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A Practical Method for the Removal of Ruthenium Byproducts by Supercritical Fluid Extraction

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Abstract:

Supercritical CO_2 was used to remove ruthenium catalyst and its derived by-products from a crude ring-closing metathesis reaction. The method was implemented in a semi-continuous fashion and allowed for efficient removal of the toxic metal impurities to meet the specifications for the final drug substance.

Introduction

In the course of our development program for the treatment of hepatitis C virus,[1] we became involved with the synthesis of macrocyclic compound BILN2061 (**1**).[2] The introduction and development of Grubbs' family of ruthenium carbene catalysts has generated enormous interest in the chemical community, and tremendous achievements and improvements have occurred in the field of olefin metathesis.[3] Our strategy for the synthesis of the core macrocycle of **1** was based on a ring-closing metathesis (RCM) of diene **3**.[4]

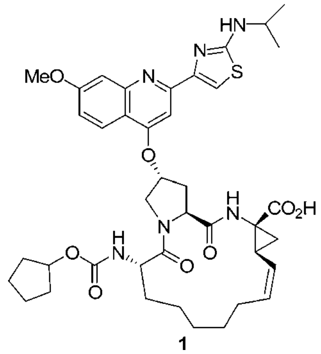

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Figure 1. **Structure of BILN 2061 (1).**

The key ring-closing metathesis step could be carried out with various ruthenium-based carbene catalysts such as the Grubbs catalysts **4** and **5** and Hoveyda catalysts **6** and **7**[5,6] (Scheme 1). Both the phosphine and the imidazoyl ligand-derived versions of the catalysts afforded yields of the desired macrocyclic compound higher than 80%.[2]

In addition to the low concentration of the macrocyclization step, removal of ruthenium byproducts rapidly emerged as an important process issue. The low tolerance to ruthenium contaminants in the final drug substance (<10 ppm)[7] made it critical that an efficient, economical, and practical method to remove the toxic metal byproducts was developed.

Several techniques have been reported to reduce the ruthenium content.[8] Table 1 shows the results obtained under

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Scheme 1. **Retrosynthetic analysis and RCM catalysts**

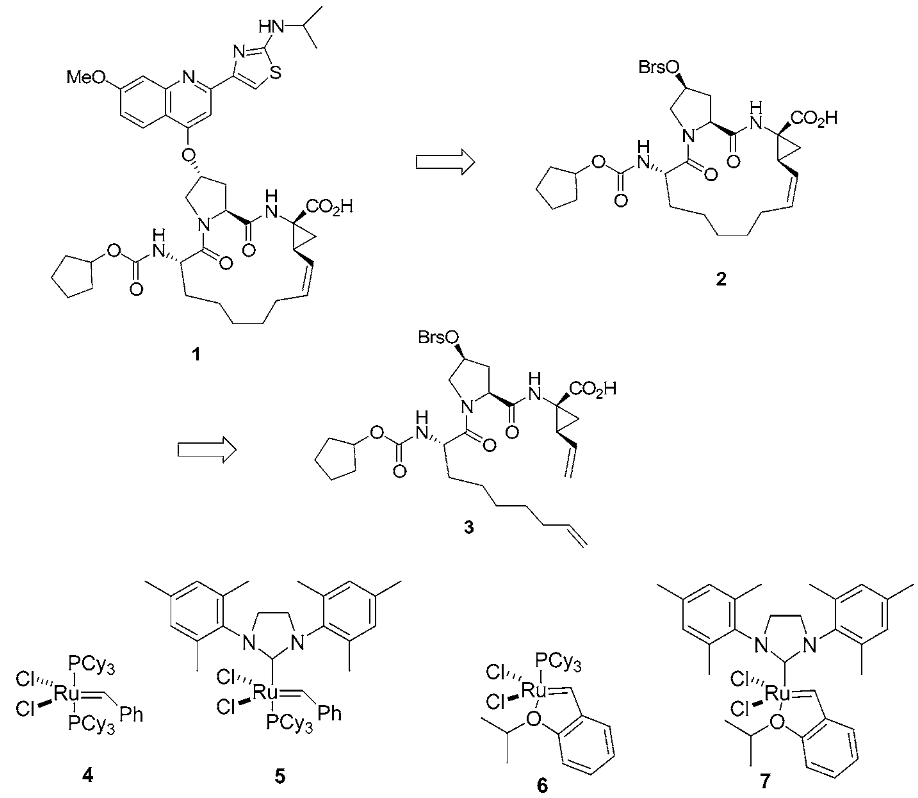

Table 1. **Screening of ruthenium scavengers**

entry	substrate (concentration)	catalyst (loading)	workup procedure	Ru level (ppm)
1	**3** ($C = 0.01$ M)	**4** (5 mol %)	THP (25 equiv)	623
2	**3** ($C = 0.1$ M)	**6** (1.5 mol %)	thiol-3 SiO_2 (10 equiv)	109
3	**3** ($C = 0.1$ M)	**6** (1.5 mol %)	PS-thiophenol SiO_2 (10 equiv)	293
4	**3** ($C = 0.01$ M)	**6** (1.5 mol %)	thiol-3 SiO_2 (100 equiv)	262
5	**3** ($C = 0.01$ M)	**5** (3.5 mol %)	THP (60 equiv)	260; 32[a]
6	**3** ($C = 0.01$ M)	**5** (3.5 mol %)	THP (40 equiv)	64[a]

[a] After charcoal treatment.

some of the reported protocols. Chelation of ruthenium byproducts with the water-soluble tris-hydroxymethyl phosphine reported by Grubbs[8b] resulted in lowering the levels of ruthenium from 1.5−5 mol % to below 700 ppm with all the catalysts tried (**4**, **5**, **6**, **7**). A rapid study showed that 40 equiv of phosphine could be used advantageously to minimize the ruthenium levels to below 70 ppm after charcoal treatment (entry 6). Pretreated metal scavenging silica and resins were also tested (entries 2−4). A correlation between the concentration of the metal and the scavenger was rapidly established which made apparent the inconvenience of heterogeneous treatments on a highly diluted crude reaction mixture. Direct charcoal treatments were also investigated. In our hands, none of the charcoals tested permitted reduction of ruthenium to acceptable levels at the API stage (two chemical transformations later) within a reasonable number of charcoal treatments. In addition, the ruthenium content seemed to reach a plateau after two to three charcoal treatments, and the metal content did not drop past this point unless a chemical transformation took place.

Various other techniques were tried which provided levels of ruthenium that met the specifications in the final drug substance. However most methods showed significant drawbacks. Long processing time, numerous washings and extractions,[2] high loading of the ruthenium scavengers, as well as patent infringement were a few of the problems encountered. Recourse to the extractive properties of supercritical carbon dioxide was therefore investigated. Herein we report a new, efficient, and practical method to remove metal byproducts associated with the RCM reaction.

Applications of supercritical fluid techniques are numerous in the area of extraction.[9] For instance, the technique has been used efficiently in nuclear chemistry for the removal of toxic metallic species.[10] One of the main advantages compared to conventional solvent extraction is the fast and selective extraction through control of the density of CO_2.

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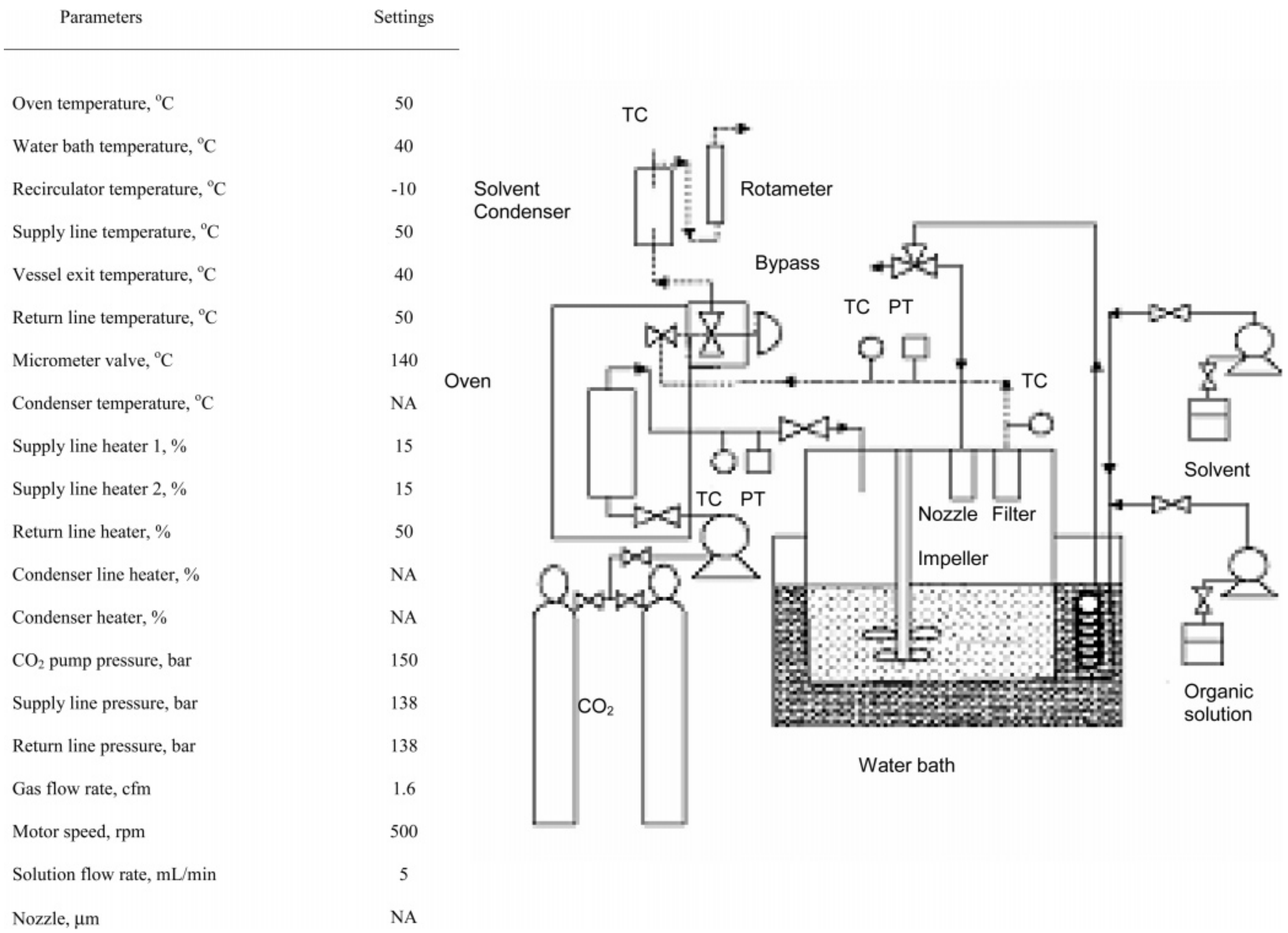

Parameters	Settings
Oven temperature, °C	50
Water bath temperature, °C	40
Recirculator temperature, °C	-10
Supply line temperature, °C	50
Vessel exit temperature, °C	40
Return line temperature, °C	50
Micrometer valve, °C	140
Condenser temperature, °C	NA
Supply line heater 1, %	15
Supply line heater 2, %	15
Return line heater, %	50
Condenser line heater, %	NA
Condenser heater, %	NA
CO_2 pump pressure, bar	150
Supply line pressure, bar	138
Return line pressure, bar	138
Gas flow rate, cfm	1.6
Motor speed, rpm	500
Solution flow rate, mL/min	5
Nozzle, μm	NA

Figure 2. **(Left) Conditions and settings for the continuous extraction. (Right) Diagram of reactor.**

The supercritical fluid (T_c 31 °C, P_c 73.75 bar, d_c 0.468 $g{\cdot}cm^{-3}$) operates as an environmentally benign medium easily recycled and possesses remarkable gas-like properties (high diffusivity and miscibility with the reactants, low viscosity, and high compressibility among others).

Selective extraction of a homogeneous transition metal catalyst with supercritical fluids (SFE) has been reported, but derivatization of the catalytic system with a CO_2-philic moiety is performed in most cases to enhance its solubility in the medium.[11]

We felt it possible to isolate substrate **2** by taking advantage of its preferential solubility in supercritical CO_2, thus leaving the ruthenium byproducts in the autoclave.[12] To the best of our knowledge, there is no report of the practical use of the technique for the removal of ruthenium catalyst and derived byproducts.

The phase behavior of the system was initially determined visually by means of a 50 mL view cell equipped with sapphire windows to render solvent expansion visible to the eye. The autoclave was charged with a 1 M solution of **2** in toluene, and the pressure was gradually increased. The experiment was repeated at various temperatures. Full expansion was determined to take place at a temperature of 40 °C and a pressure of 83−90 bar. At such pressure, a dark residue precipitated on the side of the vessel. Analysis of the content of the autoclave indicated that no decomposition had taken place at high pressure and temperature which proved the chemical compatibility of **2** with the medium.

A qualitative determination of the dynamic solubility of our substrate in sCO_2 then showed that an organic modifier was required. The experiments were carried out on an ISCO extractor, and the solubility was monitored as a function of the recovery. A 5 mL autoclave was charged with pure compound **2** neat or in solution at different concentrations. The system was maintained at 40 °C under a pressure of 100 bar for 30 min under dynamic conditions. The pressure was released slowly, and the product was collected from the CO_2 stream upon depressurization in a cold trap maintained

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Table 2. **Effect of modifiers in sCO_2 extraction**

entry	T (°C)	P (bar)	modifier (concentration)	recovery (%)
1	25	83	none	no extraction
2	25	83	CH_2Cl_2 (0.1 M)	90
3	25	83	toluene (0.1 M)	65
4	25	83	toluene (0.01 M)	90

at −78 °C. When the material was used dry, low recovery was obtained (see entry 1, Table 2) but the presence of an organic solvent drastically enhanced the solubility (see entries 2 and 3, Table 2). Dichloromethane and toluene used in the RCM worked particularly well, and metal removal was demonstrated by the dramatic color change of the extract (from dark brown to faint brown or yellow).

In addition, these preliminary experiments showed that the recovery increased with reduced concentrations (see entries 3 and 4, Table 2). Crude reaction mixtures in toluene at 0.01 M were therefore used directly for the subsequent extractions.

A preparative extraction experiment was then performed on an ISCO Speed SFE Unit. A crude solution of **2** (28 mg product at 0.01 M in toluene) containing 5 mol % ruthenium catalyst **6** was introduced in a 5 mL autoclave. The temperature was set to 40 °C with a CO_2 pressure (purity 99%) into the extractor of 138 bar. The system was held at that temperature for 30 min, and product **2** was collected from the CO_2 stream in a cold trap at −78 °C upon depressurization at a flow rate of ∼1.5 mL/min. At the end of the extraction, a clear extract containing 26 mg of product **2** (determined by assay, 92% overall recovery) was collected, and the autoclave showed a dark residue. The experiment was repeated on 80 g scale in a 1 L autoclave unit with a temperature and pressure of CO_2 of 40 °C and 97 bar, respectively, a 30 min dynamic equilibration and depressurization at a flow rate of ∼1.5 mL/min, and our earlier results were confirmed.[13] A 90% recovery of **2** was observed, and the level of residual metal was reduced from 50000 ppm (5 mol %) to 56 ppm as determined by ICP.[14] In addition, the content of the autoclave when added to a solution of diene **3** in toluene and submitted to the RCM conditions promoted the ring-closure, thus confirming the possibility to recycle the catalyst from the process.

Table 3. **sCO_2 extraction under semi-continuous fashion**

entry	recovery (%)	comments	Ru level (ppm)
1	88	dark residue in the autoclave	708
		clear extract	100[a]
2	90	dark residue in the autoclave	839
		clear extract	115[a]

[a] After charcoal treatment.

Encouraged by these results, we evaluated the extraction in a semi-continuous mode.[15] A crude mixture of **2** (*c* 0.01 M in toluene) containing 5 mol % ruthenium catalyst **6** was injected continuously at 5 mL/min to a 300 mL mixed pressure vessel, with continuous injection of CO_2 at 100 mL/min. The internal temperature and pressure were set to 40 °C and 83 bar, respectively. The product was immediately extracted without dynamic equilibration. Within 50 min, 250 mL of crude solution was injected, and 230 mL was collected (92% recovery of organic solution, 88% recovery based on **2** as determined by assay). The dried material showed a level of ruthenium of 708 ppm as determined by ICP. Subsequent charcoal treatment prior to concentration reduced the ruthenium to 100 ppm (see entry 1, Table 3 and Figure 2). The reproducibility of the technique was demonstrated by a second extraction under the same conditions which gave 90% recovery, 835 ppm ruthenium before charcoal treatment and 115 ppm after charcoal filtration (see entry 2, Table 3).[16]

In summary, we have demonstrated the utility of supercritical CO_2 to remove metathesis ruthenium alkylidene catalyst and derived byproducts from a crude ring-closing metathesis reaction. The technique is practical, economical, and environmentally friendly. It was implemented in a continuous fashion and allowed for efficient removal of the toxic metal impurities to meet the specifications required in the final drug substance.

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(13) Experimental procedure : A 1 L pressure reactor was charged with 81 g of a crude metathesis solution (**2** in toluene at 0.01 M with 5 mol % first-generation Hoveyda catalyst **10**; for preparation see ref 2). The reactor was heated to 40 °C, and CO_2 was introduced to obtain an internal pressure of 97 bar. The mixture was allowed to equilibrate under those conditions for ∼30 min and then was extracted at ∼1.5 mL/min; 639 mg of **2** was recovered (92% recovery). Ruthenium analysis by ICP indicated a level of 56 ppm.

(14) The recovered material resubmitted to the same conditions resulted in ruthenium levels below 2 ppm.

(15) Experimental procedure for semi-continuous run extraction: See Figure 2 for settings for the extraction. A 0.01 M solution of **2** in toluene (250 mL) was charged in the pump and injected continuously at 5 mL/min to a reactor with a continuous flow of CO_2 at 100 mL/min. The internal pressure in the system was set to 138 bar and the temperature to 40 °C. The product was extracted without equilibration. An aliquot of the extract was concentrated and dried under vaccum. Ruthenium analysis by ICP indicated a level of 708 ppm. Once the extraction was complete, the mixture was allowed to degas and was stirred for 2 hours with 1 g of charcoal. Filtration through a pad of celite, concentration, and drying under vacuum gave an off-white solid (1.56 g, 90% recovery). Ruthenium analysis by ICP indicated a level of 100 ppm.

(16) The isolated material resubmitted to the same conditions resulted in ruthenium levels below 15 ppm.