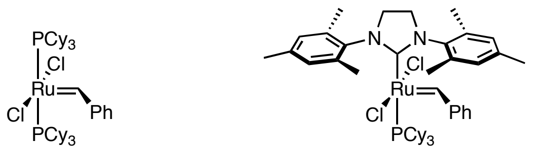
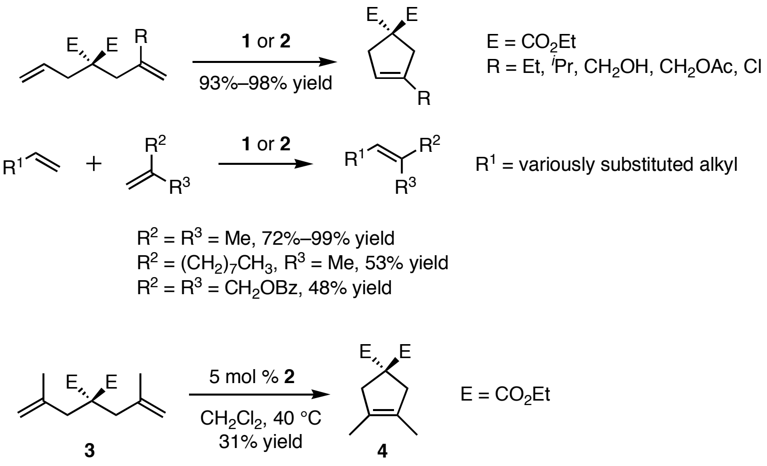
Appendix 1
Insight into Tetrasubstituted Olefin Synthesis

Although olefin metathesis has found widespread use in organic synthesis,[1] the generation of tri- and tetrasubstituted alkenes with ruthenium alkylidene catalysts still remains a challenging problem. Catalysts **1** and **2** (Figure A1.1) have been used to form trisubstituted olefins through ring-closing metathesis[2] and cross-metathesis.[3] However, when macrocycles or acyclic olefins (via cross-metathesis) are being synthesized, substitution larger than methyl on the reacting olefin is not tolerated well, and the yields for these processes are generally low (Scheme A1.1). Tetrasubstituted alkenes are even more challenging to make, and even the highly active catalyst **2** does not afford **4** in high yield.



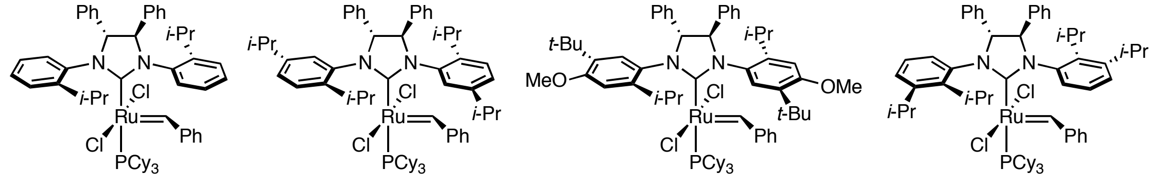
1 **2**

Figure A1.1. Ruthenium olefin metathesis catalysts.

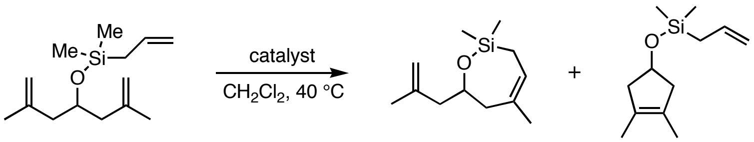


Scheme A1.1. Examples of ring-closing and cross-metathesis to form tri- and tetrasubstituted olefins.

During a routine catalyst screening of an asymmetric ring-closing metathesis (ARCM) substrate (**9**), insight into why catalyst **2** and other similar catalysts containing *N*-heterocyclic carbenes (NHCs) do not efficiently afford tetrasubstituted olefins was discovered. When **9** was treated with **2**, the expected seven-membered ring **10** was exclusively generated and was isolated in 94% yield (Figure A1.2). On the other hand, the reaction of **9** with chiral catalyst **5** afforded a 7:3 mixture of **10** and the five-membered ring, tetrasubstituted olefin **11**. Chiral catalysts **6**, **7**, and **8**, which contain bulky meta substituents on the *N*-bound aryl rings, also formed a mixture of **10** and **11**.



5 **6** **7** **8**

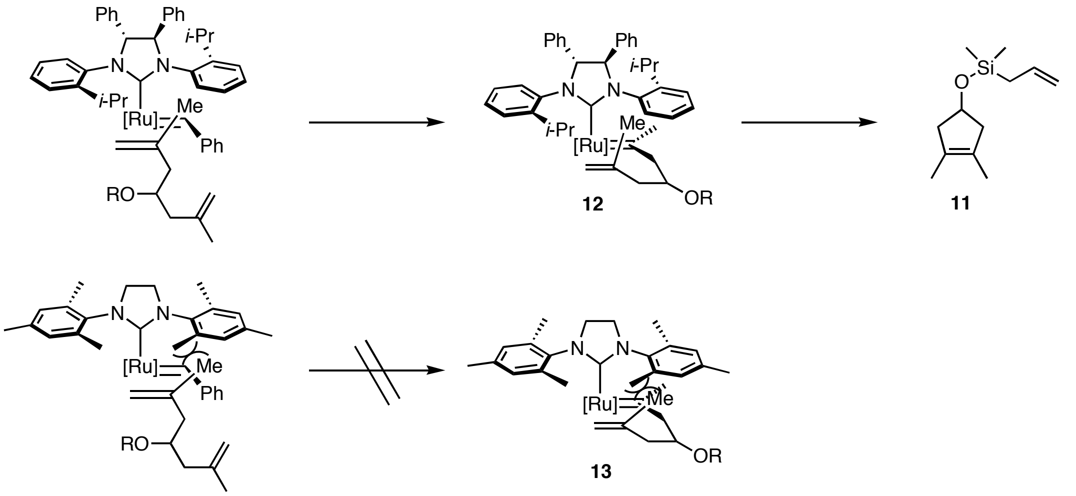


9 **10** **11**

catalyst	10	11
2	>95%	<5%
5	70%	30%
6	72%	28%
7	75%	25%
8	80%	20%

Figure A1.2. Competitive formation of a tetrasubstituted alkene using chiral ruthenium catalysts.

This result was very interesting because no **11** could be detected in the reaction with the achiral catalyst **2**. For some reason, the chiral catalysts were able to generate a tetrasubstituted alkene where the achiral variant could not. The NHC rings are saturated, and the *N*-bound aryl rings are almost orthogonal to the plane of the NHC in the chiral catalysts, so electronically, they are presumably similar to **2**. From a steric point of view, all of the chiral catalysts have only two ortho substituents, but the achiral catalyst **2** has methyl groups in all four ortho positions. Therefore, the chiral catalysts may be less crowded at the ruthenium center relative to the achiral variant with complete ortho substitution. It was proposed that the lack of ortho substitution allowed a 1,1-disubstituted olefin to react with the catalyst, affording a disubstituted ruthenium alkylidene (**12**) (Scheme A1.2). The achiral catalyst with mesityl rings would have a methyl/methyl interaction, disfavoring the formation of **13**.



Scheme A1.2. Differences in steric environments of chiral and achiral catalysts.

If it really was the lack of ortho substitution allowing **12**, and therefore **11**, to form, it would be expected that other catalysts with no ortho substituents would also generate tetrasubstituted alkenes. A few catalysts have been synthesized where the *N*-bound aryl rings have only C–H bonds or C–F bonds in the ortho positions, and they are able to catalyze the ring closing of **3** to **4** much more efficiently than **2**.[4] Although more optimization is needed, these new complexes lacking ortho substitution could lead to the development of olefin metathesis catalysts that reliably generate tri- and tetrasubstituted alkenes.

References

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