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

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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-workers⁴ 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-workers⁶ 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

⁽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.

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Börsch and Blechert⁸ utilized I in the presence of catalytic amounts of NaBH₄ to effect a tandem RCM–isomerization reaction. Nishida and co-workers⁹ have achieved indole syntheses in a tandem isomerization–RCM sequence with I in the presence of excess TMS vinylether as an olefinic reacting partner. Schmidt¹⁰ utilized a combination of the firstgeneration 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-workers¹¹ 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 selfdimerization 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

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grade, undistilled MeOH at 60 $^{\circ}$ 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

Table 1. Isomerization of C-Allyl Aromatic Derivatives

	Ar 1a-6a	10 mol % I	Ar.	
		MeOH, 60 °C 0.075 M, 3h	1b-6b	
entry	products ^a		yield (%) ^b	E/Z ^c
1	MeO MeO	(1b)	80%	14:1
2	ССОН	(2 b)	92%	11:1
3	F F F F	(3b)	80%	>20:1
4	O OR OR	(4b , R = H) (5b , R = TBS)	89% 90%	11:1 10:1
5	CI N Ts	(6b)	87%	2.7:1

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

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

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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⁽¹⁵⁾ Isomerizations were tried with 10 mol % of $RhCl_3H_2O$, $RhCl_{(PPh_3)_3}$, and $RuH_2(PPh_3)_4$ in refluxing EtOH for 12 h.

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

	10 mol % I		<u></u>	
	7a-13a	MeOH, 60 °C 0.075 M, 12h	✓ Me 7b-13b	
entry	products 7	7b-13b ^a	yield (%) ^b	E/Z ^c
1	NHR ↓	(7b , R = Cbz)	76%	4:1
	CO ₂ Me	(8b , R = Boc)	74%	4:1
2	NHBoc	(9 b)	96%	4:1
		Ле		
3	5	(10b)	80%	4:1
	° [™] N			
4	O O	(11b)	90%	5:1
5		t (12b)	95%	5:1
6 ^{<i>d</i>}	O ,H	(13b)	90%	>10:1

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

	R	10 mol% I	R. 🦟	
	14a-23a	MeOH, 60 °C 0.075 M, 12h	✓ Me 14b-23b	
entry	products 1	14b-23b ^a	yield (%) ^b	E/Z ^c
1 TBI		(14b)	90%	5:1
2	O Me O	(15b)	92%	>20:1
3	OR N	(16b, R = TBS (17b, R = Ac	s) 74%) 61% ^d	10:1 5:1
4	OR (18k Ar (19	o, R = Ac; Ar = <i>p</i> -N0 9b, R = TBS; Ar =	C ₂ C ₆ H₄) 93% ^d C ₆ H ₅) 92%	7:1 9:1
5	(20b , O Ph−P Ph	, R = TBS; Ar = <i>p</i> -C (21b)	:IC ₆ H₄) 85% 85%	9:1 >20:1
6		(22b)	75%	2:1
7 7	CHO N	(23b)	69%	4:1

^{*a*} Only the *E* isomer is shown. ^{*b*} Yields of isolated olefins after chromatography. ^{*c*} Determined by ¹H NMR. ^{*d*} >90% conversion by ¹H 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 NEt₃.^{19b} It has

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 Table 4.
 Isomerization vs Self-Dimerization/Cross-Metathesis

 with 1a

		MeO MeO	\sim	MeO MeO	j	OMe
MeO	<i>∽</i> →	2a, Isome	rization		3a, Self-dimer	rization
MeO 1a	Μ	MeO		MeO、 OMe MeO		OMe
	N	MeO 💙	~	`OMe		✓ `OMe
		4a, Isome	erization, CM	5a , /sc	merization, se	lf-dimerizatio
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>i</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 ¹H NMR of crude reaction mixtures (400 MHz, CDCl₃). ^{*c*} Reaction performed at 40 °C.

also been shown by Grubbs and co-workers²⁰ 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_a, and C_{β} as confirmed by ¹H NMR spectroscopy and HRMS analysis (Scheme 1).²² A Ru-D species generated in situ, as



observed by Grubbs²⁰ and Mol¹⁹ for the protio equivalent, could be responsible for such deuterium atom 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 1butenyl 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.

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

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(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.

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