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Alkene Chemoselectivity in Ruthenium-Catalyzed Z-Selective Olefin Metathesis

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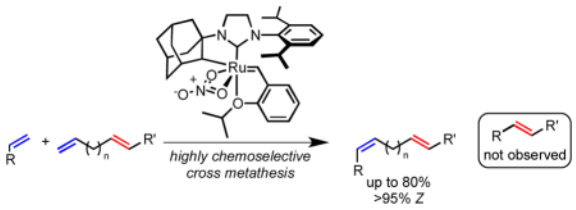
Abstract



Chelated ruthenium catalysts have achieved highly chemoselective olefin metathesis reactions. Terminal and internal *Z* olefins were selectively reacted in the presence of internal *E* olefins. Products were produced in good yield and high stereoselectivity for formation of a new *Z* olefin. No products of metathesis with the internal *E* olefin were observed. Chemoselectivity for terminal olefins was also observed over both sterically hindered and electronically deactivated alkenes.

Keywords

metathesis; chemoselectivity; ruthenium; unconjugated dienes; macrocycle

Olefin metathesis catalyzed by transition metal carbene complexes has developed as an important technique in the manipulation of carbon-carbon double bonds. [1] The development and subsequent commercial availability of highly active catalyst complexes has allowed olefin metathesis to have an important synthetic impact on fields ranging from materials science,[2] to biochemistry,[3] to natural products synthesis. [4]

Chemoselectivity, in general, is a current and outstanding problem in organic synthesis.[5] The synthetic utility of olefin metathesis is underscored by the orthogonal reactivity of carbon-carbon double bonds to many organic functional groups. However, in contrast to ring-closing metathesis, cross metathesis has received relatively fewer synthetic applications because of the low stereo- and chemoselectivity observed when previous generations of metathesis catalysts such as **1** and **2** are used.[6] Selective olefin metathesis methods would be useful for the construction of new carbon-carbon double bonds; however, chemoselective cross metathesis reactions of dienes are rare. [7,8] Until recently, metathesis of dienes where one olefin was inert to reaction was limited to olefins differentiated by either electronic or steric properties,[9] with some limited examples in macrocyclic ring-closing metathesis.[10]

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dihydroimidazol-2-ylidene)

Recent advances in catalyst development have produced new metathesis catalysts that are highly *Z*-selective (**3**–**6**, Figure 1). The Schrock and Hoveyda groups initially reported molybdenum and tungsten monoaryloxide pyrrolide (MAP) catalysts (e.g. **3** and **4**) that have now been shown to conduct *Z*-selective dimerization and cross metathesis of terminal olefins[11], ring-opening metathesis polymerization,[12] as well as macrocyclic ring-closing metathesis[13] with high levels of *Z*-selectivity. Our group then reported chelated catalysts **5** and **6** as the most effective ruthenium catalysts for *Z*-selective olefin metathesis of terminal and internal *Z*-olefins, with turnover numbers as high as 7400 and *Z*-selectivity of >95% in many cases. [14] The synthetic promise of these ruthenium complexes has been presented in the synthesis of macrocyclic musk[15] and insect pheromone natural products.[16]

The Z-selectivity exhibited by all known *Z*-selective catalysts is believed to be because of steric crowding around the transition metal center. Large ligands held over a single face of the metal center force the intermediate metallacyclobutane to be formed exclusively in an all-cis orientation (**8**), in turn producing olefin products highly enriched in the *Z* isomer (**7**, Scheme 1).[13c] In this way, catalysts **3**–**6** produce olefin products with kinetic selectivity for the higher-energy cis olefins. In the case of ruthenium catalysts **5** and **6**, this is accomplished by chelation of the NHC ligand, which positions the *N*-aryl group over the metallacyclobutane.[17]

The kinetic selectivity inherent in *Z*-selective olefin metathesis catalysts provides a platform for enhanced olefin metathesis chemoselectivity. The preference for the formation of *Z* olefins indicates that the reverse reaction should also be highly preferred for *Z* olefins. [11c,15,18] As a result, otherwise unbiased *E* olefins (**10**) should be significantly less reactive to metathesis as the intermediate metallacycle **11** is destabilized (Scheme 1). In 2012, the Schrock and Hoveyda groups made use of this principle with MAP catalysts of molybdenum (**3**) and tungsten (**4**) that selectively dimerized terminal *E*-1,3-dienes to *E*, *Z*, *E*-trienes with high *Z*-selectivity and good chemoselectivity for terminal olefins over internal *E* olefins.[19] Herein, we report the general use of chelated ruthenium catalysts (**5** and **6**) to perform chemoselective cross metathesis.[16,20] Catalyst **6** was discovered to provide products of cross metathesis with essentially complete chemo- and stereoselectivity with a wide substrate scope.

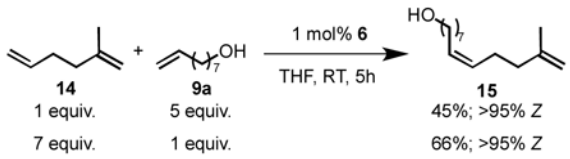
Initial catalyst investigations were conducted with 8-nonenol (**9a**) and *trans*-1,4-hexadiene (Table 1). Reactions were conducted in open vessels to facilitate efficient ethylene removal.[21] Ruthenium complex **5** provided cross product **12a** in good yield and *Z*-selectivity (entry 1). Catalyst **6**, bearing the bulkier 2,6-diisopropylphenyl group, has recently been shown to exhibit superior reactivity and *Z*-selectivity.[14d] Indeed, complex **6** provided diene **12a** in similar yields with essentially complete stereoselectivity (entry 2). Production of diene **12a** was observed with catalyst loadings as low as 0.1 mol %, though the conversion was diminished (entries 3 and 4). Unchelated dichloride catalyst **1** provided no observable amount of the desired cross product (entry 5), producing primarily oligomeric products of unselective cross metathesis of 1,4-hexadiene. Less reactive catalyst **2**, provided some **12a**, however the yield and stereoselectivity were low (entry 6). For future investigations, we chose 1 mol % of catalyst **6** in a 0.5 M solution of substrate in 1:1 THF:hexadiene as optimal conditions to achieve sufficient reaction rate with most substrates.

The scope was further investigated with *trans*-1,4-hexadiene as the metathesis partner (Table 2). A number of functionalized terminal olefins were reacted in modest to good yields. Carbonyl functionality such as aldehydes (entry 2), ketones (entry 3), and esters (entry 4) were well tolerated. Allylic amine functionality did not significantly compromise the conversion or overall yields (entries 5–6). Synthetically useful *Z*-allylic carbonates (**12h**)

and boronic esters (**12i**) could also be produced in modest yields (entries 7–8). In all cases no products derived from cross metathesis of the internal *E*-olefin were observed, providing complete chemoselectivity for the cross metathesis of terminal olefins in the presence of unbiased *E*-olefins. Comparable yields were also obtained on reactions conducted on 1 mmol scale, indicating the robustness of this methodology (Table 1, entry 2 and Table 2, entries 2 and 6).

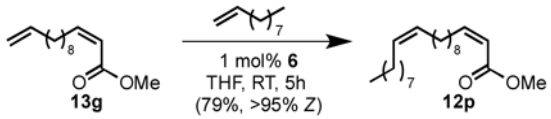
The diene partner could also be used as the limiting reagent (Table 3). The terminal olefin of diene **13a** reacted preferentially over the *E*-α,β-unsaturated ester in good yield (entry 1). Cross metathesis of diene **13b** with 1-decene occurred in similarly good yield and *Z*-selectivity (entry 1). The proximity of a functionalized *trans* olefin effects the efficiency of the reaction. Diene **13c** required higher catalyst loading to provide a modest yield of *E*, *Z*-diene **12l** (entry 3). Interestingly, *trans*-2,5-hexadiene-1-ol (**13d**) was unreactive towards cross metathesis (entries 4). This lack of reactivity is due to the oxygen functionality rather than protic substrates, as related benzoate ester **13e** was also unreactive (entry 5). Furthermore, 1,3-dienes, used as the limiting reagent or in excess, were similarly unreactive to metathesis (e.g. **13f**, entry 6).

Chelated ruthenium catalyst **6** is sensitive to the steric environment of the reacting olefin. As a result, monosubstituted terminal olefins are also preferentially reacted over disubstituted alkenes (eq 1). When diene **14** was reacted with 8-nonenol (**9a**), as either the limiting reagent or in excess, metathesis only occured at the less substituted olefin to produce diene **15** as the major product.[22]



(1)

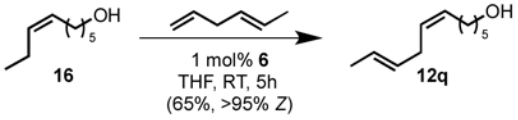
Chemoselectivity can also be driven by electronic factors. α,β-Unsaturated ester **13g** was preferentially metathesized at the terminal olefin to provide *Z*, *Z*-diene **12p** in good yield and selectivity (eq 2). The electron-withdrawing nature of the methyl ester was sufficient to deactivate the internal *Z* olefin towards metathesis with catalyst **6**. As a result, both *E*- and *Z*-α,β-unsaturated esters are unreactive to metathesis with catalyst **2**.



(2)

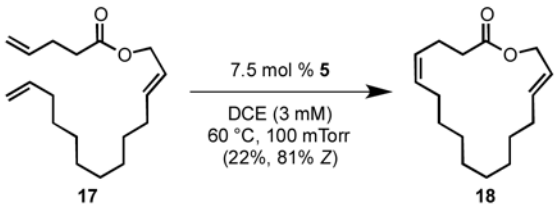
Chemoselective cross metathesis can also be performed from internal *Z*-olefins. *Cis*-6-nonen-1-ol (**16**) underwent cross metathesis with *trans*-1,4-hexadiene to provide diene **12q** as the major cross metathesis product (eq 3). Cross metathesis in this case likely occurred by initial ethenolysis of **16** to 6-hepten-1-ol by a ruthenium methylidene generated by

dimerization of *trans*-1,4-hexadiene.[16] The terminal alkene was then able to undergo further metathesis to afford *E*, *Z*-diene **12q**.



(3)

Chemoselective macrocyclic ring-closing metathesis was also possible with catalyst **5** (eq 4). Utilizing conditions previously optimized for *Z*-selective macrocyclic ring-closing metathesis of dienes (7.5 mol % catalyst loading under static vacuum of 100 mTorr),[15] the terminal alkenes of triene **17** were selectively reacted to provide 17-membered lactone **18**, which contains both internal *E* and *Z* double bonds. For this transformation, less hindered catalyst **5** was necessary for sufficient conversion.[23] High *Z* selectivity was observed for the newly formed olefin, and no products of metathesis of the *E* olefin were observed. It is important to note that this ring-closing metathesis would be extremely challenging using previous generations of metathesis catalysts (e.g. **1** or **2**). Furthermore, the mass balance of this transformation was primarily recovered triene **17**, with small amounts of oligomeric material.



(4)

In summary, chemoselective cross metathesis has been demonstrated with *Z*-selective ruthenium metathesis catalysts. Catalyst **2** preferentially reacts with terminal and internal *Z*-olefins to prepare *E*, *Z*-dienes in good yields with complete stereoselectivity. Additionally, this preference was extended to sterically and electronically deactivated olefins. Chemoselective macrocyclic ring-closing metathesis was also achieved. Ruthenium complex **6** exhibits broad substrate compatibility and scope. While there are some limitations in compatible dienes, as new catalysts are discovered, the utility and scope of these chemoselective transformations will improve. The chemoselectivity of ruthenium catalysts **5** and **6** provide new avenues for the synthesis of polyenes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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20. Our group has reported a single example of the chemoselective cross metathesis of *trans*-1,4-hexadiene with oleyl alcohol using catalyst 5. See ref. 16.

21. Reactions conducted in closed vessels would not reach complete conversion due to metathesis with ethylene generated by dimerization of the terminal alkene used in excess.

22. The low yield obtained when diene 14 was used as the limiting reagent was likely associated with the evaporation of the relatively volatile 14 when run in an open vessel.

23. It has been shown that catalyst 6 generally provides lower conversions for macrocyclic ring-closing metathesis than catalyst 5. See ref. 14d for details.

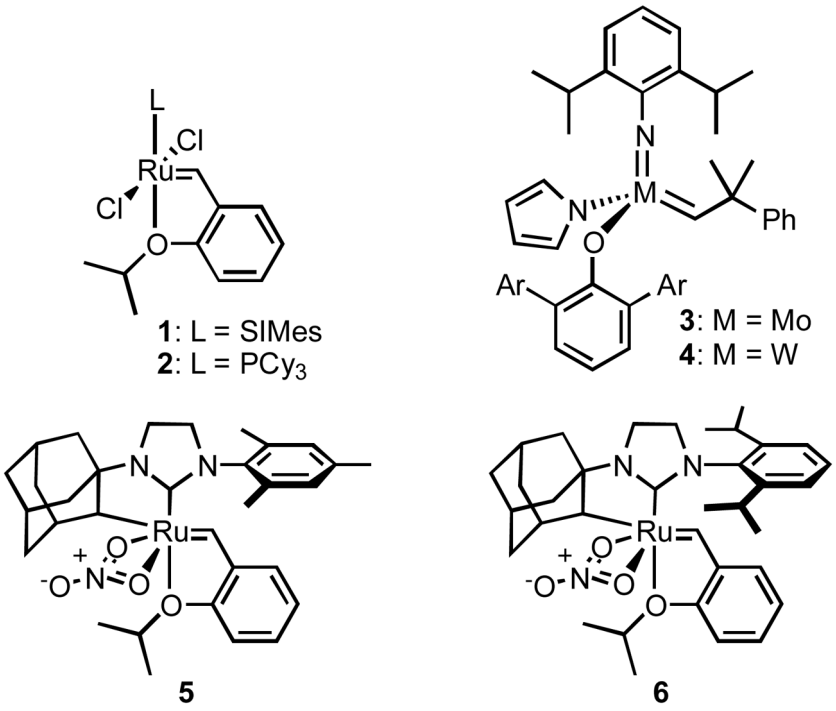
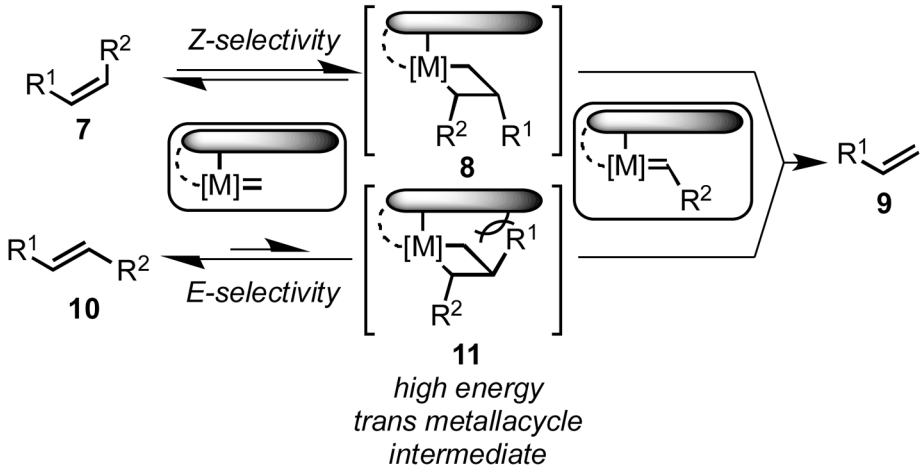


Figure 1.

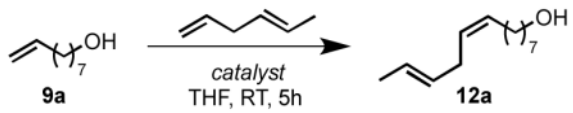
Prominent Olefin Metathesis Catalysts (Ar = 2,6-(2,4,6-$^{i}Pr_3C_6H_2)_2C_6H_3$; SIMes = 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene)



Scheme 1.
Destabilized *trans* metallacyclobutane **11** disfavors metathesis of *E*-olefins

Table 1

Catalyst investigation for chemoselective olefin metathesis.[a]



entry	catalyst	mol %	yield (%)	*Z* (%)[b]
1	**5**	1	87	89
2	**6**	1	80 (70)[c]	>95
3	**6**	0.5	77	>95
4	**6**	0.1	50	>95
5	**1**	1	<5[d]	–
6[e]	**2**	1	28[d][f]	29

[a]Reaction conditions: **9a** (0.2 mmol), 0.2 mL *trans*-1,4-hexadiene, 0.2 mL THF.

[b]Determined by ^{1}H NMR analysis.

[c]Reaction conditions: **9a** (1 mmol), 1 mL *trans*-1,4-hexadiene, 1 mL THF.

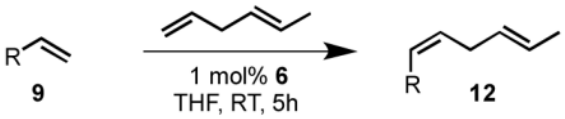
[d]Major products were oligomeric olefin material.

[e]Allyl methyl carbonate was used instead of **9a**.

[f]Determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an external standard.

Table 2

Scope of Cross Metathesis with trans-1,4-Hexadiene[a]



entry	R	12	yield[b] (%)	Z (%)[c]
1	CH_2Ph	**12b**	63[d]	>95
2	$(CH_2)_8CHO$	**12c**	70 (65)[e]	>95
3	$(CH_2)_2COCH_3$	**12d**	49	>95
4	$(CH_2)_7CO_2Me$	**12e**	82	>95
5	CH_2NHPh	**12f**	68	>95
6	CH_2NHBoc	**12g**	54 (64)[e]	>95
7	CH_2OCO_2Me	**12h**	79	>95
8	CH_2BPin	**12i**	65	>95

[a]Reaction conditions: **9** (0.2 mmol), 0.2 mL *trans*-1,4-hexadiene, 0.2 mL THF, 0.002 mmol **6**.

[b]Isolated yield.

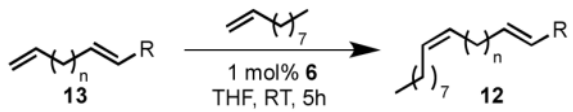
[c]Determined by ^1H NMR analysis.

[d]Yield determined by ^1H NMR analysis with 1,3,5-trimethoxybenzene as an external standard.

[e]Reaction conditions: **9** (1 mmol), 1 mL *trans*-1,4-hexadiene, 1 mL THF, 0.01 mmol **6**.

Table 3

Scope of Cross Metathesis with 1-Decene[a]



entry	R (13)	n	12	yield[b] (%)	Z(%)[c]
1	CO_2Me(**13a**)	8	**12j**	80	>95
2	CH_2OH (**13b**)	8	**12k**	60	>95
3[d]	CH_2OH (**13c**)	2	**12l**	51	>95
4	CH_2OH(**13d**)	1	**12m**	<5	–
5	CH_2OBz(**13e**)	1	**12n**	<5	–
6	*n*-$C_{10}H_{21}$(**13f**)	0	**12o**	<5	–

[a]Reaction conditions: **13** (0.2 mmol), 0.2 mL 1-decene, 0.2 mL THF, 0.002 mmol **6**.

[b]Isolated yield.

[c]Determined by ^{1}H NMR analysis.

[d]2 mol% **6**.

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