DOI: 10.1002/adsc.201500933

# Asymmetric Transfer Hydrogenation of Ketones with modified Grubbs Metathesis Catalysts: On the Way to a Tandem Process

Marc Renom-Carrasco,[a,b] Piotr Gajewski,[a,b] Luca Pignataro,[b] Johannes G. de Vries,[c] Umberto Piarulli,[d] Cesare Gennari,[b] Laurent Lefort,*[a]

[a] DSM Innovative Synthesis BV, P. O. Box 18, 6160 MD Geleen, The Netherlands
Phone: +31 464767104; e-mail: laurent.lefort@dsm.com
[b] Università degli Studi di Milano, Dipartimento di Chimica, via C. Golgi 19, 20133 Milan, Italy
[c] Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany
[d] Università degli Studi dell'Insubria, Dipartimento di Scienza e Alta Tecnologia, via Valleggio 11, 22100 Como, Italy

Received: October 2, 2015; Revised: November 16, 2015; Published online: January 26, 2016

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500933

**Abstract.** Herein, we report the successful transformation of 1st generation Grubbs metathesis catalyst into an asymmetric transfer hydrogenation (ATH) catalyst. Upon addition of a chiral amine ligand, an alcohol and a base, the 1st generation Hoveyda-Grubbs catalyst (**HG-I)** was found to promote the enantioselective reduction of acetophenone to 1-phenylethanol. After optimizing the order of addition and the reaction conditions, the substrate scope was assessed leading to enantiomeric excesses up to 97% *ee*. NMR experiments were run in order to get information about the in situ-generated ATH catalyst. Furthermore, the possibility to perform olefin metathesis and ketone transfer hydrogenation sequentially in one pot was demonstrated, and the first tandem olefin metathesis-ketone asymmetric transfer hydrogenation was carried out.

**Keywords:** Ruthenium; Asymmetric catalysis; Transfer hydrogenation; Metathesis; Tandem catalysis

Asymmetric transfer hydrogenation (ATH) of ketones is an important methodology for the production of chiral alcohols with applications in the synthesis of fine chemicals and pharmaceuticals.[1] Contrary to the direct hydrogenation with $H_2$, it employs easy to handle and cheap reagents as the hydrogen source and does not require pressure vessels. Since the seminal discovery of the Noyori catalysts,[2] ruthenium is the metal that has been used most extensively in metal catalyzed ATH.

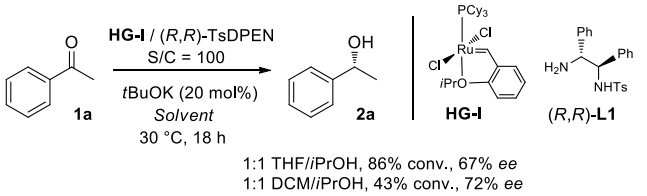
Ru-based olefin metathesis is an equally important reaction with numerous applications both in polymers and organic synthesis.[3] It has been frequently incorporated in tandem processes[4] among which the tandem metathesis-hydrogenation is probably the most studied example. First applied in the field of polymers,[5] the tandem metathesis-hydrogenation was later extended to the synthesis of small molecules.[6] Very recently, we reported the first asymmetric version of this tandem protocol, i.e. a metathesis-asymmetric hydrogenation (AH) of C=C bonds, where – after the metathesis step – the ruthenium catalyst is converted into an olefin AH catalyst upon addition of a chiral ligand.[7]

Herein, we describe our efforts to expand this concept to ATH, i.e. to achieve a tandem metathesis-ATH. The non-asymmetric tandem metathesis-TH has been previously described leading either to the reduction of the C-C double bond formed by metathesis[8] or of an adjacent carbonyl group.[6,9] However, the enantioselective version of this tandem protocol towards the formation of an enantiopure alcohol is not known. Based on our previous work, we foresaw that the addition of a chiral ligand after the metathesis could lead to such an enantioselective transformation.

In preliminary experiments, we tested whether a Ru metathesis catalyst could be turned into an ATH catalyst. For this purpose, the Hoveyda-Grubbs 1st generation catalyst (**HG-I**) and the Noyori chiral ligand (*R*,*R*)-Ts-DPEN (**L1**) were dissolved in THF or in DCM in the presence of acetophenone (**1a**) as a model substrate (Scheme 1). *t*BuOK (a necessary component to activate the Noyori catalysts) and *i*PrOH (the hydrogen donor) were added to the solutions, and the obtained mixtures were stirred at 30 °C for 18 h. Gratifyingly, GC analysis revealed the presence of the desired product, (*R*)-1-phenylethanol (**2a**) with a significant enantiomeric excess in both reactions (Scheme 1). THF/*i*PrOH led to a higher conversion and was chosen as solvent for the follow-up experiments.

When monitoring the reaction **1a** → **2a** vs time, we observed that the enantiomeric excess increased during the first 20 h (Figure 1 A). This suggests that an active catalytic species more enantioselective than the initial one(s) was forming during the course of the reaction. Stirring **HG-I**/Ts-DPEN (**L1**) with *t*BuOK in THF for 3 h before the addition of *i*PrOH did not

have any effect (Figure 1 B). From this experiment, we reasoned that the formation of the more enantioselective catalytic species was triggered by the addition of *i*PrOH. Additionally, reacting *t*BuOK with **HG-I** alone in THF before addition of the ligand had a negative effect both on the activity and enantioselectivity (Figure 1 C). This confirmed the crucial role of *i*PrOH which must quickly convert *t*BuOK into *i*PrOK. Consequently, we performed the ATH of **1a** by first adding *i*PrOH to the mixture of **HG-I**/Ts-DPEN in THF followed by *t*BuOK. In this case, the *ee* remained constant during the course of the reaction and 1-phenylethanol (**2a**) was obtained with 96% conversion and 90% *ee* after 18 h (Figure 1 D). Remarkably, no erosion of *ee* was observed even after 42 h, in contrast to what is known from other ATHs as a result of the reversible nature of this transformation.[10] When *t*BuOK was replaced by KOMe, the same behavior related to the order of addition of base and *i*PrOH was observed (Figure 1 E and 1 F). In contrary, when *i*PrONa was used as a base, a high *ee* was observed from the beginning of the reaction, no matter the order of addition (Figure 1 G and 1 H). Altogether, this set of experiments points towards a Ru-isopropoxide species as the most enantioselective catalyst or as an intermediate towards it. Notably, the reactions carried out with *i*PrONa showed a slow erosion of the *ee* during time, possibly due to a cation effect (Na *vs* K) already evidenced in some previous studies.[11]




**Scheme 1.** ATH of acetophenone **1a** using a catalyst formed in situ from HG-I and Ts-DPEN.

The optimal procedure towards the most enantioselective catalyst (D, Figure 1) was further studied by NMR and GC-MS (see the Supporting Information). In agreement with the catalytic test, no change was observed by NMR when **HG-I** and Ts-DPEN were dissolved in THF-$d_8$:*i*PrOH-$d_8$. Upon stirring this mixture in presence of *t*BuOK for 5 h at room temperature, we noticed the complete disappearance of the benzylidene proton ($\delta$ = 17.2 ppm, doublet) and the formation of *o*-isopropoxytoluene-$d_2$ by GC-MS (*m/z* = 152), arising from the hydrogenation of the benzylidene moiety. In the $^{31}$P-NMR spectrum four main peaks were observed: a singlet at 6 ppm (free $PCy_3$), a singlet at 47 ppm ($O{=}PCy_3$), and two triplets ($\delta$ = 56.8 ppm and 56.2 ppm, in a 3:1 ratio, both with a $^2J_{P,D}$ = 7.7 Hz). These NMR signals are consistent with Ru species containing both D and $PCy_3$ as ligands. In the $^1$H-NMR spectra, two doublets at -7.4 and -7.5 ppm (both with a $^2J_{H,P}$ = 52 Hz, also in 3:1 ratio) could be observed, probably belonging to the $^1$H analogs of these latter species formed from residual undeuterated *i*PrOH. Two other smaller singlets were present in the hydride zone (at -5.0 and -6.2 ppm), which were assigned to RuH species without any ligated $PCy_3$ (for more details on the qualitative identification of the active species, see the Supporting Information, pag 9-12). These observations are consistent with previous reports related to the alcoholysis of Grubbs catalysts and the concomitant formation of Ru hydrides.[12] What is remarkable in our case is the high *ee* obtained from such a mixture of potentially active Ru complexes. This suggests the presence of one enantioselective Ru species bearing the chiral Ts-DPEN ligand whose activity is superior to those of the other species present.

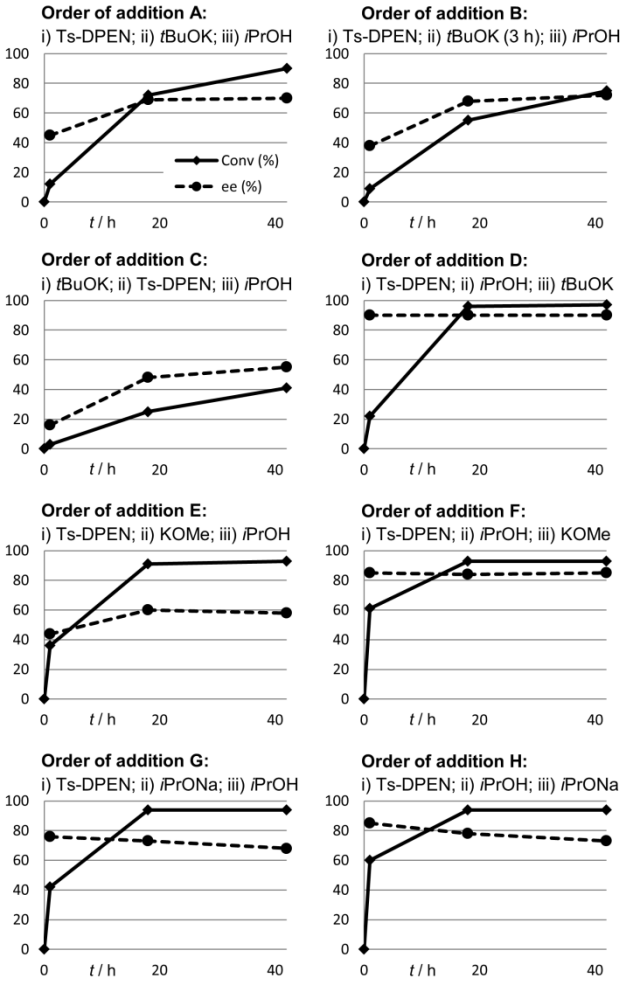
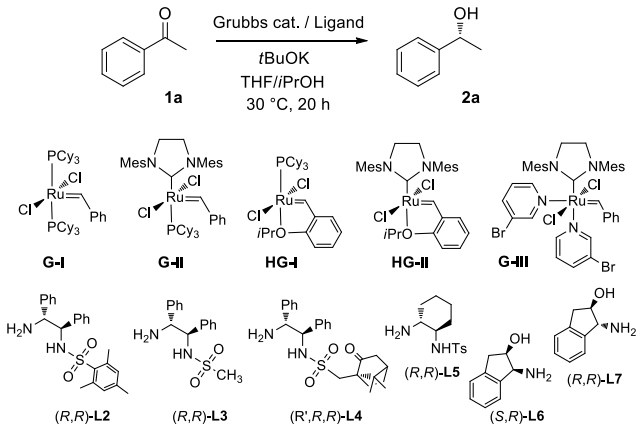



**Figure 1. 1a** and **HG-I** were mixed in THF and the other components were subsequently added in the order shown on top of each graph (stirring 5 min between each addition unless otherwise stated). Conversion and *ee vs* time for the ATH of **1a** under different conditions (molar ratio: **1a**/**HG-I**/**L1**/base = 100:1:1.1:20, 0.1 mmol **1a**, 1:1 THF/*i*PrOH (2.0 mL), 30 °C).

The ATH using **HG-I** as Ru precursor was further optimized by varying the amount of *t*BuOK (Table 1,

entries 1-4) and solvent ratio (entries 5-6). The best result was obtained with 20 equivalents of *t*BuOK and a 1:3 THF/*i*PrOH ratio leading to 97% conversion and 93% *ee* (entry 5). Other commercially available Ru–alkylidene complexes were investigated (entries 7-10). While **G-I** showed comparable results to **HG-I**, all complexes containing an NHC ligand showed very little activity. These differences between $PCy_3$ and the IMes-containing Ru complexes can be explained by their different rate of reaction with alkoxides to form the active species, as demonstrated by Fogg and co-workers.[12d] Finally, a screening of chiral ligands (entries 12-16) showed that Ts-DPEN (**L1**), Camphorsulphonyl-DPEN (**L4**) and to a lesser extent, Methanesulfonyl-DPEN (**L3**) were the best performing. Mestiylenesulphonyl-DPEN (**L2**) performed notably worse than **L1**, illustrating the high dependence of catalyst performance from the ligand structure.

**Table 1.** Optimization of the ATH of acetophenone (**1a**) to 1-phenylethanol (**2a**).[a)]




| # | Ru | Lig. | *t*BuOK (mol%) | THF / *i*PrOH | Conv (%)[b)] | *ee* (%)[b)] |
|---|---|---|---|---|---|---|
| 1 | **HG-I** | **L1** | 5 | 1:1 | 0 | - |
| 2 | **HG-I** | **L1** | 10 | 1:1 | 0 | - |
| 3 | **HG-I** | **L1** | 20 | 1:1 | 86 | 93 |
| 4 | **HG-I** | **L1** | 40 | 1:1 | 95 | 92 |
| 5 | **HG-I** | **L1** | 20 | 1:3 | 97 | 93 |
| 6 | **HG-I** | **L1** | 20 | 3:1 | 56 | 96 |
| 7 | **G-I** | **L1** | 20 | 1:3 | 96 | 95 |
| 8 | **HG-II** | **L1** | 20 | 1:3 | 4 | 10 |
| 9 | **G-II** | **L1** | 20 | 1:3 | 8 | 86 |
| 10 | **G-III** | **L1** | 20 | 1:3 | 4 | 30 |
| 11 | **HG-I** | **L2** | 20 | 1:3 | 53 | 62 |
| 12 | **HG-I** | **L3** | 20 | 1:3 | 96 | 88 |
| 13 | **HG-I** | **L4** | 20 | 1:3 | 92 | 94 |
| 14 | **HG-I** | **L5** | 20 | 1:3 | 97 | 78 |
| 15 | **HG-I** | **L6** | 20 | 1:3 | 67 | 64 |
| 16 | **HG-I** | **L7** | 20 | 1:3 | 34 | -5 |

a) The reactions were conducted with 0.1 mmol of **1a** in THF/*i*PrOH (2.0 mL) at 30 °C for 18 h. **1a**/Ru/Lig = 100:1:1.1. b) Conversion and *ee* were determined by GC analysis with Chiralsil DEX CB column.

To explore the substrate scope of this transformation, a number of ketones were tested under optimized reaction conditions (Table 2). Both conversion and enantiomeric excess were negatively affected when the steric hindrance of the alkyl group increased (entries 2-4). Similarly, *o*-substituted acetophenone (entry 8) was not reduced at all. Electron-deficient acetophenone derivatives (entries 5-6) proved more reactive than the electron-rich ones (entry 7). 2-Acetonaphtone as well as aromatic cyclic ketones (entries 9-11) were reduced with high *ee*'s up to 97%. More challenging substrates like alkyl ketones (entries 12-13) and 3-acetylpyridine (entry 14) led to poor or no conversion with low *ee*. Overall, these results are very similar to the one obtained with the Noyori catalyst. [2]

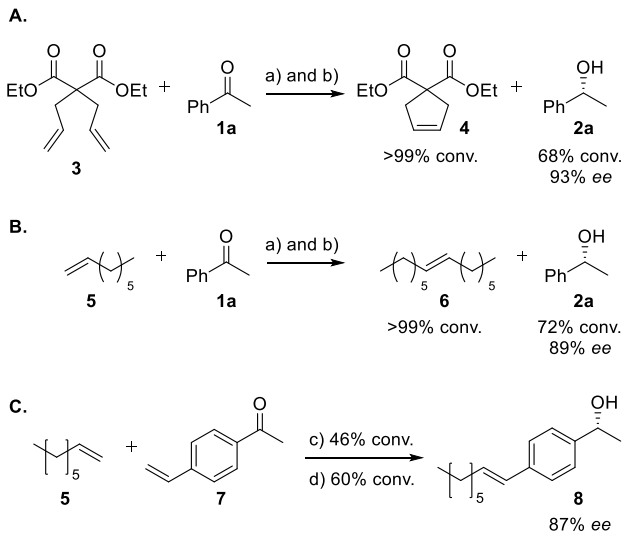
**Table 2.** Substrate scope under optimized conditions.[a)]

| # | Sub. | Conv. *ee* (%)[b)] | # | Sub. | Conv. *ee* (%)[b)] |
|---|---|---|---|---|---|
| 1 | **1a** | 97<br>93, *R* | 8 | **1h**[d)] | 0<br>n.d. |
| 2 | **1b** | 84<br>90, *R* | 9 | **1i** | 96<br>95, *R* |
| 3 | **1c** | 27<br>33, *R* | 10 | **1j** | 60<br>97, *R* |
| 4 | **1d** | 36<br>17, *R* | 11 | **1k** | 43<br>93, *R* |
| 5 | **1e** | 99<br>80, *R* | 12 | **1l** | 4<br>n.d. |
| 6 | **1f**[c)] | 100<br>73, *R* | 13 | **1m**[e)] | 45<br>30, *R* |
| 7 | **1g** | 73<br>85, *R* | 14 | **1n** | 0<br>n.d. |

a) Reactions were conducted with 0.1 mmol of **1a** in 1:3 THF/*i*PrOH (2.0 mL) at 30 °C for 20 h. **1a**/**HG-I**/**L1**/*t*BuOK = 100:1:1.1:20. b) Conversion and *ee* (including abs. config., see the Supporting Information) were determined by GC or HPLC analysis. c) 40 equivalents of base compared to the catalyst. d) Reaction run for 44 h. e) Reaction run for 90 h. n.d.= not determined.

Having shown that **HG-I** catalyst can be converted to an efficient ketone ATH catalyst, our next goal was to expand the concept towards a tandem metathesis-ATH protocol. To this purpose, two tests were performed under the optimized reaction conditions (Scheme 2 A and B). Ring closing metathesis of diethyl diallylmalonate (**3**, Scheme 2 A) and homometathesis of 1-octene (**5**, Scheme 2 B) were performed with **HG-I** in the presence of acetophenone (**1a**) in THF, followed by the addition of Ts-DPEN, *i*PrOH and *t*BuOK to perform the ketone ATH. In both cases 1-phenylethanol (**2a**) was formed with an *ee* comparable to the one obtained without previously performing the metathesis step (Table 2, entry 1), thus proving that an ATH catalyst can be generated after the metathesis reaction from a mixture of Ru precursors (unreacted or regenerated HG-I [13] and the new Ru species formed during the metathesis reaction). Remarkably, no reduction nor isomerization of the C-C double bond was observed in this case.[14]

Although electron-poor styrenes are known to be sluggish substrates with 1st generation Grubbs catalysts,[15] 4-vinylacetophenone (**7**) (Scheme 2 C) appeared to be a straightforward choice to demonstrate our concept of tandem metathesis-ATH. In the first step, we carried out the cross-metathesis of **7** with 1-octene (**5**) using **HG-I** as catalyst.




**Scheme 2.** Proof of concept for the tandem olefin metathesis-ATH. All reactions were performed using 0.05 mmol of the ketone. Conditions: a) olefin (1 eq), **HG-I** (5 mol%), THF (0.5 mL), 4 h, 40 °C; b) addition of *i*PrOH (1.5 mL), (*R*,*R*)-Ts-DPEN (5.5 mol%), *t*BuOK (0.5 eq), 20 h, 30 °C; c) 1-octene (3 eq), **HG-I** (10 mol%), dichloroethane (0.3 mL), 5 h, 50 °C; d) addition of dichloroethane (0.2 mL), *i*PrOH (1.5 mL), (*R*,*R*)-Ts-DPEN (11 mol%), *t*BuOK (1 eq), 18 h, 30 °C. Conversion and *ee* determined by GC analysis with Chiralsil DEX CB column.

Although the reaction did not reach completion, we observed good selectivity towards the desired cross-metathesized product due to the fact that **7** is a type II olefin relative to **HG-I** according to the Chatterjee/Grubbs nomenclature.[15] Without any work-up or isolation, *i*PrOH, (*R*,*R*)-Ts-DPEN and *t*BuOK were then added to the reaction mixture. After 18 h, the desired alcohol (**8**) resulting from a sequential cross metathesis-ATH was obtained with 87% *ee* (Scheme 2 C) and an overall yield of 28%. [16] In this experiment, dichloroethane was used instead of THF, as it proved beneficial for the sluggish metathesis reaction without affecting the ATH step. It is also noteworthy that in all cases the ketone was reduced selectively, and the C=C bond did not react.

In summary, we have shown that 1st generation ruthenium catalysts for olefin metathesis can be converted into highly enantioselective catalysts for ketone ATH by addition of a chiral ligand, a base and *i*PrOH. Owing to the orthogonal reactivity of the C=C and C=O bond, the first example of a tandem cross metathesis-ATH was realized with model substrate **7**. Remarkably, in this tandem process, by addition of a chiral ligand to the Ru species present at the end of the metathesis step, a number of new Ru-hydride complexes were formed (as shown by NMR), among which the most enantioselective one appears to be the most active. We believe that this simple methodology could be of broad use for the synthetic community. Additionally, it allows for multiple use of ruthenium in different catalytic processes and therefore discloses new prospects towards a more efficient and sustainable use of this precious metal.

## Experimental Section

**Procedure for the tandem cross metathesis-ATH.** In a nitrogen filled mBraun glovebox, a solution of HG-I (3.0 mg, 0.005 mmol) in dichloroethane (0.3 mL) was added to 1-octene (16.8 mg, 0.15 mmol) and 1-(4-vinylphenyl)ethanone (7.3 mg, 0.05 mmol). The reaction mixture was stirred in an open glass vial for 5 h at 50 °C. After this time, (*R*,*R*)-TsDPEN (2.0 mg, 0.0055 mmol), dichloroethane (0.2 ml), *i*PrOH (1.5 mL) and *t*BuOK (5.6 mg, 0.05 mmol) were added in this order. The vial was closed and stirred for 18 h at 30 °C. Chiral GC analysis showed a conversion of 28% and 87% ee.

## Acknowledgements

We thank the European Commission [ITN-EID "REDUCTO" PITN-GA-2012-316371] for financial support and for predoctoral fellowships (to M. R.-C. and P. G.).

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[16] Upon hydrogenation, the remaining 1-(4-vinylphenyl)ethanone was hydrogenated to 1-(4-vinylphenyl)ethan-1-ol with 79% conversion and 90% *ee*.