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Tandem Catalysis: The Sequential Mediation of Olefin Metathesis, Hydrogenation, and Hydrogen Transfer with Single-Component Ru Complexes

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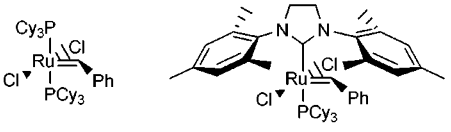
Organometallic catalysts are traditionally designed and optimized to mediate a single reaction.[1] However, the increasing demand for expedient and efficient synthetic processes requires the development of organometallic reagents that are capable of catalyzing multiple, mechanistically distinct reactions directly or by simple modification. While the Ru complex $(PCy_3)_2Cl_2Ru{=}CHPh$ (**1**)[2] has found extensive use in olefin metathesis,[3] it was also recently shown to be an effective precatalyst for mediating radical additions[4] and hydrogenation reactions.[5] We recently demonstrated all three reactions could be performed in tandem to afford well-defined block copolymers.[6] Herein, we report that complex **1**, or its more active derivative **2**,[7] is also useful in mediating a variety of other catalytic hydrogenation reactions that include regiospecific ketone and olefin reductions, transfer hydrogenations of ketones, and dehydrogenative oxidations of alcohols. In addition, we demonstrate a variety of "one-pot" tandem metathesis−hydrogenation procedures for the rapid construction of small molecules, including (*R*)-(−)-Muscone.



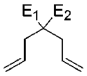
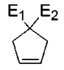
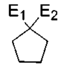
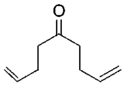
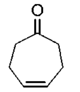
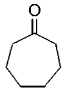
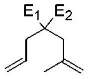
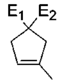
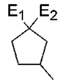
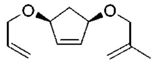
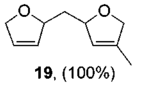
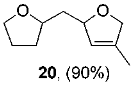
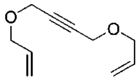
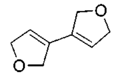
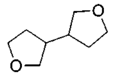
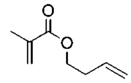
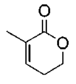
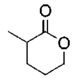
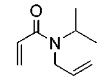
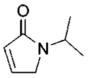
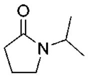
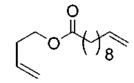
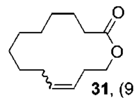
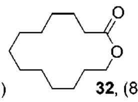
1 **2**

Figure 1. First and second generation ruthenium alkylidenes.

Addition of H_2 (1 atm, 25 °C) to complex **1** quantitatively afforded the hydride complex $RuHCl(H_2)(PCy_3)_2$,[8] an effective hydrogenation catalyst.[5,6] The same Ru hydride complex was observed upon the introduction of H_2 following a ring-closing metathesis (RCM) or cross-metathesis (CM) reaction. Thus, as shown in Tables 1 and 2, excellent yields of various saturated products were obtained by using a convenient, "one-pot" tandem catalysis protocol.[9] Upon the conclusion of the metathesis reaction (performed at 40 °C), the reaction vessel was simply pressured with hydrogen and then heated to 70 °C. The order of olefin reactivity appeared to follow the general trend cis > trans > conjugated > trisubstituted, and permitted the regioselective hydrogenation of substrate **19** (Table 1, entry 4). In some cases (Table 1, entries 2 and 8), higher pressures were employed to achieve acceptable reaction rates under the relatively dilute conditions necessary for the olefin metathesis reaction. Importantly, the Ru catalyst tolerated a wide range of functional groups without any noticeable loss in activity. In addition, the catalyst did not facilitate the hydrodehalogenation of aryl halides (Table 2, entry 4), which is a common drawback of many hydrogenation procedures. Overall, this "one pot", tandem Ru-catalyzed metathesis−hydrogenation approach is much more convenient than standard procedures where Pd/C or Rh hydrogenation catalysts are used after the olefin metathesis product has been isolated.[10]

Noyori has developed powerful diamine-coordinated Ru complexes for the regioselective hydrogenation of ketones in the presence of olefins.[11] Similarly, we found that complexes **1** or **2**

Table 1. Tandem RCM−Hydrogenation Reactions Catalyzed by **1** or **2**[a]

Entry	Substrates	Metathesis Product (% Conversion)[b]	Tandem Product (% Yield)[c]	Ru cat.	H_2
1					
a	**3**, $E_1{=}E_2{=}CO_2Et$	**4**, (100%)	**5**, (95%)	**1**	1 atm
b	**6**, $E_1{=}E_2{=}O$	**7**, (100%)	**8**, (100%)[b]	**1**	1 atm
c	**9**, $E_1{=}OH$, $E_2{=}H$	**10**, (100%)	**11**, (100%)[b]	**2**	1 atm
2[d]	 **12**	 **13**, (93)%	 **14**, (80%)	**2**	100 psi
3	 **15**, $E_1{=}E_2{=}CO_2Et$	 **16**, (90%)	 **17**, (70%)[b]	**1**	1000 psi[e]
4	 **18**	 **19**, (100%)	 **20**, (90%)	**2**	1 atm
5	 **21**	 **22**, (100%)	 **23**, (93%)	**1**	1000 psi[e]
6	 **24**	 **25**, (75%)	 **26**, (64%)	**2**	100 psi
7	 **27**	 **28**, (90%)	 **29**, (85%)	**2**	100 psi
8[d]	 **30**	 **31**, (90%)	 **32**, (84%)	**1**	600 psi

[a] Reactions conditions: 3−5 mol % catalyst **1** or **2**, 40 °C (metathesis) and 70 °C (hydrogenation), 0.1 M substrate in $ClCH_2CH_2Cl$. [b] Determined by GC. [c] Isolated yield based on starting substrate. [d] Reaction was performed under dilute conditions (see Supporting Information). [e] Hydrogenation was conducted at 100 °C.

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(3) For reviews on olefin metathesis see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, 20377. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(4) Simal, F.; Demonceau, A.; Noels, A. F. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 538.

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(6) Bielawski, C. W.; Louie, J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 12872.

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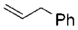
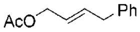
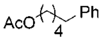
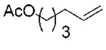
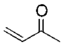
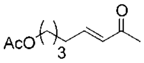
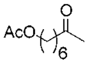
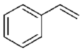
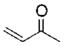
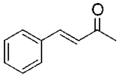
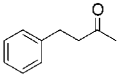
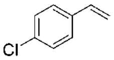
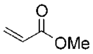
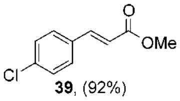
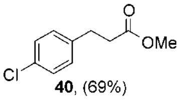
(8) (a) Wilhelm, T. E.; Belderrain, T. R.; Brown, S. N.; Grubbs, R. H. *Organometallics* **1997**, *18*, 33867. (b) Oliván, M.; Caulton, K. G. *Inorg. Chem.* **1999**, *38*, 566. (c) For an excellent mechanistic analysis of this reaction, see: Drouin, S. D.; Yap, G. P. A.; Fogg, D. E. *Inorg. Chem.* **2000**, *39*, 5412.

(9) Under relatively low pressures of H_2, chlorinated solvents (CH_2Cl_2 or $ClCH_2CH_2Cl$) appeared to be critical for successful hydrogenation as only isomerization was observed in aromatic solvents.

10.1021/ja016431e CCC: $20.00

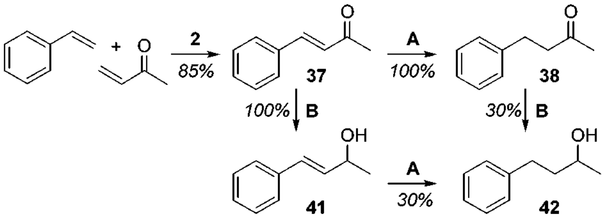
Table 2. Tandem CM−Hydrogenation Reactions Catalyzed by **1** or **2**[a]

Entry	Substrates		Metathesis Product (% Conversion)[b]	Tandem Product (% Yield)[c]
1			 **33**, (90%)	 **34**, (82%)
2			 **35**, (85%)	 **36**, (77%)
3			 **37**, (85%)	 **38**, (80%)
4			 **39**, (92%)	 **40**, (69%)

[a] Reaction conditions: 3 mol % catalyst **1** or **2**, 40 °C (metathesis) and 70 °C (hydrogenation, 100 psi H_2), 0.1 M substrate in $ClCH_2CH_2Cl$. [b] Determined by GC. [c] Isolated yield based on starting substrate.

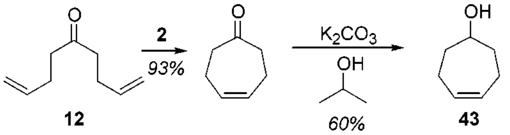
were also excellent catalysts for regiospecific ketone reductions upon the addition of ethylenediamine.[12] Thus, as shown in Scheme 1, the "one-pot" tandem metathesis−hydrogenation procedure was extended to include regiospecific ketone reductions. Following the CM of styrene with methyl vinyl ketone, the addition of ethylenediamine (1.1 equiv/Ru), NaOH (5 equiv/Ru), and H_2 (1 atm, balloon) quantitatively afforded the corresponding allyl alcohol **41** after 12 h (25 °C). No trace of olefin saturation was observed. Alternatively, reduction of both the olefin and the ketone was obtained by applying these conditions after the tandem CM−hydrogenation procedure described above to afford the secondary alcohol **42** in moderate yield (30%).[13]

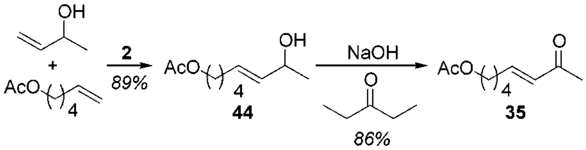
Scheme 1. Tandem Ru-Catalyzed Reactions[a]



[a] See Table 2 for the synthesis of **37**. Method A: H_2 (100 psi), 70 °C, 10 h. Method B: $H_2N(CH_2)_2NH_2$ (1.1 equiv/Ru), NaOH (5 equiv/Ru), *i*-PrOH, H_2 (1 atm), 25 °C, 12 h.

Transfer hydrogenation,[14] where H_2 is effectively transferred from a "hydrogen donor" (e.g., alcohols) to a "hydrogen acceptor" (e.g., ketones), remains a useful protocol for reducing ketones (and olefins) and oxidizing alcohols. We found that omplexes **1** and **2** were also effective transfer hydrogenation precatalysts.[15−17] As shown in eq 1, following the RCM of ketone **12**, simply adding

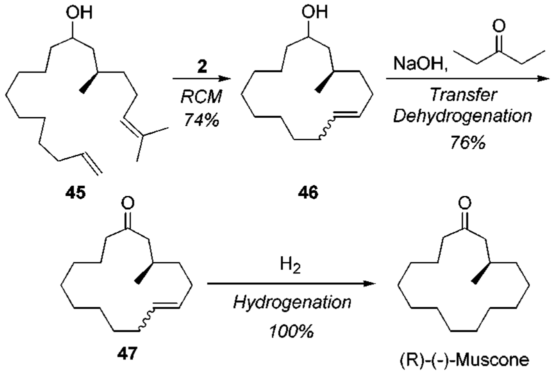




excess base (e.g., K_2CO_3 or NaOH)[18] and 2-propanol selectively afforded the unsaturated alcohol **43** in 56% overall yield from **12**. Similarly, transfer dehydrogenation of the allyl alcohol **44** (obtained via CM of 3-buten-2-ol and 5-acetoxy-1-hexene) with 3-pentanone and NaOH afforded α,β-unsaturated ketone **35** in 77% yield over the two steps (eq 2).

As shown in Scheme 2, the tandem catalytic reactions developed above were combined for a "one-pot" synthesis of (*R*)-(−)-Muscone, a natural product with a desirable fragrance.[19] Following RCM of the readily available diene **45**,[19] the addition of 3-pentanone and NaOH initiated the (Ru catalyzed) transfer dehydrogenation of the resulting alcohol (**46**) and afforded the macrocyclic ketone **47**. Finally, the addition of H_2 gave (*R*)-(−)-Muscone in 56% overall yield from **45**.

Scheme 2. A "One-Pot"/Three (Ru catalyzed)-Step Synthesis of (*R*)-(−)-Muscone



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Supporting Information Available: Full experimental procedures and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA016431E

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(12) Under H_2 (1 atm), complex **1**, NaOH (5 equiv), and 1.1 equiv of ethylenediamine (en) quantitatively afforded $RuHCl(en)(PCy_3)_2$ (^{31}P NMR: δ 52.5 ppm). Similarly, complex **2** afforded $RuHCl(en)(H_2IMes)(PCy_3)$ (^{31}P NMR: δ 52.4 ppm). The structures of both complexes were verified through independent synthesis: Louie, J.; Bielawski, C. W.; Grubbs, R. H. Unpublished results.

(13) Once the diamine Ru complex was formed, higher pressures of hydrogen (100 psi) did not facilitate olefin reduction.

(14) (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045.

(15) Transfer hydrogenation conditions: 5 mol % of Ru catalyst, NaOH or K_2CO_3 (5 equiv/Ru), *i*PrOH or 3-pentanone as solvent, 80 °C.

(16) For example, with **1** as catalyst and NaOH as base, cyclohexanone was converted to cyclohexanol in under 1 h. Similar results were obtained with complex **2**.

(17) The catalytically active species is currently under investigation. For additional mechanistic details, see ref 14.

(18) Elevated reaction rates were observed with NaOH, compare (cyclohexanone to cyclohexanol, 50% conversion): K_2CO_3, 24 h; NaOH, <1 h.

(19) A similar multistep procedure has been reported recently, see: Kamat, V. P.; Hagiwara, H.; Katsumi, T.; Hoshi, T.; Suzuki, T.; Ando. M. *Tetrahedon* **2000**, *56*, 4397.