Olefin Isomerization

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Ruthenium-Catalyzed Isomerization of Terminal Olefins: Applications to Synthesis**

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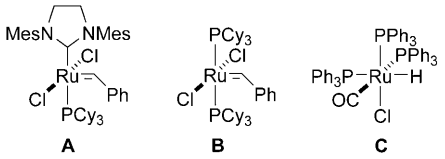
Olefin metathesis has revolutionized organic chemistry over the past decade. Catalysts such as **A** (Scheme 1) were



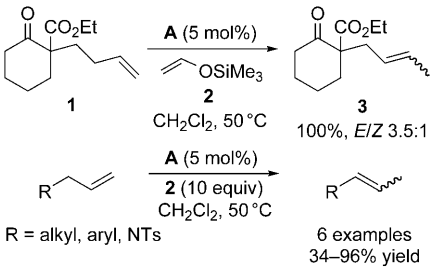
Scheme 1. Examples of ruthenium catalysts used in olefin isomerization. Cy = cyclohexyl, Mes = mesityl.

developed by Grubbs and co-workers and have expanded our options regarding C–C bond formation with reactions such as ring-closing metathesis (RCM), olefin cross-metathesis, and ring-opening olefin metathesis polymerization.[1] Catalysts derived from ruthenium carbenes have also been found to be adept at promoting the isomerization of terminal alkenes to internal alkenes.[2] This Highlight summarizes the application of this observation in the total synthesis of complex natural products.

Olefin isomerization with transition-metal catalysts is well established in organic chemistry.[3] For example, catalysts such as $[(PPh_3)_3RhCl]$ (the Wilkinson catalyst) are frequently employed in the isomerization of allylic ethers.[4] However, the use of a ruthenium hydride generated from a catalyst such as **A** provides especially mild and effective conditions that ensure that the olefin is not hydrogenated and that the terminal olefin is only isomerized to the adjacent position.

The discovery that ruthenium metathesis catalysts can be used in the isomerization of terminal olefins is potentially very useful in synthesis, especially in cases in which the introduction of a vinyl or propenyl substituent is problematic. Allyl groups have the advantage that they can be installed readily in procedures that are more convenient than the addition of a vinyl group, for example, through a radical Keck-type allylation of haloalkanes,[5] the allylation of an enolate, or the addition of an allylic organometallic reagent to a carbonyl group. Subsequent isomerization of the terminal olefin to the internal position affords a propenyl group, which can be further functionalized. Therefore, this sequence builds a bridge between the chemistry of an allyl group and that of a vinyl group; this tactic is particularly useful in synthesis.

The use of the Grubbs second-generation catalyst **A** for general olefin isomerization was reported by Nishida and co-workers in 2002.[2] During the attempted cross-metathesis of alkene **1** with silyl enol ether **2**, an unexpected reaction occurred, which resulted in the selective isomerization of the terminal olefin to give the corresponding propenyl species **3** (Scheme 2). The product was obtained as a 3.5:1 mixture of *E* and *Z* isomers. Several other terminal olefins were subjected to the reaction conditions, and the corresponding products of isomerization were obtained in moderate to excellent yield.



Scheme 2. Isomerization of terminal olefins by a ruthenium catalyst. Ts = *p*-toluenesulfonyl.

It was proposed that the ruthenium species responsible for the isomerization was a ruthenium hydride generated in situ from **A** and silyl enol ether **2**. It was shown in 2006 by Nishida and co-workers that in the presence of **2**, the ruthenium carbene complex **A** forms a Fischer carbene complex **4**, which decomposes to afford a ruthenium hydride complex **5** (Scheme 3).[6] The active ruthenium complex **5** adds reversibly to the olefin and promotes the isomerization of the terminal olefin by one carbon atom.[7] Presumably, the reaction stops with the double bond at this position for steric reasons. The ruthenium hydride **5** was previously isolated by Nolan and co-workers[8a] and Grubbs and co-workers,[8b] but

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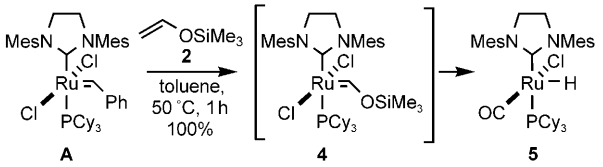


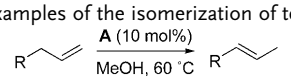
Scheme 3. Conversion of **A** into ruthenium hydride **5**.

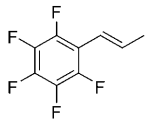
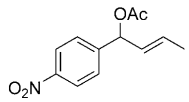
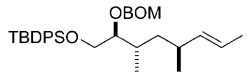
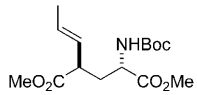
its full potential as an isomerization catalyst was not exploited.[8c]

Other methods for the decomposition of ruthenium metathesis catalysts for use in olefin-isomerization reactions include treatment with hydrogen,[9] inorganic hydrides,[10] and sodium hydroxide–2-propanol.[11] The last method was developed by Schmidt and Biernat for tandem RCM–isomerization reactions. The ruthenium hydride **C** (Scheme 1) has also been employed as an isomerization catalyst, in particular in an isomerization–RCM approach to heterocycles.[12]

Following an initial study by Dinger and Mol,[13a] Hanessian et al.[13b] reported an efficient method for the isomerization of terminal olefins with minimal self-dimerization or cross-metathesis by employing methanol to generate hydride **5** in situ from catalyst **A** (Table 1). The reaction was successful

Table 1: Selected examples of the isomerization of terminal olefins.

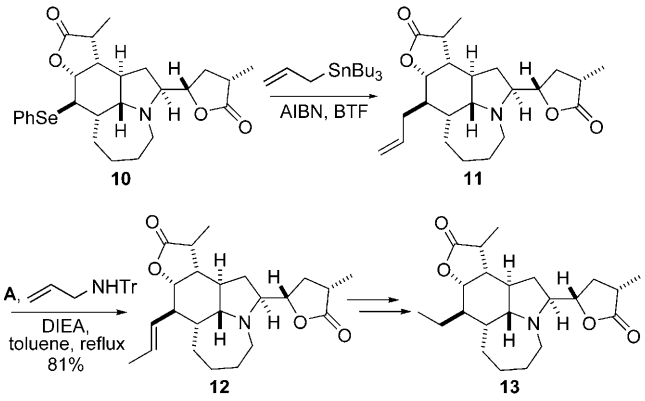


Entry	Product[a]		Yield [%][b]	*E*/*Z*[c]
1		**6**	80	>20:1
2		**7**	93	7:1
3		**8**	90	5:1
4		**9**	96	4:1

[a] Only the *E* isomer is shown [b] Yield after column chromatography. [c] The *E*/*Z* ratio was determined by ^{1}H NMR spectroscopy. Boc = *tert*-butoxycarbonyl, BOM = benzyloxymethyl, TBDPS = *tert*-butyldiphenylsilyl.

for the isomerization of a variety of allylic compounds and produced the corresponding propenyl species as *E*/*Z* mixtures of isomers. Substrates that had proven difficult to isomerize by other methods were transformed into the desired products under these conditions. For example, the electron-deficient aryl compound pentafluoroallylbenzene was isomerized to **6** in 80% yield (Table 1, entry 1).[14] A wide variety of functionality was tolerated, and no further isomerization or conjugation of the isomerized olefins was observed (Table 1, entries 2–4).

The isomerization of terminal olefins has proven to be a versatile approach to the synthesis of complex natural products. In 2005, Wipf and Spencer[15] reported the first total synthesis of (−)-tuberostemonine (**13**; Scheme 4). A

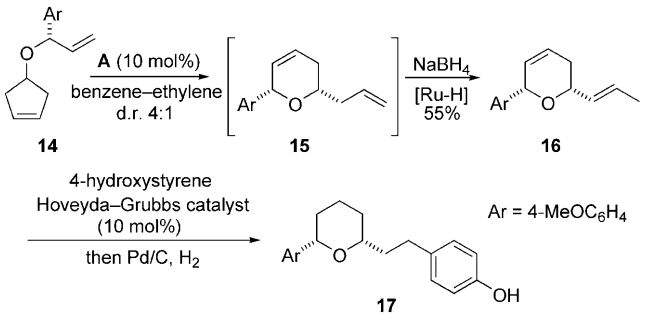


Scheme 4. Conversion of an allyl side chain into an ethyl side chain en route to (−)-tuberostemonine (**13**). AIBN = azobis(isobutyronitrile), BTF = $C_6H_5CF_3$, DIEA = diisopropylethylamine, Tr = trityl.

Keck allylation of selenide **10** provided the allyl-substituted derivative **11** in 70% yield. Attempts to convert the allyl side chain into the desired ethyl group under oxidative conditions led to extensive decomposition of **11**. However, isomerization of the terminal olefin contained in **11** by the procedure of Roy and co-workers[16] gave the propenyl intermediate **12** successfully in 81% yield. Cross-metathesis with ethylene gas, followed by hydrogenation, gave (−)-tuberostemonine (**13**).

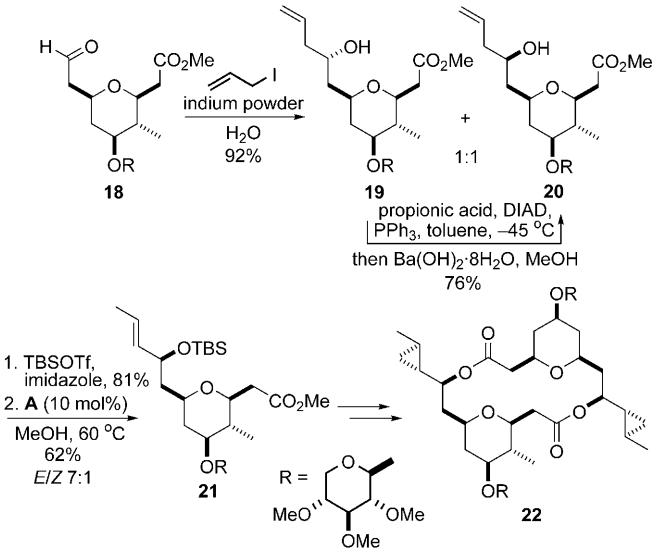
Böhrsch and Blechert employed a terminal-olefin isomerization in their synthesis of (−)-centrolobine (**17**).[17] Diastereoselective ring-rearrangement metathesis (dRRM) of cyclopentene **14** gave the intermediate dihydropyran **15** (Scheme 5). After complete conversion of **14**, sodium borohydride was added to the reaction mixture to convert the metathesis catalyst into a ruthenium hydride, which exclusively isomerized the terminal olefin in **15** to give the internal olefin **16** in 55% yield. A cross-metathesis reaction of **16** with 4-hydroxystyrene, followed by hydrogenation of the remaining alkene double bonds, gave (−)-centrolobine (**17**).

The procedure developed by Hanessian et al. was employed by Willis and co-workers in a recent total synthesis of clavosolide D (**22**).[18a] In their related synthesis of clavosoli-



Scheme 5. Isomerization strategy in the synthesis of (−)-centrolobine (**17**).

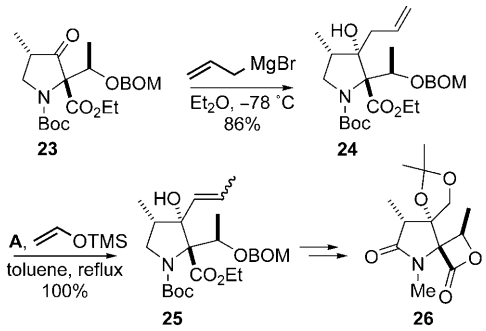
de A,[18b] the cyclopropyl side chain was originally introduced by a nonselective addition of a propenyl organometallic reagent to give a 1:1 mixture of carbinol epimers. Recycling of the undesired epimer was problematic, and therefore a more efficient method was required. The indium-mediated addition of allyl iodide to aldehyde **18** gave a 1:1 mixture of epimeric alcohols **19** and **20**, which were separated by column chromatography (Scheme 6). The undesired epimer **19** was



Scheme 6. Olefin isomerization in the synthesis of clavosolide D (**22**). DIAD = diisopropylazodicarboxylate, TBS = *tert*-butyldimethylsilyl.

recycled to give **20** in a two-step procedure. Silyl protection of **20**, followed by isomerization of the terminal olefin, gave the propenyl species **21** as predominantly the *E* isomer in good yield. Subsequent diastereoselective cyclopropanation followed by lactonization gave the natural product **22** in five steps.

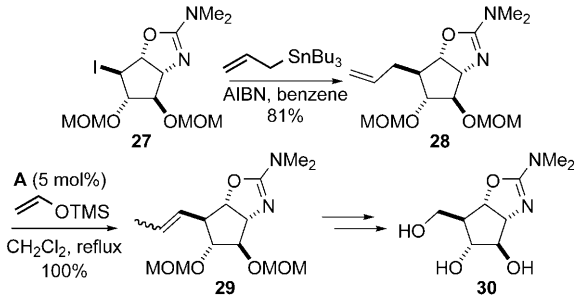
In the synthesis of the pyrrolidinone core of KSM-2690 B by Donohoe et al., the addition to ketone **23** of a nucleophile that could be converted into a hydroxymethyl functionality was required (Scheme 7). Since **23** was inert to reaction with a variety of vinyl organometallic reagents, an alternative approach was pursued.[19] The addition of allylmagnesium bromide to **23** readily provided the homoallylic alcohol **24**;



Scheme 7. Allylation and isomerization strategy in the synthesis of the pyrrolidinone core **26** of KSM-2690 B.

subsequent ruthenium-catalyzed isomerization gave the allylic alcohol **25**. Ozonolysis of the resulting olefin provided a 1,2-diol, which was transformed into the pyrrolidinone core **26** in seven steps.

Donohoe and Rosa also employed the isomerization described by Nishida and co-workers in a recent synthesis of (−)-allosamizoline.[20] Attempts to form a vinyl-substituted cyclopentane directly from iodide **27** in a radical procedure were unsuccessful. However, a Keck allylation of **27** provided the allylic derivative **28** directly (Scheme 8). The terminal olefin **28** was isomerized to the propenyl cyclopentane **29** in quantitative yield. Ozonolysis of the olefin followed by removal of the MOM protecting groups gave (−)-allosamizoline (**30**) in 13 steps and 22% overall yield.



Scheme 8. Keck allylation and isomerization in the synthesis of (−)-allosamizoline (**30**). MOM = methoxymethyl, TMS = trimethylsilyl.

The selective isomerization of terminal olefins with the modified metathesis catalyst **5** has proven to be a synthetically useful transformation. Coupled with the straightforward introduction of an allyl group into complex molecules, this transformation enables the formation of compounds that are otherwise difficult to access. The main limitation of this method is the generation of a mixture of isomers, generally in favor of the *E* isomer. However, this reaction has been utilized effectively to perform the equivalent of a radical vinylation or the addition of a vinyl organometallic reagent when other methods were unsuccessful. Hydride **5** is a highly efficient catalyst that, in some cases, is more active than other catalysts; it can be prepared readily from commercially available materials and is compatible with a wide range of functional groups. The successful application of this reaction in several total syntheses highlights its enormous potential.

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