic separation.

**Scheme 17:** Cross-metathesis of divinylated isoxazoline (\pm)-**6** with 8-(allyloxy)-1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorooctane (**7g**).

Finally, CM reactions between isoxazoline (\pm)-**6** and 4-fluorostyrene (**7h**) were studied (Scheme 18 and Table 16). HG-2 catalyst provided monocoupled (\pm)-**25a** and dicoupled (\pm)-**25c** in a comparable amount. With G-2 catalyst, both products were formed in higher yield. G-3 catalyst provided mostly monocoupled (\pm)-**25a**, but a low amount of (\pm)-**25c** was also isolated. Note, that the CM reaction was highly regioselective (alternative monocoupled product (\pm)-**25b** was not detected).

Conclusion

An insight into the study of selective functionalization of norbornadiene through nitrile oxide 1,3-dipolar cycloaddition/ROM/CM strategies was presented. The stepwise functionalization of norbornadiene across the ring olefin bonds generated fluorine-containing alkenylated cyclopentane-fused isoxazolines. The synthetic protocol was based on selective nitrile oxide cycloaddition to the norbornadiene C=C bond, followed by ROM of the resulting cyclopentane-fused isoxazolines. In the final step, selective CM by chemodifferentiation of the newly created olefin bonds on the resulting alkenylated derivatives took place. As coupling olefin partners in CM reactions, several commercial fluorine-containing alkenes have been investigated (type I and type II), and CM has been studied in order to explore the substrate effect, catalyst influence and the

chemical behavior of the olefin bonds. Second-generation Ru-based commercial catalysts G-2 and HG-2 as well as third-generation G-3 were found to be more effective in the CM transformations. Note, that first-generation catalyst HG-1 did not afford cross-metathesized products.

Our data allows to summarize some clearly visible general trends. First of all, most CM reactions of compounds (\pm)-**4** and (\pm)-**5** were only slightly regioselective (transformation of the vinyl group at C-6 was preferred, except for the reactions of isoxazoline (\pm)-**4** with **7f** and **7g**), while all CM reactions of (\pm)-**6** were completely regioselective (the vinyl group at C-6 was transformed first). This can be explained by steric hindrance: the substituent at C-3 on the isoxazoline ring shields the vinyl group at C-4 from reacting with the bulky catalyst molecules (Figure 4). For the smaller Me or Et groups, this effect is relatively weak (only some reactions of (\pm)-**5** with **7c** and **7e** were completely regioselective). The large Ph group, however, provided complete regioselectivity in all successful CM reactions.

The ratio of monometathesized products in CM reactions of (\pm)-**4** and (\pm)-**5** also depended on the catalyst. Generally, HG-2 catalyst provided the highest regioselectivity. Unfortunately,

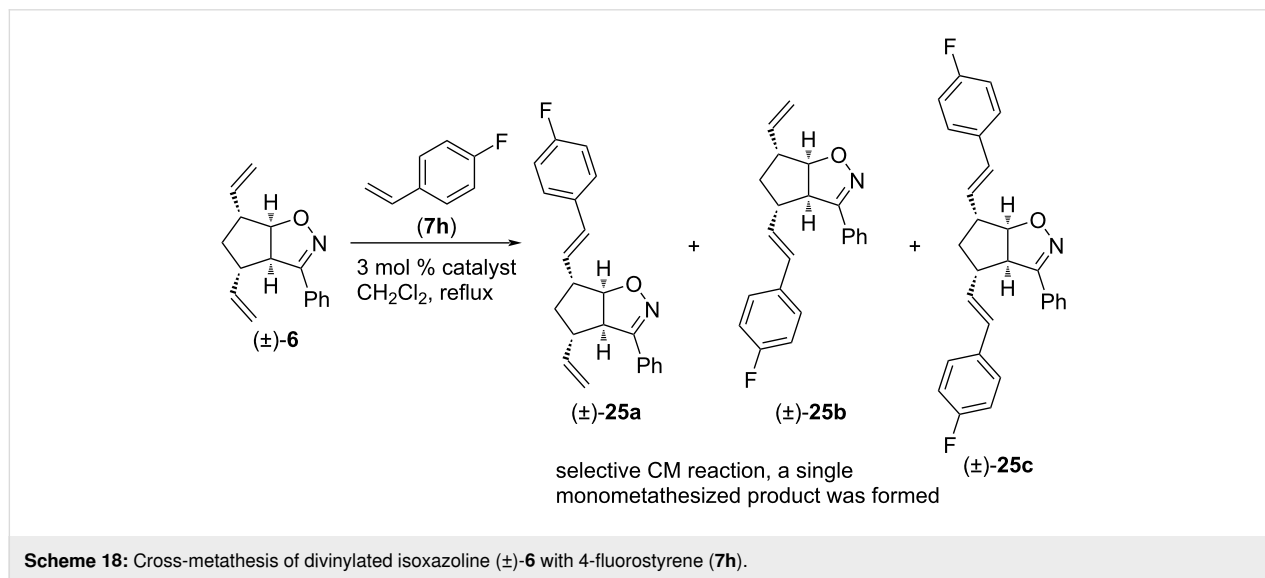
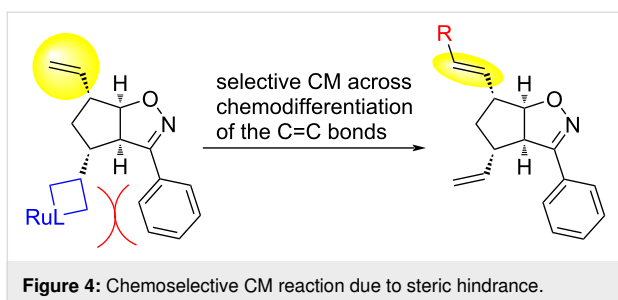


Table 16: CM of isoxazoline (\pm)-**6** with 4-fluorostyrene (**7h**).

entry	catalyst	reaction time	yield and ratio of (\pm)- 25a and (\pm)- 25b	yield of (\pm)- 25c
1	HG-2	5 h	18% (1:0)	25%
2	G-3	5 h	18% (1:0)	2%
3	G-2	5 h	28% (1:0)	49%



separation of regioisomeric monometathesized compounds proved to be impossible in most cases (only monocoupled products with olefins **7f** and **7g** were separable). However, the formed dimetathesized products could be separated from the monometathesized compounds.

Usually, the best (combined) yield of monometathesized products was achieved with G-2 catalyst, while HG-2 provided the best yield of dicoupled products. Notably, G-3 catalyst highly disfavored the formation of dimetathesized products.

Further investigations in view of the selectivity of CM reactions with other novel model compounds as well as further functionalization strategies are currently being investigated in our group.

Supporting Information

Supporting Information File 1

Experimental section and NMR spectra.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-132-S1.pdf>]

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