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Ruthenium-Catalyzed Olefin Metathesis Double-Bond Isomerization Sequence

Bernd Schmidt

FB Chemie-Organische Chemie I, Universität Dortmund, Otto-Hahn-Strasse 6, D-44227 Dortmund, Germany

bschmidt@chemie.uni-dortmund.de

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A novel ruthenium-catalyzed tandem ring-closing metathesis (RCM) double-bond isomerization reaction is described in this paper. The utility of this method for the efficient syntheses of five-, six-, and seven-membered cyclic enol ethers is demonstrated. It relies on the conversion of a metathesis-active ruthenium carbene species to an isomerization-active ruthenium−hydride species in situ. This conversion is achieved by using various additives. Scope and limitations of the different protocols are discussed, and some mechanistic considerations based on ^{31}P and ^{1}H NMR spectroscopic studies are presented.

Introduction

Over the decade that has passed since stable and defined carbene complexes of molybdenum[1] and ruthenium[2] were introduced as efficient precatalysts for olefin metathesis,[3−6] this synthetic method has become a valuable tool, especially for the synthesis of heterocycles.[7,8] From the synthetic point of view, cyclic enol ethers are particularly important heterocycles as they have widespread use in carbohydrate chemistry[9−11] and can be used as precursors for α,α′-disubstituted oxacyclic frameworks[12] and as masks for functionalized aldehydes.[13] Although significant progress has been made in enol ether metathesis over the past few years,[14−20] the reaction still appears to have some drawbacks. For instance, in most cases, the more active but less conveniently available molybdenum or second-generation ruthenium catalysts are required. Furthermore, efficient ring-closing metathesis (RCM) of enol ethers makes high dilution necessary; otherwise, dimerization of the metathesis precursors might compete. In some cases, these drawbacks have been circumvented by the ring-closing metathesis of allyl ethers,[21] which is normally an extraordinarily facile process, followed by a base-mediated[22] or transition-metal-catalyzed isomerization[23−25] of the primary RCM products. The disadvantage of the latter strategy is obviously the additional synthetic step, which often requires the use of expensive or less conveniently available catalysts (Scheme 1).

We became involved in the problem of the olefin metathesis-based synthesis of cyclic enol ethers in the course of a program directed at the synthesis of cyclic diarylheptanoids. These natural products are isolated from the plant *Alpinia blepharocalyx* and show activity against human HT-1080 fibrosarcoma and murine colon 26-L5 carcinoma cells.[26] The simplest example is (3*S*,7*R*)-5,6-dihydro-1,7-bis(4-hydroxyphenyl)de-*O*-methylcentrolobine (**A**).[27] We envisaged a synthetic strategy

(1) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886.
(2) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857.
(3) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141−8153.
(4) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2055.
(5) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013−3043.
(6) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388.
(7) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127−2198.
(8) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.
(9) Tolstikov, A. G.; Tolstikov, G. A. *Russ. Chem. Rev.* **1993**, *62*, 579−601.
(10) Postema, M. H. D. *C-Glycoside Synthesis*, 1st ed.; CRC Press: Boca Raton, FL, 1995.
(11) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Oxford, 1995.
(12) Gurjar, M. K.; Krishna, L. M.; Reddy, B. S.; Chorghade, M. S. *Synthesis* **2000**, 557−560.
(13) Williams, D. R.; Cortez, G. S.; Bogen, S. L.; Rojas, C. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4612−4615.
(14) Rainier, J. D.; Allwein, S. P. *J. Org. Chem.* **1998**, *63*, 5310−5311.
(15) Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998**, *39*, 9623−9626.
(16) Calimente, D.; Postema, M. H. D. *J. Org. Chem.* **1999**, *64*, 1770−1771.
(17) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380−1386.
(18) van Otterlo, W. A. L.; Ngidi, E. L.; de Koning, C. B. *Tetrahedron Lett.* **2003**, *44*, 6483−6486.
(19) Tuyen Nguyen, V.; De Kimpe, N. *Tetrahedron Lett.* **2004**, *45*, 3443−3446.
(20) van Otterlo, W. A. L.; Pathak, R.; de Koning, C. B. *Synlett* **2003**, 1859−1861.
(21) Schmidt, B.; Wildemann, H. *Eur. J. Org. Chem.* **2000**, 3145−3163.
(22) Nicolaou, K. C.; Veale, C. A.; Hwang, C.-K.; Hutchinson, J.; Prasad, C. V. C.; Ogilvie, W. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 299−303.
(23) Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1997**, 1263−1264.
(24) Oguri, H.; Tanaka, S.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **2000**, *41*, 975−978.
(25) Trost, B. M.; Brown, B. S.; McEachern, E. J.; Kuhn, O. *Chem.—Eur. J.* **2003**, *9*, 4442−4451.
(26) Ali, M. S.; Tezuka, Y.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 491−496.
(27) Prasain, J. K.; Tezuka, Y.; Li, J. X.; Tanaka, K.; Basnet, P.; Dong, H.; Namba, T.; Kadota, S. *Planta Med.* **1999**, *65*, 196−196.

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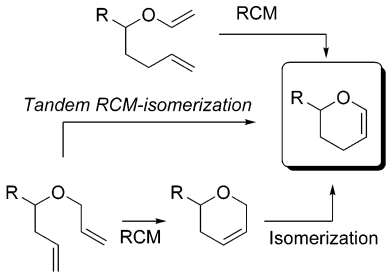
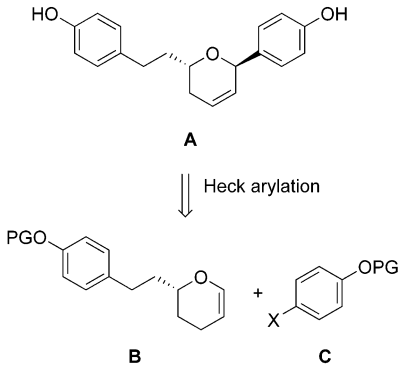
SCHEME 1. Enol Ether Metathesis versus Two-Step Allyl Ether Metathesis/Isomerization Protocol



SCHEME 2. Synthetic Strategy for Cyclic Diarylheptanoid A



that involves an intermolecular Heck arylation as the key C−C bond-forming step. This strategy obviously requires cyclic enol ether **B** and an appropriate arylating agent **C** as starting materials (Scheme 2).[28]

Our need for an efficient approach to cyclic enol ethers and recent reports in the literature describing double-bond isomerization as an undesired side reaction of olefin metathesis[29−34] inspired a novel synthesis of these heterocycles that combines the advantages of enol ether metathesis and the two-step RCM isomerization protocol. At the same time, the disadvantages of both methods are eliminated. Conceptually, this novel synthesis of cyclic enol ethers is a tandem reaction consisting of one RCM step and a nonmetathesis transformation[35] (here, olefin isomerization) mediated by a single-site catalyst. In contrast to the well-established metathesis tandem reactions, such as the ring-opening−ring-closing cross metathesis sequence,[36,37] where all of the steps are catalyzed by a ruthenium carbene species, metathesis−nonmetathesis tandem reactions require a change in the nature of the catalytically active species, which may be induced by the addition of appropriate reagents to the reaction mixture after the completion of the metathesis step. A ring-closing metathesis olefin isomerization sequence has been independently developed along the lines of this concept by Snapper et al.[38] and by us.[39,40]

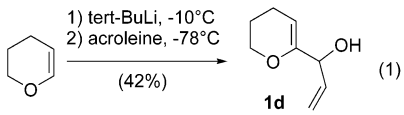
In this contribution, we provide a full account of our work on the tandem ring-closing metathesis olefin isomerization sequence. Scope and limitations of the method are evaluated for four different protocols developed in our laboratory, and some mechanistic considerations based on ^{31}P NMR and ^{1}H NMR spectroscopical studies are presented.

Results and Discussion

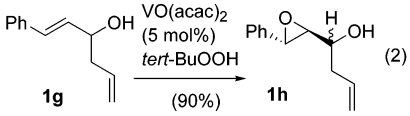
Synthesis of Starting Materials. We prepared a set of starting dienes **2a**−**w** to evaluate the scope and limitations of the method (Chart 1).

Allyl ethers **2a**−**m**, **2t**, and **2u** were obtained by allylation of the sodium salts of the corresponding alcohols **1a**−**m**, **1t**, and **1u**, respectively, with allyl bromide (Scheme 3).

These alcohols have been prepared by addition of the appropriate Grignard reagent ($n = 0$, vinyl; $n = 1$, allyl; $n = 2$, butenyl magnesium halide) to the corresponding aldehyde or ketone, except for **1d**, **1h**, **1i**, and **1t**. **1d** was synthesized by lithiation of 2,3-dihydropyran with *tert*-BuLi and trapping the resulting vinyllithium with acroleine (eq 1).[41]



1h was obtained from **1g** by vanadium-catalyzed epoxidation with *tert*-butyl hydroperoxide as a 2:1 mixture of diastereoisomers. Remarkably, no epoxidation of the homoallylic double bond was observed (eq 2).



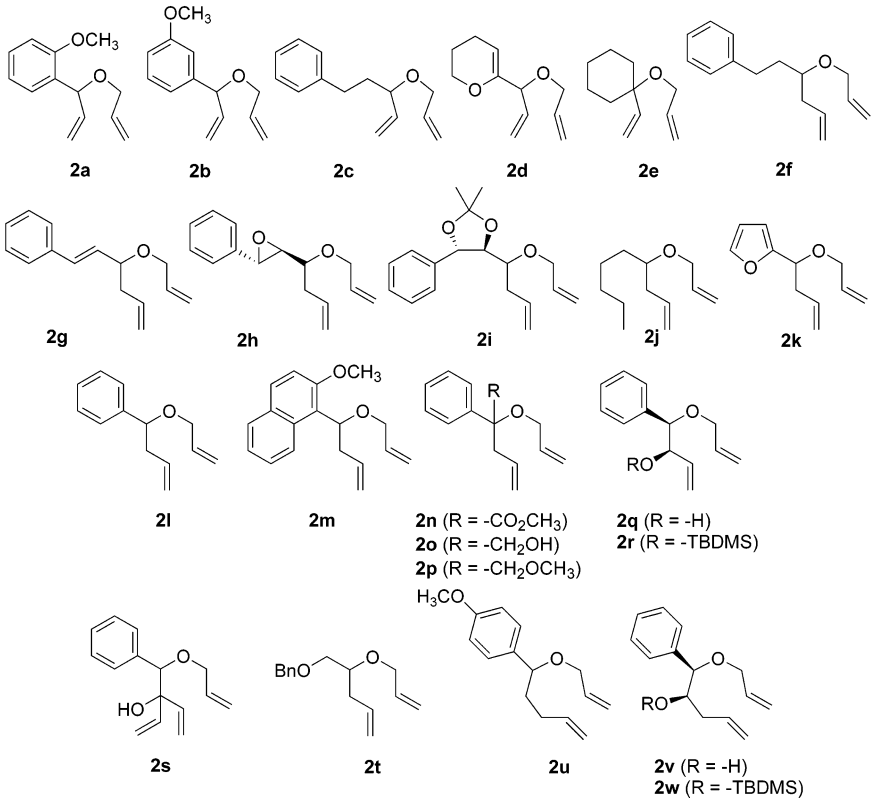
1i was prepared in a three-step procedure from methyl cinnamate by dihydroxylation with AD-mix β to give **3**, which was protected as a cyclic acetal **4**.[42] **4** was converted to a 3:2 mixture of diastereomers of **1i** by a one-pot reduction of the ester group and in situ trapping of the resulting aldehyde with allylmagnesium bromide (Scheme 4).

1t was analogously obtained from ester **5** (synthesized by benzylation of butyl glycolate with NaH and benzyl bromide, Scheme 5).

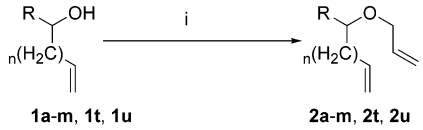
2n was prepared from DL-methyl mandelate via a tandem O-allylation Wittig rearrangement O-allylation

(28) Schmidt, B. *Chem. Commun.* **2003**, 1656−1657.
(29) Bourgeois, D.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *J. Organomet. Chem.* **2002**, *643*−*644*, 247−252.
(30) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207.
(31) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem.*−*Eur. J.* **2001**, *7*, 3236−3253.
(32) Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem.*−*Eur. J.* **2003**, *9*, 5793−5799.
(33) Cadot, C.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 1839−1841.
(34) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732−4734.
(35) Alcaide, B.; Almendros, P. *Chem.*−*Eur. J.* **2003**, *9*, 1259−1262.
(36) Arjona, O.; Csaky, A. G.; Plumet, J. *Eur. J. Org. Chem.* **2003**, 611−622.
(37) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923.
(38) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390−13391.
(39) Schmidt, B. *Eur. J. Org. Chem.* **2003**, 816−819.
(40) Schmidt, B. *Chem. Commun.* **2004**, 742−743.
(41) Lebouc, A.; Delaunay, J.; Riobé, O. *Synthesis* **1979**, 610−613.
(42) Palomo, C.; Oiarbide, M.; Landa, A. *J. Org. Chem.* **2000**, *65*, 41−46.

CHART 1

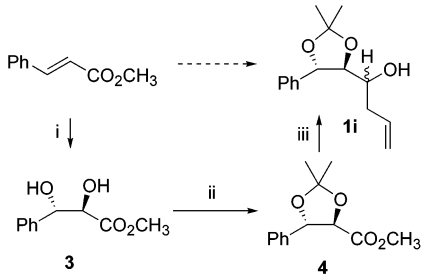


SCHEME 3. Preparation of Starting Dienes 2a−m, 2t, and 2u[a]



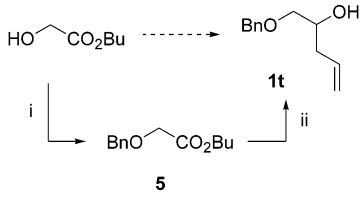
[a] Reagents and conditions: (i) NaH, THF, 65 °C, then add allyl bromide, 65 °C (74−99%; see Supporting Information for details).

SCHEME 4. Three-Step Synthesis of 1i[a]



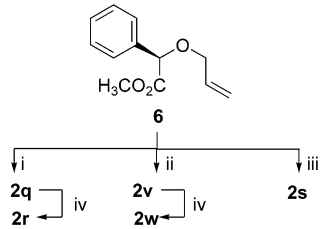
[a] Reagents and conditions: (i) AD-mix *β-tert*-BuOH/water (100%); (ii) $Me_2C(OMe)_2$, *p*-TSA (72%); (iii) DIBAL-H, $H_2C{=}CHCH_2MgBr$ (81%).

SCHEME 5. Two-Step Synthesis of 1t[a]



[a] Reagents and conditions: (i) NaH, BnBr, THF (53%); (ii) DIBAL-H, $H_2C{=}CHCH_2MgBr$ (69%).

SCHEME 6. Synthesis of 2q−s, 2v, and 2w[a]



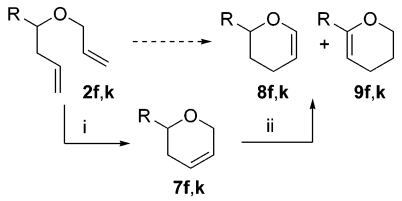
[a] Reagents and conditions: (i) DIBAL-H, $H_2C{=}CHMgCl$ (ref 45); (ii) DIBAL-H, $H_2C{=}CHCH_2MgBr$ (90%); (iii) $H_2C{=}CHMgCl$ (3 equiv) (ref 45); (iv) NaH, TBDMSCl (85% of **2r**, 95% of **2w**).

sequence. This compound is the precursor of **2o**, which was obtained by reduction of the ester group with $LiAlH_4$.[43] Methylation of **2o** with NaH and methyl iodide yields **2p**. Compound **6**, which was synthesized by allylation of methyl mandelate in the presence of silver oxide, serves as a precursor for substrates **2q−s**,**v**,**w** (Scheme 6); one-pot reduction of the ester group with DIBAL-H and in situ trapping of the aldehyde with vinylmagnesium chloride or allylmagnesium bromide gives dienes **2q** and **2v**, respectively, as 5:1 mixtures of diastereomers. Only the major diastereomer is depicted. The observed diastereoselectivity originates from chelation control, as outlined previously.[21,44] **2r** and **2w** were

(43) Schmidt, B.; Wildemann, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2916−2925.

(44) Schmidt, B.; Wildemann, H. *Synlett* **1999**, 1591−1593.

SCHEME 7. Ru-Catalyzed RCM and Rh-Catalyzed Isomerization[a]



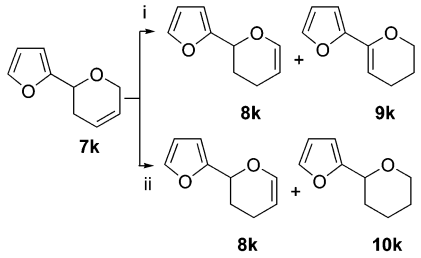
[a] Reagents and conditions: (i) $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (2 mol %), DCM (89% of **7f**, 95% of **7k**); (ii) $[ClRh(PPh_3)_3]$ (5 mol %), DBU (2 equiv), ethanol, 78 °C (79% of **8f**, 91% of a 1:1 mixture of **8k** and **9k**).

synthesized from **2q** and **2v**, respectively, by silylation with TBDMS chloride. Triene **2s** was obtained by addition of excess vinylmagnesium chloride to **6**, as previously described in the literature.[44,45]

RCM Isomerization as Two-Step Procedures. We originally envisaged a two-step procedure for the synthesis of cyclic enol ethers, consisting of the ruthenium-catalyzed ring-closing metathesis of allyl ethers **2**, followed by a rhodium-catalyzed isomerization of the resulting dihydropyrans **7** to the cyclic enol ethers **8**. For the isomerization step, a method originally introduced by Corey for the deprotection of allyl ethers was adapted and uses Wilkinson's catalyst in the presence of a base.[46] A similar isomerization protocol has more recently been applied to cyclic allyl ethers.[23,24,47] In our work, **7f** was converted to **8f** in good yield and regioselectivity in the presence of 5 mol % $[RhCl(PPh_3)_3]$ and 2 equiv of DBU. It was not possible to reduce the amount of catalyst or base without significant loss of activity. Furthermore, the transformation occasionally failed completely, and it is not possible for us to give an explanation for this unreliability. The 2-furyl-substituted dihydropyran **7k** is also isomerized in excellent yield. Regioselectivity, however, is poor as a 1:1 mixture of **8k** and the higher-substituted enol ether **9k** results under these conditions (Scheme 7).

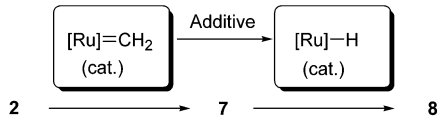
Two alternative isomerization procedures were tested for **7k**. A base-induced variant, using KO-*tert*-Bu in DMSO,[22] gives the undesired higher-substituted regioisomer **9k** as the major product along with approximately 20% of **8k**. We then considered an isomerization protocol originally developed by Frauenrath that uses the conveniently available complex $[RuCl_2(PPh_3)_3]$ in combination with $NaBH_4$ in methanol as a solvent.[48] Presumably, a Ru−hydride complex is formed in situ, which mediates olefin isomerization reactions via a hydrometalation/β-hydride elimination pathway.[49] It should be mentioned in this context that a variety of examples for olefin isomerization reactions with defined Ru−H complexes has also been published in the literature.[18,25,50−52] In our work, application of Frauenrath's protocol to **7k** resulted in the formation of **8k** and tetrahydropyran **10k** in a 2:1 ratio. The undesired regioisomer **9k** could not be detected by NMR spectroscopy. Scheme 8 summarizes these attempts toward the regioselective isomerization of **7k**.

SCHEME 8. Attempts toward Selective Isomerization of 7k[a]



[a] Reagents and conditions: (i) KO-*tert*-Bu, DMSO, 120 °C (75% of a 4:1 mixture of **9k** and **8k**); (ii) $[RuCl_2(PPh_3)_3]$ (2.7 mol %), $NaBH_4$ (25 mol %), methanol, 65 °C (41% of **8k** and 21% of **10k**).

SCHEME 9. RCM Isomerization: Single-Site Catalyst Concept



Tandem RCM Isomerization Mediated by Single-Site Catalysts. The Concept. The combination of metathesis and nonmetathesis steps of tandem sequences requires either the use of compatible catalysts[53,54] or a change in the reactivity of a single-site catalyst. For tandem olefin metathesis hydrogenation, the single-site catalyst concept has been achieved by replacing the inert gas atmosphere by an atmosphere of hydrogen.[55−61] The reaction of Grubbs' catalyst $[Cl_2(PCy_3)_2Ru{=}CHPh]$ with hydrogen leads to a Ru−H complex,[62] which effectively catalyzes olefin hydrogenation and olefin isomerization.[63] Thus, a successful realization of an RCM isomerization sequence requires the conversion of the carbene complex to a ruthenium−hydride complex with simultaneous supression of the undesired hydrogenation (Scheme 9).

Snapper et al. achieved this goal by setting the reaction mixture under an atmosphere of highly diluted hydrogen

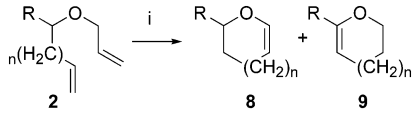
(45) Schmidt, B.; Wildemann, H. *J. Org. Chem.* **2000**, *65*, 5817−5822.
(46) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224.
(47) van Hooft, P. A. V.; El Oualid, F.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H.; Leeuwenburgh, M. A. *Org. Biomol. Chem.* **2004**, *2*, 1395−1403.
(48) Frauenrath, H.; Runsink, J. *J. Org. Chem.* **1987**, *52*, 2707−2712.
(49) McGrath, D. V.; Grubbs, R. H. *Organometallics* **1994**, *13*, 224−235.
(50) Curran, D. P.; Jacobs, P. B.; Elliott, R. L.; Kim, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 5280−5282.
(51) Wakamatsu, H.; Nishida, M.; Adachi, N.; Mori, M. *J. Org. Chem.* **2000**, *65*, 3966−3970.
(52) Krompiec, S.; Pigulla, M.; Bieg, T.; Szczepankiewicz, W.; Kuznik, N.; Krompiec, M.; Kubicki, M. *J. Mol. Catal. A* **2002**, *189*, 169−185.
(53) Cossy, J.; Bargiggia, F. C.; BouzBouz, S. *Org. Lett.* **2003**, *5*, 459−462.
(54) Grigg, R.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1998**, *39*, 4139−4142.
(55) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312−11313.
(56) Bielawski, C. W.; Louie, J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 12872−12873.
(57) Watson, M. D.; Wagener, K. B. *Macromolecules* **2000**, *33*, 3196−3201.
(58) Drouin, S. D.; Zamanian, F.; Fogg, D. E. *Organometallics* **2001**, *20*, 5495−5497.
(59) Børsting, P.; Nielsen, P. *Chem. Commun.* **2002**, 2140−2141.
(60) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308−311.
(61) Schmidt, B.; Pohler, M. *Org. Biomol. Chem.* **2003**, *1*, 2512−2517.
(62) Drouin, S. D.; Yap, G. P. A.; Fogg, D. E. *Inorg. Chem.* **2000**, *39*, 5412−5414.
(63) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865−1880.

after completion of the metathesis step.[38] We investigated four different additives used to activate the metathesis catalyst for the isomerization step. The results obtained for each protocol are summarized and discussed in the following paragraphs.

Activation by Addition of Ethyl Vinyl Ether. Grubbs et al. recently described the formation of "Fischer-type" carbene complexes derived from $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (**11a**) by treatment of this complex with electron-rich alkenes, such as ethyl vinyl ether.[64] In this case, metathetic exchange of the benzylidene ligand occurs with the formation of the new carbene complex $[Cl_2(PCy_3)_2Ru{=}CHOEt]$ (**11b**), which when heated, decomposes to the hydride complex $[Cl(CO)(PCy_3)_2Ru{-}H]$ (**12**). We assumed that the propagating species of the RCM of dienes **2**, $[Cl_2(PCy_3)_2Ru{=}CH_2]$ (**11c**), would also undergo metathetical exchange with ethyl vinyl ether to give **11b**. In a first experiment, diene **2f** was cyclized using 5 mol % $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (**11a**) in toluene. Ring-closing metathesis is complete under these conditions within 20 min, and ^{31}P NMR reveals the presence of $[Cl_2(PCy_3)_2Ru{=}CH_2]$ (**11c**, $\delta(^{31}P) = 44$ ppm).[65] Addition of ethyl vinyl ether led to a rapid disappearance of the signal at 44 ppm, and a new signal at 37 ppm, which is indicative for the Fischer-type carbene complex **11b**,[64] was observed. Subsequent heating of the reaction mixture to reflux induced a color change from deep red to orange yellow, and simultaneously, a new signal in the ^{31}P NMR spectrum appeared at 48 ppm, which is in good agreement with the literature value for hydride complex **12**.[64] Although a hydride complex is obviously formed, isomerization of the intermediate metathesis product **7f** to enol ether **8f** is very slow; after 8 h in refluxing toluene, only 10% of **8f** and 90% of **7f** could be detected in the proton NMR spectrum of the crude reaction mixture. A similar result was obtained for **2l**. In contrast to these six-membered heterocycles, five-membered oxacycles are isomerized to the corresponding enol ethers in preparatively useful rates of conversion and isolated yields. Thus, when dienes **2a**−**e** were subjected to the protocol outlined above, quantitative conversion to the corresponding cyclic enol ethers was observed within 5−7 h. Except for **2e**, which has a quaternary center in the 2-position, the RCM isomerization sequence results in the formation of regioisomers **8** and **9** in a 4:1 ratio. In the case of **2a**, the selectivity for the formation of the less-substituted cyclic enol ether **8a** was significantly better, probably due to steric effects. Ratios of regioisomers were determined by ^1H NMR spectroscopy of the crude reaction mixture. Isolated yields, however, refer to pure **8** because the regioisomers **9** decompose selectively upon chromatography on silica. Scheme 10 and Table 1 summarize the results.

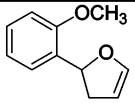
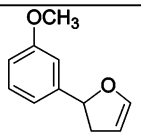
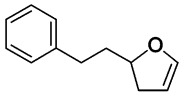
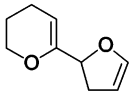
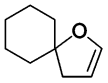
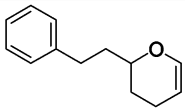
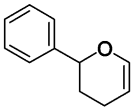
Activation by Addition of Inorganic Hydrides. It is known that complex hydrides, especially $NaBH_4$, reduce Ru(II) or Ru(III) compounds to Ru−hydride complexes.[66−70] This observation has been exploited by Frauenrath for the development of an olefin isomerization protocol that relies on the formation of a ruthenium−hydride complex from $[RuCl_2(PPh_3)_3]$ and $NaBH_4$ in situ.[48,71,72] To the best of our knowledge, the reaction of

SCHEME 10. Tandem RCM Isomerization: Activation of the Ru Catalyst with Ethyl Vinyl Ether[a]



[a] Reagents and conditions: (i) toluene, $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (5 mol %), 25 °C, add $EtOCH{=}CH_2$ after completion of the metathesis reaction, 25 °C for 10 min, and then 110 °C (see Table 1 for details).

TABLE 1. Tandem RCM Isomerization: Activation of the Metathesis Catalyst with Ethyl Vinyl Ether

2	8	Ratio 8 : 9	Yield[a]
2a	 8a	8 : 1	77%
2b	 8b	4 : 1	61%
2c	 8c	4 : 1	68%
2d	 8d	4 : 1	69%
2e	 8e	---	74%
2f	 8f	---	---[b]
2l	 8l	---	---[b]

[a] Isolated yield of pure **8**. [b] With <10% conversion after 10 h.

(64) Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153−2164.
(65) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.
(66) Harris, R. O.; Hota, N. K.; Sadavoy, L.; Yuen, J. M. C. *J. Organomet. Chem.* **1973**, *54*, 259−264.
(67) Holah, D. G.; Hughes, A. N.; Hui, B. C. *Can. J. Chem.* **1976**, *54*, 320−328.
(68) Peet, W. G.; Gerlach, D. H. *Inorg. Synth.* **1974**, *15*, 38−42.
(69) Young, R.; Wilkinson, G. *Inorg. Synth.* **1977**, *17*, 75−77.
(70) Bennett, M. A.; Bruce, M. I.; Matheson, T. W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 4, pp 692−820.
(71) Frauenrath, H.; Philips, T. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 274−275.
(72) Bennett, M. A.; Matheson, T. W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 4, pp 932−965.

Grubbs' catalyst [$Cl_2(PCy_3)_2Ru{=}CHPh$] with $NaBH_4$ has not been investigated so far. We assumed that introduction of a hydride by nucleophilic attack might take place, which should give an isomerization-active Ru−H species. In an initial experiment, $NaBH_4$ (0.5 equiv) was added to a completed metathesis reaction of substrate **2f** in toluene. When the mixture was heated to reflux, slow conversion of the RCM product **7f** to the cyclic enol ether **8f** was observed, which was complete after 8 h. **8f** was obtained with a regioselectivity better than 95:5, and no isomer **9f** could be detected in the NMR spectrum of the crude reaction mixture. The use of NaH was found to reduce the reaction times slightly without affecting yields and selectivities. In contrast, addition of DIBAL-H (0.5 equiv) resulted in an incomplete conversion of the primary metathesis product to the cyclic enol ether **8f**. Scope and limitations of this protocol have been evaluated for the examples listed in Table 2. Only for dihydrofurans **8a**−**d** were significant amounts of the higher-substituted regioisomers **9** observed. Ratios of regioisomers **8** and **9** are in the same range as those observed for the products obtained via the ethyl vinyl ether protocol (Table 1), except for **8d**, which has a donor atom in the side chain. It might be speculated that the dihydropyran substituent coordinates to the isomerization catalyst and exerts a directing effect, resulting in a larger amount of **9d**. With this protocol, isomerization of the five-membered heterocycles is normally complete within 2−3 h. For six-membered oxacycles **8f**−**t**, reaction times are generally longer (normally in the range of 5−7 h), but the higher-substituted dihydropyrans **9** are normally not observed in the ^{1}H NMR spectrum of the crude reaction mixture. An exception is 2-furyl-substituted **8k**, which was obtained with approximately 10% of its regioisomer **9k**. Ethers, epoxides, acetals, and silyl ethers are compatible with the reaction conditions. No conversion was observed for unprotected alcohols, and incomplete conversion was observed for **8g**, **8j**, and **8m**. **8g** was obtained after prolonged heating with 30% of RCM product **7g**. We speculate that intramolecular coordination of the exocyclic double bond to the ruthenium center occurs, resulting in an inhibition of the catalytically active species. Application of the protocol to **2j** and **2m** results in incomplete isomerization of the intermediate dihydropyrans **7j** and **7m** to the cyclic enol ethers **8j** and **8m**, respectively. In these cases, the isomers **13j** and **13m** were obtained as byproducts; isomers **9j** and **9m**, however, could not be detected (Scheme 11).

At this point, control experiments were conducted to address three questions. (a) Is the isomerization really ruthenium-catalyzed or probably a base-induced process? To answer this question, which arises in those cases where the strong base NaH is used as an activating agent, **7a** was synthesized by ring-closing metathesis of **2a**, purified by flash chromatography, and then distilled. This purification should be sufficient for removing any ruthenium residues. Pure, colorless **7a** was then treated with 1 equiv of NaH in refluxing toluene for several hours. Upon hydrolysis and evaporation of the solvent, ^{1}H NMR analysis of the mixture revealed the absence of any isomerized products **8a** or **9a**. The starting material, **7a**, was recovered unchanged in quantitative yield. (b) Is an activating agent really required for isomerization activity? The interference of isomerization side reactions with olefin metathesis is often attributed to ruthenium−hydride species that either are present in the precatalyst as an impurity[31] or result from unimolecular decomposition of the propagating species.[73,74] It was therefore necessary to check whether an activating reagent is required to induce isomerization activity. To this end, **2a** was reacted with 5 mol % Grubbs' catalyst **11a** in toluene and then heated to reflux for 5 h. A sample of the reaction mixture was analyzed by ^{1}H NMR spectroscopy and found to contain exclusively the metathesis product **7a**. Isomerization product **8a** or **9a** could not even be detected in trace amounts. When 30 mol % $NaBH_4$ was added to the residual reaction mixture and the mixture was heated to reflux, complete isomerization of **7a** to **8a** and **9a** (8:1 ratio) occurred in <2 h. (c) Does the isomerization occur with racemization? As mentioned above, we have observed minor amounts of isomerized dihydropyrans **13** in two cases. Isomerization of **13** might give either **7** or achiral **9**. If enantiomerically pure starting materials are employed in the sequence, racemization might occur when the double bond in enol ethers **9** migrates (via **13** and **7**) to give **8**, which then would obviously be a racemic mixture (Scheme 12). This scenario appears to be quite unlikely since no significant amounts of products **9** (except for **2k**) could be detected in the case of dihydropyrans. Furthermore, the higher-substituted enol ethers **9** can be expected to be the thermodynamically preferred products.

Nevertheless, the sequence was repeated for enantiomerically enriched (*R*)-**2f**, which was obtained from (*R*)-**1f**. This homoallylic alcohol was synthesized in 90% ee via allylboration following a literature procedure.[75] (*R*)-**2f**, subjected to the conditions of the tandem RCM isomerization process, yields (*R*)-**8f** with the same enantiomeric excess determined for the homoallylic alcohol. This control experiment has also been conducted by Snapper et al. for their protocol with the same result.[38] Furthermore, dienes **2h** and **2i**, which have been used as mixtures of diastereomers, are converted to **8h** and **8i**, respectively, without alteration of the diastereomeric ratio. From these observations, we conclude that the racemization scenario outlined in Scheme 12 does not play a significant role in this tandem process.

To gain some insight into the nature of the isomerization catalyst, the tandem sequence was monitored by ^{31}P NMR for the example of diene **2p**. After ring-closing metathesis of **2p** was completed, a signal at 43.8 ppm was observed, which can be assigned to the methylidene complex **11c**. When $NaBH_4$ is added and the mixture heated to reflux, this signal disappears within 1 h and a new species is formed with a ^{31}P NMR resonance at 47.1 ppm. This signal is still observed after the isomerization step is complete. Ruthenium−hydride species could be detected by repeating the reaction in perdeuterated toluene with 20 mol % catalyst **11a**. The high-field region of the NMR spectrum obtained from the reaction mixture shows three signals originating from the ruthenium−hydride species: a broad signal at −7.58 ppm, a doublet with a coupling constant of 43 Hz at −10.63 ppm, and a

(73) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202−7207.
(74) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414−7415.
(75) Ram Reddy, M. V.; Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.* **2001**, *624*, 239−243.

TABLE 2. RCM Isomerization Sequence: Activation of the Metathesis Catalyst with Inorganic Hydrides (Protocol a) or Isopropanol/Base (Protocol b)

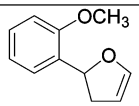
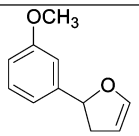
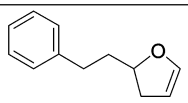
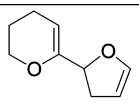
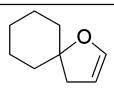
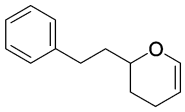
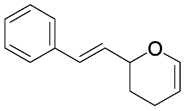
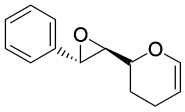
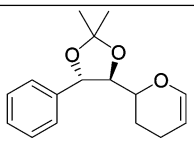
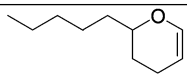
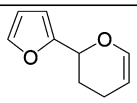
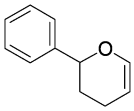
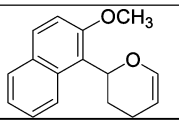
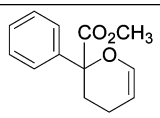
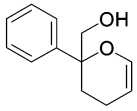
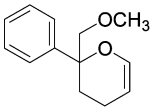
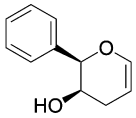
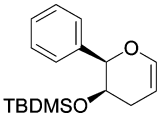
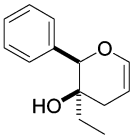
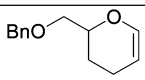
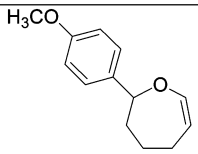
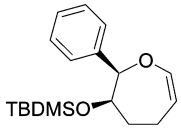
2	8	Protocol [a]			Protocol [b]	
		Hydride	**8** : **9**	Yield	**8** : **9**	Yield
2a	 **8a**	NaH $NaBH_4$	8 : 1 8 : 1	79% 75%	---	---[c]
2b	 **8b**	NaH $NaBH_4$	3.6 : 1 4 : 1	64% 67%	---	---
2c	 **8c**	NaH	4.8 : 1	70%	---	---
2d	 **8d**	$NaBH_4$	2 : 1	53%	---	---
2e	 **8e**	NaH	---	72%	---	---
2f	 **8f**	NaH $NaBH_4$	>19 : 1 >19 : 1	94% 92%	>19 : 1	72%
2g	 **8g**	NaH	---	---[d]	>19 : 1	65%[e]
2h	 **8h**	$NaBH_4$	>19 : 1	91%[f]	>19 : 1	63%[f]
2i	 **8i**	$NaBH_4$	>19 : 1	73%[f]	>19 : 1	69%[f]
2j	 **8j**	NaH	>19 : 1	74%[g]	>19 : 1	70%
2k	 **8k**	NaH	11 : 1	95%	11 : 1	86%
2l	 **8l**	NaH	>19 : 1	87%	>19 : 1	82%
2m	 **8m**	NaH	---	---[h]	>19 : 1	80%

Table 2 (Continued)

2n	 **8n**	---	---	---	---	70%
2o	 **8o**	NaH $NaBH_4$	--- ---	---[i] ---[i]	---	48%[j]
2p	 **8p**	NaH $NaBH_4$	--- ---	80% 72%	---	76%
2q	 **8q**	---	---	---	>19 : 1	40%[j]
2r	 **8r**	$NaBH_4$	>19 : 1	87%	>19 : 1	84%
2s	 **8s**	NaH $NaBH_4$	--- ---	---[i] ---[i]	---	66%[k]
2t	 **8t**	NaH	>19 : 1	87%	>19 : 1	91%
2u	 **8u**	NaH	>19 : 1	44%	>19 : 1	51%
2w	 **8w**	$NaBH_4$	>19 : 1	82%	>19 : 1	74%

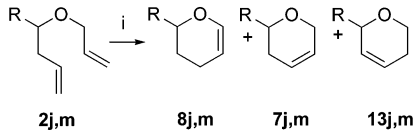
[a] Reagents and conditions: toluene (0.2 M), [$Cl_2(PCy_3)_2Ru$=CHPh] (5 mol %), 25 °C, and then add NaH or $NaBH_4$ (50 mol %), 110 °C (complete conversion was observed after 5 h for **8a**−**e**, 8 h for **8f**−**t**, and 10 h for **8u**,**w**, unless otherwise stated). [b] Reagents and conditions: toluene (0.2 M), [$Cl_2(PCy_3)_2Ru$=CHPh] (5 mol %), 25 °C, and then add 2-propanol (25% v/v) and NaOH (50 mol %), 110 °C (complete conversion was observed after 2 h for all examples except **8k** (1 h) and **8s** (7 h)). [c] Complex mixture of products. [d] Reaction stops at 70% conversion. [e] Obtained as an inseparable mixture with 10% of **8f** and an unidentified byproduct. [f] Dienes **2** are 3:2 mixtures of diastereoisomers; products **8** are obtained with the same diastereomeric ratio. [g] Incomplete conversion. [h] Incomplete conversion, 10:4:1 ratio of products **8m**, **7m** and **13m**. [i] Only RCM product **7** observed. [j] Obtained with 10% of **10**. [k] [$Cl_2(PCy_3)_2Ru$=CHPh] (8 mol %) and longer reaction times required.

triplet with a coupling constant of 18 Hz at −14.24 ppm. Although the exact structure of the ruthenium−hydride species involved is not clear, it is most likely that the triplet originates from a complex containing two phosphine ligands. The observed coupling constant of 18 Hz is in good agreement with literature values reported for other Ru−H complexes.[64,76] The experiment was repeated without addition of $NaBH_4$ or any other additive to check if the observed signals originate from an impurity present in the precatalyst or from decomposition products resulting from monomolecular degradation of the propagating species after completion of the metathesis reaction. After the substrate was heated in the presence of 20 mol % precatalyst **11a** for 2 h, no trace of isomerized products was observed and the high-field region of the NMR spectrum did not show any signals that might be assigned to Ru−hydride species.

Activation by Addition of 2-Propanol and Base. The development of this protocol has been inspired by

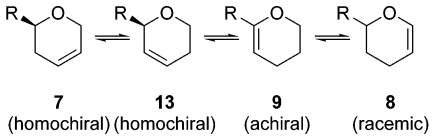
(76) Christ, M. L.; Sabo-Etienne, S.; Chaudret, B. *Organometallics* **1994**, *13*, 3800−3804.

SCHEME 11. Product Distribution for Tandem RCM Isomerization of 2j,m[a]

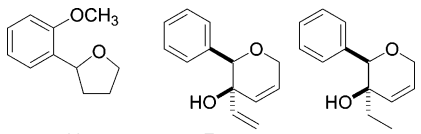


[a] Reagents and conditions: (i) toluene, $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (5 mol %), 25 °C, add NaH after completion of the metathesis reaction, 110 °C for 8 h (74% of a 12:1:1 **8j**/**7j**/**13j** mixture, 100% of a 10:4:1 **8**m/**7**m/**13**m mixture).

SCHEME 12. Potential Racemization Pathway



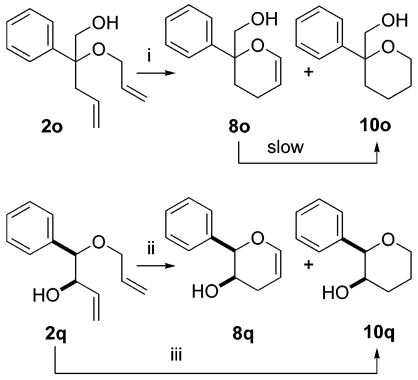
recent reports that Grubbs' catalyst (**11a**), like other ruthenium complexes,[77−79] mediates transfer hydrogenation and dehydrogenation[80] in the presence of secondary alcohols and ketones, respectively.[55,81] It is believed that ruthenium−hydrides are the catalytically active species in these transformations, and that they are formed by β-hydride elimination of a ruthenium−alkoxide. Thus, we assumed that addition of a secondary alcohol and a base to a completed metathesis reaction should induce a conversion of the ruthenium−carbene species to a ruthenium−hydride species. To test this hypothesis, 2-propanol and K_2CO_3 (as a base) were added to a completed metathesis reaction of **2k** in toluene. When the mixture was heated, slow formation of the isomerized product **8k** was observed by TLC. Use of triethylamine as a base also resulted in the slow but incomplete formation of **8k**. However, addition of 2-propanol and solid NaOH to the reaction mixture turned out to be very effective; under these conditions, the intermediate RCM product **7k** was converted quantitatively to **8k** within 1 h in excellent regioselectivity. The reaction time is significantly reduced, compared to that of the protocol based on catalyst activation by inorganic hydrides; for this example, 5 h is required to achieve complete conversion. It has recently been reported by Dinger and Mol that primary alcohols in the presence of a base also react with Grubbs' catalyst to yield ruthenium−hydride complexes.[82,83] Therefore, methanol and ethanol were also tested instead of 2-propanol, but they turned out to be significantly less effective. In these cases, incomplete isomerization was observed. Having established the protocol for the conversion of **2k** → **8k**, we investigated the scope and limitations for the examples listed in Table 2. Surprisingly, the first example, **2a**, which undergoes the tandem sequence readily with both protocols discussed above, does not react to **8a** cleanly under these conditions. Instead, a 3:2:1 mixture of **8a**, tetrahydrofuran **10a**, and the higher-substituted regioisomer of **8a**, **9a** is obtained. The formation of tetrahydrofuran **10a** is quite interesting because this is obviously the product of a hydrogen transfer from 2-propanol to either **7a**, **8a**, or **9a**. Hydrogen transfer from alcohols to alkenes is a known process but comparatively rare.[84] We assumed that hydrogenation is facilitated for five-membered ring systems and, therefore, did not investigate this protocol for substrates **2b**−**e**. All other substrates listed in Table 2 that undergo the tandem RCM isomerization process mediated by inorganic hydrides also react to enol ethers **8** using the 2-propanol/NaOH additive combination. Reaction times are significantly reduced and are normally in the range of 2−3 h. Isolated yields are comparable, and regioselectivities are generally excellent. However, the use of 2-propanol/NaOH does not lead only to reduced reaction times. A range of substrates that undergo no or only incomplete isomerization with the inorganic hydride protocol react smoothly under these conditions. For instance, tandem RCM isomerization of **2g** using NaH as an additive resulted in the formation of a 7:3 mixture of **7g** and **8g**, and addition of 2-propanol/NaOH results in complete conversion of **7g** to **8g**. Interestingly, **8f**, resulting from a hydrogenation of the exocyclic double bond, is formed as an inseparable byproduct. Similarly, **2j** and **2m**, which do not give **8j** and **8m** in preparatively useful yields and selectivities if inorganic hydrides are added, undergo quantitative conversion in excellent selectivities under the present conditions. The inorganic hydride protocol also fails for **2s** as only the RCM product **7s** was obtained. Application of the 2-propanol/NaOH protocol to this substrate yields, surprisingly, dihydropyran **8s**, where the exocyclic double bond is hydrogenated. Monitoring the conversion of **2s** to **8s** by NMR spectroscopy reveals that the primary metathesis product **7s** (formed as a 4:1 mixture of diastereomers)[45] first undergoes hydrogenation of the exocyclic double bond (giving intermediate **14**) which then isomerizes slowly to **8s**. Thus, formation of **8s** can be described as a tandem RCM transfer hydrogenation−isomerization reaction.



Apart from the functional groups tolerated by the inorganic hydride protocol, activation of the catalyst with 2-propanol/NaOH allows the use of esters (**2n** → **8n**) and unprotected primary (**2o** → **8o**) and secondary (**2q** → **8q**) alcohols. As for the conversion of tertiary alcohol **2s**, transfer hydrogenation interferes with the isomerization step. Carefully monitoring the reaction by TLC allows the isolation of **8o** and **8q** in preparatively useful yields and selectivities; application of the protocol to

(77) Sasson, Y.; Blum, J. *J. Org. Chem.* **1975**, *40*, 1887−1896.
(78) Johnson, J. B.; Bäckvall, J.-E. *J. Org. Chem.* **2003**, *68*, 7681−7684.
(79) Ito, M.; Osaku, A.; Kitahara, S.; Hirakawa, M.; Ikariya, T. *Tetrahedron Lett.* **2003**, *44*, 7521−7523.
(80) Gladiali, S.; Mestroni, G. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Vol. 2, pp 97−119.
(81) (a) Cho, C. S.; Kim, B. T.; Choi, H.-J.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2003**, *59*, 7997−8002. (b) Cho, C. S.; Kim, B. T.; Kim, H.-S.; Kim, T.-J.; Shim, S. C. *Organometallics* **2003**, *22*, 3608−3610. (c) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Org. Chem.* **2001**, *66*, 9020−9022.
(82) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089−1095.
(83) Dinger, M. B.; Mol, J. C. *Eur. J. Inorg. Chem.* **2003**, 2827−2833.
(84) Edwards, M. G.; Jazzar, R. F. R.; Paine, B. M.; Shermer, D. J.; Whittlesey, M. K.; Williams, J. M. J.; Edney, D. D. *Chem. Commun.* **2004**, 90−91.

SCHEME 13. Tandem RCM Isomerization and Subsequent Transfer Hydrogenation[a]



[a] Reagents and conditions: (i) toluene (0.2 M), $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (5 mol %), 25 °C, and then add 2-propanol (25% v/v) and NaOH (50 mol %), 110 °C, 4 h (48% of **8o** and 10% of **10o**); (ii) toluene (0.2 M), $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (5 mol %), 25 °C, and then add 2-propanol (25% v/v) and NaOH (50 mol %), 110 °C, 0.5 h (40% of **8q**); (iii) toluene (0.2 M), $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (5 mol %), 25 °C, and then add 2-propanol (25% v/v) and NaOH (50 mol %), 110 °C, 8 h (46% of **10q**).

2o and **2q** gives first the enol ethers **8o** and **8q**, which are subsequently slowly hydrogenated to tetrahydropyrans **10o** and **10q** under the reaction conditions (Scheme 13).

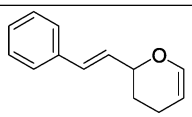
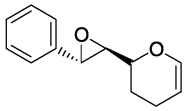
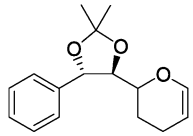
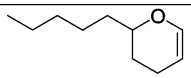
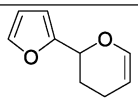
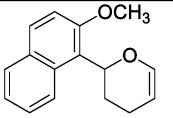
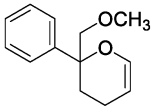
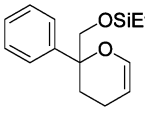
While the hydrogenation step observed for examples **2s** and **2o** is a true hydrogen transfer from 2-propanol to an alkene, a mechanistic alternative must be considered for **2q**; enol ether **8q** might undergo isomerization to a cyclic ketone, which then undergoes transfer hydrogenation to yield the secondary alcohol **10q**. Although we could not observe a cyclic ketone during the reaction, we cannot exclude this pathway. It is quite striking that hydrogen transfer occurs as a competing or subsequent reaction to double-bond isomerization, preferably in those cases where an unprotected alcohol functionality is present in the molecule. We assume that coordination of the ruthenium catalyst to the hydroxy group occurs, which facilitates hydrogen transfer. This aspect will be investigated in detail in the future. As described above, we also checked if the isomerization, according to this protocol, was base-induced rather than ruthenium-catalyzed. To this end, a sample of pure **7l** was treated with NaOH and 2-propanol under the reaction conditions in the absence of any ruthenium compounds. No isomerization to enol ether **8l** was observed after several hours.

Preliminary mechanistic investigations have also been conducted for this protocol. Monitoring the reaction by ^{31}P NMR spectroscopy reveals that the propagating species of olefin metathesis, $[Cl_2(PCy_3)_2Ru{=}CH_2]$ (**11c**), is rapidly converted to a new phosphorus-containing complex, which exhibits a resonance in the ^{31}P NMR spectrum at 51.7 ppm. In the search for a ruthenium−hydride species, a typical isomerization sequence using this protocol was repeated in toluene-d_8. We were able to detect two very weak resonances at −8.45 (t, J = 22 Hz) and −10.64 ppm (d, J = 43 Hz).

Activation by Addition of Silanes. Recently, Lee et al. described the dehydrogenative silylation of alcohols and the hydrosilylation of α,β-unsaturated carbonyl compounds catalyzed by $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (**11a**).[85] These reactions had previously been reported for other transition-metal complexes, and it is generally believed that activation of the Si−H bond occurs by oxidative addition of the silane to the metal complex, giving a metal−hydride complex.[86,87] On the basis of this assumption, we investigated the use of silanes to convert the propagating species of olefin metathesis, $[Cl_2(PCy_3)_2Ru{=}CH_2]$ (**11c**), to an isomerization catalyst. Lee et al. reported a decreasing activity of silanes in dehydrogenative silylation of alcohols in the order Ph_2SiH_2 > Me_2PhSiH > Et_3SiH. Guided by this observation, we subjected **2k** to the conditions of this tandem protocol because its RCM product, **7k**, was found in the protocols discussed above to undergo isomerization significantly faster than all other dihydropyrans. After diphenylsilane was added to the completed metathesis reaction and the mixture was heated, a color change from deep red to orange yellow rapidly occurred. Simultaneously, the signal of **11c** in the ^{31}P NMR spectrum disappeared and two new signals at 46.2 and 34.2 ppm were observed. However, after the reaction mixture was heated to reflux for 4 h, it was not possible to detect any isomerization product in the reaction mixture. Using Me_2PhSiH as an activating agent led to the rapid formation of a new phosphorus-containing species [$\delta(^{31}P)$ = 46.5 ppm] and the partial isomerization to the desired enol ether **8k** with 30% conversion after 7 h in refluxing toluene. Finally, triethylsilane was found to give the most active isomerization catalyst in this series. Although a comparatively long reaction time of 10 h was required, **8k** was obtained in yields and selectivities comparable to those of the previously discussed conditions. ^{31}P NMR spectroscopy of the reaction mixture revealed the presence of a new signal at 47.5 ppm. The ^{31}P NMR signals observed for the three different silanes differ only slightly in their chemical shift value, but the significantly distinct isomerization activity suggests that indeed a different species is involved in each protocol. We have applied the optimized conditions found for the conversion of **2k** → **8k** to dienes **2** listed in Table 3. Only **2g** gave a complex mixture of products, which contained the desired **8g** as a major component. All other dienes that were subjected to these conditions were converted cleanly to the cyclic enol ethers **8** in good yields and excellent regioselectivities within 10−16 h at 110 °C. Noteworthy is the conversion of diene **2o**, which contains a primary alcohol. This starting material was employed because we assumed that Lee's dehydrogenative silylation procedure might be incorporated as an additional step in our tandem sequence; after ring-closing metathesis of **2o** was completed, 1.1 equiv of triethylsilane was added to the reaction mixture. When the mixture was heated, the expected dehydrogenative silylation of the primary alcohol occurred rapidly and was completed before the reaction mixture reached reflux temperature. The isomerization reaction took place subsequently over the usual time scale of several hours in refluxing toluene,

(85) Maifeld, S. V.; Miller, R. L.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 6363−6366.
(86) Lukevics, E.; Dzintara, M. *J. Organomet. Chem.* **1985**, *295*, 265−315.
(87) Marciniec, B. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim, Germany, 1996; Vol. 1, pp 487−506.

TABLE 3. RCM Isomerization Sequence: Activation of the Metathesis Catalyst with Triethylsilane[a]

2	8	Yield[b]
2g	 8g	---[c]
2h	 8h	71%
2i	 8i	77%
2j	 8j	72%[d]
2k	 8k	83%
2m	 8m	79%
2p	 8p	74%
2o	 8x	84%

[a] Reagents and conditions: toluene (0.2 M), $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (5 mol %), 25 °C, and then add Et_3SiH (1.1 equiv). [b] All products were obtained with regioselectivities >19:1. [c] Complex mixture of products. [d] Approximately 10% of **7j** and **13j** present in the reaction mixture after 12 h.

making the transformation of **2o** to **8x** a tandem RCM O-silylation isomerization sequence.

Close examination of the high-field region of a ^{1}H NMR spectrum obtained from the reaction mixture revealed the presence of three major signals at −10.71 (dd, J = 43 and 8 Hz), −11.46 (d, J = 33 Hz), and −13.47 ppm after triethylsilane was added. On the basis of these results, it can only be stated that, most likely, a ruthenium−hydride species is involved, but whether this species is different from those active in the other protocols is not clear. It is, however, striking that for all of the protocols where the high-field region of the ^{1}H NMR spectrum was investigated a doublet structure at −10.6 ppm with a coupling constant of 43 Hz was observed.

Comparison of the Protocols. ^{1}H NMR-Derived Time-Conversion Graphs for Selected Examples. Time-conversion curves have been recorded for the individual protocols for selected examples by analyzing the composition of the reaction mixtures using ^{1}H NMR spectroscopy. Figures 1 and 2 show the isomerization step in the tandem sequence **2c** → **7c** → **8c** + **9c**. With ethyl vinyl ether as an additive (Figure 1), only a very short induction period is observed, which is obviously required for the formation of the isomerization catalyst by decomposition of the Fischer-type carbene complex **11b**. After this induction period, a steady decrease of the concentration of RCM product **7c** is observed. A significantly longer induction period is observed for $NaBH_4$ as the additive (Figure 2). However, once the catalyst is formed, it appears to be much more active than the one working in the ethyl vinyl ether protocol. In both protocols, the ratio of regioisomers **8c** and **9c** appears to be nearly constant during the reaction.

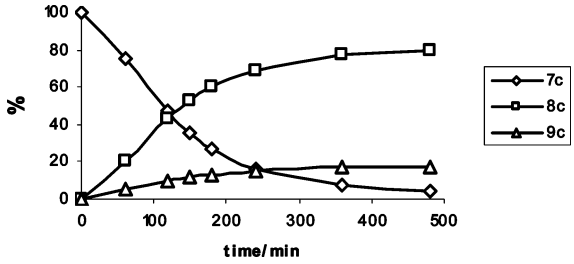


FIGURE 1. Time-conversion curve for the isomerization of **7c**, with ethyl vinyl ether as the additive.

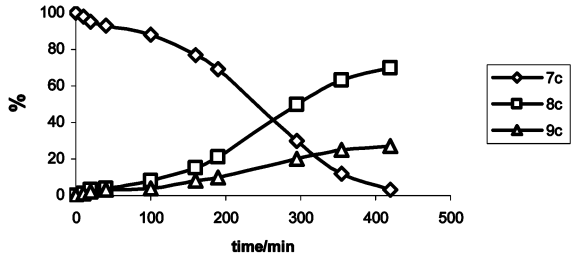


FIGURE 2. Time-conversion curve for the isomerization of **7c**, with $NaBH_4$ as the additive.

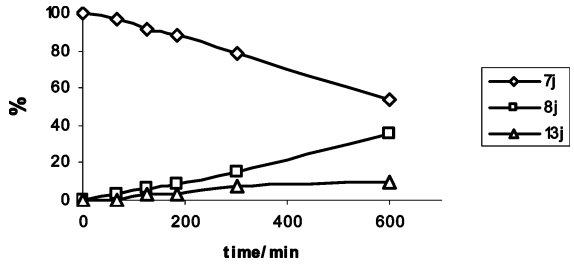


FIGURE 3. Time-conversion curve for the isomerization of **7j**, with $NaBH_4$ as the additive.

As an example for a dihydropyran isomerization, the tandem sequence **2j** → **7j** → **8j** was chosen because this transformation was found to be comparatively slow for all protocols. Figure 3 shows the time-conversion curve for the activation with $NaBH_4$. For this particular example, this protocol turns out to be inefficient; even after 10 h, <50% of **7j** was isomerized to the expected **8j** and dihydropyran **13j**. Formation of the higher-substituted enol ether **9j**, which is a consecutive product of **13j**, could not be observed (Scheme 14).

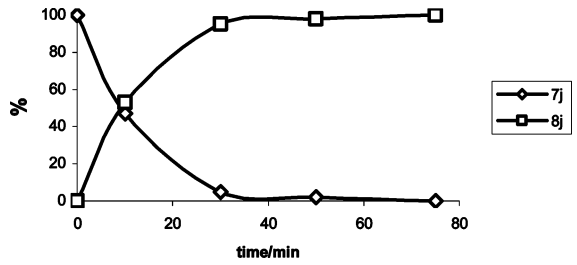


FIGURE 4. Time-conversion curve for the isomerization of **7j**, with 2-propanol/NaOH as the additive.

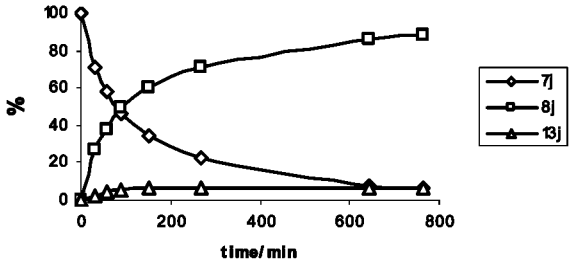


FIGURE 5. Time-conversion curve for the isomerization of **7j**, with Et_3SiH as the additive.

SCHEME 14. Isomerization of 7j to 8j and 13j

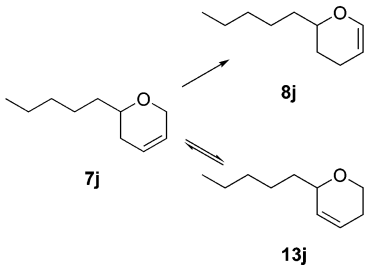


Figure 4 illustrates that the 2-propanol/NaOH protocol is superior in cases, such as **2j** → **7j** → **8j**, where virtually quantitative conversion to **8j** is observed in <1 h. We were unable to detect significant amounts of **13j**, which does not mean that this product is not formed during the isomerization step; however, the isomerization catalyst working here is obviously so efficient that **7j** and **13j** rapidly equilibrate, and **7j** is consecutively removed from the equilibrium by isomerization to **8j**.

Finally, a time-conversion curve was recorded for the triethylsilane protocol (Figure 5). This additive yields an isomerization catalyst which is intermediate in activity; the concentration of **7j** rapidly decreases with virtually no induction period. After 13 h, 90% of **7j** is converted to **8j** and the residual 10% is a 1:1 mixture of **7j** and **13j**. The ratio of **8j** to **13j** appears to be constant over the reaction time, and it may be concluded that **13j** is probably a "dead end" in this isomerization protocol.

Conclusion

Olefin isomerization, normally considered to be an undesired side reaction in olefin metathesis, can be a synthetically valuable reaction if conditions are found that allow one to distinguish strictly between metathesis and isomerization activity. We have developed four protocols that allow for the use of ruthenium−carbene complexes in clean isomerization reactions and incorporation of these isomerization steps in tandem sequences. The concept is exemplified for the regioselective synthesis of cyclic enol ethers, which are valuable synthetic intermediates. Evidence is presented that ruthenium−hydride species are responsible for the isomerization reaction. Currently, we are working toward application of this novel synthetic methodology in the synthesis of target molecules and identification of the actual isomerization catalysts.

Experimental Section

General Remarks. All of the experiments were conducted in dry reaction vessels under an atmosphere of dry argon. Solvents were purified by standard procedures. ^{1}H NMR spectra were obtained at 400, 500, or 600 MHz in $CDCl_3$, with $CHCl_3$ (δ = 7.24 ppm) as an internal standard, or in C_6D_6, with C_6D_5H (δ = 7.18 ppm) as an internal standard. Coupling constants (J) are given in hertz. Signal assignments are based on H−H correlation spectroscopy. ^{13}C NMR spectra were recorded at 100, 125, or 150 MHz in $CDCl_3$, with $CDCl_3$ (δ = 77.0 ppm) as an internal standard, or in C_6D_6, with C_6D_6 (δ = 128.0 ppm) as an internal standard. The number of coupled protons was analyzed by DEPT or APT experiments and is denoted by a number in parentheses following the chemical shift value. IR spectra were recorded as films on NaCl or KBr plates. The peak intensities are defined as strong (s), medium (m), or weak (w). Mass spectra were obtained at 70 eV. Optical purities were determined by HPLC using a HPLC-1050 system equipped with a Daicel Chiralcel OD column. The following compounds have been prepared following procedures described in the literature: **1c**,[88] **1d**,[41] (*R*)-**1f**,[75] **1g**,[89] **1l**,[90] **1t**,[91] **1u**,[92] **2e**,[21] **2l**,[93] **2n**,[43] **2o**,[43] **2q**,[21] **2s**,[45] **2t**,[94] and **7k**.[95]

Representative Procedures for the Synthesis of Cyclic Enol Ethers 8. Rhodium-Catalyzed Double-Bond Isomerization (Protocol a). To a solution of **7f** (1.34 g, 7.1 mmol) in ethanol (40 mL) were added DBU (2.24 mL, 15.0 mmol) and $[RhCl(PPh_3)_3]$ (330 mg, 5 mol %). The mixture was heated to reflux until the starting material was fully consumed, as indicated by TLC. All volatiles were evaporated in vacuo, and the residue was purified by flash chromatography on silica using cyclohexane/MTBE mixtures as eluent to give **8f** (1.06 g, 79%).

Ruthenium-Catalyzed Double-Bond Isomerization (Protocol b). To a solution of **7k** (0.70 g, 4.7 mmol) in methanol (20 mL) were added $[RuCl_2(PPh_3)_3]$ (120 mg, 2.7 mol %) and $NaBH_4$ (45 mg, 25 mol %). The mixture was heated to reflux for 2 h and filtered, and the solvent was evaporated. The residue was purified by flash chromatography on silica to give **8k** (0.29 mg, 41%) and tetrahydropyran **10k** (0.15 g, 21%).

Tandem RCM Isomerization Process with Ethyl Vinyl Ether as an Additive (Protocol c). To a solution of **2c** (0.41 g, 2.0 mmol) in toluene (10 mL) was added $[Cl_2(PCy_3)_2$-Ru=CHPh] (75 mg, 4.6 mol %). The solution was stirred until the starting material was fully consumed (approximately 20 min, TLC), and ethyl vinyl ether (1.0 mL, 10 mmol) was added. The mixture was continuously stirred at ambient temperature

(88) Gazzard, L. J.; Motherwell, W. B.; Sandham, D. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 979−993.
(89) Shibata, I.; Yoshimura, N.; Yabu, M.; Baba, A. *Eur. J. Org. Chem.* **2001**, 3207−3211.
(90) Jurd, L.; Roitman, J. N. *Tetrahedron* **1978**, *34*, 57−62.
(91) Gravestock, M. B.; Knight, D. W.; Lovell, J. S.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3143−3155.
(92) Hartung, J.; Hiller, M.; Schmidt, P. *Liebigs Ann.* **1996**, 1425−1436.
(93) Schmidt, B. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2627−2637.
(94) Aragonès, S.; Bravo, F.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1847−1856.
(95) Marco, J. A.; Carda, M.; Rodríguez, S.; Castillo, E.; Kneeteman, M. N. *Tetrahedron* **2003**, *59*, 4085−4101.

for 15 min to allow formation of the intermediate ethoxy-substituted carbene complex, and the solution was then heated to reflux until the primarily formed metathesis product was completely converted to the enol ether (TLC). A color change from deep red to yellow occured when the solution was heated to reflux, which indicates the formation of the ruthenium−hydride species. Evaporation of the solvent and flash chromatography on silica yielded **8c** (0.24 g, 67%).

Tandem RCM Isomerization Process with NaH or $NaBH_4$ as an Additive (Protocol d). To a solution of **2f** (0.98 g, 4.5 mmol) in toluene (30 mL) was added $[Cl_2(PCy_3)_2$-Ru=CHPh] (186 mg, 5.0 mol %). The solution was stirred until the starting material was fully consumed (approximately 30 min, TLC), and NaH (60% dispersion in mineral oil, 80 mg, ~2.0 mmol) was added. The solution was then heated to reflux until the primarily formed metathesis product was completely converted to the enol ether (TLC). After the reaction mixture was cooled to ambient temperature, it was diluted with MTBE and washed with water. The organic layer was separated, dried with $MgSO_4$, filtered, and evaporated. Flash chromatography on silica yielded **8f** (0.80 g, 94%).

Tandem RCM Isomerization Process with 2-Propanol and NaOH as an Additives (Protocol e). To a solution of **2f** (0.43 g, 2.0 mmol) in toluene (8 mL) was added $[Cl_2(PCy_3)_2$-Ru=CHPh] (82 mg, 5.0 mol %). The solution was stirred until the starting material was fully consumed (approximately 30 min, TLC), and 2-propanol (2.0 mL) and NaOH (20 mg, 0.5 mmol) were added. The solution was then heated to reflux until the primarily formed metathesis product was completely converted to the enol ether (TLC). After the reaction mixture was cooled to ambient temperature, it was diluted with MTBE and washed with water. The organic layer was separated, dried with $MgSO_4$, filtered, and evaporated. Flash chromatography on silica yielded **8f** (0.34 g, 90%).

Tandem RCM Isomerization Process with Triethylsilane as Additive (Protocol f). To a solution of **2m** (0.27 g, 1.0 mmol) in toluene (10 mL) was added $[Cl_2(PCy_3)_2Ru$=CHPh] (42 mg, 5.0 mol %). The solution was stirred until the starting material was fully consumed (approximately 30 min, TLC), and triethylsilane (0.16 mL, 1.0 mmol) was added to the solution via syringe. The solution was then heated to reflux until the primarily formed metathesis product was completely converted to the enol ether (TLC). The solvent was evaporated and the residue purified by flash chromatography on silica to give **8m** (0.19 g, 79%) as a colorless solid.

Analytical Data of Cyclic Enol Ethers 8. 2-(2-Methoxyphenyl)-2,3-dihydrofuran (8a). Protocol c. **8a** was obtained from **2a** (204 mg, 1.0 mmol) as an 8:1 mixture of regioisomers. Flash chromatography on silica yields **8a** as a single isomer (136 mg, 77%). **Protocol d**. **8a** was obtained from **2a** (408 mg, 2.0 mmol) as an 8:1 mixture of regioisomers. Flash chromatography on silica yields **8a** as a single isomer (280 mg, 79%). **Protocol e**. A 3:2:1 mixture of **8a**, **10a**, and **9a** was obtained from **2a** (204 mg, 1.0 mmol): ^{1}H NMR (500 MHz, C_6D_6) δ 2.43 (dddd, J = 15.2, 8.2, 2.3, 2.3, 1 H), 3.09 (dddd, J = 15.2, 10.7, 2.3, 2.3, 1 H), 3.25 (s, 3 H), 4.73 (ddd, J = 2.5, 2.3, 2.3, 1 H), 6.02 (dd, J = 10.7, 8.2), 6.39 (ddd, J = 2.5, 2.3, 2.3), 6.53 (d, J = 8.2, 1 H), 6.95 (dd, J = 7.5, 7.5, 1 H), 7.10 (ddd, J = 8.2, 7.5, 1.7, 1 H), 7.68 (dd, J = 7.5, 1.2, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 37.7 (2), 54.8 (3), 78.0 (1), 99.1 (1), 110.4 (1), 120.9 (1), 125.9 (1), 128.3 (1), 132.4 (0), 145.7 (1), 156.1 (0); IR (film, NaCl plates) ν 754 (s), 1051 (s), 1243 (s), 1491 (s), 1621 (s), 2937 (s) cm^{-1}; MS (EI) m/z 176 (100) [M$^+$], 147 (86), 91 (92). Anal. Calcd for $C_{11}H_{12}O_2$ (176.2): C, 75.0; H, 6.9. Found: C, 74.9; H, 6.7. **Protocol e**. A 3:2:1 mixture of **8a**, tetrahydrofuran **10a**, and the regioisomer of **8a** (**9a**) was obtained from **2a** (204 mg, 1.0 mmol). Tetrahydrofuran **10a** was identified by comparison with the NMR spectrum of an authentic sample.[61]

2-(3-Methoxyphenyl)-2,3-dihydrofuran (8b). Protocol c. **8b** was obtained from **2b** (408 mg, 2.0 mmol) as a 4:1 mixture of regioisomers. Flash chromatography on silica yields **8b** as a single isomer (215 mg, 61%). **Protocol d**. **8b** was obtained from **2a** (343 mg, 1.7 mmol) as a 3.6:1 mixture of regioisomers. Flash chromatography on silica yields **8b** as a single isomer (191 mg, 64%): ^{1}H NMR (400 MHz, C_6D_6) δ 2.43 (dddd, J = 15.1, 8.5, 2.5, 2.5, 1 H), 2.73 (dddd, J = 15.1, 10.5, 2.5, 2.5, 1 H), 3.33 (s, 3 H), 4.68 (ddd, J = 2.5, 2.5, 2.5, 1 H), 5.40 (dd, J = 10.5, 8.5), 6.31 (ddd, J = 2.5, 2.5, 2.5), 6.74 (dd, J = 7.8, 1.8, 1 H), 6.92 (d, J = 7.8, 1 H), 7.04 (dd, J = 1.8, 1.8, 1 H), 7.12 (dd, J = 7.8, 7.8, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 38.2 (2), 54.7 (3), 82.4 (1), 98.9 (1), 111.4 (1), 113.3 (1), 118.1 (1), 129.8 (1), 145.4 (0), 145.8 (1), 160.4 (0); IR (film, NaCl plates) ν 697 (s), 783 (s), 1264 (s), 1484 (s), 1586 (s), 1603 (s), 2936 (s) cm^{-1}; MS (EI) m/z 176 (54) [M$^+$], 147 (93), 135 (82), 91 (100). Anal. Calcd for $C_{11}H_{12}O_2$ (176.2): C, 75.0; H, 6.9. Found: C, 74.9; H, 7.2.

2-Phenethyl-2,3-dihydrofuran (8c). Protocol c. **8c** was obtained from **2c** (405 mg, 2.0 mmol) as a 4:1 mixture of regioisomers. Flash chromatography on silica yields **8c** as a single isomer (235 mg, 68%). **Protocol d**. **8c** was obtained from **2c** (500 mg, 2.5 mmol) as a 4.8:1 mixture of regioisomers. Flash chromatography on silica yields **8c** as a single isomer (305 mg, 70%): ^{1}H NMR (500 MHz, C_6D_6) δ 1.61 (dddd, J = 13.7, 9.5, 8.2, 5.5, 1 H), 1.92 (dddd, J = 13.7, 10.0, 6.7, 5.2, 1 H), 1.99 (dddd, J = 15.0, 7.7, 2.5, 2.5, 1 H), 2.38 (dddd, J = 15.0, 10.2, 2.5, 2.5, 1 H), 2.60 (ddd, J = 13.8, 9.5, 6.7, 1 H), 2.70 (ddd, J = 13.8, 9.7, 5.5, 1 H), 4.36 (dddd, J = 10.2, 8.2, 7.7, 5.2, 1 H), 4.67 (ddd, J = 2.5, 2.5, 2.5), 6.22 (ddd, J = 2.5, 2.5, 2.5), 7.07 (d, J = 7.8, 1 H), 7.15−7.20 (3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 32.2 (2), 34.9 (2), 38.3 (2), 80.5 (1), 98.7 (1), 126.1 (1), 128.6 (1), 128.8 (1), 142.1 (0), 145.5 (1); IR (film, NaCl plates) ν 699 (s), 1055 (s), 1140 (s), 1619 (s), 2856 (s), 2930 (s) cm^{-1}; MS (EI) m/z 174 (25) [M$^+$], 130 (100), 91 (98). Anal. Calcd for $C_{12}H_{14}O$ (174.3): C, 82.7; H, 8.1. Found: C, 82.7; H, 8.4.

6-(2,3-Dihydrofuran-2-yl)-3,4-dihydro-2*H*-pyran (8d). Protocol c. **8d** was obtained from **2d** (360 mg, 2.0 mmol) as a 4:1 mixture of regioisomers. Flash chromatography on silica yields **8d** as a single isomer (210 mg, 69%). **Protocol d**. **8d** was obtained from **2d** (416 mg, 2.3 mmol) as a 2:1 mixture of regioisomers. Flash chromatography on silica yields **8d** as a single isomer (175 mg, 53%): ^{1}H NMR (500 MHz, C_6D_6) δ 1.37−1.45 (2 H, $-OCH_2CH_2CH_2-$), 1.70−1.80 (2 H, $-OCH_2CH_2CH_2-$), 2.56 (dddd, J = 15.0, 11.0, 2.5, 2.5, 1 H, H3), 2.76 (dddd, J = 15.0, 8.5, 2.5, 2.5, 1 H, H3′), 3.69−3.77 (2 H, $-OCH_2CH_2CH_2-$), 4.71 (ddd, J = 2.5, 2.5, 2.5, 1 H, H4), 4.81−4.87 (2 H, $-OC$=$CH-$, H2), 6.26 (ddd, J = 2.5, 2.5, 2.5, 1 H, H5); ^{13}C NMR (125 MHz, C_6D_6) δ 20.1 (2), 22.6 (2), 33.5 (2), 66.1 (2), 80.8 (1), 96.9 (1), 99.0 (1), 145.7 (1), 153.5 (0); IR (film, NaCl plates) ν 910 (s), 1052 (s), 1069 (s), 1138 (s), 1621 (s), 1674 (s), 2931 (s) cm^{-1}; MS (EI) m/z 152 (54) [M$^+$], 95 (46), 69 (45), 55 (100). Anal. Calcd for $C_9H_{12}O_2$ (152.2): C, 71.0; H, 8.0. Found: C, 70.7; H, 8.3.

1-Oxaspiro[4.5]dec-2-ene (8e). Protocol c. **8e** (225 mg, 74%) was obtained from **2e** (360 mg, 2.2 mmol) after flash chromatography on silica. **Protocol d**. **8e** (200 mg, 72%) was obtained from **2e** (326 mg, 2.0 mmol) after flash chromatography on silica: ^{1}H NMR (400 MHz, C_6D_6) δ 1.15−1.48 (6 H, $-CH_2-$), 1.68−1.85 (4 H), 2.20 (dd, J = 2.3, 2.3, 2 H), 4.65 (dt, J = 2.5, 2.3, 1 H), 6.22 (dt, J = 2.5, 2.3, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 23.2 (2), 25.5 (2), 37.4 (2), 41.1 (2), 86.0 (0), 97.8 (1), 144.7 (1); IR (film, NaCl plates) ν 1062 (s), 1621 (s), 2857 (s), 2933 (s) cm^{-1}; MS (EI) m/z 138 (42) [M$^+$], 81 (100). Anal. Calcd for $C_9H_{14}O$ (138.2): C, 78.2; H, 10.2. Found: C, 78.6; H, 10.0.

2-Phenethyl-3,4-dihydro-2*H*-pyran (8f). Protocol a. **8f** (1.06 g, 79%) was obtained from **2f** (1.34 g, 7.1 mmol) after flash chromatography on silica. **Protocol d**. **8f** (0.80 g, 94%) was obtained from **2f** (0.98 g, 4.5 mmol) after flash chromatography on silica. **Protocol e**. **8f** (0.27 g, 72%) was obtained from **2f** (0.43 g, 2.0 mmol) after Kugelrohr distillation (0.1 mbar, 120 °C): ^{1}H NMR (400 MHz, C_6D_6) δ 1.39−1.45 (2 H), 1.58 (dddd, J = 13.8, 10.8, 7.0, 4.3, 1 H), 1.68−1.92 (3 H), 2.64 (ddd, J = 13.8, 9.5, 7.0, 1 H), 2.78 (ddd, J = 13.8, 9.8, 5.3, 1

H), 3.63 (m, 1 H), 4.59 (ddd, J = 6.3, 5.5, 2.5, 1 H), 6.48 (d, J = 6.3, 1 H), 7.07−7.22 (5 H); ^{13}C NMR (100 MHz, C_6D_6) δ 20.1 (2), 28.2 (2), 31.9 (2), 37.5 (2), 74.1 (1), 100.2 (1), 126.1 (1), 128.6 (1), 128.8 (1), 142.4 (0), 144.3 (1); IR (film, NaCl plates) ν 1066 (s), 1240 (s), 1650 (s), 2924 (s) cm^{-1}; MS (EI) m/z 188 (28) [M$^+$], 91 (100). Anal. Calcd for $C_{13}H_{16}O$ (188.3): C, 82.9; H, 8.6. Found: C, 82.9; H, 8.4.

(*R*)-2-Phenethyl-3,4-dihydro-2*H*-pyran ((*R*)-8f). Protocol d. (*R*)-**8f** (0.20 g, 71%) was obtained from (*R*)-**2f** (0.33 g, 1.5 mmol) after flash chromatography on silica. The enantiomeric excess of (*R*)-**8f** was determined by HPLC analysis (eluent, 95:5 heptane/2-propanol; flow 1.0 mL min^{-1}, 20 °C) to be 90% after comparison with that of racemic **8f** under identical conditions: $[\alpha]^{20}_D$ +17° (c 1.02, CH_2Cl_2) for 90% ee.

2-Styryl-3,4-dihydro-2*H*-pyran (8g). Protocol d. An inseparable 2.5:1 mixture of **8g** and **7g** (0.35 g, 90%) was obtained from **2g** (0.45 g, 2.1 mmol) after flash chromatography on silica. **Protocol e**. **8g** (0.24 g, 65%) was obtained from **2g** (0.42 g, 2.0 mmol) after flash chromatography on silica, contaminated with approximately 10% **8f** and 10% of another unidentified byproduct. All attempts to isolate **8g** in pure form failed. NMR data were obtained from the mixture: ^{1}H NMR (500 MHz, C_6D_6) δ 1.55−1.70 (2 H, H3,4), 1.75−1.95 (2 H), 4.34 (m, 1 H), 4.63 (m, 1 H), 6.19 (dd, J = 16.0, 5.7, 1 H), 6.52 (d, J = 6.2, 1 H), 6.62 (d, J = 16.0, 1 H), 7.06 (t, J = 7.5, 1 H), 7.13 (dd, J = 7.5, 7.5, 2 H), 7.25 (d, J = 7.5, 2 H); ^{13}C NMR (125 MHz, C_6D_6) δ 19.7 (2), 28.6 (2), 75.3 (1), 100.3 (1), 126.8 (1), 127.8 (1), 128.8 (1), 129.6 (1), 130.7 (1), 137.3 (0), 144.1 (1). **Protocol f**. A mixture obtained from **2g** (0.38 g, 1.7 mmol) contained, among several other products, **8g**. Attempts to isolate **8g** were unsuccessful.

2-(3-Phenyloxiranyl)-3,4-dihydro-2*H*-pyran (8h). Protocol d. An inseparable 3:2 mixture of diastereomers of **8h** (0.12 g, 91%) was obtained from **2h** (0.15 g, 0.7 mmol, 3:2 mixture of diastereomers) after flash chromatography on silica. **Protocol e**. An inseparable 3:2 mixture of diastereomers of **8h** (0.23 g, 63%) was obtained from **2h** (0.42 g, 1.8 mmol, 3:2 mixture of diastereomers) after flash chromatography on silica, followed by Kugelrohr distillation (0.17 mbar, 150 °C). **Protocol f**. An inseparable 3:2 mixture of diastereomers of **8h** (0.08 g, 71%) was obtained from **2h** (0.13 g, 0.6 mmol, 3:2 mixture of diastereomers) after flash chromatography on silica. NMR data of the major isomer: ^{1}H NMR (500 MHz, C_6D_6) δ 1.55−1.80 (4 H), 2.95 (dd, J = 5.2, 2.0, 1 H), 3.65 (ddd, J = 9.5, 5.2, 2.7, 1 H), 3.74 (d, J = 2.0, 1 H), 4.55 (m, 1 H), 6.35 (dm, J = 6.2, 1 H), 7.05−7.20 (5 H); ^{13}C NMR (125 MHz, C_6D_6) δ 10.0 (2), 24.8 (2), 56.9 (1), 63.2 (1), 74.4 (1), 100.8 (1), 125.9 (1), 128.3 (1), 128.7 (1), 137.8 (0), 143.6 (1). Characteristic ^{1}H NMR data of the minor isomer: ^{1}H NMR (500 MHz, C_6D_6) δ 2.97 (dd, J = 5.0, 2.0, 1 H), 3.62 (ddd, J = 10.2, 5.0, 2.2, 1 H), 3.71 (d, J = 2.0, 1 H), 4.55 (m, 1 H), 6.42 (dm, J = 6.2, 1 H). Full ^{13}C NMR data of the minor isomer: ^{13}C NMR (125 MHz, C_6D_6) δ 19.5 (2), 24.6 (2), 54.9 (1), 63.8 (1), 74.6 (1), 100.4 (1), 125.9 (1), 128.3 (1), 128.7 (1), 137.8 (0), 143.9 (1); IR (film, NaCl plates) ν 890 (s), 1068 (s), 1239 (s), 1650 (s), 1925 (m) cm^{-1}; MS (EI) m/z 202 (3) [M$^+$], 175 (13), 145 (30), 117 (75), 91 (100). Anal. Calcd for $C_{13}H_{14}O_2$ (202.3): C, 77.2; H, 7.0. Found: C, 77.1; H, 7.2.

2-(2,2-Dimethyl-5-phenyl[1,3]dioxolan-4-yl)-3,4-dihydro-2*H*-pyran (8i). Protocol d. An inseparable 3:2 mixture of diastereomers of **8i** (0.36 g, 73%) was obtained from **2i** (0.58 g, 1.9 mmol, 3:2 mixture of diastereomers) after flash chromatography on silica. **Protocol e**. An inseparable 3:2 mixture of diastereomers of **8i** (0.36 g, 69%) was obtained from **2i** (0.58 g, 2.0 mmol, 3:2 mixture of diastereomers) after flash chromatography on silica, followed by Kugelrohr distillation (0.17 mbar, 150 °C). **Protocol f**. An inseparable 3:2 mixture of diastereomers of **8i** (0.20 g, 77%) was obtained from **2i** (0.29 g, 1.0 mmol, 3:2 mixture of diastereomers) after flash chromatography on silica. NMR data of the major isomer: ^{1}H NMR (500 MHz, C_6D_6) δ 1.47 (s, 3 H, −OC(CH_3)$_2$O−), 1.51 (s, 3 H, −OC(CH_3)$_2$O−), 1.60−1.88 (4 H, H3,4), 3.94 (ddd, J = 9.7, 6.5, 2.0, 1 H, H2), 4.08 (dd, J = 7.2, 6.7, 1 H, PhCH(OC(CH_3)$_2$O)-CH−), 4.50 (m, 1 H, H5), 5.11 (d, J = 7.2, 1 H, PhCH(OC-(CH_3)$_2$O)CH−), 6.25 (d, J = 6.0, 1 H, H6), 7.13 (t, J = 7.5, 1 H, −Ph), 7.22 (dd, J = 7.5, 7.5, 1 H, −Ph), 7.53 (d, J = 7.5, 1 H, −Ph); ^{13}C NMR (125 MHz, C_6D_6) δ 19.3 (3), 24.8 (3), 27.3 (2), 27.4 (2), 76.3 (1), 81.7 (1), 84.1 (1), 100.6 (1), 109.3 (0), 127.0 (1), 127.5 (1), 128.7 (1), 140.3 (0), 143.6 (1). Characteristic ^{1}H NMR data of the minor isomer: ^{1}H NMR (500 MHz, C_6D_6) δ 1.37 (ddm, J = 13.5, 6.3, 1 H, H3′), 1.58 (s, 3 H, −OC(CH_3)$_2$O−), 1.59 (s, 3 H, −OC(CH_3)$_2$O−), 2.01 (dddd, J = 13.5, 11.0, 11.0, 6.3, 1 H, H3), 3.68 (ddd, J = 11.0, 2.0, 2.0, 1 H, H2), 3.77 (dd, J = 8.5, 2.3, 1 H, PhCH(OC(CH_3)$_2$O)CH−), 4.57 (m, 1 H, H5), 5.37 (d, J = 8.5, 1 H, PhCH(OC(CH_3)$_2$O)-CH−), 6.48 (d, J = 6.0, 2 H, −Ph), 7.46 (d, J = 7.5, 2 H, −Ph). Full ^{13}C NMR data of the minor isomer: ^{13}C NMR (125 MHz, C_6D_6) δ 20.2 (3), 25.3 (3), 27.0 (2), 27.5 (2), 71.9 (1), 78.3 (1), 85.5 (1), 100.8 (1), 109.6 (0), 127.0 (1), 127.5 (1), 128.3 (1), 140.3 (0), 144.3 (1); IR (film, NaCl plates) ν 890 (s), 1069 (s), 1242 (s), 1651 (s), 2986 (s) cm^{-1}; MS (EI) m/z 260 (1) [M$^+$], 202 (79), 119 (86), 91 (100). Anal. Calcd for $C_{16}H_{20}O_3$ (260.3): C, 73.8; H, 7.7. Found: C, 74.6; H, 8.1.

2-Pentyl-3,4-dihydro-2*H*-pyran (8j). Protocol d. **8j** and **7j** were obtained from **2j** (0.40 g, 2.2 mmol) as an inseparable 5:1 mixture (0.25 g, 74%) after flash chromatography on silica. **Protocol e**. **8j** (0.15 g, 70%) was obtained from **2j** (0.26 g, 1.4 mmol) after flash chromatography on silica. **Protocol f**. **8j** (0.07 g, 72%) was obtained from **2j** (0.11 g, 0.6 mmol) after flash chromatography on silica: ^{1}H NMR (500 MHz, C_6D_6) δ 0.89 (t, J = 7.2, 3 H), 1.16−1.68 (10 H), 1.79 (dm, J = 17.2, 1 H), 1.92 (dm, J = 17.2, 1 H), 3.67 (m, 1 H), 4.61 (m, 1 H), 6.49 (d, J = 6.3, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 14.2 (3), 20.3 (2), 23.0 (2), 25.4 (2), 28.2 (2), 32.2 (2), 35.7 (2), 75.1 (1), 100.0 (1), 144.5 (1); IR (film, NaCl plates) ν 1072 (s), 1242 (s), 1650 (s), 2930 (s) cm^{-1}; MS (EI) m/z 154 (32) [M$^+$], 98 (37), 57 (91), 55 (100). Anal. Calcd for $C_{10}H_{18}O$ (154.2): C, 77.9; H, 11.8. Found: C, 77.9; H, 12.2.

2-Furan-2-yl-3,4-dihydro-2*H*-pyran (8k). Protocol a. **8k** and its regioisomer **9k** were obtained from **2k** (0.33 g, 2.2 mmol) as an inseparable 1:1 mixture (0.30 g, 91%) after flash chromatography on silica. Regioisomer **9k** was independently obtained by base-promoted isomerization of **7k**. To a solution of **7k** (1.60 g, 10.7 mmol) in DMSO (10 mL) and THF (20 mL) was added KO-*tert*-Bu (2.24 g, 20.0 mmol). The mixture was heated to reflux for 2 h, cooled to ambient temperature, diluted with MTBE, and washed with brine. The organic layer was isolated, dried with $MgSO_4$, filtered, and evaporated. The residue was purified by flash chromatography on silica to give **9k** and **8k** as an inseparable 4:1 mixture (1.20 g, 75%). NMR data of **9k**: ^{1}H NMR (500 MHz, C_6D_6) δ 1.46 (m, 2 H), 1.86 (td, J = 6.5, 4.0, 2 H), 3.80 (m, 2 H), 5.50 (t, J = 4.0, 1 H), 6.08 (dd, J = 3.3, 1.7, 1 H), 6.56 (d, J = 3.5, 1 H), 7.05 (dd, J = 1.7, 0.8, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 20.2 (2), 22.6 (2), 66.1 (2), 105.4 (1), 111.2 (1), 141.8 (1), 145.6 (1), 151.2 (0). **Protocol b**. **8k** (0.29 g, 41%) and tetrahydropyran **10k** (0.15 g, 21%) were obtained from **7k** (0.70 g, 4.7 mmol) after flash chromatography on silica. NMR data of tetrahydropyran **10k**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50−1.95 (6 H), 3.57 (ddd, J = 11.3, 11.3, 2.5, 1 H), 4.03 (dm, J = 11.3, 1 H), 4.37 (dd, J = 9.0, 4.3, 1 H), 6.22 (d, J = 3.3, 1 H), 6.29 (dd, J = 3.3, 1.8, 1 H), 7.34 (dd, J = 1.8, 0.8, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (2), 25.6 (2), 29.5 (2), 68.5 (2), 72.9 (1), 106.0 (1), 109.9 (1), 141.9 (1), 155.1 (0). **Protocol d**. **8k** (0.34 g, 95%) was obtained from **2k** (0.40 g, 2.2 mmol) after flash chromatography on silica. A small amount (<10%) of the regioisomeric dihydropyran **9k** could be observed in the ^{1}H NMR spectrum of the crude reaction mixture. **Protocol e**. **8k** (0.36 g, 86%) was obtained from **2k** (0.50 g, 2.8 mmol) after flash chromatography on silica. **Protocol f**. **8k** (0.13 g, 83%) was obtained from **2k** (0.18 g, 1.0 mmol) after flash chromatography on silica: ^{1}H NMR (500 MHz, C_6D_6) δ 1.70−1.87 (3 H), 2.00 (m, 1 H), 4.56 (m, 1 H), 4.76 (dd, J = 10.2, 2.2, 1 H), 6.09 (dd, J = 3.0, 0.8, 1 H), 6.18 (d, J = 3.0, 1 H), 6.43 (d, J = 6.3, 1 H), 7.10 (d, J = 0.8,

1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 19.7 (2), 26.6 (2), 70.6 (1), 100.4 (1), 106.8 (1), 110.4 (1), 142.1 (1), 144.0 (1), 154.9 (0); IR (film, NaCl plates) ν 1060 (s), 1073 (s), 1238 (s), 1650 (s), 2928 (m) cm^{-1}; MS (EI) *m*/*z* 150 (24) [M$^+$], 94 (100). Anal. Calcd for $C_9H_{10}O_2$ (150.2): C, 72.0; H, 6.7. Found: C, 72.1; H, 6.9.

2-Phenyl-3,4-dihydro-2*H*-pyran (8l). Protocol d. **8l** (0.28 g, 87%) was obtained from **2l** (0.38 g, 2.0 mmol) after flash chromatography on silica. **Protocol e**. **8l** (0.25 g, 82%) was obtained from **2l** (0.35 g, 1.9 mmol) after flash chromatography on silica: ^{1}H NMR (400 MHz, C_6D_6) δ 1.70−1.80 (3 H), 1.94 (m, 1 H), 4.64 (m, 1 H), 4.70 (dd, *J* = 8.0, 4.5, 1 H), 6.57 (d, *J* = 5.8, 1 H), 7.11 (t, *J* = 7.3, 1 H), 7.19 (dd, *J* = 7.3, 7.3, 2 H), 7.29 (d, *J* = 7.3, 2 H); ^{13}C NMR (100 MHz, C_6D_6) δ 20.2 (2), 30.4 (2), 76.8 (1), 100.2 (1), 125.8 (1), 127.3 (1), 128.2 (1), 142.4 (0), 144.3 (1); IR (film, NaCl plates) ν 1059 (s), 1076 (s), 1241 (s), 1650 (s), 2847 (s), 2922 (s), 3060 (s) cm^{-1}; MS (EI) *m*/*z* 160 (16) [M$^+$], 131 (23), 104 (100). Anal. Calcd for $C_{11}H_{12}O$ (160.2): C, 82.5; H, 7.6. Found: C, 82.1; H, 7.7.

2-(2-Methoxynaphthalen-1-yl)-3,4-dihydro-2*H*-pyran (8m). Protocol d. A crude reaction mixture was obtained (0.23 g, 100%) from **2m** (0.27 g, 1.0 mmol) after 10 h in refluxing toluene, which contains **8m**, **7m**, and its isomer **13m** in a 10:4:1 ratio. **Protocol e**. **8m** (0.46 g, 80%) was obtained from **2m** (0.65 g, 2.4 mmol) after flash chromatography as a viscous oil, which solidifies upon standing at 0 °C. Mp 93 °C. **Protocol f**. **8m** (0.19 g, 79%) was obtained from **2m** (0.27 g, 1.0 mmol) after flash chromatography: ^{1}H NMR (500 MHz, C_6D_6) δ 1.82−1.93 (2 H), 2.24 (m, 1 H), 2.67 (ddd, *J* = 12.0, 12.0, 5.7, 1 H), 3.33 (s, 3 H), 4.77 (m, 1 H), 6.17 (dd, *J* = 12.0, 1.8, 1 H), 6.68 (d, *J* = 6.2, 1 H), 6.86 (d, *J* = 9.0, 1 H), 7.23 (dd, *J* = 7.7, 7.2, 1 H), 7.38 (dd, *J* = 8.2, 7.2, 1 H), 7.57 (d, *J* = 9.0, 1 H), 7.68 (d, *J* = 8.2, 1 H), 8.71 (d, *J* = 8.7, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 21.4 (2), 28.0 (2), 56.1 (3), 72.4 (1), 100.8 (1), 113.3 (1), 122.8 (0), 123.7 (1), 126.2 (1), 126.3 (1), 128.8 (1), 130.1 (1), 130.4 (0), 133.2 (0), 144.8 (1), 154.3 (0); IR (film, NaCl plates) ν 808 (s), 1051 (s), 1076 (s), 1242 (s), 1252 (s), 1649 (s) cm^{-1}; MS (EI) *m*/*z* 240 (30) [M$^+$], 184 (100). Anal. Calcd for $C_{16}H_{16}O_2$ (240.3): C, 80.0; H, 6.7. Found: C, 79.9; H 6.9.

2-Phenyl-3,4-dihydro-2*H*-pyran-2-carboxylic Acid Methyl Ester (8n). Protocol e. **8n** (0.32 g, 70%) was obtained from **2n** (0.52 g, 2.1 mmol) after flash chromatography on silica, followed by Kugelrohr distillation (0.25 mbar, 150 °C): ^{1}H NMR (500 MHz, C_6D_6) δ 1.70 (dm, *J* = 17.2, 1 H), 1.99 (ddd, *J* = 13.2, 9.7, 5.7, 1 H), 2.09 (m, 1 H), 2.65 (ddd, *J* = 13.0, 5.0, 4.5, 1 H), 3.23 (s, 3 H), 4.61 (m, 1 H), 6.56 (d, *J* = 6.2, 1 H), 7.07 (t, *J* = 7.5, 1 H), 7.18 (dd, *J* = 7.5, 7.5, 2 H), 7.72 (d, *J* = 7.5, 2 H); ^{13}C NMR (100 MHz, C_6D_6) δ 18.2 (2), 31.1 (2), 52.0 (3), 81.1 (0), 101.4 (1), 125.5 (1), 128.2 (1), 128.6 (1), 140.7 (1), 143.1 (0), 172.5 (0); IR (film, NaCl plates) ν 1073 (s), 1231 (s), 1274 (s), 1654 (s), 1732 (s), 1753 (s), 3062 (m) cm^{-1}; MS (EI) *m*/*z* 218 (30) [M$^+$], 159 (100), 103 (85). Anal. Calcd for $C_{13}H_{14}O_3$ (218.3): C, 71.5; H, 6.5. Found: C, 71.6; H, 6.8.

(2-Phenyl-3,4-dihydro-2*H*-pyran-2-yl)methanol (8o). Protocol d. No amount of **8o** was obtained from **2o** (0.45 g, 2.1 mmol), but **7o** was exclusively obtained as the primary metathesis product[43] (0.36 g, 90%). **Protocol e**. **8o** (0.23 g, 48%) and **10o** (0.05 g, 10%) were obtained from **2o** (0.55 g, 2.5 mmol) after chromatography on silica. **8o** was further purified by Kugelrohr distillation (0.25 mbar, 150 °C) and thus obtained as a colorless solid. Mp 72 °C. Analytical data for **8o**: ^{1}H NMR (500 MHz, C_6D_6) δ 1.55 (ddddd, *J* = 17.2, 11.5, 5.7, 2.2, 2.2, 1 H), 1.65 (dm, *J* = 17.2, 1 H), 1.76 (s br, 1 H), 1.91 (dd, *J* = 13.7, 4.5, 1 H), 2.14 (ddd, *J* = 13.7, 11.5, 5.7, 1 H), 3.50 (dd, *J* = 11.5, 8.0, 1 H), 3.60 (dd, *J* = 11.5, 2.0, 1 H), 4.50 (m, 1 H), 6.42 (d, *J* = 6.2, 1 H), 7.09 (t, *J* = 7.2, 1 H), 7.18 (dd, *J* = 7.7, 7.2, 2 H), 7.26 (d, *J* = 7.7, 2 H); ^{13}C NMR (100 MHz, C_6D_6) δ 17.4 (2), 27.0 (2), 70.4 (2), 81.0 (0), 101.3 (1), 125.9 (1), 127.3 (1), 128.5 (1), 142.0 (0), 142.5 (1); IR (film, NaCl plates) ν 696 (s), 757 (s), 1055 (s), 1080 (s), 1241 (s), 1447 (s), 1651 (s), 3261 (s) cm^{-1}; MS (EI) *m*/*z* 190 (10) [M$^+$], 159 (100). Anal. Calcd for $C_{12}H_{14}O_2$ (190.2): C, 75.8; H, 7.4. Found: C, 75.7; H, 7.4. Analytical data for (2-phenyltetrahydropyran-2-yl)methanol (**10o**): colorless solid; mp 68 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 1.38 (dm, *J* = 12.6, 1 H), 1.46 (dddd, *J* = 12.6, 12.6, 3.8, 3.8, 1 H), 1.61 (dddd, *J* = 12.0, 12.0, 4.3, 4.3, 1 H), 1.68 (dm, *J* = 12.0, 1 H), 2.05 (ddd, *J* = 14.3, 13.1, 3.8, 1 H), 2.20 (dm, *J* = 14.3, 1 H), 2.27 (s br, 1 H), 3.35 (d, *J* = 11.3, 1 H), 3.48 (d, *J* = 11.3, 1 H), 3.51 (ddd, *J* = 11.8, 11.8, 2.5, 1 H), 3.74 (dm, *J* = 11.8, 1 H), 7.22−7.42 (5 H); ^{13}C NMR (100 MHz, C_6D_6) δ 19.4 (2), 25.9 (2), 28.1 (2), 62.8 (2), 72.0 (2), 79.1 (0), 127.0 (1), 127.2 (1), 128.5 (1), 140.5 (0); IR (film, NaCl plates) ν 1041 (s), 1082 (s), 1446 (s), 2941 (s), 3442 (s) cm^{-1}; MS (EI) *m*/*z* [M$^+$] not observed, 161 (100), 105 (98). Anal. Calcd for $C_{12}H_{16}O_2$ (192.3): C, 75.0; H, 8.4. Found: C, 74.7; H, 8.6.

2-Methoxymethyl-2-phenyl-3,4-dihydro-2*H*-pyran (8p). Protocol d. **8p** (0.30 g, 80%) was obtained from **2p** (0.45 g, 1.9 mmol) after flash chromatography on silica. **Protocol e**. **8p** (0.31 g, 76%) was obtained from **2p** (0.46 g, 2.0 mmol) after flash chromatography on silica, followed by Kugelrohr distillation (0.15 mbar, 150 °C). **Protocol f**. **8p** (0.09 g, 74%) was obtained from **2p** (0.13 g, 0.6 mmol) after flash chromatography on silica: ^{1}H NMR (400 MHz, C_6D_6) δ 1.62 (ddm, *J* = 17.2, 10.5, 1 H), 1.74 (dm, *J* = 17.2, 1 H), 2.09 (ddd, *J* = 13.7, 4.7, 4.5, 1 H), 2.25 (ddd, *J* = 13.7, 10.5, 5.5, 1 H), 3.08 (s, 3 H), 3.39 (d, *J* = 10.0, 1 H), 3.48 (d, *J* = 10.0, 1 H), 4.52 (m, 1 H), 6.49 (d, *J* = 6.2, 1 H), 7.12 (t, *J* = 7.5, 1 H), 7.22 (dd, *J* = 7.5, 7.5, 2 H), 7.46 (d, *J* = 7.5, 2 H); ^{13}C NMR (100 MHz, C_6D_6) δ 17.5 (2), 27.8 (2), 59.2 (3), 79.7 (2), 80.3 (0), 100.8 (1), 126.2 (1), 127.3 (1), 128.3 (1), 142.7 (1), 142.9 (0); IR (film, NaCl plates) ν 1065 (s), 1109 (s), 1246 (s), 1652 (s), 2924 (s) cm^{-1}; MS (EI) *m*/*z* 204 (10) [M$^+$], 159 (100). Anal. Calcd for $C_{13}H_{16}O_2$ (204.3): C, 76.4; H, 7.9. Found: C, 76.9; H, 7.9.

(2*R,3*R**)-2-Phenyl-3,4-dihydro-2*H*-pyran-3-ol (8q). Protocol e**. **8q** (0.12 g, 40%) was obtained from **2q** (0.34 g, 1.7 mmol) after flash chromatography on silica. The isomerization step must be carefully monitored by TLC and stopped when tetrahydropyran **10q** is detected. Following the same protocol, we obtained tetrahydropyran **10q** (0.13 g, 46%) from **2q** (0.32 g, 1.6 mmol) by heating the reaction mixture until **8q** was completely consumed. Analytical data for **8q**: ^{1}H NMR (400 MHz, C_6D_6) δ 1.59 (s br, 1 H), 1.90 (dm, *J* = 17.3, 1 H), 2.07 (dm, *J* = 17.3, 1 H), 3.78 (s br, 1 H), 4.49 (m, 1 H), 4.56 (s br, 1 H), 6.43 (d, *J* = 6.0, 1 H), 7.12 (t, *J* = 7.5, 1 H), 7.20 (dd, *J* = 7.5, 7.5, 2 H), 7.33 (d, *J* = 7.5, 2 H); ^{13}C NMR (100 MHz, C_6D_6) δ 29.4 (2), 66.9 (1), 78.4 (1), 98.1 (1), 126.7 (1), 127.8 (1), 128.4 (1), 139.3 (0), 144.0 (1); IR (film, NaCl plates) ν 701 (s), 734 (s), 1071 (s), 1239 (s), 1652 (s), 2923 (s), 3416 (s) cm^{-1}; MS (EI) *m*/*z* 176 (6) [M$^+$], 120 (100), 91 (77). Anal. Calcd for $C_{11}H_{12}O_2$ (176.2): C, 75.0; H, 6.9. Found: C, 75.0; H, 7.3. Analytical data for (2*R**,3*R**)-2-phenyltetrahydropyran-3-ol (**10q**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (m, 1 H), 1.72 (s br, 1 H), 1.88 (m, 1 H), 2.05−2.15 (2 H), 3.65 (ddd, *J* = 12.2, 10.5, 2.0, 1 H), 3.92 (s br, 1 H), 4.19 (dd, *J* = 10.5, 3.0, 1 H), 4.50 (s br, 1 H), 7.20−7.45 (5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8 (2), 30.1 (2), 67.9 (1), 68.9 (2), 81.1 (1), 125.7 (1), 127.4 (1), 128.4 (1), 139.5 (0); IR (film, NaCl plates) ν 731 (s), 1091 (s), 1451 (s), 2927 (s), 3432 (s) cm^{-1}; MS (EI) *m*/*z* 178 (39) [M$^+$], 107 (100), 79 (61).

(2*R,3*R**)-*tert*-Butyldimethyl(2-phenyl-3,4-dihydro-2*H*-pyran-3-yloxy)silane (8r). Protocol d**. **8r** (0.20 g, 87%) was obtained from **2r** (0.25 g, 0.8 mmol) after flash chromatography on silica. **Protocol e**. **8r** (0.27 g, 84%) was obtained from **2r** (0.36 g, 1.1 mmol) after flash chromatography on silica: ^{1}H NMR (400 MHz, C_6D_6) δ −0.40 (s, 3 H, −Si(CH$_3$)$_2$), −0.18 (s, 3 H, −Si(CH$_3$)$_2$), 0.88 (s, 9 H, −C(CH$_3$)$_3$), 1.90 (dm, *J* = 17.0, 1 H, H4), 2.17 (dm, *J* = 17.0, 1 H, H4′), 3.87 (s br, 1 H, H3), 4.55 (m, 1 H, H5), 4.70 (s br, 1 H, H2), 6.56 (d, *J* = 6.0, 1 H, H6), 7.12 (t, *J* = 7.5, 1 H, −Ph), 7.22 (dd, *J* = 7.5, 7.5, 2 H, −Ph), 7.41 (d, *J* = 7.5, 2 H, −Ph); ^{13}C NMR (100 MHz, C_6D_6) δ −5.4 (3), −5.1 (3), 18.2 (0), 25.9 (3), 29.8 (2), 68.3 (1), 78.9 (1), 97.2 (1), 127.2 (1), 127.5 (1), 127.8 (1), 139.1 (0), 144.1 (1); IR (film, NaCl plates) ν 836 (s), 1074 (s), 1103 (s), 1241 (s), 1657 (s), 2856 (s), 2928 (s), 2955 (s) cm^{-1}; MS (EI) *m*/*z* [M+]

not observed, 233 (90), 177 (90), 91 (100). Anal. Calcd for $C_{17}H_{26}O_2Si$ (290.5): C, 70.3; H, 9.0. Found: C, 70.5; H, 9.1.

3-Ethyl-2-phenyl-3,4-dihydro-2*H*-pyran-3-ol (8s). Protocol d. No **8s** was obtained from **2s** (0.23 g, 1.0 mmol), but **7s** was obtained exclusively as the primary metathesis product[45] (0.17 g, 84%). **Protocol e**. **8s** (0.27 g, 66%) was obtained from **2s** (0.46 g, 2.0 mmol) as a 4:1 mixture of diastereoisomers after flash chromatography on silica. A higher catalyst loading (131 mg, 8 mol % $[RuCl_2(PCy_3)_2{=}CHPh]$) was required for this example. NMR data of the major isomer: ^{1}H NMR (600 MHz, C_6D_6) δ 0.75 (t, J = 7.3, 1 H, $-CH_3$), 1.00 (dq, J = 13.9, 7.3, 1 H, $-CH_2CH_3$), 1.18 (dq, J = 13.9, 7.3, 1 H, $-CH_2CH_3$), 1.82 (dd, J = 17.2, 4.8, 1 H, H4), 1.90 (dm, J = 17.2, 1 H, $-CH_2CH_3$), 4.37 (s, 1 H, H2), 4.54 (ddd, J = 5.9, 4.8, 2.6, 1 H, H5), 6.44 (d, J = 5.9, 1 H, H6), 7.10−7.21 (3 H, −Ph), 7.39 (d, J = 7.5, 2 H, −Ph); ^{13}C NMR (150 MHz, C_6D_6) δ 6.7 (3), 30.6 (2), 32.6 (2), 69.7 (0), 83.3 (1), 98.8 (1), 128.0 (1), 128.2 (1), 128.9 (1), 137.6 (0), 144.1 (1). NMR data of the minor isomer: ^{1}H NMR (600 MHz, C_6D_6) δ 0.74 (t, J = 7.5, 1 H, $-CH_3$), 1.10 (dq, J = 14.3, 7.5, 1 H, $-CH_2CH_3$), 1.50 (dq, J = 14.3, 7.5, 1 H, $-CH_2CH_3$), 2.01 (d, J = 16.9, 1 H, H4), 2.09 (dd, J = 16.9, 3.3, 1 H, $-CH_2CH_3$), 4.51 (m, 1 H, H5), 4.79 (s, 1 H, H2), 6.38 (d, J = 6.2, 1 H, H6), 7.10−7.21 (3 H, −Ph), 7.41 (d, J = 7.3, 2 H, −Ph); ^{13}C NMR (150 MHz, C_6D_6) δ 6.7 (3), 25.7 (2), 30.4 (2), 70.0 (0), 84.5 (1), 98.8 (1), 128.0 (1), 128.1 (1), 128.3 (1), 138.1 (0), 143.5 (1); IR (film, NaCl plates) ν 1071 (s), 1240 (s), 1652 (s), 2939 (s), 2970 (s), 3536 (s) cm^{-1}; MS (EI) m/z 204 (4) [M$^+$], 148 (30), 98 (100). Anal. Calcd for $C_{13}H_{16}O_2$ (204.3): C, 76.4; H, 7.9. Found: C, 76.4; H, 8.0.

2-Benzyloxymethyl-3,4-dihydro-2*H*-pyran (8t). Protocol d. **8t** (0.18 g, 87%) was obtained from **2t** (0.23 g, 1.0 mmol) after Kugelrohr distillation (0.2 mbar, 150 °C). **Protocol e**. **8t** (0.39 g, 91%) was obtained from **2t** (0.49 g, 2.1 mmol) after Kugelrohr distillation (0.2 mbar, 150 °C): ^{1}H NMR (500 MHz, C_6D_6) δ 1.58−1.65 (2 H), 1.73 (m, 1 H), 1.85 (m, 1 H), 3.38 (dd, J = 10.0, 5.2, 1 H), 3.51 (dd, J = 10.0, 5.5, 1 H), 3.96 (m, 1 H), 4.36 (s, 2 H), 4.56 (m, 1 H), 6.44 (d, J = 6.2, 1 H), 7.11 (t, J = 7.5, 1 H), 7.18 (dd, J = 7.5, 7.5, 2 H), 7.29 (d, J = 7.5, 2 H); ^{13}C NMR (125 MHz, C_6D_6) δ 19.6 (2), 25.0 (2), 72.7 (2), 73.4 (2), 74.4 (1), 100.3 (1), 127.6 (1), 128.5 (1), 139.1 (0), 144.1 (1); IR (film, NaCl plates) ν 698 (s), 734 (s), 1071 (s), 1100 (s), 1241 (s), 1650 (s), 2853 (s), 2922 (s), 3061 (s) cm^{-1}; MS (EI) m/z 204 (6) [M$^+$], 113 (58), 91 (100). Anal. Calcd for $C_{13}H_{16}O_2$ (204.3): C, 76.4; H, 7.9. Found: C, 76.7; H, 8.3.

2-(4-Methoxyphenyl)-2,3,4,5-tetrahydrooxepine (8u). Protocol d. **8u** (0.09 g, 44%) was obtained from **2u** (0.23 g, 1.0 mmol) after flash chromatography on silica. **Protocol e**. **8u** (0.21 g, 51%) was obtained from **2u** (0.47 g, 2.0 mmol) after flash chromatography on silica: ^{1}H NMR (500 MHz, C_6D_6) δ 1.39 (m, 1 H), 1.78−2.01 (4 H), 2.11 (m, 1 H), 3.33 (s, 3 H), 4.72−4.78 (2 H), 6.50 (dd, J = 7.0, 1.0, 1 H), 6.82 (d, J = 8.5, 1 H), 7.28 (d, J = 8.5, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 26.1 (2), 26.2 (2), 39.4 (2), 54.7 (3), 84.2 (1), 109.7 (1), 113.9 (1), 127.3 (1), 136.1 (0), 148.0 (1), 159.4 (0); IR (film, NaCl plates) ν 1248 (s), 1514 (s), 1613 (s), 1649 (s), 2930 (s) cm^{-1}; MS (EI) m/z 204 (48) [M$^+$], 147 (100). Anal. Calcd for $C_{13}H_{16}O_2$ (204.3): C, 76.4; H, 7.9. Found: C, 76.5; H, 8.0.

(2*R,3*R**)-*tert*-Butyldimethyl(2-phenyl-2,3,4,5-tetrahydrooxepin-3-yloxy)silane (8w). Protocol d**. **8w** (0.18 g, 82%) was obtained from **2w** (0.22 g, 0.7 mmol) after flash chromatography on silica. **Protocol e**. **8w** (0.18 g, 74%) was obtained from **2w** (0.26 g, 0.8 mmol) after flash chromatography on silica: ^{1}H NMR (500 MHz, C_6D_6) δ −0.49 (s, 3 H, $-Si(CH_3)_2$), −0.21 (s, 3 H, $-Si(CH_3)_2$), 0.86 (s, 9 H, $-C(CH_3)_3$), 1.81 (dddd, J = 13.5, 8.5, 5.7, 2.0, 1 H, H4), 2.00 (ddm, J = 16.7, 10.5, 1 H, H3), 2.09 (m, 1 H, H3′), 2.12 (dddd, J = 13.5, 10.2, 7.7, 2.5, 1 H, H4′), 3.91 (ddd, J = 7.5, 5.5, 2.0, 1 H, H3), 4.68 (ddd, J = 6.2, 6.2, 4.2, 1 H, H6), 4.91 (s br, 1 H, H2), 6.46 (dd, J = 6.2, 1 H, H7), 7.10 (t, J = 7.5, 1 H, −Ph), 7.20 (dd, J = 7.5, 7.5, 1 H, −Ph), 7.35 (d, J = 7.5, 1 H, −Ph); ^{13}C NMR (125 MHz, C_6D_6) δ −5.6 (3), −4.8 (3), 18.2 (2), 21.7 (0), 26.0 (3), 35.5 (2), 75.7 (1), 86.7 (1), 108.9 (1), 127.2 (1), 127.9 (1), 128.1 (1), 140.7 (0), 149.0 (1); IR (film, NaCl plates) ν 836 (s), 1099 (s), 1254 (s), 1649 (s), 2929 (s), 2952 (s) cm^{-1}; MS (EI) m/z [M$^+$] not observed, 247 (75), 191 (100), 155 (75). Anal. Calcd for $C_{18}H_{28}O_2Si$ (304.5): C, 71.0; H, 9.3. Found: C, 71.4; H, 9.3.

Triethyl(2-phenyl-3,4-dihydro-2*H*-pyran-2-ylmethoxy)-silane (8x). Protocol f. **8x** (0.51 g, 84%) was obtained from **2o** (0.44 g, 2.0 mmol) after Kugelrohr distillation (0.30 mbar, 175 °C). When the reaction was monitored by TLC [hexane/MTBE, 10:1 (v/v)], it was revealed that after addition of triethylsilane and after the mixture had been heated to reflux within 1 h silylation of the hydroxy group occurs and then (within 8 h) isomerization to **8x**: ^{1}H NMR (500 MHz, C_6D_6) δ 0.52−0.60 (6 H), 0.96 (t, J = 8.0, 9 H), 1.65 (ddm, J = 17.0, 11.2, 1 H), 1.76 (dm, J = 17.0, 1 H), 2.15 (dm, J = 13.7, 1 H), 2.26 (ddd, J = 13.7, 11.2, 5.7, 1 H), 3.69 (d, J = 10.5, 1 H), 3.82 (d, J = 10.5, 1 H), 4.53 (m, 1 H), 6.49 (d, J = 6.0, 1 H), 7.12 (t, J = 7.5, 1 H), 7.22 (dd, J = 7.5, 7.5, 2 H), 7.45 (d, J = 7.5, 2 H); ^{13}C NMR (100 MHz, C_6D_6) δ 4.8 (2), 7.0 (3), 17.6 (2), 27.2 (2), 70.8 (2), 80.6 (0), 100.9 (1), 126.3 (1), 127.3 (1), 128.3 (1), 142.7 (0), 142.8 (1); IR (film, NaCl plates) ν 698 (s), 727 (s), 1066 (s), 1121 (s), 1246 (s), 1652 (s), 2876 (s), 2913 (s), 2954 (s) cm^{-1}; MS (EI) m/z 304 (2) [M$^+$], 275 (20), 219 (30), 159 (100). Anal. Calcd for $C_{18}H_{28}O_2Si$ (304.5): C, 71.0; H, 9.3. Found: C, 71.3; H, 9.5.

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Supporting Information Available: Experimental procedures and analytical data for compounds **1**, **2**, and **7**. Experimental procedures and analytical data for the control experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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