<u>LETTERS</u>

E- and *Z*-Selective Transfer Semihydrogenation of Alkynes Catalyzed by Standard Ruthenium Olefin Metathesis Catalysts

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Supporting Information

ABSTRACT: Selective transfer semihydrogenation of alkynes to yield alkenes was achieved with commercial first and second generation Hoveyda–Grubbs catalysts and formic acid as a hydrogen donor. This catalytic system is distinguished by its selectivity and compatibility with many functional groups (halogens, cyano, nitro, sulfide, alkenes). The metathetic activity of the ruthenium catalysts may be utilized in tandem sequences of olefin metathesis plus alkyne reduction.

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he Lindlar semireduction of alkynes¹ is a long-standing synthetic transformation, present in classical textbooks. Due to its well-established stereochemical course, Z selectivity is the intrinsic feature of this transformation. The small amounts of isomeric or over-reducted byproducts that sometimes accompany the (*Z*)-alkenes are derived from secondary processes.² The formation of (E)-alkenes by catalytic hydrogenation is, however, more difficult.³ Therefore, active research has been started in the area of E-selective alkyne reductions, and some promising catalytic systems have been very recently developed, employing transition metal complexes in combination with hydrogen gas or with various transfer hydrogenation agents. Two years ago Fürstner et al. reported on the revolutionary (E)-selective semihydrogenation of alkynes employing commercial complex [Cp*Ru(cod)Cl] under a H₂ pressure of 10 bar.³ This system is characterized by excellent E/Z selectivity and a wide scope of alkyne substrates.³ More recent examples of a triple bond semireduction catalyzed by a ruthenium complex were published by Mandkad (2015)⁴ and Lindhardt (2016).⁵ The first publication refers to application of heterobimetallic $(IMes)Ag-RuCp(CO)_2$ in the reduction of tolanes. The second one describes semihydrogenation of tolanes and terminal arylalkynes with the use of commercial $Ru(PPh_3)_3(CO)(H)Cl$ under low H₂ pressure. The quest for more environmentally benign and inexpensive catalysts is another recently observed trend. In 2014, Liu et al. described an interesting approach for *E*-selective tolane reduction with Na₂S and water.⁶ In 2013, Milstein et al. proposed an innovative *E*-selective semireduction of various internal alkynes as well as phenylacetylene by means of a newly synthesized iron pincer complex under H₂ pressure.

It must be stressed that the compatibility of the recently developed catalytic systems with reducible functional groups (such as NO_2) is high in many cases, and the sometimes observed over-reduction of a triple bond to a single bond can usually be avoided. However, despite the enormous progress in alkyne semireduction, only a few catalyst systems can allow switchable selectivity leading to either the (*E*)- or (*Z*)-olefin isomer according to ligand alteration,^{8,9} and to the best of our

knowledge, none of them use ruthenium alkylidene complexes, commonly employed as olefin metathesis catalysts.¹⁰

Our recent observation that ruthenium metathesis catalysts in the presence of HCO_2H and NaH form [Ru]–H species capable of reduction of C–C double bond¹¹ encouraged us to translate this methodology to the reduction of triple bonds. First, in a model hydrogenation reaction of diphenylacetylene (tolane, 1a)¹² various ruthenium complexes were tested, from the simplest ones to the contemporary alkylidene olefin metathesis catalysts (Figure 1). In a typical run the addition of substrate and internal standard (durene) solutions to a vessel



Figure 1. Selected ruthenium complexes tested in this study.

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containing a ruthenium complex and NaH (0.2 equiv) was followed by addition of HCO_2H (50 equiv). The conditions were similar to those previously used by us for olefin reduction,¹¹ with the difference that the reduction of acetylene **1a** was carried out in an open Schlenk tube under argon, not in a sealed ampula under pressure.¹¹

Again, THF was chosen as the best solvent, and the progress of the reaction was analyzed by GC. In most cases, good to complete conversion of **1a** was observed; however, in addition to the expected stilbenes, other products were also obtained in some cases (Table 1). Namely, the use of $Ru(PPh_3)_3Cl_2$ and

Table 1. Screening of Ruthenium Cataly
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	1a	(Z)-2a	(<i>E</i>)-2a
entry	catalyst	conversion [%] ^c	E/Z^{c}
1^a	RuCl ₃	11	10/90
2^a	$Ru(PPh_3)_3Cl_2$	100^b	98/2
3 ^{<i>a</i>}	$Ru(PPh_3)_3(CO)(H)Cl$	100^b	99/1
4 ^{<i>a</i>}	$[Ru(COD)Cl_2]_n$	19	14/86
5 ^{<i>a</i>}	Gru I	55	5/95
6 ^{<i>a</i>}	Gru II	100	85/15
7^a	Gru III	100	50/50
8 ^{<i>a</i>}	Hov I	65	3/97
9 ^{<i>a</i>}	Hov II	100	99/1
10^a	nitro-Hov I	50	4/96
11^a	nitro-Hov II	100	97/3
12^a	M1	37	8/92
13^a	M2	100	87/13
14^a	M10	98	93/7
15^a	M11	32	4/96
16^a	M20	83	14/86
17^a	M52	100	98/2

^{*a*}Conditions: 0.02 equiv of catalyst, 0.2 equiv of NaH, 50 equiv of HCO₂H, 80 $^{\circ}$ C, 6 h, THF. ^{*b*}Two additional products, substantial decomposition of HCO₂H. ^{*c*}Conversion and product distribution were determined by GC analysis.

Ru(PPh₃)₃(CO)(H)Cl resulted in formation of additional products and intensive decomposition of HCO_2H to CO_2 and H_2 . The screening indicated that the ruthenium–alkylidene complexes (entries 5–17) led to more clean reactions. As a consequence, we focused our efforts on the use of commercial Ru olefin metathesis catalysts for semireduction.

The results indicated that first generation ruthenium– benzylidene complexes, containing aliphatic phosphine ligands (PCy₃), favor production of (*Z*)-stilbene (entries 5, 8, 10, 15) while the second generation benzylidene complexes, bearing the N-heterocyclic (NHC) ligand, promote production of (*E*)-stilbene (entries 6, 9, 11, 17). The third generation catalyst **Gru III** showed low selectivity (entry 7). The standard indenylidene-based complexes **M1** and **M2** lead to lower conversion or selectivity (entries 12, 13) but followed the general trend. Interestingly, complex **M10** gave predominantly the (*E*)-stilbene, while belonging formally to the first generation of Ru metathesis catalysts. The second PPh₃-containing catalysts tested by us, **M20**, gave, in contrast, a relatively high content of the (*Z*)-isomer. Based on the results of this preliminary screening, the most simple and very stable **Hov I** and **Hov II** complexes were chosen for further studies, as they showed both good reactivity and high *Z*- and *E*-selectivity (Table 1).

During optimization of the hydrogenation reaction conditions, we found that the amount of added sodium hydride affects the conversion of the starting material and the selectivity of the reaction.¹¹ In the case of 0.8 equiv of NaH, the reaction is complete after 0.5 h while the conversion of **1a** in the reaction conducted without NaH reached only 10%. On the other hand, use of NaH in amounts greater than 0.2 equiv led to worse selectivity (see the Supporting Information for details). Therefore, we decided to use 0.2 equiv of the base and carry out the reaction for the time required to obtain maximal conversion (6-24 h).

To understand better the relation between Hoveyda–Grubbs catalyst generation and selectivity of the semireduction, we examined the consumption of a substrate and formation of products according to the time of reaction. The results are presented in the form of molar fraction changes with time (Figures 1 and 2). Based on the results, we can state that



Figure 2. Reduction of diphenylacetylene **1a** with Hoveyda–Grubbs first generation catalyst. Conditions: 0.02 equiv of **Hov I**, 0.2 equiv of NaH, 50 equiv of HCO₂H, 80 °C, THF.

(*Z*)-stilbene seems to be in all cases the initial product of the reaction that undergoes, with time, isomerization¹³ to more thermodynamically stable (*E*)-stilbene (Scheme 1). In the case of

Scheme 1. Proposed Reduction-Isomerization Sequence



the less active first generation Hoveyda–Grubbs catalyst, this process may be stopped at the first step, to afford the (Z)-product with good selectivity (Figure 2). In the case of the more reactive second generation Hoveyda–Grubbs catalyst, (Z)-stilbene is also an initial product (Figure 3), but during the first hour of the reaction it was almost completely isomerized to the (E)-product (Figure 3).

To find the factor responsible for the isomerization process we carried out three separate experiments. In the first one, a THF solution of (*Z*)-stilbene was heated in the presence of 50 equiv of HCO_2H at 80 °C. In the second one, 0.02 equiv of Hov II was used together with only 0.02 equiv of HCO_2H . The third experiment was similar to the previous one, but HCO_2H was left out. After 24 h, the substrate (*Z*)-2a remained intact in the first case, while in the second and third reaction (*Z*)-2a was completely isomerized to (*E*)-2a. Based on the above results,



Figure 3. Reduction of diphenylacetylene **1a** with Hoveyda–Grubbs second generation catalyst. Conditions: 0.02 equiv of **Hov II**, 0.2 equiv of NaH, 50 equiv of HCO₂H, 80 °C, THF.

it seems probable that the ruthenium complex in both the presence and absence of HCO₂H is the factor responsible for isomerization of (Z)-stilbene to its (E)-isomer. This intriguing reactivity of olefin metathesis complexes encouraged us to investigate the scope of the method in more detail. As can be seen from the results compiled in Table 2, Grubbs-Hoveyda catalysts (0.02 equiv) in the presence of HCO₂H (50 equiv) and NaH (0.2 equiv) in THF allowed an assortment of substrates to be reduced by HCO_2H (50 equiv) with excellent E/Z selectivity control. In the presence of the Hov I catalyst the semihydrogenation proceeded cleanly to afford (Z)-olefins in very good yields and selectivity (Table 2. entries 1-3). To obtain (E)-products, the Hov II complex was used instead (Table 2, entries 4-11). The observed high *E*-selectivity renders the latter method to be stereocomplementary to the classical Lindlar reduction.

Importantly, substrates containing various functional groups, both electron-donating and -withdrawing, are tolerated (Table 2). For example, there was no sign of protodebromination of the aryl bromide fragment of tollane 1c (Table 2, entries 3 and 8), which offers additional flexibility, as compared with Pd-based Lindlar semihydrogenation methods. Even a thioether moiety did not poison the catalyst, as can be observed from the case of tollane 1h bearing a 1,3-dithiane ring that underwent transfer hydrogenation without deprotection or desulphurization (Table 2, entry 11). Moreover, a reducible nitro group remained intact (Table 2, entries 9). However, in the case of a nitrile group, 0.03 equiv of Hov II catalyst had to be used, and the reaction was carried out for 48 h to obtain full conversion with a trace of amine derivative (Table 2, entry 10). The possible reason why this substrate requires a higher catalyst loading and longer reaction time may be due to coordination of this functional group to a ruthenium complex.¹⁴ It shall be noted that many, otherwise excellent systems for alkyne semireduction are not compatible with the nitro group.⁷ Furthermore, the reduction of aryl-alkyl alkynes 1i-1k and cycloalkyne 1l with the use of Hov II led to formation of corresponding *E*-alkenes (Table 2, entries 12-15), serving as proof that our catalytic system has a wider scope of potential applications than just substituted diphenylacetylenes. Lower yields in those cases were caused by overreduction of alkynes and formation of other unidentified products. We found our catalytic system incompatible with terminal alkynes.

Procedures commonly known as "one-pot" processes have found numerous applications in laboratories and industry.¹⁵ This technique allows for the more effective use of solvents and other materials than in traditional stepwise procedures and can

 Table 2. Substrate Scope and Functional Group Tolerance of the Title Reaction

entry	substrate	product ^a	method, yield [%] ^h	E/Z^i
1	1a	(Z)-2a	A , 94	5/95
2	()	(Z)-2b	A , 91	5/95
3	1c		<mark>A</mark> , 96	6/94
4	1a	(E)-2a	<mark>B</mark> , 98	99/1
5	1d	(E)-2d	<mark>B</mark> , 95	99/1
6	() OMe	(E)-2b	B , 93	95/5
7	OMe OMe 1e	(E)-2e	B , 96	99/1
8	1c	(E)-2c	<mark>B</mark> , 98	99/1
9	1f	(E)-2f	<mark>B</mark> , 99	99/1
10^b	1g	(E)-2g	B , 79 ⁱ	only E
11 ^c	$\left(\begin{array}{c} & & \\ & $	(E)-2h	<mark>B</mark> , 100	95/5
12^d		(E)-2i	<mark>B</mark> , 68	97/3
13 ^e	MeO-	MeO (E)-2j	B , 71	95/5
14 ^{<i>f</i>}	0 ₂ N-	O ₂ N (E)-2k	B , 73 ^{<i>k</i>}	91/9
15 ^g			B , 44, 53 ^k	90/10

⁴⁰Only major isomer of the product was shown. ^b0.03 equiv of **Hov II**, 24 h. ^c24 h. ^d1 h. ^e4.5 h. ^f2 h. ^g0.04 equiv of **Hov II**, 3 h, 90 °C. ^hMethod A: 0.02 equiv of **Hov I**, 0.2 equiv of NaH, 50 equiv of HCO₂H, 80 °C, 24 h, THF. Method B: 0.02 equiv of **Hov II**, 0.2 equiv of NaH, 50 equiv of NaH, 50 equiv of HCO₂H, 80 °C, 6 h, THF. Isolated yield. ⁱRatio of crude determined by GC analysis. ^j6% of formylated amine derivative was formed. ^kGC yield.

allow the synthesis of highly complex products by using simple substrates.¹⁵ Owing to the current global interest in one-pot transformations, and being aware of the high metathetical activity

of Hoveyda–Grubbs complexes used by us in alkyne reduction, we decided to test a model one-pot metathesis–semireduction. To do so, we carried out a single-pot reaction of 1j which consisted of ring closing metathesis (RCM) and triple C–C bond hydrogenation (Scheme 2). After completion of RCM,

Scheme 2. One-Pot RCM—Semireduction and Ortep Drawing of Product (*E*)-2m



 a 0.04 equiv of Hov II, 40 °C, 5 h, THF. b 0.2 equiv of NaH, 50 equiv of HCO₂H, 80 °C, 6 h, THF.

formic acid and sodium hydride were added into the reaction mixture to convert **Hov II** into the catalytic system for semireduction, ¹¹ leading to product (*E*)-**2m** in a total yield of 49% after two steps. Although product (*E*)-**2m** can be obtained by other means (in two or more steps), this example is useful to demonstrate the high selectivity of this reduction system. Notably, the C–C double bond formed during the RCM step did not undergo further reduction to a single bond or isomerization. The latter transformation (a double bond shift) is a rather common process, triggered by decomposed Ru olefin metathesis catalysts.¹⁶

Outlined herein are our preliminary results on a ligandcontrolled semihydrogenation of alkynes to form either (E)- or (Z)-alkenes using classical Hoveyda—Grubbs olefin metathesis catalysts and formic acid as a safe hydrogen source. Importantly, the second generation of benzylidene ruthenium complexes led almost exclusively to (E)-selective alkyne hydrogenation, rendering this method to be stereocomplementary to the classical Lindlar reduction. The metathetic capability of the ruthenium complexes used by us for the reduction may be also utilized in tandem sequences composed of olefin metathesis alkyne reduction. As the developed system operates under mild conditions and tolerates a host of sensitive functional groups we believe that it holds great promise for future applications in target-oriented syntheses.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03254.

Crystallographic data (CIF)

Full experimental details, copies of spectral data, X-ray crystal structure (PDF)

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Notes

The authors declare no competing financial interest.

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