

Ru-Catalyzed Rearrangement of Styrenyl Ethers. Enantioselective Synthesis of Chromenes through Zr- and Ru-Catalyzed Processes

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The present studies arose from our interest in the enantioselective synthesis of 2-substituted chromenes,¹ a structural unit found within a myriad of medically important agents.² In this context, extensive efforts by us to use the Zr-catalyzed kinetic resolution of unsaturated pyrans³ to obtain nonracemic chromenes led to uncharacteristically low levels of selectivity (~10% ee at 60% conversion). Alternatively, as shown in Scheme 1, we envisioned that styrenyl allylic ethers, possess alkenes with appropriate electronic attributes⁴ so that, with the Grubbs metathesis catalyst (PCy₃)₂Cl₂Ru=CHCH=CPh₂ (**3**),⁵ they might undergo a net skeletal rearrangement to yield the desired isomeric heterocyclic products.⁶ Importantly, rearrangement substrates would be synthesized in the nonracemic form by the Zr-catalyzed kinetic resolution.⁷

Previous reports suggest that Ru-catalyzed ring-closing metatheses can be influenced by thermodynamic factors;⁸ we thus selected **4** as our initial case study. We surmised that strain energy of the seven-membered ring would serve as the driving force for the formation of the less-strained chromene. When **4** is treated with 5 mol % of **3**, as shown in entry 1 of Table 1, **5** is obtained in 44% yield. In addition, dimer **6** is isolated in 56% yield (mixture of alkene isomers). Products from independent rupture of the cycloheptene, or any of the derived dimeric adducts, were not detected. Under more dilute conditions (entry 2), **5** becomes the major product, albeit the reaction proceeds less readily and with low monomer/dimer selectivity. When the Ru-catalyzed rearrangement is carried out under ethylene atmosphere, monomeric **5** is obtained in 92% yield.

A plausible mechanism for the Ru-catalyzed rearrangement is presented (Scheme 2). Reaction of **4** with **3** delivers **7**, which is cleaved to provide **8**. Subsequent intramolecular addition affords **9**, which rearranges to chromene-containing **10**, reaction of which with a second equivalent of **4** yields **5** and regenerates **8**. Additionally, as increasing amounts of **5** are produced, **10** may react with **5** to afford **6**. With ethylene present (entry 3, Table 1), less dimer is formed, likely because the olefinic additive competitively reacts with **10** to produce **5** and L_n-

Scheme 1

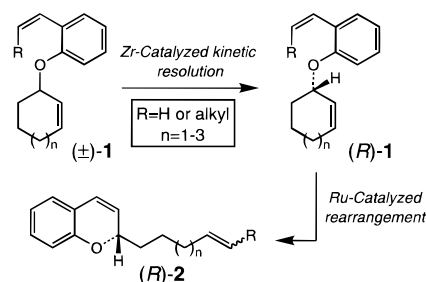


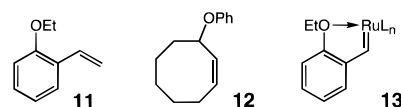
Table 1. Ru-Catalyzed Rearrangement of the Styrenyl Ether of 1-Cyclohepten-2-ol

entry	[4], M	conditions ^a	yield (5 : 6 , %) ^b
1	0.1	A	44;56
2	0.05	A	50;29
3	0.1	B	92;<2

^a Conditions: (A) 5 mol % of **3**, CH₂Cl₂, 22 °C, Ar atmosphere, 10–14 h; (B) same as A, except under 1 atm of C₂H₄. ^b Isolated yields.

Ru=CH₂. This modification is perhaps effective since larger amounts of the external alkene are present, leading to the formation of the more reactive (toward styrenyl ether) L_nRu=CH₂.⁹

The catalytic cycle may also commence with reaction of **3** with the carbocyclic olefin. Several observations, however, imply that terminal alkene of styrene reacts first. For example, the intermolecular variant (cross-metathesis)¹⁰ of this process is inoperative; treatment of an equimolar mixture of **11** and **12** with 5 mol% **3** leads to <2% reaction. Without **11**, under



otherwise identical conditions, large amounts of oligomeric products are isolated.¹¹ These observations imply that **11** effectively competes with allylic ether **12** for the active Ru complex. It is tenable that chelated complex **13** sequesters the active Ru system to inhibit oligomerization of **12**.¹²

As illustrated in Table 2, styrenyl ethers derived from 1-cyclohepten-2-ol and 1-cycloocten-2-ol, which are of diverse electronic properties, undergo efficient rearrangement to afford the derived chromene system in excellent yield. The electronic properties of the aromatic moiety do not have a significant influence on the reactivity of the diene substrates. In all cases,

(9) If any dimeric product (e.g., **6**) is formed, L_nRu=CH₂ can reconvert it to its corresponding monomer. Treatment of **6** with 5 mol % of **3** (ethylene atmosphere, 12 h) leads to an equal mixture of **5** and **6** (400 MHz ¹H NMR).

(10) (a) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162–5163. (b) Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610–9611. (c) Schneider, M. F.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 411–412. (d) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1979–1980.

(11) Hillmyer, M. A.; Laredo, W. R.; Grubbs, R. H. *Organometallics* **1995**, *28*, 6311–6316.

(12) Complex **13** may suffer lower reactivity for electronic reasons as well (Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110). For related observations in connection to the influence of internal chelation on metal–carbene reactivity, see: (a) Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260–2265. (b) Reference 5a.

(1) The Mn-catalyzed kinetic resolution of 2,2-disubstituted chromenes was recently reported (Vander Velde, S. L.; Jacobsen, E. N. *J. Org. Chem.* **1995**, *60*, 5380–5381). One instance of resolution of a 2-substituted chromene was reported; the low level of selectivity observed (*k*_{rel} = 2.7) was attributed to “competitive decomposition pathways”.

(2) Van Lommen, G.; De Bruyn, M.; Schroyen, M. *J. Pharm. Belg.* **1990**, *45*, 355–360 and references cited therein.

(3) (a) Morken, J. P.; Didiuk, M. T.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1994**, *116*, 3123–3124. (b) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291–4298.

(4) Crowe, W. E.; Zhang, Z. *J. Am. Chem. Soc.* **1993**, *115*, 10998–10999.

(5) (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324–7325. (b) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634–6640 and references cited therein. (c) Bazan, G. C.; Schrock, R. R.; Cho, H.-N.; Gibson, V. C. *Macromolecules* **1991**, *24*, 4495–4502.

(6) Unlike what is typically observed with Ru-catalyzed ring-closing metatheses (ref 5a,b), the products of reactions reported herein are isomers of the starting materials; the Ru-catalyzed reactions thus constitute a rearrangement.

(7) Visser, M. S.; Harrity, J. P. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 3779–3780. For a recent review, see: Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262–1284.

(8) Miller, S. J.; Kim, S.; Chen, Z.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108–2109.

Scheme 2

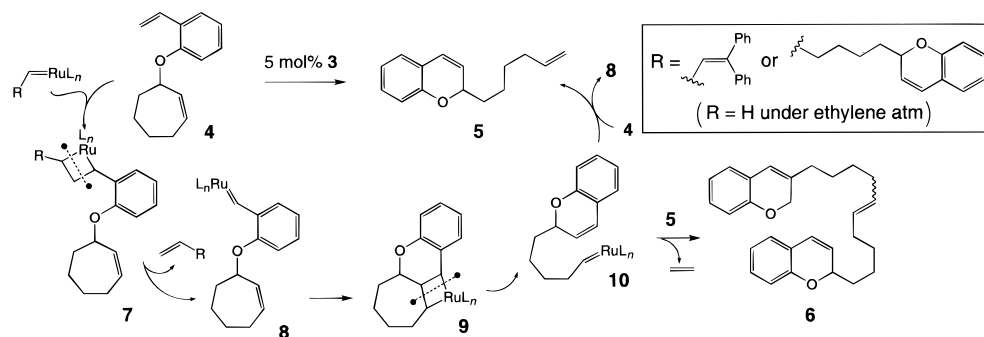


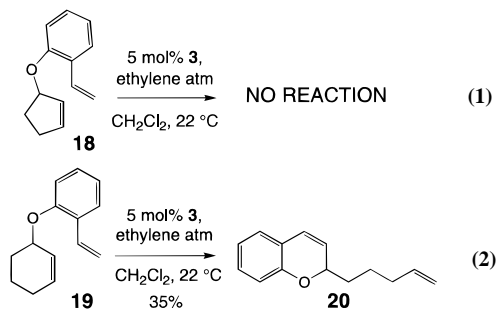
Table 2. Ru-Catalyzed Rearrangements of Seven- and Eight-Membered Ring Styrenyl Ethers^a

entry	substrate	product	R	conditions	yield ^b mono-;dimer (%)
1			a OMe b F	A B	68 ; 23 100 ; 0
2			a H b NO ₂	B B	86 ; <2 90 ; <2 84 ; <2

^a For conditions A and B, see the legend for Table 1. ^b Isolated yields.

the rearranged monomer is obtained in high efficiency with little or no formation of the corresponding dimer.

In contrast to seven- and eight-membered rings, under identical conditions, cyclopentenyl styrenyl ether (**18**) does not provide any reaction products after 16 h (eq 1).¹³ Ru-catalyzed



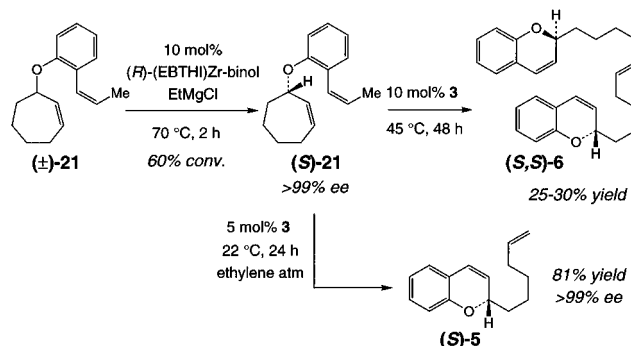
rearrangement of **19** proceeds less efficiently than the larger ring **4** and **16a** to afford **20** in 35% yield (ethylene atmosphere; 65% recovered **19**, <2% dimer).¹⁴ Elevated temperatures and prolonged reaction times (10 mol % of **3**, 48 h, 45 °C, Ar atmosphere) lead to exclusive formation of the derived dimer in 92% isolated yield. With regard to the lower reactivity of smaller rings, it is possible that the reduction in reactivity for the five- and six-membered ring systems may be due to the higher degree of angle strain present in the metallacycle intermediates represented by **9** in Scheme 2.

As was mentioned before, an attractive feature of the Ru-catalyzed process is that racemic allylic ether substrates can be catalytically resolved. The Zr-catalyzed kinetic resolution of styrenyl systems described above is inefficient, however, due

(13) Since the strain energy of cyclopentene and cycloheptene are nearly identical (Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 2377–2386), release of strain provided by cleavage of the carbocycle is likely not the only critical factor.

(14) Treatment of the dimer from **20** with 5 mol % of **3** under ethylene atmosphere (15 h) leads to a 2:1 mixture of **20**/dimer; there is <2% of **19** (400 MHz ¹H NMR). Subjection of **20** to 5 mol % of **3** (Ar atm) affords 1:10 ratio of **20**/dimer; under ethylene atmosphere, a 1:1 mixture of **20**/dimer is obtained. These results indicate that the activation barrier for reversion of **20** to **19** is likely higher than that for dimerization of the former.

Scheme 3



to competitive and nonselective alkylation of the resident terminal olefin. Hence, we turned our attention to cyclic allylic ethers that bear substituted styrenes. As shown in Scheme 3, β -methylstyrenyl ether **21** is resolved effectively by the Zr-catalyzed protocol (98% yield based on percent conversion). The latter plan proved undesirable, however, because (1) the Ru-catalyzed reaction of β -methyl styrene system is inefficient (~20–45% yield) and (2) since the rearrangement only proceeds under more forcing conditions, it exclusively affords chromene dimer (*S,S*)-**6**. This difficulty is easily overcome when the optically pure substrate (e.g., (*S*)-**21**) is subjected to the catalytic rearrangement conditions (22 °C, 24 h) under ethylene atmosphere; (*S*)-**5** is obtained readily in 81% yield (after chromatography).¹⁵ It is not clear at present whether ruthenium–carbene complex (*S*)-**8** (Scheme 2) is directly generated and subsequently converted to (*S*)-**5**, or if styrenyl ether (*S*)-**4** is formed first (cross-metathesis)¹⁰ and then proceeds through (*S*)-**8** to give the chiral heterocycle (both intermediates may be involved as well). With the less reactive disubstituted styrene **21**, the cycloalkene site may be where reaction is initiated. If so, rearrangement under ethylene could be more effective because the more reactive $L_nRu=CH_2$ (vs $L_nRu=CH(CH_3)$) is then responsible for initiating a new catalytic cycle; these and other mechanistic details are under scrutiny.

We have demonstrated that a Zr-catalyzed kinetic resolution can be followed by a Ru-catalyzed rearrangement to deliver 2-substituted chromene systems efficiently and with outstanding enantiopurity. The application of the tandem catalytic resolution/rearrangement to the enantioselective synthesis of biologically important agents will be the subject of future disclosures from these laboratories.

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Supporting Information Available: Experimental procedures and spectral and analytical data for all reaction products (27 pages). See any current masthead page for ordering and Internet access instructions. JA9636597

(15) In addition, 10% of the dimer **6** was isolated.