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Catalysts

Large-Scale Synthesis of a Niche Olefin Metathesis Catalyst Bearing an Unsymmetrical N-Heterocyclic Carbene (NHC) Ligand and its Application in a Green Pharmaceutical Context

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Abstract: A large-scale synthesis of known Ru olefin metathesis catalyst **VII** featuring an unsymmetrical N-heterocyclic carbene (NHC) ligand with one 2,5-diisopropylphenyl (DIPP) and one thiophenylmethylene *N*-substituent is reported. The optimised procedure does not require column chromatography in any step and allows for preparation of up to 0.5 kg batches of the catalyst from simple precursors. The application profile of the obtained catalyst was studied in environmentally friendly dimethyl carbonate (DMC). Although **VII** exhibited low efficiency in cross-metathesis (CM) with electron-deficient partners, good to excellent results were noted for substrates featuring easy to isomerise C–C double bonds. This includes polyfunctional substrates of medicinal chemistry interest, such as analogues of psychoactive 5F-PB-22 and NM-2201 and two PDE5 inhibitors—Sildenafil and Vardenafil. Finally, a larger scale ring-closing metathesis (RCM) of a Vardenafil derivative was conducted in DMC, allowing for straightforward isolation of the expected product (23 g) in high yield and with low Ru contamination level (7.7 ppm).

Introduction

One of the main challenges faced by the chemical industry is to provide effective technologies to enable performing reactions in a truly environmentally friendly manner.[1] This involves the development of cleaner and more efficient catalytic processes based on new types of catalysts, which exhibit high activity and selectivity, even in the presence of varying levels of impurities present in biomass-based substrates and solvents.[2] Such approaches not only give access to many products that have not been available owing to synthetic limitations, but also allow to reduce generation of waste, reduce reaction times and decrease general production costs. The trend is closely associated with the so-called Circular Economy,[3] aimed at "minimizing waste and making the most of resources", and encouraging use of renewable raw materials instead of fossil ones as substrates and solvents. Given the mild reaction conditions and high atom-economy, the catalytic olefin metathesis reaction[4] is currently undergoing a thriving development as a powerful transformation leading to complex organic molecules, including natural products, Active Pharmaceutical Ingredients (APIs),[5] and much more.[6]

In the same context, it is important to note that the particular class of metathesis catalysts belonging to the family of ruthenium(II) carbene complexes is not very sensitive towards air and moisture, and in general is compatible with so-called "green solvents", such as 2-MeTHF, ethyl and methyl carbonate, ethyl acetate,[7] and even more polar media, such as water,[8] alcohols[9] or ethyl lactate.[10] This attribute is primarily because of the existing consensus regarding the pressing need to switch away from fuel-based aromatic or chlorinated solvents to their more ecologically friendly and green alternatives.[11] This is especially important in pharmaceutical production, which is highly material inefficient (*E*-factor of 25 to 100) and uses relatively large volumes of solvents.[12] According to our best knowledge, only one example of a pharmaceutically relevant larger scale (1.5 kg) metathesis reaction in such solvent is the known synthesis of IDX320, a hepatitis C virus protease inhibitor by Idenix Pharmaceuticals Inc. performed in ethyl acetate (Figure 1).[13] Other APIs described in recent review literature[5c,14] were prepared in non-green solvents, usually in chlorinated ICH Class 1 solvents or in toluene (ICH Class 2 solvent).

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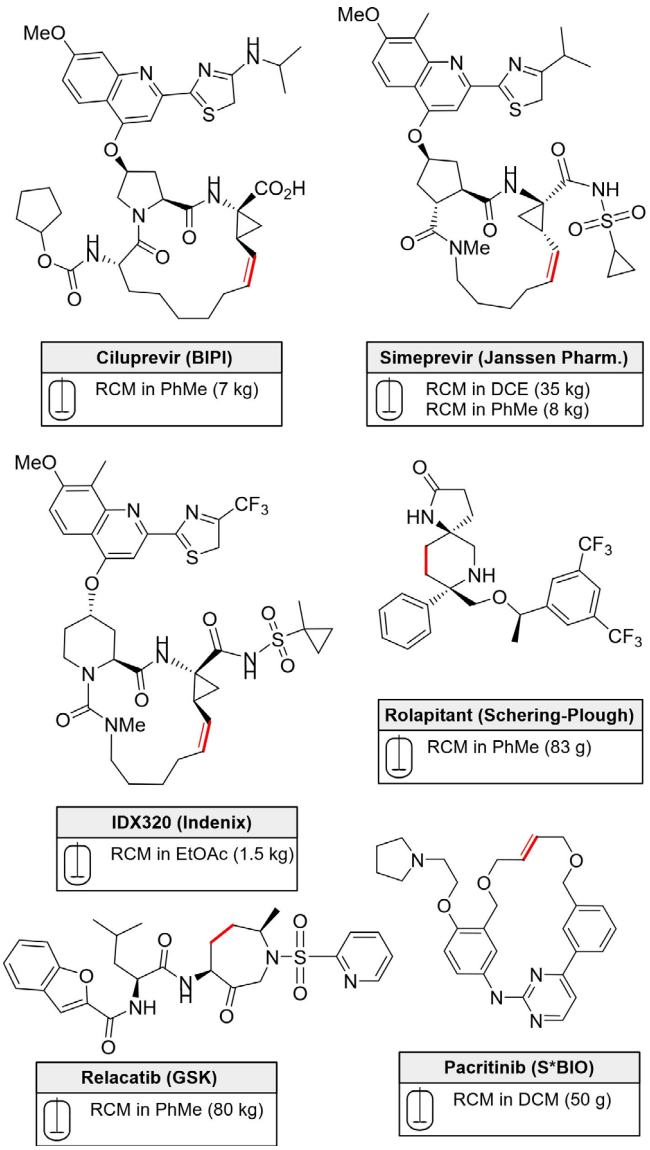


Figure 1. Selected examples of APIs and drug candidates prepared by RCM, including reported scale and solvent (DCM = dichloromethane; DCE = 1,2-dichloroethane; PhMe = toluene).

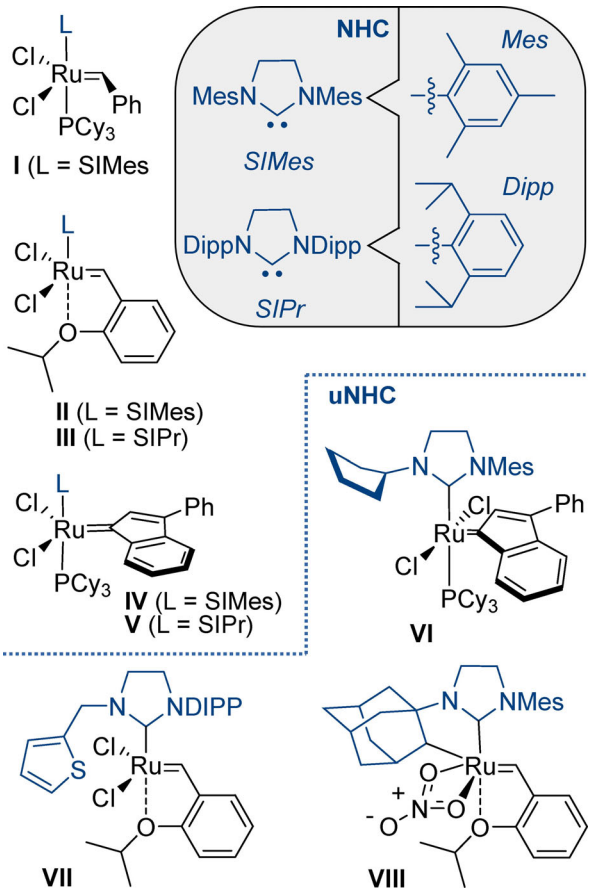


Figure 2. Representative general-purpose Ru catalysts bearing SIMes and SIPr ligands (**I**–**V**) and selected specialised complexes with uNHC ligands (**VI**–**VIII**).

Results and Discussion

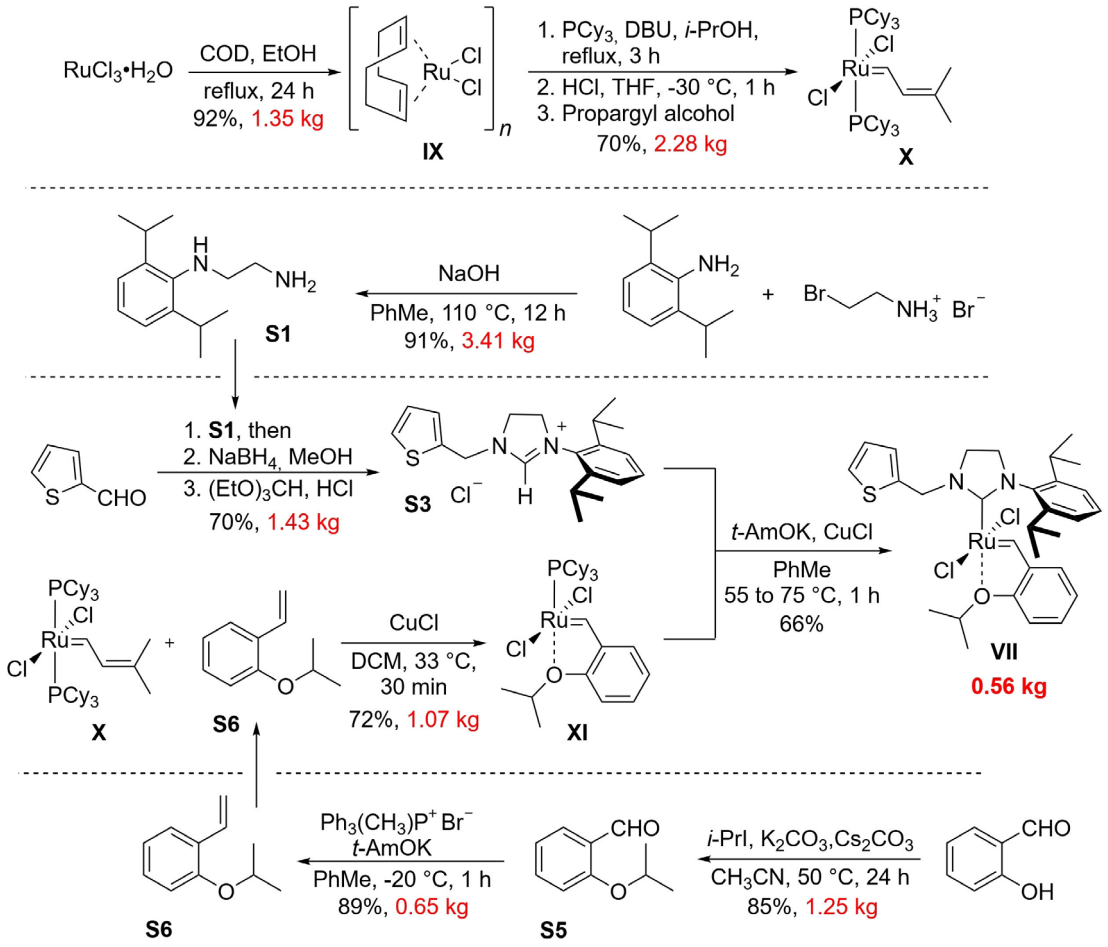
The soaring popularity of ruthenium olefin metathesis catalysts is strongly associated with the introduction of N-heterocyclic carbene (NHC) ligands.[15] Although the vast majority of Ru catalyst applications is dominated by complexes **I**–**III**—true top-sellers bearing symmetrical NHC ligands (Figure 2a)—their analogues with unsymmetrical NHC (uNHC) ligands, although usually displaying lower general activity than their symmetrical counterparts, have carved a niche for themselves in demanding transformations such as high-concentration macrocyclisation,[16] ethenolysis[17] or self-metathesis of α-olefins[18] and others, owing much higher selectivity.[19] Additionally, engineered uNHC Ru catalysts, such as **VIII** are very useful in the stereocontrolled formation of *Z*-configured C–C double bonds.[6g]

Herewith, we present for the first time the large-scale synthesis of a "niche" olefin metathesis uNHC catalyst **VII**; its scope and limitations study in diverse metathesis reactions were carried out in a green solvent—dimethyl carbonate (DMC). This study was additionally extended to the small- and large-scale synthesis of some pharmaceutically relevant compounds, such as new analogues of Sildenafil and Vardenafil, popular drugs used in a treatment of erectile dysfunction.

Large-scale preparation of uNHC catalyst VII

For the scale-up study, we selected known uNHC catalyst (**VII**),[20] which was found to offer good results in a number of "difficult" self-metathesis reactions of α-olefins and in macrocyclisation reactions.[16,20a] The low-scale (up to 320 mg) synthesis of this catalyst was reported,[20a] however, the larger scale synthesis was never attempted. The growing demand for this catalyst forced us to start a scale-up study to prepare this complex in at least 0.5 kg scale (Scheme 1).

The first decision to make in the planned large-scale synthesis was the choice of suitable ruthenium source. Therefore, the first step in our synthesis was transformation of the simplest commercially available ruthenium source—ruthenium(III) chloride hydrate—into an appropriate Ru^{II} complex, on which the



Scheme 1. Large-scale synthesis of catalyst **VII** from inexpensive commercially available reagents (*t*-Am = *tert*-pentyl (*tert*-amyl); COD = 1,5-cyclooctadiene; DCM = dichloromethane; DBU = 1,8-diazabicyklo(5.4.0)undec-7-en; Cy = cyclohexyl).

ligand exchange can be performed. Considering the present high cost of platinum metals on the market, and the limited number of ruthenium producers,[21] we were looking for a high-yielding but also cost-effective route. For example, in a number of protocols, ruthenium(III) chloride is converted by a reaction with triphenylphosphine into a common precursor "$RuCl_2(PPh_3)_3$" and then into more elaborate carbene complexes.[22] However, after calculating the estimated material–operation costs for this route, as well as for a number of alternative strategies, and considering various risks (such as the formation of impurities and safety aspects), it was decided instead to use a route proceeding via known ruthenium(II) complex **X** (Scheme 1).[23] Synthesis of the above precursor was possible in a few straightforward steps. First, $RuCl_3{\cdot}H_2O$ was reacted with cycloocta-1,5-diene and ethanol,[24] a reaction which even at > 1 kg scale went uneventfully in our hands. Next, the product—poorly soluble polymer **IX**—was transformed into complex **X** as a result of a one-pot, two-step procedure. In the first step of this transformation, an oxygen and moisture-sensitive ruthenium hydride complex was obtained, which then without isolation was reacted with propargyl alcohol providing 2.25 kg of complex **X** with an overall 70% yield. Independently, the benzylidene and uNHC ligands precursors were prepared in an appropriate quantity, based on scaled-up and optimised original procedures.[20a] The thiophene-based uNHC ligand precursor (salt **S3**) was synthesised in three steps, which consisted of imine formation by reaction of thiophene-2-carbaldehyde with *N*,*N*′-(2,6-diisopropylphenyl)ethane-1,2-diamine (**S1**), reduction the resulting imine with $NaBH_4$ and condensation of the newly formed diamine with triethyl orthoformate in 70% total yield (Scheme 1). 2-Isopropoxystyrene (**S6**) was obtained in > 75% yield in two straightforward steps—Williamson alkylation of salicylaldehyde with 2-iodopropane (1.25 kg scale) and subsequent Wittig reaction at 0.65 kg scale. Next, the reaction of styrene **S6** with **X** in the presence of CuCl as the phosphine scavenger gave > 1 kg of the Hoveyda–Grubbs first-generation complex (**XI**, 72%) without much difficulty. With all precursors in hand, we attempted the large-scale synthesis of **VII** for the first time. The exploratory runs were made at 55 and 200 g scale giving reproducibly 64–66% yield. Analytical data of the produced complex were in full agreement with those obtained in a previously published low-scale procedure.[20a] Encouraged by these results, we moved to the final scale-up experiment, using a 60 L reactor and starting from 0.58 kg of salt **S3**, which under deprotonation with potassium *tert*-amylate (0.92 L of 1.7 M solution in toluene) afforded in situ a corresponding car-

bene, which was then installed on Ru^{II} complex **XI** (0.79 kg), yielding finally 0.56 kg (66% yield) of the expected complex **VII**, isolated as a green microcrystalline solid.

Having secured a suitable amount of catalyst **VII**, we attempted to study its scope and limitations in diverse metathesis reactions carried out in a green solvent—dimethyl carbonate (DMC).[7a,b,25]

Application of catalyst VII in RCM of simple and moderately complex substrates in DMC

Our previous studies on this type of thiophene-based uNHC catalysts in solvents such as toluene[20a] or 2-methyltetrahydrofuran[20a] suggest that although relatively poorly potent at ambient temperature, these complexes activate at 50–70 °C; however, in general, they exhibit lower productivity levels compared with general-purpose catalysts featuring symmetrical NHC ligands.[20a] To complete this picture, a model RCM of **1** (DEDAM) has been performed in DMC, comparing uNHC **VII** with **II** and **III**. Time-conversion curves presented in Figure 3 show, as it may be expected from previously published studies,[20a] that **VII** was slightly less active than SIMes and SIPr complexes. However, at 0.1 mol%, **VII** still gave 91% conversion and at 0.2 mol% full conversion was observed (see Table 1).

We noted that even relatively low amounts of catalyst **VII** in DMC were enough to form five- and six-membered carbocycles with high selectivity (entries 1–4). The same was the case for RCM and enyne cycloisomerisation with 0.5 mol% of **VII** leading to various five- to seven-membered O- and N-heterocycles (entries 5–9). It should be noted that uNHC catalyst **VII** gave generally high selectivity levels,[18,20a,26] which was especially visible in the case of **12**, which is sensitive to a C–C double bond shift.[27]

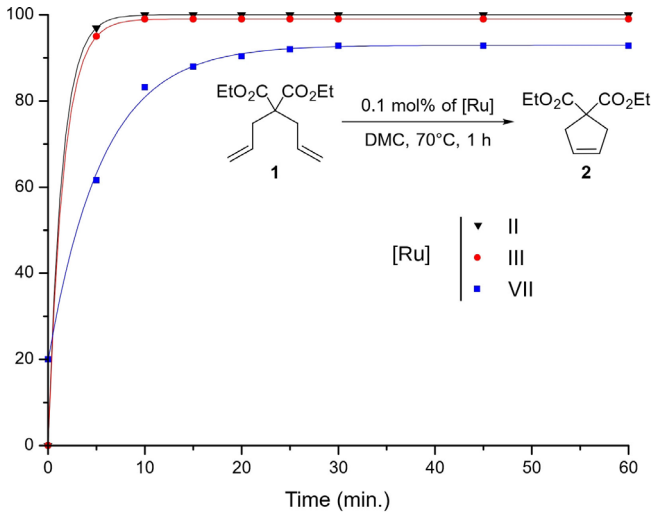
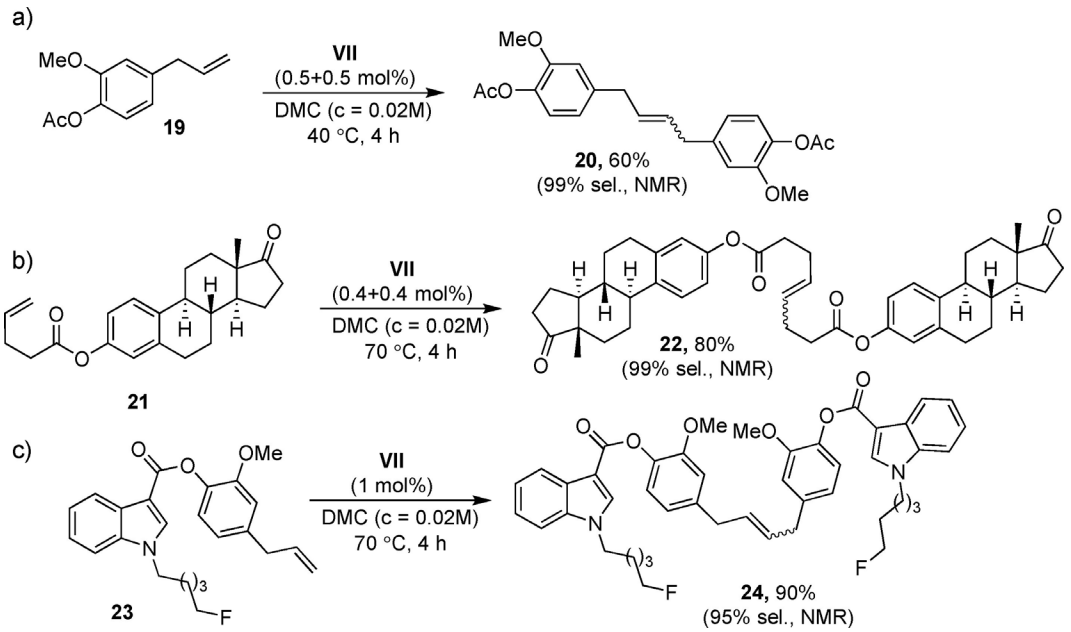


Figure 3. Time/conversion curves for the RCM reaction of diethyl 2,2-diallylmalonate (**1**) with 0.1 mol% of Ru complexes at 70 °C in DMC (monitored by GC). Lines are visual aids only.

Application of catalyst VII in CM and self-CM in DMC

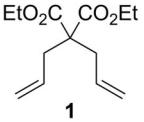
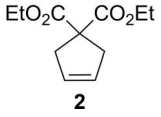
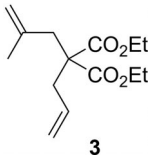
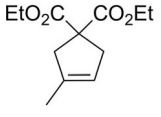
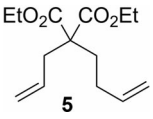
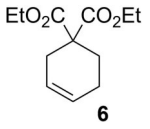
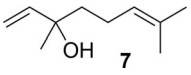
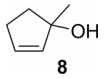
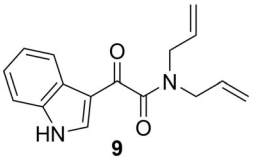
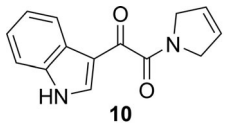
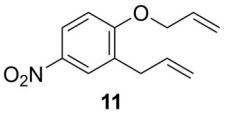
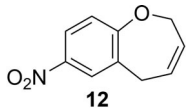
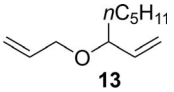
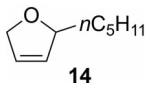
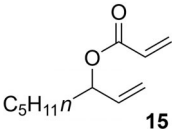
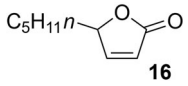
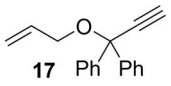
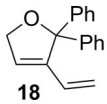
Next, we attempted to study more challenging self-cross metathesis (self-CM) and cross-metathesis (CM) reactions.

First, we planned to examine the self-CM (sometimes referred as "homodimerisation") reaction (Scheme 2) of selected functionalised alkenes belonging either to natural product families (such as **19**) or containing structural fragments of pharmaceutical interest (**21**, **23**). Self-CM is sometimes used in a medicinal chemistry context to obtain "homodimers" of products such as steroids, carbohydrates, or antibiotics.[28] In our previous work, we have noted that standard symmetrical NHC-bearing Ru catalysts produce unsatisfactory selectivity



Scheme 2. Self-CM reactions catalysed by **VII**. Sel. = 100 × (moles of the desired product)/(moles of all products created in the reaction).

Table 1. RCM and enyne reactions in the presence of **VII** and **II** performed in DMC.

Entry	Substrate	Product	Loading [mol%]/ Time [h]	Catalyst: Conversion [%]
1	 **1**	 **2**	0.2/1	**VII**: 99 **III**: 99
2	 **3**	 **4**	0.2/1	**VII**: 91
3	 **5**	 **6**	0.5/1	**VII**: > 99
4	 **7**	 **8**	0.5/24	**VII**: 94 (sel. 92%) **III**: 99 (sel. 94%)
5	 **9**	 **10**	0.5/1	**VII**: > 99
6	 **11**	 **12**	0.5/24	**VII**: 98 (sel. 97%) **III**: 98 (sel. 44%)
7	 **13**	 **14**	0.5/24	**VII**: 94
8	 **15**	 **16**	0.5/24	**VII**: 90
9	 **17**	 **18**	0.5/24	**VII**: 86

Conditions: $c = 0.02$ M, 70 °C, 1 or 24 h. Sel. = 100 × (moles of the desired product)/(moles of all products created in the reaction).

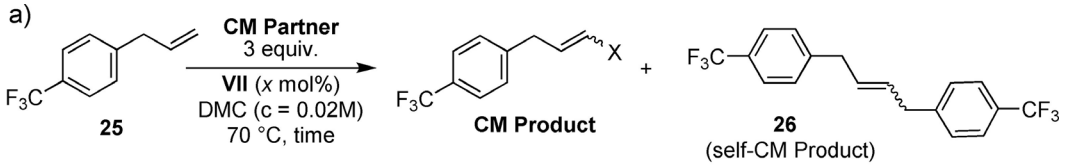
levels in such reactions, owing to their tendency to isomerise (shift) C–C double bonds in the course of the metathesis process.[29] Therefore, we were pleased to find that in the case of reactions presented in Scheme 2, no severe isomerisation was found for uNHC **VII** catalyst, and the reactions were in general very clean. This was especially visible in the case of substrate **23**—a close analogue of 5F-PB-22[30] and NM-2201,[31] designer drugs acting as cannabinoid agonists. Self-CM reaction of this compound performed in the presence of catalyst **VII** produced the conjugate **24** in high selectivity and yield (Scheme 2c).

Next, we decided to study CM reactions of selected terminal olefins with a set of CM partners, such as 1,4-diacetoxybut-2-ene (**27**), crotonaldehyde (**28**) and ethyl acrylate (**29**) (Scheme 3).[32] Importantly, we noted rather disappointing results when crotonaldehyde or acrylic ester were used. In such cases, large proportions of self-CM "dimers" were formed, demonstrating the low reactivity of uNHC catalyst **VII** towards electron-poor CM partners. This is in strong contrast with the usually excellent results noted in analogous reactions for Hoveyda–Grubbs NHC catalysts.[33] Interestingly, with non-electron-poor partner-1,4-diacetoxybut-2-ene (**27**), the uNHC catalyst gave good to very good isolated yields of the expected CM products (Scheme 3), which is in agreement with the previously published results.[20a] These show some serious limitations in thus-far very good application profile of **VII**, restricting its use in CM to only non-electron-deficient partners.

Scope and limitations study of catalyst VII in a medicinal chemistry context

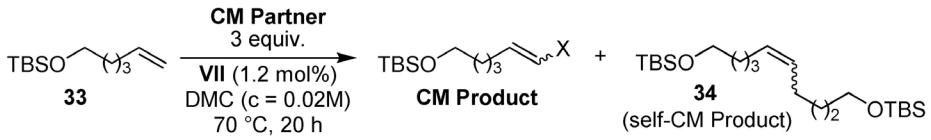
Having secured the route to larger quantities of **VII** and knowing its general reactivity picture, we looked for more challeng-

a)



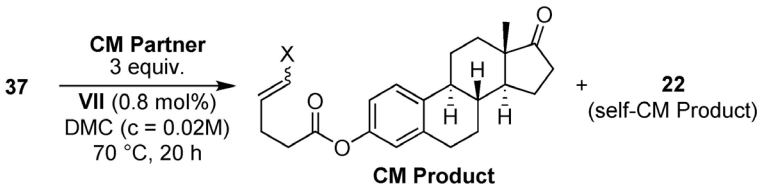
Conditions	CM partner	X	CM Product	self-CM Product
5 mol%, 3 h	AcO–(=)–OAc **27**	CH_2OAc	**30**, 73% (*E*/*Z* = 2.5:1)	10% (*E*/*Z* = 2.6:1)
1.2 mol%, 20 h	CHO **28**	CHO	**31**, 21% (*E*-only)	62% (*E*/*Z* = 4.7:1)
0.8 mol%, 4 h	CO_2Et **29**	CO_2Et	**32**, 37% (*E*/*Z* = 4.7:1)	53% (*E*/*Z* = 5:1)

b)



CM partner	X	CM Product	self-CM Product
27	CH_2OAc	**35**, 87% (*E*/*Z* = 2.1:1)	11% (*E*/*Z* = 2.6 :1)
29	CO_2Et	**36**, 25% (*E*/*Z* = 6.1:1)	53% (*E*/*Z* = 2.9 :1)

c)



CM partner	X	CM Product	self-CM Product
27	CH_2OAc	**38**, 62% (*E*/*Z* = 1.7:1)	27% (*E*/*Z* = 1.8:1)
29	CO_2Et	**39**, 24% (*E*/*Z* = 4:1)	73% (*E*/*Z* = 3.6:1)

Scheme 3. CM reactions catalysed by **VII**.

ing targets of practical interest. The opportunity for such "reconnaissance by fire" came from an industrial doctoral project related to new phosphodiesterase type 5 inhibitors (PDE5 inhibitors).[34] In the framework of this programme, we opted to apply self-CM and RCM to obtain some new analogues of Sildenafil[35] (marketed inter alia under the brand name Viagra) and Vardenafil[36] (sold inter alia under the trade name Levitra)—popular drugs used to treat erectile dysfunction and pulmonary arterial hypertension. Although both Vardenafil and Sildenafil share the same mode of action as PDE5 inhibitors, the major structural difference between them is a nitrogen atom position and the change of the Sildenafil piperazine ring methyl group to an ethyl group (Figure 4). From the point of view of catalytic olefin metathesis, both of these structures exhibit some potential risks, as they contain a number of Lewis basic centres that can chelate (arrest) the propagating $14e^-$ Ru species, thus inhibiting the catalytic activity of an olefin metathesis catalyst.

First, we attempted to obtain precursors of Vardenafil and Sildenafil "dimers" through self-CM reaction (Scheme 4). Analysing potential hazards associated with this transformation, we focused on known problems regarding the metathesis of *N*-allyl sulfonamides, which are considered as rather reluctant substrates for CM.[37] When the N(H)-allyl derivative of Vardenafil was used (Scheme 4a) only less than 10% of the expected self-CM product was formed, accompanied by the same amount of *N*-desallyl derivative.[38] Other catalysts, such as **III**, unfortunately gave no better results. Also Lewis acid additives,

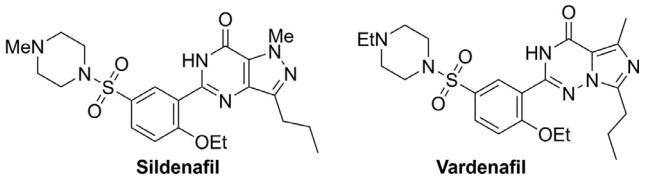
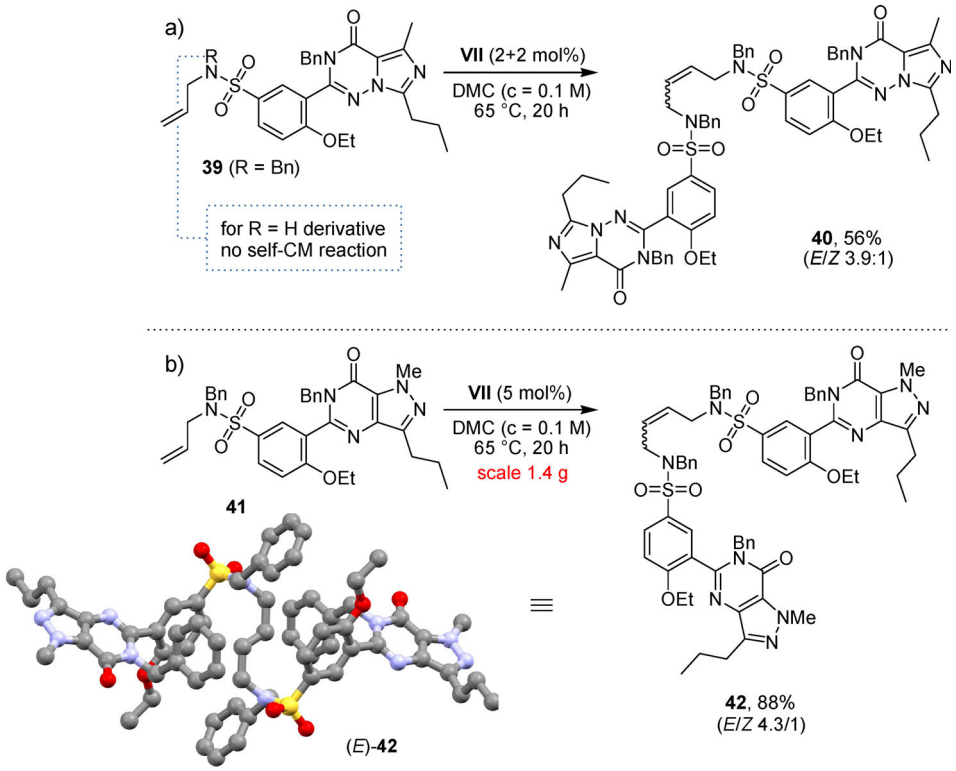


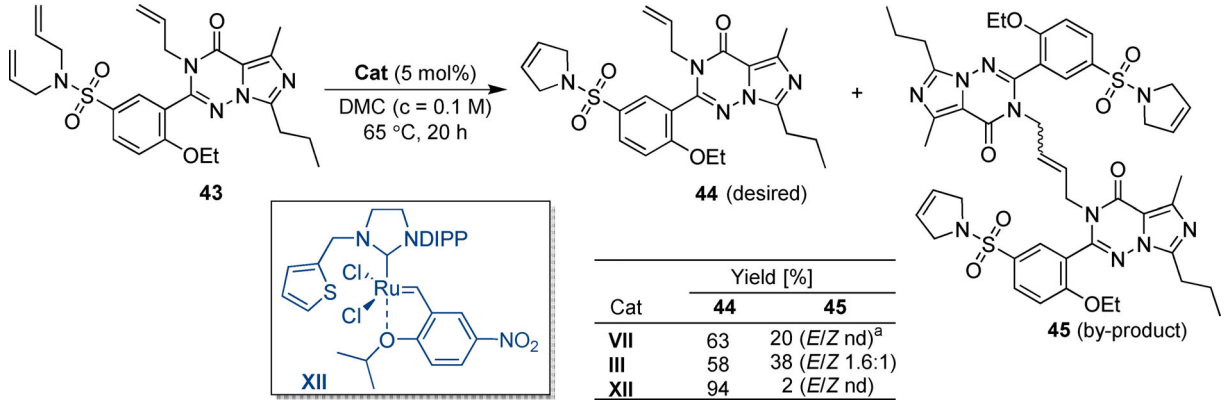
Figure 4. Chemical structures of Sildenafil and Vardenafil.



Scheme 4. Preparation of Vardenafil and Sildenafil "dimers" by CM catalysed by **VII** and the solid-state structure of the (*E*)-**42** isomer. Isolated yields.

such as $B(OMe)_3$ made no improvement in this challenging self-CM. Fortunately, when the N(Bn)-allyl derivative **39** was used, the clean metathesis reaction occurred in the presence of 4–5 mol% of **VII** in dimethyl carbonate, giving **40** in 56% isolated yield (Scheme 4a). A slightly higher yield was noted in the case of **41**, which gave 75% isolated yield on a scale of 100 mg, and 88% in 1.4 g scale (Scheme 4b).

Another challenge was related to triallyl derivative **43** (Scheme 5). We hoped that the rate of the RCM reaction (intramolecular) should be sufficiently higher than the rate of the alternative self-CM intermolecular reaction, thus allowing for selective formation of the desired product **44**. Indeed, when catalyst **VII** was applied in this reaction, 63% of only-RCM product **44** was isolated, however, accompanied by a second, more polar fraction, which was a mixture of **45** (formed from a sequence of two RCM and one self-CM reactions) and its not-fully cyclised derivatives (unfortunately we were not able to separate and fully characterise this side product mixture). Interestingly, SIPr-bearing catalyst **III**, although giving a lower yield of **44**, produced **45** as the only side product, which was isolated in pure form in 38% yield. Looking for a way to manufacture the desired RCM product **44** with higher efficiency, we speculated that the unsatisfactory results obtained above were related to the insufficient RCM activity of catalyst **VII**. Although



Cat	Yield [%] 44	45
VII	63	20 (*E*/*Z* nd)[a]
III	58	38 (*E*/*Z* 1.6:1)
XII	94	2 (*E*/*Z* nd)

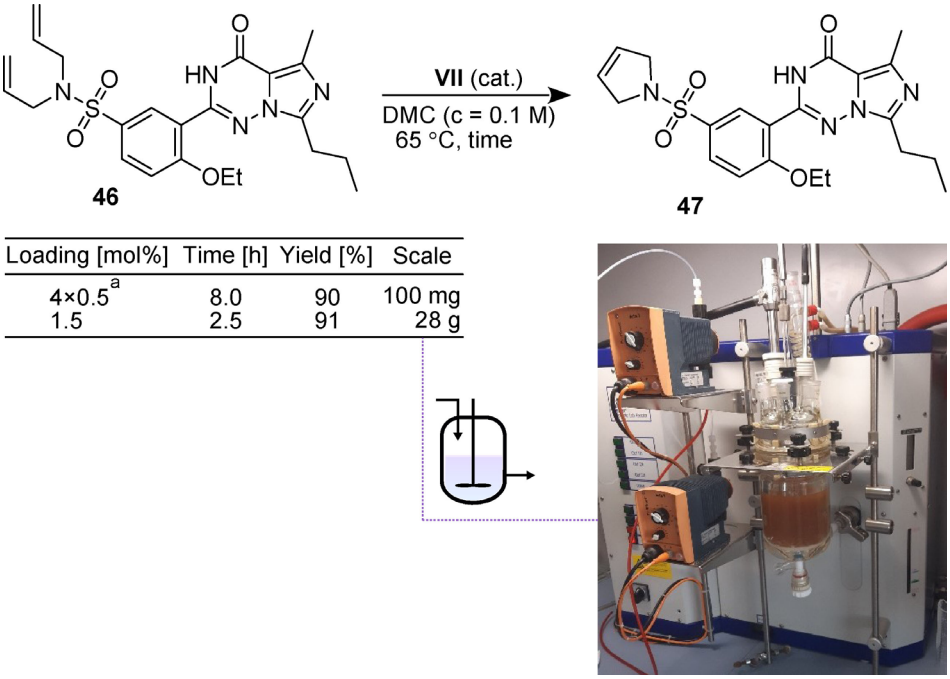
Scheme 5. RCM versus CM in metathesis of the triallyl derivative of Vardenafil. Isolated yields. [a] Total yield of an inseparable mixture of **45** and its not-fully cyclised derivatives. n.d. = not determined.

the Hoveyda–Grubbs' catalyst **III** was able not only to fully cyclise the five-membered ring in **43**, it also catalysed the unwanted self-CM reaction. In contrast, catalyst **VII** acted apparently slower, being unable to react with all *N*,*N*-diallylsulfonamide fragments even. Therefore, we looked at the electron-withdrawing group-activated[39] version of the same catalyst (**XII**) published by us previously.[20a] In this case, we were satisfied to see that CM product **44** was formed in 94% isolated yield, and only as low as 2% of the more polar self-CM product was observed (Scheme 5).[40]

Finally, we decided to prepare Vardenafil analogues bearing other heterocyclic moieties at the sulfonamide fragment. One such, **47** (Scheme 6), seemed to be easily accessible by RCM of similar *N*,*N*-diallylsulfonamide substrates as tested above. In this case, having no concerns about the chemo- and regioselectivity of the attempted metathesis process, we focused on more practical aspects of this transformation, such as scale-up, product separation and Ru catalyst removal. After checking that the target RCM reaction proceeds well on a small scale, a set of larger scale experiments was initiated. After a number of minor optimisation steps, we worked out a procedure in which the catalyst (weighed and handled on air) was added as a powder to a stirred solution of **46** (28 g, 60 mmol) in dimethyl carbonate (650 mL) placed in a 1 L reactor. The reaction mixture was stirred under a protective atmosphere of argon at 65 °C until TLC monitoring showed complete conversion (2 h). The reaction mixture was then cooled to 5 °C and stirred for 60 min. The precipitated product was filtered off and dried in vacuum dryer (see the Supporting Information). The product of HPLC purity of 99.7% was obtained as a cream-coloured solid (23.9 g, 91%). Interestingly, the crude product contained only 7.7 ppm of Ru (as checked by ICP-MS). We believe that this low contamination level is related to the slow crystallisation of **47** from the cooling of the reaction mixture, during which the Ru complexes remained in DMC solution. In a control experiment, when half of the solvent volume was evaporated before the reactor content was cooled down, crystallisation from a more concentrated solution gave the product containing a ten-times higher amount of Ru (86.0 ppm, Table 2, entry 2). Finally, when the reaction mixture was evaporated to dryness, the obtained residue exhibited 1694 ppm of Ru. It shall be noted that it was then relatively difficult to purify such contaminated product. For example, the purification procedure consisted of dissolving the crude product (1697 ppm of Ru) in 10% aqueous solution of NaOH at 80 °C, treatment with activated charcoal and precipitation by drop-wise addition of concentrated HCl, which led to a product containing 11 ppm of Ru, so actually more than in the case where product **47** precipitated freely after the reaction. An alternative purification protocol, consisting of use of a scavenger developed in our laboratories[41] led to 9.6 ppm of Ru (Table 2, entry 5).

Conclusion

A large-scale synthesis of known 2-isopropoxybenzylidene ruthenium catalyst **VII**[20a] bearing an unsymmetrical NHC ligand with one 2,6-diisopropylphenyl (DIPP) and one thiophenylmethylene *N*-substituent has been reported. This procedure, staring from simple precursors and not using column chromatography in any step, allowed preparation of up to 0.5 kg batches of the catalyst. The application profile of the obtained catalyst was studied in environmentally friendly dimethyl carbonate (DMC) to explore the limitations of this system. Although a number of metathesis reactions can be successfully



Loading [mol%]	Time [h]	Yield [%]	Scale
4×0.5[a]	8.0	90	100 mg
1.5	2.5	91	28 g

Scheme 6. Preparation of Vardenafil analogue RCM catalysed with **VII**. [a] Catalyst added in 4 portions over 8 h.

Table 2. Purification attempts after RCM of **46** in DMC.[a]

Entry	Purification method	Trace Ru [ppm]
1	Precipitated from the reaction mixture	7.72
2	Precipitated from the concentrated ($^1/_2$) reaction mixture	86.02
3	Reaction mixture evaporated to dryness	1694.60
4	As in entry 3, then the residue was dissolved in NaOH, treated with charcoal, precipitated with HCl	11.03
5	As in entry 3, then the residue dissolved in DCM, treated with SnatchCat metal scavenger	9.64

[a] For detailed procedures, see the Supporting Information. DCM = dichloromethane.

performed with **VII**, its low efficiency in CM with electron-deficient partners such as α,β-unsaturated aldehydes or esters is of note. Accordingly, in this specific field of applications, complexes **I**–**V** bearing symmetrical SIMes and SIPr ligands are superior to **VII**. Next, we focused on polyfunctional substrates of medicinal chemistry interest, such as 5F-PB-22 and NM-2201 and a number of new analogues of PDE5 inhibitors—Sildenafil and Vardenafil. We were pleased to find that with these substrates, catalyst **VII** (and its nitro-activated analogue **XII**) shows high levels of selectivity and productivity. Finally, a larger scale (28 g) RCM of Vardenafil derivative was attempted in DMC, allowing the straightforward isolation of the expected product in high yield and with a low Ru contamination level (7.7 ppm). Therefore, we believe that catalyst **VII** can find a niche in applications where high selectivity is required, such as metathesis of substrates featuring easy to isomerise C–C double bonds.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: large-scale synthesis · medicinal chemistry · N-heterocyclic carbene (NHC) ligands · olefin metathesis · ruthenium catalysts

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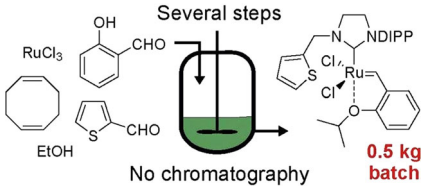
FULL PAPER

A large-scale synthesis of known Ru olefin metathesis catalyst **VII** featuring an unsymmetrical N-heterocyclic carbene (NHC) ligand with one 2,6-diisopropylphenyl (DIPP) and one thiophenylmethylene *N*-substituent is reported. The optimised procedure does not require column chromatography in any step and allows for preparation of up to 0.5 kg batches of the catalyst from simple precursors.



Catalysts

T. Nienałtowski, P. Szczepanik, P. Małecki, D. Czajkowska-Szczykowska, S. Czarnocki, J. Pawłowska, A. Kajetanowicz, K. Grela**

■■ – ■■

Large-Scale Synthesis of a Niche Olefin Metathesis Catalyst Bearing an Unsymmetrical N-Heterocyclic Carbene (NHC) Ligand and its Application in a Green Pharmaceutical Context