Organic LETTERS
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Tandem Ring-Closing Metathesis/Transfer Hydrogenation: Practical Chemoselective Hydrogenation of Alkenes

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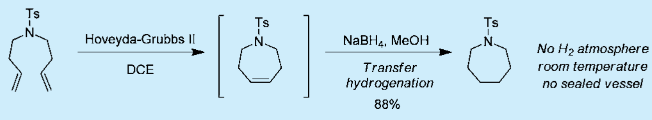
Supporting Information

ABSTRACT: An operationally simple chemoselective transfer hydrogenation of alkenes using ruthenium metathesis catalysts is presented. Of great practicality, the transfer hydrogenation reagents can be added directly to a metathesis reaction and effect hydrogenation of the product alkene in a single pot at ambient temperature without the need to seal the vessel to prevent hydrogen gas escape. The reduction is applicable to a range of alkenes and can be performed in the presence of aryl halides and benzyl groups, a notable weakness of Pd-catalyzed hydrogenations. Scope and mechanistic considerations are presented.



Over the past two decades Ru-catalyzed alkene metathesis has transformed the design and practice of organic synthesis.[1] Since the early days, chemists have sought to improve the utility of alkene metathesis reactions through incorporation in tandem processes in which the Ru catalyst is repurposed for a second transformation.[2] The simplest of these sequences, metathesis/hydrogenation, has long been known; yet, a truly practical protocol has proven elusive, as repurposing of Ru metathesis catalysts for hydrogenation often requires high pressure hydrogen and/or elevated temperatures (Figure 1).[2−4] Ru-catalyzed alkene metathesis is of considerable practical utility due to the high chemoselectivity, excellent functional group compatibility, and commercial availability of the Ru metathesis catalysts (Figure 2). In contrast, tandem Ru-catalyzed metathesis/hydrogenation either using H_2[3] or under transfer hydrogenation conditions[5] has been sparsely utilized due to the inconvenience of current protocols. In particular, the relative rarity of tandem Ru-catalyzed metathesis/hydrogenation under transfer hydrogenation conditions reflects the uncommon prevalence of Ru-catalyzed transfer hydrogenation of alkenes as opposed to the more commonly seen transfer hydrogenation of polar functional groups.[6,7] Identification of practical conditions for Ru-catalyzed tandem metathesis/hydrogenation sequence remains an unsolved problem.

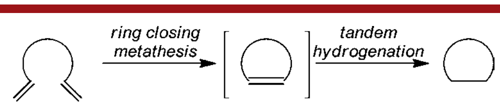


Figure 1. Tandem ring-closing metathesis/hydrogenation.

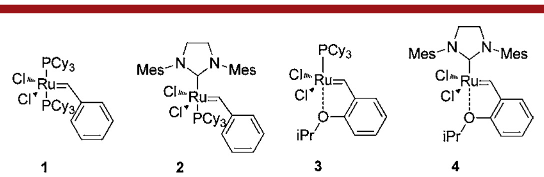


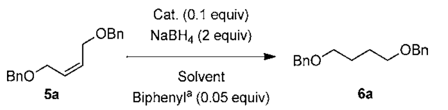
Figure 2. Ruthenium metathesis catalysts.

Recently, we serendipitously encountered the concomitant hydrogenation of an unactivated alkene during a $NaBH_4$/EtOH carbonyl reduction carried out at ambient temperature. This hydrogenation process was considered to be mediated by a residual Hoveyda−Grubbs second generation catalyst (**4**) from an earlier ring-closing metathesis (RCM) reaction. Ru-catalyzed transfer hydrogenation using $NaBH_4$ has previously been reported.[8,9] However, these conditions have not been applied to a tandem Ru metathesis/hydrogenation sequence presumably due to the known ability of **1** and **2** to mediate alkene isomerization in the presence of $NaBH_4$.[10] Recognizing the potential utility of transfer hydrogenation of an alkene under mild conditions, we sought first to optimize the transfer hydrogenation reaction and second to explore whether it could be adapted to a tandem metathesis/hydrogenation sequence.

Optimization of the hydrogenation reaction was carried out using (*Z*)-1,4-bis(benzyloxy)but-2-ene (**5a**) as the alkene hydrogenation substrate and the Hoveyda−Grubbs second generation catalyst **4** to generate the hydrogenation product 1,4-bis(benzyloxy)butane (**6**) (Table 1). Evaluation of protic solvents in combination with dichloroethane demonstrated methanol as the optimum protic solvent. Use of water or ethylene glycol resulted in rapid hydrogen evolution (Table 1, entries 3 and 7) while sterically larger alcohols provided slower reaction times (i.e., ethanol and isopropanol) (Table 1, entries 5 and 6). More acidic protic solvents, trifluoroethanol (TFE) and acetic acid, led to incomplete conversion (Table 1, entries 8 and 9). The proportion of protic solvent could be reduced to a ratio of dichloroethane/methanol (20:1) without loss of activity (Table 1, entry 10). Other common Ru metathesis catalysts

Received: July 8, 2014
Published: August 20, 2014

Table 1. Optimization of Alkene Hydrogenation



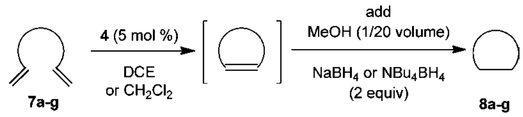
entry	cat.	solvent	1 h[b] (5a/6a)	4 h[b] (5a/6a)	24 h[b] (5a/6a)
1	**4**	EtOH[c]	17:52	6:58	0:53
2	**4**	DCE[d]	84:4	81:6	72:10
3	**4**	DCE/H_2O (10:1)[c,e]	7:72	0:>95	0:83
4	**4**	DCE/MeOH (10:1)[c]	0:84	0:79	0:87
5	**4**	DCE/EtOH (10:1)	49:31	0:>95	0:80
6	**4**	DCE/IPA (10:1)	28:2	14:8	0:102
7	**4**	DCE/$(CH_2OH)_2$ (10:1)[c]	43:8	27:4	7:79
8	**4**	DCE/TFE (10:1)	>95:0	93:4	72:14
9	**4**	DCE/AcOH (10:1)	66:21	54:34	54:34
10	**4**	DCE/MeOH (20:1)	0:>95	0:>95	0:>95
11	**4**	DCE/MeOH (60:1)[f]	21:4	15:7	0:>95
12	**1**	DCE/MeOH (20:1)	83:16	10:80	0:89
13	**2**	DCE/MeOH (20:1)	19:67	0:82	0:91
14	**3**	DCE/MeOH (20:1)	6:87	0:>95	0:89

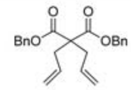
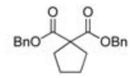
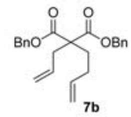
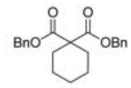
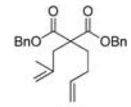
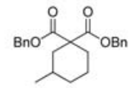
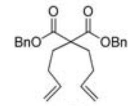
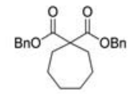
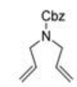
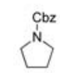
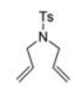
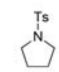
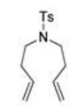
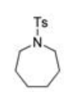
[a]Biphenyl used as internal standard. [b]Absolute HPLC conversion based on biphenyl standard (**5a**%:**6a**%). [c]Visible gas evolution. [d]Reactivity likely due to adventitious water. [e]Biphasic. [f] ~4 equiv of MeOH.

Grubbs first generation **1**, Grubbs second generation **2**, and Hoveyda–Grubbs first generation catalyst **3** also demonstrated competency in the transfer hydrogenation reaction (Table 1, entries 12–14). Qualitatively, however, the Hoveyda–Grubbs second generation catalyst **4** was the most efficient. Two other hydride sources, $NaBH_3CN$ and $NaBH(OAc)_3$, were inferior providing no conversion or low conversion, respectively. Minimization of the protic solvent leads to little/no hydrogen evolution being observed and presumably prevents premature consumption of $NaBH_4$. In fact, at low concentrations of protic solvent including our optimum conditions of dichloroethane/methanol (20:1), $NaBH_4$ is not fully soluble likely resulting in a slow release to the reaction. Rapid hydrogen evolution usually resulted in incomplete product formation (Table 1, entry 1). In most conditions evaluated, the mass balance apart from starting alkene **5a** and alkane product **6a** was composed of alkene isomerization products. This isomerization process was suppressed by minimization of the protic solvent.

Having identified optimal conditions for the hydrogenation process, we turned next to evaluation of the tandem metathesis/transfer hydrogenation sequence. To our delight, the hydrogenation conditions coupled well with a typical ring-closing metathesis (RCM) reaction providing the reduced RCM product in a simple one-pot operation (Table 2). Five, six, and seven membered alkene RCM products readily underwent hydrogenation with sodium borohydride (typically within 2–4 h) to provide the cycloalkanes in good yield, 76%–92% (Table 2, entries 1–2, 4–6) (method **A**). Alkene **7c** (Table 2, entry 3) underwent RCM; however, the trisubstituted alkene product did not undergo reduction, reflecting the steric sensitivity of the transfer hydrogenation (see below). Recognizing that the poor solubility of sodium borohydride may be rate-limiting, we also investigated tetrabutylammonium borohydride as a soluble hydride source (method **B**). Results with tetrabutylammonium borohydride demonstrated that using tetrabutylammonium as the counterion produces a homogeneous solution resulting in

Table 2. Tandem RCM/Hydrogenation Substrate Scope



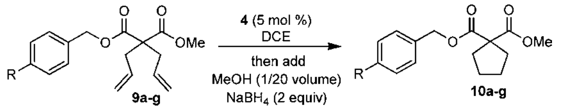
entry	substrate	product	Method **A** isolated yield[a]	Method **B** isolated yield[b]
1	 **7a**	 **8a**	86%	83%
2	 **7b**	 **8b**	91%	84%
3	 **7c**	 **8c**	0%[c]	0%[c]
4	 **7d**	 **8d**	92%	81%
5	 **7e**	 **8e**	76%	96%
6	 **7f**	 **8f**	85%	91%
7	 **7g**	 **8g**	88%	93%

[a]Method **A**: **4**, DCE; upon completion of RCM, add $NaBH_4$ (2 equiv) and 1/20 volume MeOH. [b]Method **B**: **4**, DCM; upon completion of RCM, add Bu_4NBH_4 (2 equiv) and 1/20 volume MeOH. [c]Complete RCM observed, but <10% reduction occurred upon addition of MeOH and hydride.

faster conversion (typically less than 1 h). However, the drawback of tetrabutylammonium borohydride compared to sodium borohydride is that tetrabutylammonium borohydride is much less atom economical and much more expensive than sodium borohydride. In most cases, the isolated yields are comparable justifying the use of method A (sodium borohydride) as the default procedure.

Chemoselectivity is one of the primary strengths of the Ru-catalyzed metathesis reaction. Investigation of the chemoselectivity of our tandem metathesis/transfer hydrogenation sequence demonstrated excellent chemoselectivity for alkene reduction (Table 3). Utilizing benzyl malonate **9a** as a template, we introduced substitution on the phenyl ring of the benzyl ester in order to evaluate the compatibility of various functional groups with the tandem metathesis/transfer hydrogenation conditions. The parent **9a** and related **9b** underwent an efficient tandem metathesis/transfer hydrogenation reaction (87% and 86% yield) (Table 3, entries 1 and 2). Aryl halides **9c** and **9d** also

Table 3. Tandem RCM/Hydrogenation Chemoselectivity



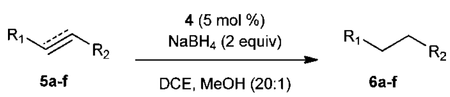
entry	R	substrate	product	isolated yield[a]
1	–H	**9a**	**10a**	87%
2	–Me	**9b**	**10b**	86%
3	–Br	**9c**	**10c**	77%
4	–I	**9d**	**10d**	81%
5	AcNH–	**9e**	**10e**	87%
6	–CN	**9f**	**10f**	0%[b]
7	$-NO_2$	**9g**	**10g**	0%[c]

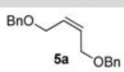
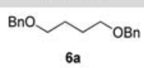
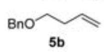
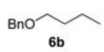
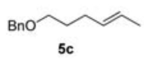
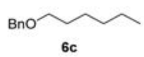
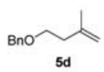
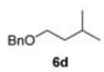
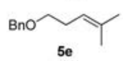
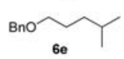
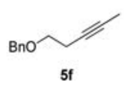
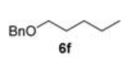
[a]Method **A** ($NaBH_4$). [b]Nitrile slowly reduced to primary amine. [c]Nitro group partially reduced to multiple products.

showed excellent compatibility providing tandem metathesis/transfer hydrogenation products **10c** and **10d** in high yields (77% and 81%) (Table 3, entries 3 and 4). Amide **9e** demonstrated compatibility providing **10e** (87%) (Table 3, entry 5). However, nitrile **9f** and nitro **9g** were not compatible with the tandem metathesis/transfer hydrogenation conditions instead providing products resulting from reduction of the nitrile and nitro functional groups including the relatively clean but slow conversion of nitrile **9f** to the primary benzylic amine (Table 3, entries 6 and 7).

These conditions also work quite well as a standalone transfer hydrogenation (Table 4). Both terminal alkenes, **5b** and **5g**, and

Table 4. Alkene Hydrogenation Scope



entry	substrate	product	isolated yield[a]
1	 **5a**	 **6a**	86%
2	 **5b**	 **6b**	90%
3	 **5c**	 **6c**	83%
4	 **5d**	 **6d**	80%
5	 **5e**	 **6e**	0% (60%)[c]
6	 **5f**	 **6f**	22%[a,d] / 73%[b]

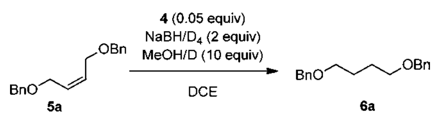
[a]Method **A** ($NaBH_4$). [b]Method **B** (NBu_4BH_4). [c]~60% conversion observed after 18 h, inseparable from alkene by chromatography. [d]Average of two runs, 23% and 20%.

internal disubstituted alkenes, **5a** and **5c**, readily undergo hydrogenation (Table 4, entries 2 and 7, entries 1 and 3). The ipso disubstituted alkene **5d** participated well (Table 4, entry 4), but the trisubstituted alkene **5e** was a poor substrate (Table 4, entry 5). This low reactivity, however, is not surprising, as Ru-catalyzed hydrogenations usually demonstrate high steric sensitivity.[6] The alkyne **5f** provided the product alkane **6f** in a poor yield of 22% (Table 4, entry 6). We hypothesized that this low yield may be due to competitive isomerization to an allene intermediate, a species previously reported to undergo significant polymerization under metathesis conditions.[11] Considering that the poor solubility of sodium borohydride may contribute to a slow rate of hydrogenation, we substituted tetrabutylammonium borohydride for sodium borohydride (method **B**) resulting in a much faster reaction and a significantly improved yield of 73%.

The scope and chemoselectivity of this protocol parallels that of other reported Ru transfer hydrogenations.[5,7,8] Benzyl group, aryl halides, and esters are typically stable. Nitro groups normally undergo reduction.[5b,7c] Nitriles have previously been observed to be stable whereas we observe slow reduction.[8a] This difference, however, may be a result of reaction rates. The hydrogenation protocol proceeds under milder conditions than previously reported $NaBH_4$-mediated Ru transfer hydrogenations.[8] Based on our observations, selectivity over nitrile groups should be attainable given a suitably short reaction time. Steric selectivity also follows previously reported Ru transfer hydrogenations.[5,7,8] Trisubstituted alkenes are generally reported to be inert to hydrogenation under these conditions, and we observe only very slow hydrogenation of trisubstituted alkenes. The advantages of our method are the relatively mild conditions, i.e. ambient temperature and pressure, and that the reaction is readily coupled with RCM reactions.

The precise details of the catalytic cycle are unclear and likely complex. A key question of the hydrogenation mechanism is whether hydrogen gas is formed *in situ* and is the active source of hydrogen. In a control experiment of the reduction of **5a** to **6a**, a hydrogen atmosphere was used in place of added borohydride. Under a hydrogen atmosphere, only trace hydrogenation product **6a** was observed confirming that our system is not simply forming hydrogen gas *in situ*. This suggests that entry into the catalytic cycle is likely achieved via conversion of Ru catalyst **4** into a Ru hydride species consistent with previous observations in the literature.[12] However, this observation does not exclude the possibility that once a Ru hydride is formed, hydrogen gas formed *in situ* is the active reductant. In fact, this pathway has previously been proposed when NaH is used to form the ruthenium hydride species.[3b] To gain additional insight into the mechanism, we ran three experiments using the deuterated reagents $NaBD_4$ and MeOD (Table 5). The results of these

Table 5. Deuterium Incorporation Experiments



entry	hydride source	proton source	$\%D_0/\%D_1/\%D_2$
1	$NaBD_4$	MeOH	54/36/10
2	$NaBH_4$	CD_3OD	44/43/13
3	$NaBD_4$	CD_3OD	19/43/38

experiments demonstrate surprisingly that both combinations $NaBD_4$/MeOH and $NaBH_4/CD_3OD$ provide substoichiometric deuterium incorporation into the hydrogenation product, ~0.6 equiv of deuterium in each case (Table 5, entries 1 and 2). In the case of $NaBD_4/CD_3OD$, incorporation of 1.2 equiv of deuterium was observed (Table 5, entry 3). The less than complete deuterium incorporation found in the double labeling experiment can be accounted for by the presence of adventitious water.[13] This scenario is consistent with equilibration of the hydrogen sources such that a majority of hydrogen could come from either the borohydride or the alcohol. In addition, the

dx.doi.org/10.1021/ol5019739 | Org. Lett. 2014, 16, 4444–4447

deuterium incorporation results suggest the involvement of a bis-hydride species in the catalytic cycle in order to allow equilibration of the hydrogen sources. The observed preference for hydrogen versus deuterium implies a kinetic isotope effect in the rate-determining step.[14] Based on these observations, a potential catalytic cycle consistent with these observations can be proposed (Figure 3). The catalytic cycle is initiated by

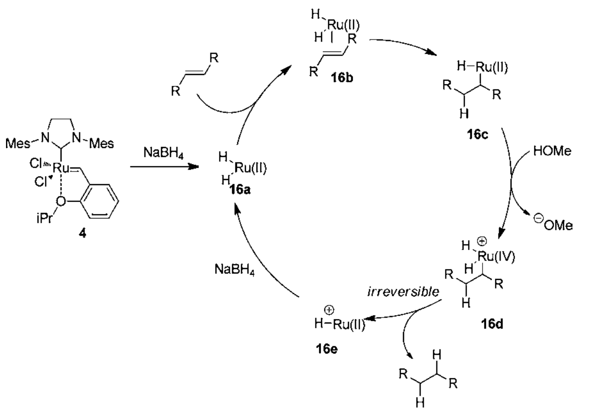


Figure 3. Proposed catalytic cycle of alkene hydrogenation.

conversion of Ru catalyst **4** into bis-hydride **16a**. Following complexation of the alkene, **16b**, the Ru hydride adds across the alkene to form alkyl ruthenium **16c**. Next, protonation by methanol provides **16d** and finally reductive elimination delivers product and ruthenium **16e**. Hydride transfer to **16e** from sodium borohydride would then reform ruthenium hydride **16a**. All interconversions in the catalytic cycle prior to the irreversible reductive elimination of **16d** to **16e** are all likely reversible under the reaction conditions allowing for alkene isomerization commonly observed during Ru-catalyzed transfer hydrogenation reactions. However, further work is needed to clarify the mechanism.

In conclusion, a simple and practical hydrogenation protocol for alkenes has been demonstrated. The method works well coupled with Ru-catalyzed metathesis allowing for a convenient tandem RCM/transfer hydrogenation sequence. The hydrogenation process has high functional group tolerance, a notable advantage over more common Pd-catalyzed hydrogenations. The selective and practical nature of the tandem metathesis/hydrogenation sequence provides a useful addition to the pantheon of Ru metathesis chemistry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and product characterization (^{1}H and ^{13}C NMR, MS). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Prof. Phil Baran (the Scripps Research Institute) and Eric Gillis (Bristol-Myers Squibb) are gratefully acknowledged for helpful discussions. Mark Saulnier (Bristol-Myers Squibb), Nick Meanwell (Bristol-Myers Squibb), Eric Gillis (Bristol-Myers Squibb), and John Kadow (Bristol-Myers Squibb) are thankfully acknowledged for reading the manuscript. Dieter Drexler (Bristol-Myers Squibb) is gratefully acknowledged for deuterium isotopic analysis. This paper is dedicated to the memory of Prof. David Y. Gin (1967–2011).

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