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Efficient Allyl to Propenyl Isomerization in Functionally Diverse Compounds with a Thermally Modified Grubbs Second-Generation Catalyst

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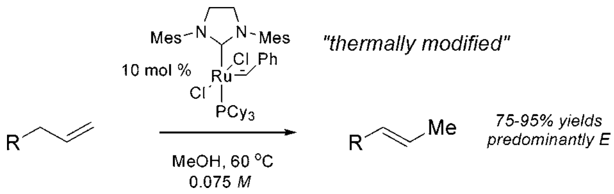
ABSTRACT



Heating compounds containing *C*-allylic appendages in MeOH in the presence of 10 mol % of Grubbs second-generation catalyst at 0.075 M substrate concentration leads to the corresponding 2-propenyl derivatives without further conjugation in the cases of ketones, esters, and lactams. The reaction is applicable to a large variety of functionally relevant terminal olefins, including *O*- and *N*-allyl ethers.

Alkene metathesis including the venerable ring-closure metathesis (RCM) variant reactions, with ruthenium catalysts such as **I** developed by Grubbs and co-workers,[1] has markedly influenced our thought process regarding strategic C−C bond formation. Characterized by its compatibility with a wide cross section of functionalities, this remarkable internal olefin-forming reaction under mild and requisite dilution conditions has been used as a key carbo- and heterocyclization step in a large number of natural product syntheses.[2] Occasionally, and depending on the nature of the reacting olefinic partners, isomerization to a 2-alkenyl-type motif may occur with terminal olefins, thereby detracting from the usually high-yielding metathesis reaction.[3] To address this problem, Grubbs and co-workers[4] have developed methods that minimize the unwanted isomerization reaction.

Olefin isomerization with ruthenium carbene catalysts in conjunction with RCM reactions has been reported by several groups.[5] For example, Snapper and co-workers[6] utilized a N_2/H_2 atmosphere in a tandem RCM−isomerization sequence for the syntheses of 2,3-dihydropyrans from terminal olefinic precursors in the presence of **I** (Figure 1).[7]

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[1] For an authoritative collection of relevant work in this area, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinhem, Germany, 2003; Vols. 1, 2, & 3. See also pertinent reviews: (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140. (c) Schmidt, B.; Hermanns, J. *Top. Organomet. Chem*. **2004**, *7*, 223−267. (d) Connon, S. J.; Blechert, S. *Top. Organomet. Chem*. **2004**, *7*, 93−124. (e) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923. (f) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18−29. (g) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043.

[2] (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed*. **2005**, *44*, 4490−4527. (b) Deiters, A.; Martin, S. F. *Chem. Rev*. **2004**, *104*, 2199−2238.

[3] For selected observations of unwanted isomerizations during or subsequent to RCM reactions, see: (a) Bourgeois, D.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *J. Organomet. Chem*. **2002**, *643−644*, 247−254. (b) Fürstner, A.; Theil, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem*. **2000**, *65*, 2204−2207. (c) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137−4140. (d) Joe, D.; Overman, L. E. *Tetrahedron Lett*. **1997**, *38*, 8635−8638 (with Mo−carbene).

[4] Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160−17161.

[5] Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865−1880.

[6] Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390−13391.

[7] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

10.1021/ol062167o CCC: $33.50

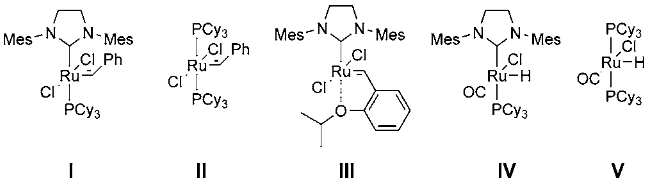


Figure 1. Ru carbene and hydride complexes **I**−**V**.

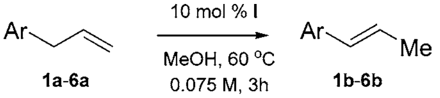
Börsch and Blechert[8] utilized **I** in the presence of catalytic amounts of NaBH$_4$ to effect a tandem RCM−isomerization reaction. Nishida and co-workers[9] have achieved indole syntheses in a tandem isomerization−RCM sequence with **I** in the presence of excess TMS vinylether as an olefinic reacting partner. Schmidt[10] utilized a combination of the first-generation catalyst **II** and ethyl vinylether to perform tandem isomerization−Claisen rearrangements. Prunet and Nolan[3a] observed isomerization in the presence of the IMes derivative of **I** in their attempt to obtain a cyclooctene intermediate. Wagener and co-workers[11] have studied olefin isomerization in conjunction with ADMET polymerization. Competing olefin isomerization to the detriment of an intended RCM reaction has also been noted by Fürstner,[3b] Grubbs,[3c] and Overman.[3d]

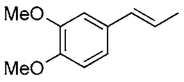
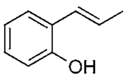
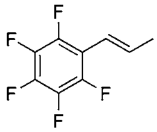
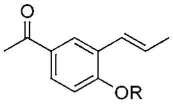
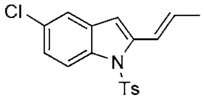
However, the intentional isomerization of a terminal double bond to its internal counterpart with Ru catalysts can also be of particular importance in natural product synthesis.[12] To the best of our knowledge, there are no catalytic methods of *preparative utility* for the isomerization of unsubstituted terminal olefins in polyfunctional compounds into their 2-alkenyl equivalents in the presence of **I**. The availability of such a method that is compatible with the presence of one or more polar substituents in polyfunctional substrates bearing a *C*-allyl appendage, for example, would greatly expand the repertoire of olefin chemistry.[13]

We report herein a mild, efficient, and versatile method for the isomerization of unsubstituted terminal allyls to their 2-propenyl counterparts, with minimal if any self-dimerization or cross-metathesis products[1e] in the examples studied. The method consists of heating a suspension of the Grubbs second-generation catalyst and the olefin in reagent grade, undistilled MeOH at 60 °C for 3−12 h depending on the nature of the substrates. A catalyst loading of 10 mol % and a concentration of 0.075 M in substrate is highly effective.

Starting with simple allyl aromatics, isomerization is complete with minimal self-dimerization taking place (Table 1). There is a high tolerance for a variety of aromatic substituents. Pentafluoro allylbenzene (**3a**), which was reported to isomerize with 50% conversion in the presence of an Ir catalyst,[14] was isomerized with 100% conversion and 80% isolated yield under the present conditions (Table 1, entry 3). Functionalized rings such as **4a** and **5a** (Table 1, entry 4) were isomerized, whereas other catalysts failed to react.[15] A 2-allyl-indole analogue (**6a**) underwent isomerization to afford the propenyl derivative **6b** (Table 1, entry 5). In general, these allyl aromatics were fully converted to their 2-propenyl counterparts in less than 3 h giving a preponderance of the trans isomers.[14]

Table 1. Isomerization of *C*-Allyl Aromatic Derivatives



entry	products[a]		yield (%)[b]	E/Z[c]
1		(**1b**)	80%	14:1
2		(**2b**)	92%	11:1
3		(**3b**)	80%	>20:1
4		(**4b**, R = H)	89%	11:1
		(**5b**, R = TBS)	90%	10:1
5		(**6b**)	87%	2.7:1

[a] Only the *E* isomer is shown. [b] Yields of isolated olefins after chromatography. [c] Determined by ^{1}H NMR.

In Table 2 are listed the results from the isomerization of a variety of *C*-allyl groups appended to functionally diverse and preparatively useful substrates (**7a**−**13a**). Thus, *N*-substituted amino acid esters and lactams (Table 2, entries 1−3), ketones, esters, and lactones (entries 4−6) harboring *C*-allyl groups are smoothly isomerized to the corresponding 2-propenyl olefins in high yields, *without further conjuga-*

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(8) Böhrsch, V.; Blechert, S. *Chem. Commun.* **2006**, 1968−1970.

(9) (a) Terada, Y.; Arisawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4063−4067. (b) Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 4255−4261.

(10) Schmidt, B. *Synlett* **2004**, 1541−1544. See also: Ammar, H. B.; Le Nôtre, J.; Salem, M.; Kaddachi, M. T.; Dixneuf, P. H. *J. Organomet. Chem.* **2002**, *662*, 63−69. For a similar approach to tandem isomerization−Claisen using Ir-based catalysts, see: Nelson, S. G.; Bungard, C. J.; Wang, K. *J. Am. Chem. Soc.* **2003**, *125*, 13000−13001. See also: Stevens, B. D.; Bungard, C. J.; Nelson, S. G. *J. Org. Chem.* **2006**, *71*, 6397−6402.

(11) Lehman, S. E.; Schwendeman, J. E.; O'Donnell, P. M.; Wagener, K. B. *Inorg. Chim. Acta* **2003**, *345*, 190−198.

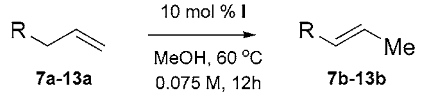
(12) For recent isomerizations of terminal double bonds in total synthesis, see: (a) Shen, X.; Wasmuth, A. S.; Zhao, J.; Zhu, C.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 7438−7439. (b) Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 225−235.

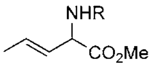
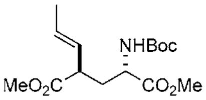
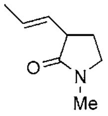
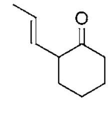
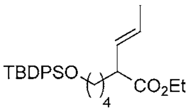
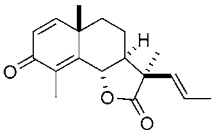
(13) For reviews on double-bond isomerizations with Ru hydride catalysts, see: (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096. (b) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599−2660.

(14) For a recent report on trans-selective isomerizations of allylbenzene derivatives, see: Baxendale, I. R.; Lee, A.-L.; Ley, S.V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1850−1857.

(15) Isomerizations were tried with 10 mol % of RhCl$_3$·H$_2$O, RhCl(PPh$_3$)$_3$, and RuH$_2$(PPh$_3$)$_4$ in refluxing EtOH for 12 h.

Table 2. Isomerization of α-*C*-Allyl Carbonyl Derivatives



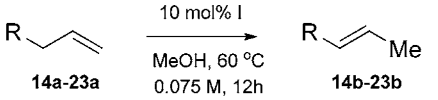
entry	products **7b-13b**[a]		yield (%)[b]	*E/Z*[c]
1		(**7b**, R = Cbz) (**8b**, R = Boc)	76% 74%	4:1 4:1
2		(**9b**)	96%	4:1
3		(**10b**)	80%	4:1
4		(**11b**)	90%	5:1
5		(**12b**)	95%	5:1
6[d]		(**13b**)	90%	>10:1

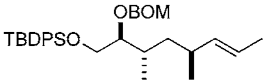
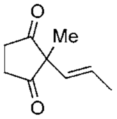
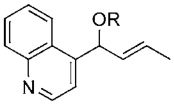
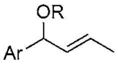
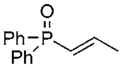
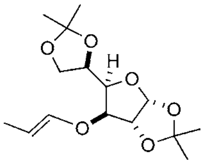
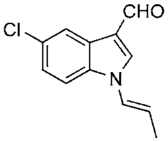
[a] Only the *E* isomer is shown. [b] Yields of isolated olefins after chromatography. [c] Determined by ^{1}H NMR. [d] Run in the absence of light and with 12 mol % of **I**.

tion.[16] Although these functionalized olefins with multiple coordination sites were isomerized at lower rates than the aromatic olefins, they were complete after 12 h at 60 °C giving the trans isomers as major or exclusive products. Again, when isomerization of substrates such as **9a** was tried with other well-known isomerization catalysts,[15] only starting material was recovered in each case.

The isomerizations listed in Table 3 were done following the same simple protocol, and the results further validate the generality of the method. Remarkably, benzylic acetates and ethers (**16a**−**20a**) in a variety of aromatic and heteroaromatic substrates are not subject to methanolysis or hydrolysis under these conditions (Table 3, entries 3 and 4). Allyl diketone (**15a**) and allylphosphine oxide (**21a**) undergo isomerization with high *E*/*Z* ratios (Table 3, entries 2 and 5). The isomerization of *O*-allyl ethers under mild conditions (Table 3, entry 6) obviates the need to include excess amounts of *N*-allylic reagents as in the commonly used protocol.[17] *N*-Allyl-indole derivatives are converted to the *N*-2-propenyl counterparts in good yields (Table 3, entry 7).[18]

Table 3. Isomerization of Differently Functionalized *C*-, *P*-, *O*-, and *N*-Allyl Compounds



entry	products **14b-23b**[a]		yield (%)[b]	*E/Z*[c]
1		(**14b**)	90%	5:1
2		(**15b**)	92%	>20:1
3		(**16b**, R = TBS) (**17b**, R = Ac)	74% 61%[d]	10:1 5:1
4		(**18b**, R = Ac; Ar = *p*-$NO_2C_6H_4$) (**19b**, R = TBS; Ar = C_6H_5) (**20b**, R = TBS; Ar = *p*-ClC_6H_4)	93%[d] 92% 85%	7:1 9:1 9:1
5		(**21b**)	85%	>20:1
6		(**22b**)	75%	2:1
7		(**23b**)	69%	4:1

[a] Only the *E* isomer is shown. [b] Yields of isolated olefins after chromatography. [c] Determined by ^{1}H NMR. [d] >90% conversion by ^{1}H NMR.

We next studied the effect of solvents using 3,4-dimethoxy allylbenzene **1a** as a model substrate (Table 4). All four expected products of isomerization, self-dimerization, and cross-metathesis were prepared separately as controls. The results are listed in Table 4. Clearly, the most efficient solvent for isomerization of **1a** was MeOH. Benzene, dichloromethane, and dichloroethane were the least efficient, affording mixtures due to the occurrence of cross-metathesis with a still viable catalyst prior to isomerization. Alternatively, heating the catalyst **I** in DME[3a] at 60 °C for 1 h, followed by addition of **1a**, gave **2a** in 84% yield (NMR).

Mol[19a] and co-workers have reported the isomerization of neat 1-nonene with **V** and the partial conversion of **I** to **IV** and **V** in MeOH at 60 °C in the presence of NEt_3.[19b] It has

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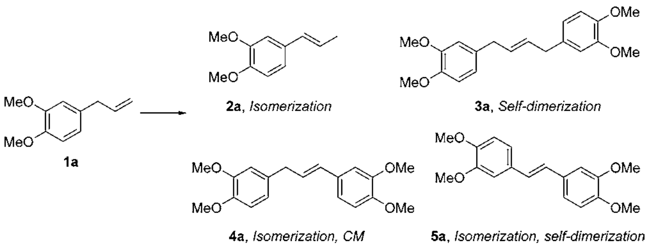
[16] For a review of α-vinylic and related amino acids, see: Berkowitz, D. B.; Charette, B. D.; Karukurichi, K. R.; McFadden, J. M. *Tetrahedron: Asymmetry* **2006**, *17*, 869−882.

[17] Hu, Y.-J.; Dominique, R.; Das, S. K.; Roy, R. *Can. J. Chem.* **2000**, *78*, 838−845.

[18] Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem.*−*Eur. J.* **2003**, *9*, 5793−5799.

[19] (a) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089−1095. (b) Dinger, M. B.; Mol, J. C. *Eur. J. Inorg. Chem.* **2003**, 2827−2883.

Table 4. Isomerization vs Self-Dimerization/Cross-Metathesis with **1a**



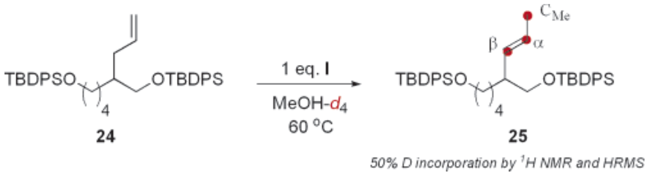
entry[a,b]	solvent	**1a** (%)	**2a** (%)	**3a** (%)	**4a** (%)	**5a** (%)
1	C_6H_6	36	11	28	24	1
2	MeOH	0	80	0	7	13
3	*i*-PrOH	0	54	2	32	12
4	DCE	11	18	22	39	10
5	DME	0	47	1	19	33
6[c]	CH_2Cl_2	36	9	29	24	2

[a] Substrate and catalyst heated at 60 °C for 90 min. [b] Ratios determined by ^{1}H NMR of crude reaction mixtures (400 MHz, $CDCl_3$). [c] Reaction performed at 40 °C.

also been shown by Grubbs and co-workers[20] that **I** could be transformed in part to the hydrido−carbonyl complex **IV** in the presence of MeOH, even at room temperature after 12 h. We surmised that the catalytic species in the isomerizations reported herein involved the Ru hydrido−carbonyl complex **IV** (and possibly **V**) formed in situ, although no precautions were taken to avoid air or moisture in the methanol used.[21]

To gain evidence toward this assumption, we conducted the isomerization of **24** with *1 equiv* of **I** in MeOH-d_4. Deuterium incorporation (50%) was observed at C_{Me}, C_α, and C_β as confirmed by ^{1}H NMR spectroscopy and HRMS analysis (Scheme 1).[22] A Ru-D species generated in situ, as observed by Grubbs[20] and Mol[19] for the protio equivalent, could be responsible for such deuterium atom incorporation.

Scheme 1. Deuterium Incorporation



The complex nature of the prevailing Ru species formed from the Grubbs catalyst **I** under the reaction conditions precludes any speculations regarding a precise catalytic cycle.[23]

In conclusion, we have developed a simple, mild, and efficient method for the isomerization of terminal unsubstituted olefins into their 2-alkenyl counterparts with minimal if any self-dimerization products even at a concentration of 0.075 M in substrate.[24] Applications to a diverse set of *C*-allylic substrates, including amino acid derivatives, and of *O*-allyl ethers demonstrate the versatility of the method. Particularly useful are isomerizations of α-*C*-allyl carbonyl compounds to their α-2-propenyl counterparts, which are formally equivalent to a two-step α-propenylation of an enolate, without further conjugation. Isomerization of 1-butenyl benzylic acetates and *O*-TBS ethers to the corresponding 2-butenyl isomers without solvolysis in MeOH is noteworthy. The catalytic species are most likely Ru hydride complexes generated during the initial heating period in MeOH.[21] The facile allyl to propenyl isomerizations reported herein should find utility in a variety of synthetic applications.

Acknowledgment. We thank NSERC (Canada) and the Wenner-Gren foundation (Sweden) for financial assistance to A.L.

Supporting Information Available: Experimental details and characterization data for relevant new compounds. Copies of selected ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546−2558.

[21] For a study of the Ru complexes formed from **I** in MeOH in the presence of NEt_3, see ref 19b. For the formation of **IV** in the presence of TMS vinylether, see ref 9. For the formation of **V** in the presence of ethylvinylether, see: Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153−2164. For the synthesis of the IMes derivative of **IV** from **V**, see: Lee, H. M.; Smith, D. C.; He, Z.; Stevens, E. D.; Y, C. S.; Nolan, S. P. *Organometallics* **2001**, *20*, 794−797. See also: Dharmasena, U. L.; Foucault, H. M.; dos Santos, E. N.; Fogg, D. E.; Nolan, S. P. *Organometallics* **2005**, *24*, 1056−1058.

[22] For a related experiment in a Pd-catalyzed olefin isomerization, see: Davies, N. R. *Aust. J. Chem.* **1964**, *17*, 212−218.

[23] Preliminary results showed that catalyst **II** was less efficient than **I** for isomerization. As expected, the Hoveyda−Grubbs catalyst **III** led to self-dimerization of **1a**.

[24] Representative procedure: To a solution of the olefin (1 equiv) in MeOH (0.075 M) was added **I** (10 mol %) at room temperature. The suspension was then heated at 60 °C. After a few minutes, the insoluble catalyst (purple) dissolved and the resulting orange−brown solution was stirred for 3 h (Table 1) or 12 h (Tables 2 and 3) after which time the solution was evaporated. The residue was purified by flash chromatography to give the isomerized olefin. See Supporting Information for details.