High-Performance Isocyanide Scavengers for Use in Low-Waste Purification of Olefin Metathesis Products

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Three isocyanides containing a tertiary nitrogen atom were investigated for use as small-molecule ruthenium scavenging agents in the workup of olefin metathesis reactions. The proposed compounds are odorless, easy to obtain, and highly effective in removing metal residues, sometimes bringing the metal content below 0.0015 ppm. The most successful of the tested compounds, II, performs very well, even with challenging polar products. The performance of these scavengers is compared and contrasted with other known techniques, such as silica gel filtration and the use of self-scavenging catalysts. As a result, a new hybrid purification method is devised, which gives better results than using either a self-scavenging catalyst or a scavenger alone. Additionally, isocyanide II is shown to be a deactivating (reaction quenching) agent for olefin metathesis and superior to ethyl vinyl ether.

Introduction

Transition-metal complexes are the catalysts of many organic reactions of key research and industrial significance.[1–3] One of the most important issues related to their use is the removal of metal residues from reaction products. If not removed, these residues can cause the decomposition or isomerization of the product over time or negatively affect the yield of subsequent steps of the synthesis. Additionally, they preclude the use of such products in the synthesis of active pharmaceutical ingredients (API),[4–10] which are subject to strict legal limits on heavy-metal contamination (less than 10 ppm).[11]

Thanks to the discovery of well-defined ruthenium catalysts Ru1–Ru6 (Figure 1),[12–17] olefin metathesis (OM) became a very useful tool in organic synthesis. It creates carbon–carbon double bonds under mild conditions, with high yield and selectivity.[18] It has been used in the total synthesis of a wide variety of natural compounds[19] and increasingly finds its way into the syntheses of pharmaceutical products.[20]

Over the last 20 years, tremendous progress was made in the design of new OM catalysts.[21] Many details of the relationship between structure, activity, and stability have been elucidated.[22,23] Several auxiliary traits to enhance the practical usefulness of metathesis catalysts were also proposed.[24] In recent years, increasing attention has been given to the purification of OM products from ruthenium residues.[25,26]

The problem of metal residues can be addressed in a variety of ways: 1) classic methods of purification, such as recrystallization, extraction, or chromatography; 2) heterogeneous catalysis; 3) custom-designed self-scavenging catalysts; and 4) addition of metal scavengers.

Classic methods of purification are often insufficient to bring the metal content below 10 ppm.[27] Some of them are also difficult to scale to industrial applications. For example, chromatography is usually avoided in industrial settings due to the cost of adsorbents, high solvent use, and other factors that result in high total process costs.

Heterogeneous catalysts can be easily separated from the reaction mixture through filtration to afford a product with...
a low metal content. Unfortunately, in the case of OM, immobilization on a heterogeneous support often has adverse effects on catalytic activity due to steric interactions with the support and inhibited diffusion to and from catalytic sites.

Self-scavenging catalysts contain a structural element that allows the efficient removal of both the catalyst and its residues from the postreaction mixture through extraction, adsorption, filtration, or thermomorphic separation. However, the syntheses of such catalysts are often quite involved and, as a result, few of them are commercially available.

Metal scavengers are added to the postreaction mixture during workup and readily bind to transition metals, which facilitates their removal through classic methods of purification. Their use does not require structural modifications of the catalyst, so the same scavenger can potentially be used together with a wide variety of commercially available catalysts, which gives a measure of versatility. However, they require an additional workup step and introduce another possible contaminant: the scavenger itself.

The perfect scavenger should exhibit the following traits: 1) quick, irreversible, and quantitative binding of transition metals complexed with diverse ligands and in various oxidation states; 2) effectiveness at small stoichiometric excess with respect to the catalyst; 3) easy removal of both the metal–scavenger complex and unbound excess scavenger; 4) simple and cost-effective preparation; 5) stability in air and in the presence of moisture; 6) ease of handling, safety of use, and lack of toxicity or strong odor; and 7) a solubility profile that permits use in a wide variety of solvents.

Several ruthenium scavengers are described in the literature, for example, P(CH$_2$OH)$_3$, Pb(OAc)$_2$, DMSO or triphenylphosphine oxide (TPPO), polymer-bound chelating phosphines, functionalized mesoporous silicas, mercaptocynicotinic acid, d(ethylene glycol) vinyl ether, and silica-based heterogeneous particles. Most of these compounds are commercially available, but none of them satisfy all of the above conditions. Their most important disadvantages are the necessity of using them in large excess (more than 10 equiv with respect to the metal), a long binding time (more than 1 h), and high residual ruthenium content (above 10 ppm).

Our present work is inspired by the publications of Diver et al. In 2007, they presented a new method of purifying OM products with the polar isocyanide D1 (Figure 2). Isocyanides are widely used in the synthesis of organometallic complexes. Similar to N-heterocyclic carbenes (NHCs), they bind very strongly to ruthenium. In the case of second-generation OM catalysts, such as Ru2, coordination of isocyanides to the ruthenium atom initiates the Büchner reaction, which causes an insertion of the benzylidene ligand into an aromatic ring of the NHC ligand. The result is the creation of complex 1 and the immediate loss of metathetic activity. In the case of first-generation catalyst Ru1, the isocyanide D1 forms the inactive complex 2 and the phosphine ylide 3 (Scheme 1).

The presence of the –CO$_2$K moiety in compound D1 causes the newly formed, catalytically inactive complex to be highly polar, which makes it easy to remove from the mixture by means of column chromatography. Binding takes 30 min at room temperature and only a moderate excess of the scavenger is required (4.4 equiv with respect to the catalyst).

Compound D1 is a crystalline salt. It is easy to handle and devoid of the intolerable smell typical of volatile isocyanides. Unfortunately, the ionic structure restricts its solubility to highly polar solvents, such as alcohols and water. The residual ruthenium content in the products purified with the use of D1 is between 120 and 2200 ppm. These values are significantly higher than the allowable limits for pharmaceutical uses.

Recently, the group of Diver presented an isocyanide scavenger immobilized on silica gel, D2 (Figure 2). Compared with D1, it was necessary to use a much larger excess (60 equiv). The purified product contained 132 ppm of ruthenium. To bring the ruthenium content below 10 ppm, an additional chromatography step was required. A possible drawback of this method is the decomposition of the isocyanide groups of D2 over time, which may occur due to the acidic character of the silica gel.

Herein, we investigated new isocyanide metal scavengers with a polar fragment containing a tertiary nitrogen atom (Scheme 2). Compounds I–III bind strongly to silica gel and are soluble in common organic solvents. Similar to D1, they do not exhibit a strong odor; furthermore, unlike D1 and D2, there are no malodorous intermediates formed during their synthesis. Isocyanide II is a colorless, odorless, crystalline solid that is stable in air and in the presence of moisture. All three compounds can be easily obtained in two steps from inexpensive starting materials (Scheme 2). Additionally, compounds I and II are commercially available.
Results and Discussion

Use of scavengers combined with SiO₂ filtration

To test and compare the performance of compounds I–III with the Diver scavenger D1, a ring-closing metathesis (RCM) reaction of diethyl diallylmalonate (4a) was performed with 1.0 mol% of Ru4 (Scheme 3). After 1 h, the scavenger (0.35–8.8 equiv) dissolved in solvent (1 mL; methanol in the case of D1 and the reaction solvent in all other cases) was added, and the reaction was stirred for a further 30 min at room temperature. The mixture was then gravitationally filtered through a plug of silica gel (200 mg of gel for every 1 mmol of the catalyst). After removing the solvent, the ruthenium content in the final product was determined by inductively coupled plasma mass spectrometry (ICP-MS). Additionally, a control experiment was performed, in which no scavenger was added (Table 1, entry 1).

Purification only by filtering through silica gel in the control experiment afforded a product with 334 ppm of ruthenium. The use of D1 reduced this to 91 ppm (Table 1, entry 4). To eliminate the confounding effect of methanol required to dissolve D1, which affected the performance of filtration through silica gel, an extra experiment was performed in which the solvents were removed through evaporation and the residue was dissolved in pure dichloromethane before filtration; see text.

Table 1. Performance of the investigated scavengers and Diver’s isocyanide D1 in the model RCM reaction.

| Entry | Solvent | T [°C] | Scavenger | Equiv [a] | Ru content [ppm] |
|-------|---------|--------|-----------|-----------|-----------------|
| 1     | CH₂Cl₂ | 22     | D₁       | 2.2       | 334             |
| 2     | CH₂Cl₂ | 22     | D₁       | 4.4       | 299             |
| 3     | CH₂Cl₂ | 22     | D₁       | 8.8       | 138             |
| 4     | CH₂Cl₂ | 22     | D₁       | 8.8       | 91              |
| 5     | CH₂Cl₂ | 22     | D₁       | 2.2       | 40              |
| 6     | toluene| 70     | D₁       | 8.8       | 247             |
| 7     | CH₂Cl₂ | 22     | I        | 4.4       | 17              |
| 8     | CH₂Cl₂ | 22     | I        | 8.8       | 11              |
| 9     | CH₂Cl₂ | 22     | II       | 1.1 (2.2) | 22              |
| 10    | CH₂Cl₂ | 22     | II       | 2.2 (4.4) | 18              |
| 11    | toluene| 70     | II       | 2.2 (4.4) | 11              |
| 12    | CH₂Cl₂ | 22     | II       | 4.4 (8.8) | 1.6             |
| 13    | toluene| 70     | II       | 4.4 (8.8) | < 0.0015        |
| 14    | toluene| 70     | II       | 4.4 (8.8) | < 0.0015        |
| 15    | CH₂Cl₂ | 22     | III      | 0.35 (1.1) | 143             |
| 16    | CH₂Cl₂ | 22     | III      | 0.7 (2.2) | < 0.0015        |
| 17    | CH₂Cl₂ | 22     | III      | 1.5 (4.4) | 6.1             |
| 18    | CH₂Cl₂ | 22     | III      | 2.9 (8.8) | 7.1             |
| 19    | toluene| 70     | III      | 0.7 (2.2) | < 0.0015        |

[a] Equivalents of scavenger with respect to the catalyst. Values in parentheses indicate equivalents of isocyanide groups. [b] Solvent replaced with pure dichloromethane before filtration; see text.

For isocyanide III, an interesting and counterintuitive trend was observed (Table 1, entries 16–18): the less III used, the better were the results. The optimal amount turned out to be approximately 0.7 equivalents of the compound, or 2.2 equivalents of isocyanide groups, with respect to ruthenium. A further decrease to 0.35 equivalents caused a dramatic increase in ruthenium content to 143 ppm. These observations were reproducible. No such phenomenon was present for isocyanides I and II. This may be explained by the fact that two isocyanide groups will bind to each atom of ruthenium, whereas compound III has three such groups. In amounts lower than one equivalent, compound III probably forms polycentric, macro-molecular complexes with ruthenium, which are easier to remove than the small-molecule complexes formed when III is used in excess. However, no attempt was made to further corroborate this hypothesis.

After these initial experiments, we tested the performance of II, III, and D1 in removing several commonly used OMe catalysts. Compound 1a was reacted in toluene at 70 °C for 1 h to ensure both full conversion of the substrate and extensive decomposition of the catalyst (Scheme 4). The results are presented in Table 2. It should be noted that because toluene is
less polar than dichloromethane, it will elute as a smaller amount of ruthenium-containing contaminants from the silica gel plug, which is generally polar. This explains the difference in final ruthenium content between reactions in toluene and in CH$_2$Cl$_2$, and should not be interpreted as a solvent effect in the ruthenium binding process.

In the case of catalysts Ru2 and Ru3, scavengers II and III reduced the residual ruthenium content below 5 ppm. In the case of D1, ruthenium contamination was two orders of magnitude higher and equal to 251 and 142 ppm, respectively (Table 2, entries 4 and 7). The residues of Ru1 and Ru6 were more difficult to remove. The use of compounds II and III afforded products with ruthenium contents between 14 and 23 ppm, compared with 370 and 159 ppm obtained with D1. The results summarized in Table 2 indicate that II and III can be successfully applied with a variety of OM catalysts.

From a practical point of view, the physical properties and stability of a scavenger are just as important as its performance. At room temperature, the obtained compound III is a viscous oil, which slowly decomposes over time, even when refrigerated. In comparison, compound II is an easy to handle, crystalline solid that is insensitive to moisture and air. Therefore, despite promising results obtained with III, further investigation focused only on compound II.

To establish the scope of applicability of II, its effectiveness was evaluated for a variety of widely used variants of the OM reaction (Scheme 5). The ruthenium content in the products never exceeded 10 ppm, even with high catalyst loadings (5 mol%).

A potential drawback of using a scavenger is the risk of contaminating the product with the scavenger itself, especially when it is used in a large excess. Therefore, we investigated whether II contaminated the product. We verified that II produced a distinct peak in GC chromatograms. GC analysis of the reaction mixture before filtration through silica gel showed the

| Entry | Catalyst | Scavenger | Equiv[a] | Ru content [ppm] |
|-------|----------|-----------|----------|-----------------|
| 1     | Ru1      | D1        | 8.8      | 370             |
| 2     | Ru1      | II        | 4.4      | 14              |
| 3     | Ru1      | III       | 0.7      | 16              |
| 4     | Ru2      | D1        | 8.8      | 251             |
| 5     | Ru2      | II        | 4.4      | 1.2             |
| 6     | Ru2      | III       | 0.7      | 1.2             |
| 7     | Ru3      | D1        | 8.8      | 142             |
| 8     | Ru3      | II        | 4.4      | 2.4             |
| 9     | Ru3      | III       | 0.7      | <0.0015         |
| 10    | Ru6      | D1        | 8.8      | 159             |
| 11    | Ru6      | II        | 4.4      | 14              |
| 12    | Ru6      | III       | 0.7      | 23              |

[a] Equivalents with respect to the catalyst.

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| 4     | Ru2      | D1        | 8.8      | 251             |
| 5     | Ru2      | II        | 4.4      | 1.2             |
| 6     | Ru2      | III       | 0.7      | 1.2             |
| 7     | Ru3      | D1        | 8.8      | 142             |
| 8     | Ru3      | II        | 4.4      | 2.4             |
| 9     | Ru3      | III       | 0.7      | <0.0015         |
| 10    | Ru6      | D1        | 8.8      | 159             |
| 11    | Ru6      | II        | 4.4      | 14              |
| 12    | Ru6      | III       | 0.7      | 23              |

[a] Equivalents with respect to the catalyst.
presence of unreacted scavenger, whereas analysis of the filtrate showed an absence of a peak in the relevant region. This indicates that excess II binds strongly to silica gel and is thus removed, even when using polar eluents, such as ethyl acetate.

Use of scavengers combined with self-scavenging catalysts

Although 4a is a widely used model substrate for RCM, the results in Table 1 show that it is not particularly hard to purify it from metal residues. The next avenue of investigation was to check whether II would also work satisfactorily for more challenging, polar substrates that contained groups with high affinity to ruthenium; this is typical of biologically active compounds. Based on our experience, we selected proline derivative 13a and aromatic amide 14a as our “problem substrates” (Scheme 6). Both of these compounds contain an amide group in close proximity to the double bonds, which makes them likely to bind to ruthenium. A further adjustment was changing the solvent to ethyl acetate (ACS grade), which is more environmentally benign and more attractive for use in the pharmaceutical industry.[37, 68] Finally, the reaction was carried out under an ambient atmosphere.[69]

Compounds 13b and 14b purified only by filtration through silica gel were still significantly contaminated by ruthenium: 1530 and 2550 ppm, respectively (Table 3, entries 1 and 5). The use of scavenger II decreased the ruthenium levels to 30 (13b) and 60 ppm (14b; Table 3, entries 2 and 6, respectively).

Recently, we reported a new self-scavenging Hoveyda-type catalyst, Ru8, which contained a quaternary ammonium tag in the NHC ligand.[37] Crude products 13b and 14b obtained in a reaction with Ru8 have ruthenium contents equal to 5.9 and 15 ppm (Table 3, entries 3 and 7).

The results in Table 3, entries 5–7, showcase a situation in which every conventional strategy (classic purification, use of a scavenger, and use of a self-scavenging catalyst) fails to give a product with less than 10 ppm of ruthenium. This prompted us to search for a new, more effective method.

We found that simply combining the use of a self-scavenging catalyst with the use of a scavenger improved the results considerably. The use of Ru8 followed by the addition of II, when the reaction was complete, reduced the metal content by a factor of 5, to less than 5 ppm, when compared with the use of Ru8 alone. This strategy also allowed us to obtain 13b with a ruthenium content as low as 1.2 ppm (Table 3, entry 4), compared with the earlier result of 5.9 ppm (Table 3, entry 3).

Ruthenium removal without SiO2 filtration

Compounds 13b and 14b, in addition to being difficult to purify from ruthenium residues, bind strongly to silica gel, which complicates their efficient recovery. Filtration requires the use of a large amount of polar eluent (20 mL of EtOAc per 1 mmol of substrate). We observed that, after adding scavenger II to a solution of Ru8 in ethyl acetate, a precipitate formed. We decided to exploit this finding to improve the purification process of 6b. Another experiment was conducted, with both Ru8 and II, but instead of silica gel, the postreaction mixture was filtered through cotton wool (Scheme 7). We recovered 14b quantitatively, with a ruthenium content equal to 21 ppm. The control experiment, in which no II was added, afforded a product with 313 ppm of ruthenium, which was 15 times more. This approach is very practical because it does not require the use of silica gel, conserves solvents, and shortens the purification time.

Evaluation of II as a quenching agent

Fast-acting quenching agents (inhibitors of catalysis) facilitate the kinetic studies of organic reactions by allowing one to “freeze” their progress at a specific point in time and use off-

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**Table 3.** Comparison of the performance of classical methods, scavenger II, self-scavenging catalyst Ru8, and a hybrid method for problem substrates.

| Entry | Substrate | Catalyst | Scavenger [equiv][a] | Ru content [ppm] |
|-------|-----------|----------|---------------------|------------------|
| 1     | 13a       | Ru3      | –                   | 1530             |
| 2     | 13a       | Ru3      | II (4.4)            | 30               |
| 3     | 13a       | Ru8      | –                   | 5.9              |
| 4     | 13a       | Ru8      | II (4.4)            | 1.2              |
| 5     | 14a       | Ru7      | –                   | 2550             |
| 6     | 14a       | Ru7      | II (4.4)            | 60               |
| 7     | 14a       | Ru8      | –                   | 15               |
| 8     | 14a       | Ru8      | II (4.4)            | 3.0              |

[a] Equivalents with respect to the catalyst.
line analytic methods, such as GC, to analyze the samples. Furthermore, they enable the high-throughput acquisition of reaction profiles without the need for real-time, online, parallel analytics, which would require expensive hardware. Fogg et al. proposed the following set of traits desirable in a quenching agent:

1. complete interruption of all activity;
2. stability against decomposition into species that may cause further organic reactions under the conditions required for the completion of analysis;
3. solubility in common organic solvents to facilitate robotic dispensing;
4. a lack of volatility at the reaction temperature;
5. fast and irreversible action;
6. effectiveness at low loadings to minimize interference with analysis; and
7. commercial availability or simple, cost-effective preparation.

One of the most well-known traditional quenching agents for OM is ethyl vinyl ether (EVE). It works by competing with the substrate and forming an inactive Fischer carbene. This mechanism of action necessitates the use of a large excess of EVE. Furthermore, the formed Fischer carbene can exhibit residual catalytic activity in some cases. Thus, EVE does not satisfy criteria 1, 4, and 6.

In 2005, Diver et al. reported the use of CO and isocyanides to immediately interrupt an enyne metathesis reaction. CO does not compete with the substrate, but instead promotes the Bök-McGill insertion of the benzylidene fragment into the aromatic rings of the NHC ligand. This results in the complete and irreversible loss of catalytic activity in second-generation Grubbs-type complexes. Thanks to this mechanistic difference, it is much faster acting and can be used in lower excess. Unfortunately, CO is gaseous and toxic, which complicates its use. The isocyanide group is isoelectronic to CO, which inhibits metathetic activity through the same mechanism, and agents containing it are easier to handle. The reactions between isocyanides and Grubbs-type complexes were explored in detail in a 2009 publication from the same group.

To evaluate the performance of II as a quenching agent and compare it to EVE, mixtures of 15a with either II or EVE were prepared. We selected 15a because it is commonly used in kinetic experiments, reacts very fast, and the product 15b undergoes a number of postmetathesis reactions under certain conditions, such as unwanted C≡C bond shifts. A solution of catalyst Ru7 was added to these mixtures. Each of the combined solutions contained 4.4 equivalents of the deactivating agent with respect to the catalyst. After 3 h at room temperature, the conversion of the substrate was measured by GC. The sample with II showed no conversion, compared with 11% of the substrate undergoing a reaction in the sample with EVE. This confirms the expectation that II would be a much faster acting inhibitor of catalytic activity (Scheme 8).

The practical utility of II as a quenching agent was tested to measure the reaction profile of another popular catalyst. Figure 3 shows the profile of RCM of 15a with 1.0 mol% of the highly active nitro-Hoveyda catalyst Ru4, obtained by using II as the deactivating agent. Aliquots of the reacting mixture were added to a solution of II at selected points of time and then analyzed by GC.
Unlike EVE, CO, and D1, compound II satisfies all requirements for an ideal quenching agent for OM, as proposed by Fogg et al. The only notable drawback is the fact that it forms a distinct peak in GC analysis, which can overlap with product and/or substrate peaks. In the event of such a coincidence, changing the column or adjusting the thermal program should be sufficient to obtain usable data. On the other hand, the fact that II does not accumulate at the beginning of the column extends its service life and leads to improved reproducibility.

Conclusions

Three compounds containing a tertiary nitrogen atom and one, two, or three isocyanide groups were evaluated as ruthenium scavengers. Compound II outperforms other scavengers previously described in the literature. When combined with the use of self-scavenging catalysts, such as Ru8,[17] it provides a highly efficient de-activating agent for OM catalysts.

Compound III is also a highly effective scavenger and shows interesting multidentate binding behavior, but its physical properties and poor stability make it a less attractive choice from a practical standpoint.

This work shows new ways to attack the problem of ruthenium contamination in the products of OM intended for pharmaceutical use, and may prove to have significant importance in both laboratory and industrial practice.

Experimental Section

General

Commercially available chemicals were used as received. Ruthenium catalysts were obtained from Apeiron Catalysts. Scavenger III was prepared according to a procedure reported in the literature.[18] Merck silica gel 60 (230–400 mesh) was used for filtration through silica gel. NMR (1H and 13C) spectra were recorded on Agilent Mercury 400 MHz spectrometers, with CDCl3 as the solvent. Chemical shifts (δ) are given in ppm, with the solvent signal of CDCl3 used as a point of reference. Coupling constants (J) are reported in Hertz (Hz). IR spectra were recorded on a Thermo Scientific Nicolet iS 50 FT-IR spectrometer; wavenumbers (ν) are given in cm⁻¹. MS measurements were recorded on a Shimadzu LCMS-IT-TOF spectrometer. GC measurements were performed on a Perkielmer Clarus 580 instrument with an InertCap SMS-Sil column. Elemental analyses were performed by the Institute of Organic Chemistry, PAS, Warsaw. The determination of ruthenium content was performed by the Certified Chemical Laboratory of Multielemental Analyses, Wrocław University of Technology.

Synthesis of 1,4-Bis(3-isocyanopropyl)piperazine (II)

1,4-Bis(3-aminopropyl)piperazine (50 mL, 243 mmol) was added slowly to a stirred solution of ethyl formate (100 mL) and ethyl acetate (150 mL). The resulting mixture was vigorously stirred at RT for 2 h, with the crude product forming as a precipitate. After 2 h, an additional portion of EtOAc (100 mL) was added, and the mixture was filtered under reduced pressure. The residue was washed with EtOAc (2×75 mL) and dried at 50 °C under reduced pressure to afford quantitatively the corresponding diformamide (IIb) as a white solid, which was used without further purification. In the next step, triethylamine (33.4 mL, 12.0 equiv) dried over 4 Å molecular sieves was added to a stirred solution of IIb (5.13 g, 20.0 mmol) dissolved in CH2Cl2 (100 mL). The resulting mixture was cooled to 0 °C and phosphoryl chloride (5.58 mL, 3.0 equiv) was added dropwise. After 15 min, the cooling bath was removed and the reaction mixture was stirred for 1 h. Afterwards, the suspension was poured into an ice-cooled aqueous solution of K2CO3 (150 mL, 25 % w/v). The obtained solution was vigorously stirred for 30 min. CH2Cl2 (100 mL) was added and the layers were separated. The aqueous phase was washed with CH2Cl2 (2×50.0 mL). The combined organic phases were dried with anhydrous MgSO4. The solution was transferred into a flask containing a portion of silica gel (6.0 g) and the solvent was removed in vacuo. The dry residue was transferred onto a short pad of silica gel (12.0 g) and washed with a solution of triethylamine in CH2Cl2 (200 mL, 2:100). The product was recrystallized from cyclohexane (100 mL) to afford the target compound (2.57 g, 11.7 mmol, 58 %) as white crystals. Analytical data were in good agreement with previously reported values.[62]

Synthesis of (S)-N,N-diallyl-1-tosylpyrrolidin-2-carboxamide (13 a)

TsCl (24.0 g, 1.2 equiv) in Et2O (100.0 mL) was added to a stirred solution of l-proline (12.1 g, 105.0 mmol) dissolved in 1.5 M NaOH (170 mL). The resulting mixture was stirred at RT for 4 h. Then concentrated HCl (15 mL) was added to the solution until pH 2 was achieved. The organic layer was separated and the aqueous layer was extracted with Et2O (2×50.0 mL). The combined extracts were dried over MgSO4 and concentrated under reduced pressure. The crude product was recrystallized from CH2Cl2/n-hexane to give pure N-tosyl-l-proline as a white solid (23.2 g, 86.1 mmol, 82 %). Analytical data were in good agreement with previously reported values.[63] Under an argon atmosphere, N-tosyl-l-proline (13.5 g, 50.0 mmol) was dissolved in dry CH2Cl2 (50.0 mL), thionyl chloride (7.25 mL, 0.2 equiv) was added, and the resulting mixture was stirred at RT for 16 h. The solvent was then evaporated under reduced pressure to give a yellow viscous liquid. This was dissolved in dry CH2Cl2 (100.0 mL). The solution was cooled to 0 °C and diallylamine (7.5 mL, 1.2 equiv) was added dropwise followed by dry triethylamine (20.8 mL, 3.0 equiv). The resulting mixture was warmed to RT and stirred under an argon atmosphere for 2 h. Afterwards, the suspension was poured into a 10% solution of K2CO3 (100 mL). CH2Cl2 (100 mL) was added and the layers were separated. The organic layer was washed with a saturated solution of K2CO3 (3×100 mL) and dried with MgSO4. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (5% EtOAc/CH2Cl2) and then recrystallized from CH2Cl2/n-hexane to afford the target compound as a white solid (11.0 g, 31.6 mmol, 63 %). 1H NMR (400 MHz, 25 °C, CDCl3): δ = 7.77–7.71 (m, 2H, CHAr); 5.48–5.39 (m, 1H, CH=CHJ); 5.92–5.79 (m, 1H, CH); 5.78–5.65 (m, 1H, CH); 2.40 (s, 3H, CH3); 1.89–1.83 (m, 3H, CH2); 1.00–0.98 (m, 3H, CH3).
Synthesis of \(N,N\)-diallyl-4-bromobenzamide (14a)

Under an argon atmosphere, 4-bromobenzoyl chloride (8.6 g, 38.6 mmol) was dissolved in dry \(CH_2Cl_2\) (120 mL). The mixture was cooled to 0 °C. Diallylamine (5.3 mL, 1.2 equiv) was added dropwise, followed by dry triethylamine (16.1 mL, 3.0 equiv). The resulting reaction mixture was warmed to RT and stirred for 1 h. Then the suspension was poured into a 10% solution of HCl (75 mL). \(CH_2Cl_2\) (50 mL) was added and the layers were separated. The organic layer was washed with a 10% solution of HCl (75 mL), water (50 mL), and 10% solution of \(K_2CO_3\) (2 x 75 mL) and dried with MgSO\(_4\). The solvent was removed under reduced pressure. The crude product was recrystallized from \(n\)-hexane to afford compound 14a as colorless crystals (10.5 g, 37.5 mmol, 97%). \(^1H\) NMR (400 MHz, 25 °C, CDCl\(_3\)): \(\delta = 7.54–7.49\) (m, 2H; \(CH\)), 7.34–7.29 (m, 2H; \(CH\)), 5.86 (brs, 1H; \(CH\)), 5.72 (brs, 1H; \(CH\)), 5.30–5.13 (m, 4H; 2CH = \(CH\)), 4.11 (brs, 2H; \(NCH\)), 3.81 ppm (brs, 2H; \(NCH\)). \(^13C\) NMR (100 MHz, 25 °C, CDCl\(_3\)): \(\delta = 170.8, 135.2, 133.0, 132.7, 131.7, 128.5, 124.1, 117.9, 50.8, 47.33\) ppm; IR (neat): \(\tilde{\nu} = 3085, 3016, 2984, 2911, 1645, 1658, 1590, 1453, 1407, 1256, 1188, 1148, 1068, 1007, 950, 913, 834, 752, 634, 576, 555, 501, 426\) cm\(^{-1}\); MS (ESI, MeOH): \(m/z: 304.0\) [\(M+Na^+\)], 288.0 [\(2M+Na^+\)]; elemental analysis calcd (%) for \(C_{11}H_8BrNO\): C 55.73, H 5.04, Br 28.52, N 5.06; found: C 55.54, H 5.19, Br 28.65, N 5.06.

Method I: General procedure for the removal of ruthenium residues with isocyanide scavengers (Tables 1 and 2 and Scheme 2)

The substrate (4a–11a) (1.25 mmol) was placed in a Schenk flask. In the case of 11a, the cross-metathesis coreagent 12a (2.75 mmol) was added. The flask was flushed with argon and the contents were dissolved in a dry solvent (25 mL; \(CH_2Cl_2\) or toluene). The solution was heated to the predetermined temperature. Subsequently, an appropriate amount of the solid Ru catalyst (0.0125–0.6 mmol, 1.0–5.0 mol%) was added. The reaction mixture was stirred at the chosen temperature for 1 h. From this point onwards, all manipulations were carried out under an ambient atmosphere with ACS-grade solvents. The reaction mixture was cooled to RT, the chosen amount of the isocyanide scavenger (0.35–8.8 mol%) dissolved in the reaction solvent (1 mL; in the case of D1 in 1 mL of MeOH) was added, and the resulting mixture was stirred at RT for 30 min. Afterwards, the reaction mixture was gravitationally filtered through silica gel (200 mg of silica gel per 1 mg of catalyst; column diameter: 1.6 cm for 1.0–2.0 mol% catalyst loading, 2.7 cm for 5 mol% loading). The silica gel plug was washed with an additional portion of solvent (30 mL in the case of 6b, 100 mL in the case of 11b, 20 mL per 1 mol% of the catalyst in all other cases). Finally, the solvent was removed under reduced pressure to give 4b–11b quantitatively.

Method II: General procedure for the removal of ruthenium residues from 5b and 6b by II (Table 3)

Compound 13a or 14a (1.0 mmol) was dissolved in ACS-grade EtOAc (5 mL). The solution was warmed to 70 °C, then the ruthenium catalyst (0.01 mmol, 1.0 mol%) was added. The reaction mixture was stirred at 70 °C for 1 h under an ambient atmosphere. Then scavenger II (9.7 mg, 0.044 mmol, 4.4 mol%) was added and the resulting mixture was stirred at 70 °C for 30 min. The reaction mixture was gravitationally filtered through silica gel (200 mg of gel per 1 mg of the used catalyst; column diameter 1.6 cm). The silica gel plug was washed with an additional portion of EtOAc (20 mL). The solvent was removed under reduced pressure to give 13b or 14b quantitatively as white solids.

Compound 13b: \(^1H\) NMR (400 MHz, 25 °C, CDCl\(_3\)): \(\delta = 7.58–7.51\) (m, 2H; \(CH\)), 7.44–7.37 (m, 2H; \(CH\)), 5.94–5.88 (m, 1H; \(CH = CH\)), 5.77–5.71 (m, 1H; \(CH = CH\)), 4.46–4.40 (m, 2H; \(NCH\)), 4.42–4.15 ppm (m, 2H; \(NCH\)). \(^13C\) NMR (100 MHz, 25 °C, CDCl\(_3\)): \(\delta = 168.9, 135.8, 131.8, 128.7, 126.2, 125.2, 124.4, 55.9, 53.6 ppm; IR ( neat): \(\tilde{\nu} = 3083, 3056, 2930, 2893, 2850, 1634, 1584, 1562, 1431, 1392, 1340, 1275, 1257, 1194, 1159, 1144, 1066, 998, 962, 910, 893, 802, 785, 748, 709, 688, 626, 598, 487, 442\) cm\(^{-1}\); MS (ESI, MeOH): \(m/z: 343.1\) [\(M+Na^+\)], 663.2 [\(2M+Na^+\)]; elemental analysis calcd (%) for \(C_{11}H_8BrNO\) (252:11): C 52.41, H 4.00, Br 31.69, N 5.56; found: C 52.37, H 4.11, Br 31.49, N 5.45.

Compound 14b: \(^1H\) NMR (400 MHz, 25 °C, CDCl\(_3\)): \(\delta = 7.78–7.74\) (m, 2H; \(CH\)), 7.31–7.25 (m, 2H; \(CH\)), 5.89–5.83 (m, 1H; \(CH = CH\)), 4.67–4.52 (m, 2H), 4.35–4.11 (m, 3H), 3.51–3.36 (m, 2H; \(NCH\)), 2.40 (s, 3H; \(CH\)), 2.20–1.90 ppm (m, 3H), 1.85–1.73 ppm (m, 1H); \(^13C\) NMR (100 MHz, 25 °C, CDCl\(_3\)): \(\delta = 169.7, 143.5, 136.0, 129.6, 127.6, 126.0, 125.1, 59.2, 53.6, 53.3, 48.5, 30.5, 25.0, 21.7 ppm; IR ( neat): \(\tilde{\nu} = 2958, 2913, 2871, 1656, 1623, 1597, 1449, 1440, 1351, 1325, 1306, 1290, 1263, 1195, 1147, 1095, 1015, 991, 941, 887, 814, 750, 715, 679, 592, 549, 526, 507, 483\) cm\(^{-1}\); MS (ESI, MeOH): \(m/z: 276.0\) [\(M+Na^+\)], 527.0 [\(2M+Na^+\)]; elemental analysis calcd (%) for \(C_{11}H_8Na_2O_3\) (320:41): C 59.98, H 6.29, N 8.74, S 10.01; found: C 60.05, H 6.59, S 8.68, S 10.16.
Deactivation of OM reactions and GC studies of the catalytic activity of Ru4 (Schemes 7 and 8)

Compound 15a (251 mg, 1.0 mmol) and a deactivating agent (0.044 mmol; II or EVE) were dissolved in ACS-grade CH2Cl2 (20 mL). Then Ru7 (7.56 mg, 0.01 mmol) was added and the resulting mixture was stirred at RT for 3 h. The conversion of 15a was analyzed by GC.

Catalyst Ru4 (6.72 mg, 1.0 mol%) was added to a mixture of 15a (251 mg, 1.0 mmol) in ACS-grade CH2Cl2 (20 mL). At the same time, a handheld stopwatch was started. The resulting mixture was stirred at RT for 15 min. At regular time intervals, the reaction mixture (0.2 mL) was sampled by using a microsyringe and added to a solution of scavenger II (1 mL, 1 mg mL−1) in CH2Cl2; the sampling time was recorded at the moment of injection of the sample into the solution of the scavenger. The solutions obtained in this manner were analyzed by GC.

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