Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201500359

Assisted Tandem Catalysis: Metathesis Followed by Asymmetric Hydrogenation from a Single Ruthenium Source

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Received: April 10, 2015; Revised: May 7, 2015; Published online: July 14, 2015

Dedicated to Prof. Stephen L. Buchwald on the occasion of his 60th birthday.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500359.

Abstract: Here we report the first example of a tandem metathesis–asymmetric hydrogenation protocol where the prochiral olefin generated by metathesis is hydrogenated with high enantioselectivity by an *in situ* formed chiral ruthenium catalyst. We show that either the ruthenium metathesis catalysts or the ruthenium species formed during the metathesis reaction can be converted into an efficient asymmetric hydrogenation catalyst upon addition of a chiral ligand and an alcohol. The performance in asymmetric hydrogenation appears to be very dependent on the solvent, the chiral ligand, and the prochiral substrate.

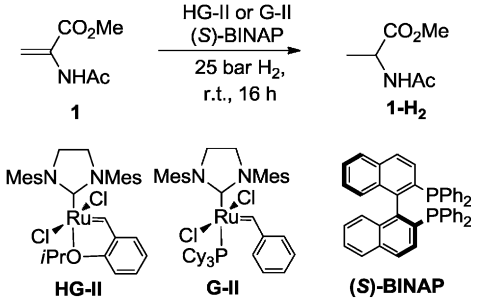
Keywords: asymmetric catalysis; hydrogenation; metathesis; ruthenium; tandem catalysis

In sequential tandem catalysis,[1] two consecutive catalytic transformations are carried out within a single reaction vessel where the product of the first catalytic cycle is the substrate of the second cycle. Fogg et al.[1b] in their review on the taxonomy of tandem reactions proposed the term "assisted tandem catalysis" for processes where the initial catalyst is converted into a new species able to catalyze the second reaction upon the addition of a reagent or a change in the reaction conditions. In addition to the main advantages associated with every one-pot multi-step transformation (i.e., high process and work-up efficiency), such a process allows multiple use of the catalyst or, at least, of its precious metal component.

Ru-catalyzed olefin metathesis[2] followed by hydrogenation is a typical example of assisted tandem catalysis and has been the subject of numerous publications,[3] initially in the field of polymers[4] and later in the synthesis of small molecules.[5] Although Ru is commonly used in asymmetric hydrogenation,[6] there are no reports about a sequential tandem metathesis–asymmetric hydrogenation. We anticipated that this could be achieved *via* addition of a chiral ligand after the metathesis step and prior to introducing hydrogen. However, such an approach is risky considering the fact that different Ru species are present at the end of the metathesis reaction.[7] Under hydrogen pressure, these may form different complexes which may or may not contain the chiral ligand, and which will have dissimilar efficiency in asymmetric hydrogenation. In this communication, we report our stepwise approach where we first show that Grubbs metathesis catalysts can be converted into enantioselective hydrogenation catalysts followed by several examples of sequential tandem metathesis–asymmetric hydrogenation.

In initial experiments, we tested whether Hoveyda–Grubbs 2nd generation metathesis catalyst (**HG-II**) in the presence of (*S*)-BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] as a chiral ligand was active in the enantioselective hydrogenation of 2-acetamidoacrylic acid methyl ester (**1**) (Scheme in Table 1). The choice of **HG-II** was based on the simple consideration that this catalyst does not contain any phosphine that could compete with BINAP in the com-

Table 1. Asymmetric hydrogenation with Grubbs metathesis precursor and (*S*)-BINAP.[a]



Entry	Ru	Ligand	Solvent[d]	Conversion [%][b]	*ee* [%][b]
1	**HG-II**	none	DCM	2	0
2	**HG-II**	none	THF	0	0
3	**HG-II**	(*S*)-BINAP	DCM	2	0
4	**HG-II**	(*S*)-BINAP	THF	0	0
5	**HG-II**	(*S*)-BINAP	DCM:MeOH	100	59
6	**HG-II**	(*S*)-BINAP	THF:MeOH	100	61
7	**HG-II**	none	DCM:MeOH	15	0
8	**HG-II**	none	THF:MeOH	16	0
9	**HG-II**	none; Et_3N[c]	DCM:MeOH	29	0
10	**HG-II**	(*S*)-BINAP; Et_3N[c]	DCM:MeOH	35	4
11	**HG-II**	(*S*)-BINAP[e]	DCM:MeOH	99	82
12	**HG-II**	(*S*)-BINAP[e]	THF:MeOH	5	0
13	**G-II**	(*S*)-BINAP	DCM:MeOH	100	0
14	**G-II**	none	DCM:MeOH	100	0

[a] *Reaction conditions:* **1** (1 mmol), Ru catalyst (1 mol%), (*S*)-BINAP (1.1 mol%), H_2 (25 bar), solvent (5 mL), 16 h, room temperature.
[b] Determined by GC analysis with a CP-Chirasil-DEX CB column.
[c] 3 equiv. Et_3N relative to Ru.
[d] Solvent mixtures: DCM:MeOH 1:4 or THF:MeOH 1:4.
[e] H_2: 2 bar (see the Supporting Information for other tests at *P* between 2 and 25 bar).

plexation of Ru and lead to the formation of an achiral hydrogenation catalyst after hydrogenolysis. In THF and DCM, the conversion of substrate **1** was very low, no matter whether the bisphosphine ligand was added or not (Table 1, entries 1–4). As reported by Fogg and co-workers,[8] the activity of Grubbs catalysts in hydrogenation can be enhanced by addition of an alcohol. Indeed, repeating the experiments in DCM:MeOH 1:4 or THF:MeOH 1:4 led to full conversions (entries 5 and 6).

Gratifyingly, a significant enantiomeric excess was also observed in both solvent mixtures, indicating that a Ru-BINAP complex active in hydrogenation had formed (possibly the same complex, considering that the same *ee* was obtained, entries 5 and 6). In the absence of the chiral ligand (entries 7 and 8), the conversion was much lower, suggesting that the hydrogenation was ligand-accelerated, that is, the best possible case for our goal to achieve high enantiomeric excesses. This is consistent with another observation by Fogg,[8c] who showed that the post-metathesis addition of a phosphine increases the activity in hydrogenation of precursors devoid of phosphine, most certainly by stabilizing the resting state of the catalyst. Et_3N was also reported as a beneficial additive when a mixture of DCM/MeOH was used as a solvent.[8] However, this appears not to be the case for substrate **1** (entries 9 and 10). The effect of lowering the hydrogen pressure to 2 bar (entries 11 and 12) was profound, but highly dependent on the solvent used: we obtained full conversion and a higher *ee* in DCM/MeOH but very low conversion towards the racemate in THF/MeOH. Finally, with the phosphine-containing Grubbs 2nd generation catalyst (**G-II**), we observed a very fast formation of the racemate even in presence of the chiral ligand (entries 13 and 14). Consequently, considering our goal to design a protocol for tandem metathesis–asymmetric hydrogenation, we decided to focus on **HG-II**.

It is well known that the solvent plays a crucial role in asymmetric hydrogenation.[9] It is even more so in our case where the solvent also determines the nature of the active hydrogenation species and their rate of formation. Therefore, we pursued our study by carrying out a solvent screening focusing on mixtures of THF or DCM with different amounts of alcohols

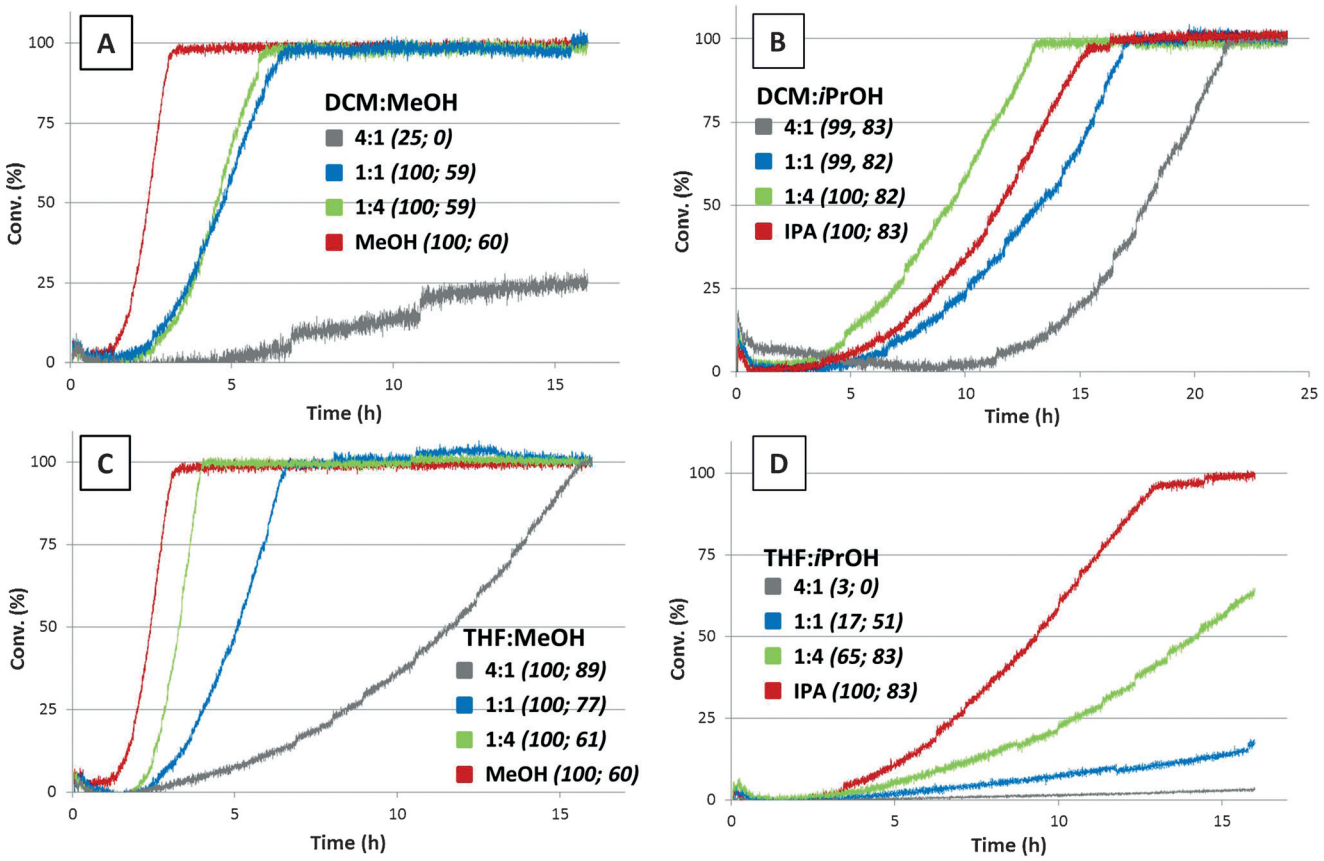


Figure 1. Asymmetric hydrogenation of **1** with **HG-II**/(*S*)-BINAP in different solvent mixtures [A: DCM:MeOH; B: DCM:*i*-PrOH; C: THF:MeOH; D: THF:*i*-PrOH; The kinetic profiles (conv. *vs.* time) are derived from hydrogen consumption measurement; in parenthesis, the conversion and *ee* at the end of the reaction are reported]. *Reaction conditions:* **1** (1 mmol), Ru catalyst (1 mol%), (*S*)-BINAP (1.1 mol%), H_2 (25 bar), solvent (5 mL), room temperature. Conversion and *ee* determined by GC analysis with CP-Chirasil-DEX CB column.

(MeOH and *i*-PrOH). The experiments were performed in a parallel Endeavour™ (Biotage) autoclave where the hydrogen consumption, and consequently the rate of reaction, could be monitored (Figure 1).

For all solvent systems, the addition of an alcohol leads to an increase of activity and, in almost all cases, the formation of enantiomerically enriched product. An induction period ranging from 1 hour up to 10 h is observed for all reactions. However, the kinetic profiles reveal some significant differences between DCM and THF. In DCM (Figure 1A), for the 4:1 DCM:MeOH mixture, some hydrogenation activity is observed, but without enantioselectivity. Upon addition of more MeOH (50 vol% and 80 vol%) and all the way up to pure MeOH, the asymmetric hydrogenation occurs with rates (denoted by the slope of the curves in Figure 1A) and enantiomeric excesses which do not vary significantly with the methanol content. The same is true with *i*-PrOH (Figure 1B), even at the lowest alcohol content (4:1 DCM:*i*-PrOH). The activity in DCM:*i*-PrOH is overall lower (longer induction periods, lower rate) than in DCM:MeOH, but the enantiomeric excesses are higher (82% *ee vs.* 60% *ee*). In THF (Figure 1C and D), a very different behavior is observed. The reactions start after a constant induction period of roughly 2 h and with a rate that is strongly increasing with the amount of alcohol. The enantiomeric excess is also varying greatly with the amount of alcohol, but in an opposite manner depending on the nature of the alcohol. The highest *ee*s are obtained with the lowest amount of MeOH (89% *ee* for the 4:1 THF:MeOH mixture) and with the highest amount of *i*-PrOH (83% *ee* for the 1:4 THF:*i*-PrOH mixture). A ligand screening performed under these optimized conditions confirmed (*S*)-BINAP as the best ligand (see the Supporting Information).

A detailed understanding of the molecular processes that take place in the different solvent combinations is difficult. The solvent influences both the formation of the hydrogenation catalyst and its activity/enantioselectivity. The catalytic performances result from the sum of both effects which, at this stage, cannot be deconvoluted. However, several observations can be made. First of all, the induction period observed for all solvent mixtures is certainly caused

by the relatively slow conversion of **HG-II** into one or more active hydrogenation catalysts *via* alcoholysis and/or hydrogenolysis. This transformation seems to occur more readily in DCM than in THF when *i*-PrOH is used (Figure 1B *vs.* D). With MeOH (Figure 1A *vs.* C), the difference is less pronounced indicating that MeOH is more efficient than *i*-PrOH for the alcoholysis of **HG-II**. Furthermore, for any amounts of *i*-PrOH (but also for a low amount of MeOH – see Figure 1C, grey curve) the rate of hydrogenation increases with time, suggesting that some additional catalyst is being formed as the asymmetric hydrogenation proceeds. In contrast, at a high ratio of MeOH or in pure MeOH, the reaction profiles resemble zero order kinetics which may be a proof that **HG-II** undergoes a rapid and complete transformation before significant hydrogenation takes place. The lack of variation of the *ee*s upon addition of DCM to the pure alcohol is consistent with the limited coordination ability of this solvent. On the contrary, THF – which is known to bind to ruthenium – affects the *ee*s significantly in the presence of either MeOH or *i*-PrOH.

In an effort to determine the nature of the Ru catalyst, the reaction of **HG-II** with (*S*)-BINAP in a mixture of THF:MeOH (1:4) was followed by ^{31}P NMR. No changes were observed after 16 h indicating that the chiral ligand remained uncoordinated. This experiment carried out in the absence of H_2 suggests that hydrogenolysis of the chelating benzylidene moiety is certainly a prerequisite for the binding of the chiral ligand to the Ru center.

Two other standard prochiral substrates (methyl 2-acetamidocinnamate, **2** and dimethyl itaconate, **3**) were tested in two solvent systems: 4:1 THF:MeOH, where we obtained the highest *ee* for the asymmetric hydrogenation of **1**, and 1:4 DCM:*i*-PrOH, the *i*-PrOH-containing system where the catalyst was the fastest. As shown in Figure 2, the prochiral olefin **2**, which is very similar to **1**, behaves in a very different way. For both solvent systems, only small amounts of product were obtained from which no reliable *ee* could be determined. With substrate **3**, the hydrogenated product was formed with an acceptable yield. The solvent system in which we obtained the best

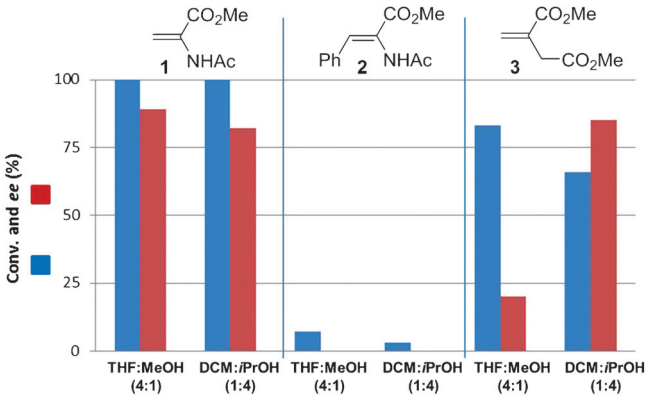
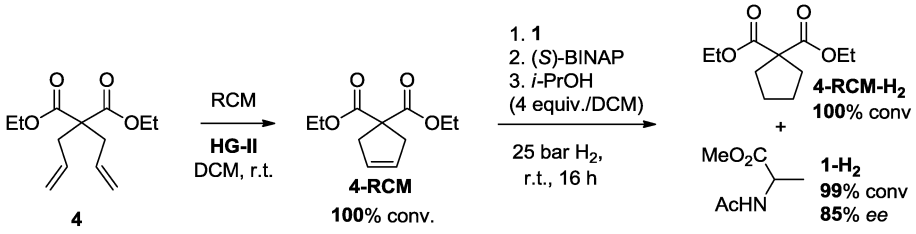


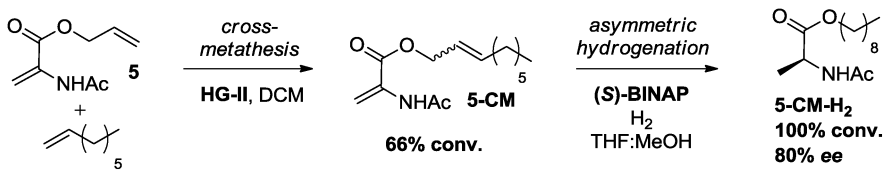
Figure 2. Comparison of the asymmetric hydrogenation of **1**, **2** and **3** with **HG-II**/(*S*)-BINAP in two solvent mixtures. *Reaction conditions:* **1** or **2** or **3** (1 mmol), Ru catalyst (1 mol%), (*S*)-BINAP (1.1 mol%), H_2 (25 bar), solvent (5 mL), 16 h, room temperature. Conversion and *ee* determined by GC analysis with CP-Chirasil-DEX CB (for **1**, **2**) and Astec® Chiraldex® G-TA (for **3**) columns.

enantiomeric excess with **1** (4:1 THF:MeOH) only led to 20% *ee*, far lower than the other tested solvent (85% *ee* in 1:4 DCM:*i*-PrOH). Nevertheless, this latter result confirms that the conversion of **HG-II** into an enantioselective hydrogenation catalyst is not limited to substrate **1**. However, it is well-known that in asymmetric hydrogenation every new substrate requires a new optimization of the solvent mixture and the chiral ligand – hence, the importance of high throughput experimentation.

Having demonstrated that the metathesis precatalyst **HG-II** could be converted into an asymmetric hydrogenation catalyst, we decided to test whether the same was true for the active species generated from this precursor during a metathesis reaction. For this purpose, we selected diethyl diallylmalonate (**4**) as a metathesis substrate. After having performed the ring-closing metathesis of **4**, we added (*S*)-BINAP, an alcohol and the prochiral substrate **1** to the reaction mixture and performed the asymmetric hydrogenation (Scheme 1). Gratifyingly, the same activity and enantiomeric excess were obtained as starting from the precatalyst, thus opening the path towards a tandem protocol.



Scheme 1. Proof of concept of the tandem metathesis–asymmetric hydrogenation. *Reaction conditions:* **4** and **1** (1 mmol), Ru catalyst (1 mol%), (*S*)-BINAP (1.1 mol%), H_2 (25 bar), solvent (5 mL), 16 h, room temperature. Conversion and *ee* determined by GC analysis with a CP-Chirasil-DEX CB column.

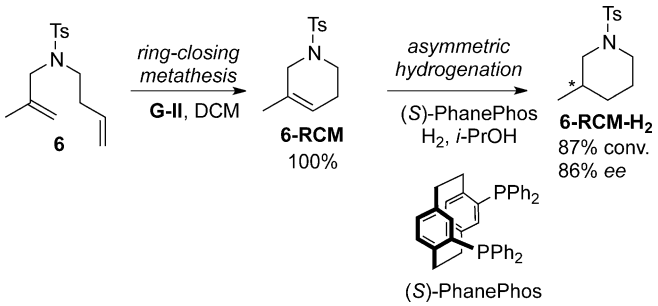


Scheme 2. Tandem metathesis–asymmetric hydrogenation. *Reaction conditions:* **5** (0.15 mmol), 1-octene (100 equiv.), Ru catalyst (5 mol%), (*S*)-BINAP (5.5 mol%), H_2 (50 bar), solvent for cross-methatesis: DCM (1.5 mL), solvent for asymmetric hydrogenation: THF:MeOH 4:1 (2 mL), 16 h, room temperature.

Substrate **5**, engineered to undergo a metathesis reaction followed by an asymmetric hydrogenation is a modified version of **1** with a terminal olefin as part of the ester group. This substrate was submitted to a cross-metathesis with 1-octene (Scheme 2). Although the metathesis reaction was not optimized and did not reach completion,[10] the ensuing asymmetric hydrogenation allowed us to obtain the fully hydrogenated product with a good enantiomeric excess, thus demonstrating the concept.

The recent work of Andersson and co-workers provided us with a second example for our tandem protocol.[11] These authors indeed disclosed the enantioselective synthesis of 3-substituted piperidines *via* metathesis followed by asymmetric hydrogenation. The first step was catalyzed by **G-II** and the second by an Ir/phosphine-thiooxazoline ligand. The prochiral olefin formed by metathesis was isolated prior to hydrogenation. Such a substrate (**6** in Scheme 3) perfectly fits our one-pot tandem metathesis–asymmetric hydrogenation protocol. Using our high throughput screening platform, 11 chiral ligands in combination with **HG-II** in 5 different solvents were tested. Considering that our parallel multireactor can accommodate up to 96 catalytic mixtures, we also tested **G-II**, that had been disclosed to be efficient in the ring closing metathesis of **6**.[11] **G-II** was tested only in one solvent system (1:1 DCM:*i*-PrOH) in view of the lack of enantiomeric excess obtained earlier with this Ru complex (Table 1, entry 11). Surprisingly, for substrate **6**, the best result was obtained with **G-II** in combination with PhanePhos as the chiral ligand.[12] Although **HG-II**–PhanePhos induced a comparable enantioselectivity, the catalyst was much less active. The detrimental effect of PCy_3 – as initially observed for substrate **1** – is therefore substrate-dependent. For substrate **6**, PCy_3 may act as a labile ligand that prevents a deactivation pathway of the catalyst.

In summary, we report the first proof of concept for a tandem metathesis–asymmetric hydrogenation protocol. Such a single-pot protocol is obviously advantageous in terms of cost due to the use of the same noble metal source to carry out two different transformations efficiently. What is also remarkable in this case is that high enantioselectivities can be obtained from the mixture of Ru species present at the end of the metathesis reactions. Indeed, it is well-known that asymmetric hydrogenation is a very sensitive transformation, and practitioners in this field usually take great care of using very pure metal precursors. This may not be needed, as long as a very active and enantioselective catalyst is formed from a mixture of pre-catalysts as seems to be the case in our protocol. Considering the latest development in Ru-based metathesis where the formation of tri- and tetra-substituted pro-chiral olefins is becoming more common,[13,14] we believe that our methodology could be applied to an increasing number of substrates and therefore be of great value for synthetic chemists.



Scheme 3. Tandem ring-closing metathesis–asymmetric hydrogenation. *Reaction conditions:* **6** (0.07 mmol), Ru catalyst (5 mol%), and (*S*)-PhanePhos (5.5 mol%), H_2 (50 bar), DCM:*i*-PrOH (1:1, 1 mL), 16 h, room temperature.

Experimental Section

Protocol for the Ligand Screening for the Tandem Ring-Closing Metathesis–Asymmetric Hydrogenation of 6

Under an inert atmosphere, a solution of **G-II** in DCM (0.144 mmol, 5 mol%) was added to **6** (2.87 mmol). After 15 min at room temperature, the reaction was complete. Using a liquid handling robot, small aliquots of the solution (170 μL, 0.07 mmol of **6-RCM**, 0.0035 mmol of Ru) were dispensed to 5-mL vials containing the chiral ligand in DCM solution (330 μL, 0.0039 mmol, 5.5 mol%). *i*-PrOH (0.5 mL) was added. The reaction mixtures were placed in the Premex A96 parallel reactor and stirred overnight under 50 bar of hydrogen at room temperature. Conversions and *ee*s were determined by gas chromatography.

Acknowledgements

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

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[10] In addition to the cross-metathesis product, we also observed 18% of remaining starting material and 16% of ring-closing metathesis product. Upon hydrogenation, only the remaining starting material was hydrogenated with 71% *ee*. See the Supporting Information for details.

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