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Homo- and heterogeneous Ru-based metathesis catalysts in cross-metathesis of 15-allylestrone—towards 17β-hydroxysteroid dehydrogenase type 1 inhibitors

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Abstract

The cross-metathesis of allylestrone with acrylic acid derivatives using homogeneous and heterogenized Ru-catalysts was evaluated for the synthesis of a new 17β-hydroxysteroid dehydrogenase type 1 inhibitor. Hoveyda-type catalyst containing an additional diethylamino group turned out to be comparably active as homogeneous Grubbs II catalyst after immobilization on an acidic ion exchange resin which greatly facilitated workup.

Keywords: Catalysis; Enzyme inhibitor; Immobilization; Cross-olefin metathesis; Ru-catalyst; Steroids

The estradiol-synthesizing enzyme 17β-hydroxysteroid dehydrogenase type 1 (17βHSD1) is mainly responsible for the conversion of estrone (E1) to the potent estrogen estradiol (E2). It is a key player in controlling the tissue levels of E2. It is therefore an attractive target in estradiol dependent diseases like breast cancer or endometriosis.[1]

Non-steroidal structures like pyrimidone,[2a] biphenyl[2b] and naphthalene derivatives[2c] and steroidal structures namely estrone and estradiol derivatives[2d–i] show inhibitory activity of 17βHSD1. We have been focussing on the synthesis of C15 estrone derivatives leading to a new drug candidate **4**.[2d] For further development a scalable process had to be developed which is practical and allows to access other side chain analogues of **4**. Compound **2** can straightforwardly be prepared following the sequence described by Künzer,[2j] starting from *O*-benzyl-15,16-dehydro estrone **1**. The protected 15-allyl estrone **2** finally can be used in a cross-metathesis reaction with acrylic acid derivatives yielding the protected and unsaturated key intermediate **3** en route to **4** (deprotection, hydrogenation) (Scheme 1).

During recent years, olefin metathesis using modern ruthenium catalysts such as Grubbs I–III (**5**, **6**, **9**), Hoveyda–Grubbs carbene (**7**) and Hoveyda–Blechert–Grubbs carbene (**8**) as well as therefrom derived indenyl and phenylthio carbenes **10**–**12** has become a key reaction in organic synthesis.[3] Heterogenization of homogeneous catalysts for removing catalysts at the end of the catalytic process is an active field of research[4] with an increasing impact on industrial processes.[5]

In this context, the removal of various ruthenium byproducts[6] has been achieved following diverse strategies such as scavengers,[7a–d] biphasic extraction,[7e,h] and silica-gel chromatography.[7f–h] An alternative concept is the immobilization of these homogeneous catalyst on a solid

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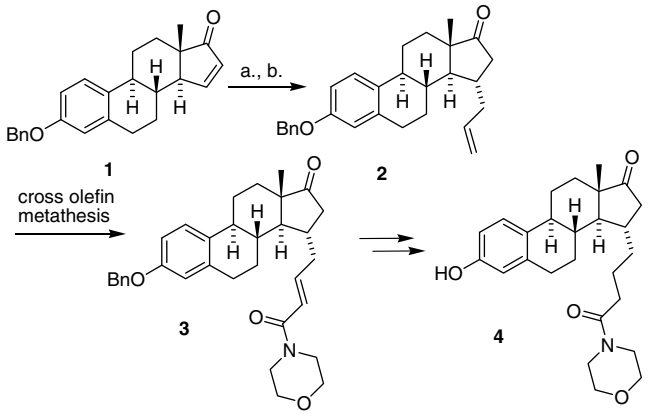


Scheme 1. Synthesis of estrone derivative **4** with 17βHSD1 inhibitory property. Reagents and conditions: (a) allyl-MgBr, THF, 2.5 h, 0 °C, 85%; (b) KH, 18-crown-6, THF, 12 h, rt, 75%.

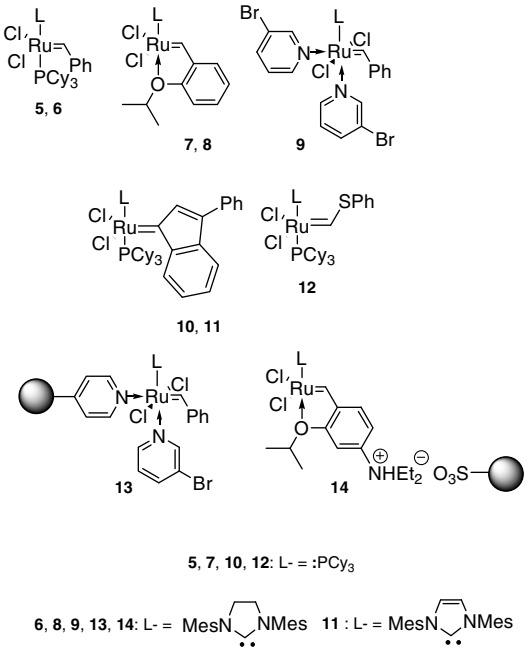


Fig. 1. Ru-complexes **5**–**14** (Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl).

support which has been achieved for carbenes **5** and **6** via ligand L or via the alkylidene moiety.[8] Hoveyda established catalysts **7** and **8**[9] as remarkably robust complexes promoting olefin metathesis by a release/return mechanism.[10] Recently, various Hoveyda–Grubbs carbenes were attached to different resins or soluble supports preferentially via the 2-alkoxy-benzylidene fragment.[11] As a part of our research dedicated to catalysis under continuous-flow conditions[12] which ideally requires facile regeneration of immobilized homogeneous catalysts we developed two modified Grubbs-type catalysts **13**[13] and **14**[14] which are attached to a polymeric phase by coordinative attachment or ion exchange, respectively.[15]

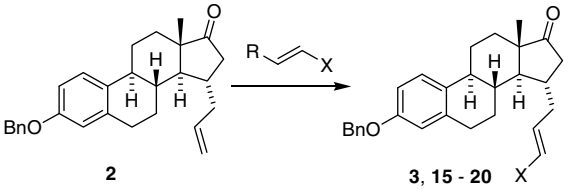
In the present work, we disclose a detailed evaluation of several Ru-based metathesis catalysts including heterogenized catalysts **13** and **14** (powder) in the cross-metathesis reaction[16] between alkene **2** and several acrylic acid derivatives (see Fig. 1).

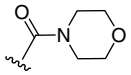
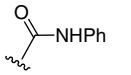
Cross-metathesis of alkene **2** with methyl acrylate using Ru-complex **6** proceeded in dichloromethane at 40 °C led to 97% conversion (determined by LCMS–ELSD; liquid chromatography mass spectrometry with evaporative light scattering detection) within 2.5 h. The reaction can be accelerated under microwave irradiating conditions[17] (10 min at 80 °C; 79%) but the conversion never exceeded 80% even at elevated temperatures (100–120 °C). The use of sealed microwave vials can be made responsible because the byproduct ethylene inside the vial is trapped at an internal pressure of 3–7 bar. Besides dichloromethane, also 1,2-dichloroethane (80 °C) gave satisfactory results. In contrast, conversions in toluene, chlorobenzene, dichlorobenzene and ethyl acetate ranged between 25% and 30% yield while in dioxane, THF, chloroform, acetone, methanol, DMF and DMSO it was determined to be between 10% and 0%.

From a practical point of view, it was important for us that not only Grubbs II catalyst **6** can be employed for this cross-metathesis reaction but also heterogenized Ru-complexes **13** and **14** gave excellent yields in dichloromethane after 5.5 h (70% and 95%, respectively). Hoveyda's Ru-complex **8** operates with similar efficiency, however, it reacts more sluggishly compared to complex **6**. Industrial catalysts **10**–**12** did not yield appreciable amounts (<10%) of methyl ester **15** under these conditions. Surprisingly, also Grubbs III catalyst **9** did not perform as well as its immobilized variant **13** as coupling product **15** was only formed in about 40% yield even after prolonged reaction time. The performance of **9** could not be improved when the cross-metathesis was carried out in toluene or 1,2-dichloroethane at 40 °C and 80 °C, respectively (<20% conversion). The solvent switch was only beneficial for immobilized catalyst **13** as the yield of transformation could be raised to 95% in 1,2-dichloroethane at 80 °C after a reaction time of 5.5 h. In essence, the two immobilized Ru-complexes **13** and **14** perform with similar efficiency as the homogeneous counterparts **6** and **8** while all other homogeneous catalysts **9**–**12** are not well suited for the model cross-metathesis.[18]

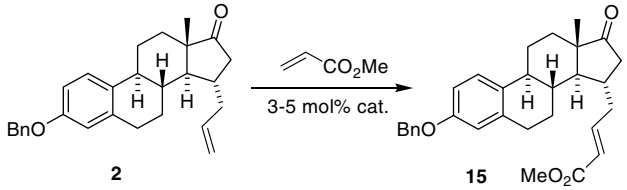
Therefore, the following studies were exclusively conducted with Ru-complexes **6**, **13** and **14** (Table 1). The data presented in Table 1 show that no single catalyst outperforms any other in the cases listed. For example, in the CM of three acrylamide derivatives, Grubbs catalyst **6** gave best conversion in two cases (entries 4 and 5), while the immobilized complex **14** was the most optimal catalyst for the third amide (entry 6). This observation is another indication for the current difficulty in anticipating the activity of pre-catalysts with respect to a specific substrate.[19] Still, the very good results achieved with complex **14** are noteworthy because in comparison to Grubbs II **6** it allows easy purification of reaction mixtures and facile regeneration (see Scheme 2).

Table 1
[22] Cross-metathesis of 15-propenyl estrone **2** with various alkenes using Ru-complexes **6**, **13** and **14**[a]



Entry	X	R	Product	Yield[b] (%)		
				6	**13**	**14**
1	$-CO_2Me$	H	**15**	97	95	95
2	$-CO_2Me$	Me	**15**	94	58	73
3	$-CO_2H$	H	**16**	88	0	99
4	$-CONH_2$	H	**17**	61	0	12
5		H	**3**	51	1	3
6		H	**18**	62	58	85
7	–OAc	H	**19**	86	0	32
8	–Ph	H	**20**	76	55	74

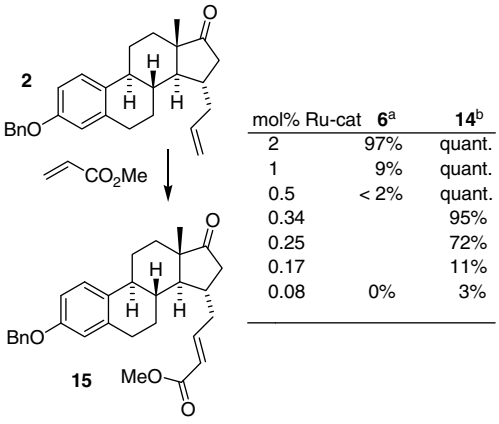
[a] Conditions: **6**: CH_2Cl_2, 40 °C, 2.5 h; **13**: $(CH_2Cl)_2$, 80 °C, 5.5 h; **14**: CH_2Cl_2, 40 °C, 5.5 h.
[b] Isolated yields (only *E*-isomers).



Catalyst	Optimized conditions
6	CH_2Cl_2, 40°C, 2.5h; 97%
8	CH_2Cl_2, 40°C, 4h; 90%
9	CH_2Cl_2, 40°C, 5.5h; 34%
13	$(ClCH_2)_2$, 80°C, 5.5h; 95%
14	CH_2Cl_2, 40°C, 5.5h; 95%

Scheme 2. Optimization of cross-metathesis of 15-allylestrone **2** with methyl acrylate.

Even more importantly, the concentration of catalyst **14** could be reduced to <0.5 mol % in contrast to the Grubbs II catalyst **6** which has to be added in at least 2 mol % to achieve complete transformation (Scheme 3). This result may be attributed to the enhanced activity exhibited by the EWG-activated[20] Hoveyda catalyst **14** combined with its pronounced thermal stability,[14] although Nolan et al.[19] clearly state that the indenylidene catalyst possesses even improved stability. In our case, this catalyst failed in the present study. The reaction time for **14** is doubled compared to **6**, which is a common phenomenon for biphasic systems. At the end of the reaction, catalyst **14** can be simply removed by filtration and rinsed with minimal amounts of dichloromethane, producing minimal solvent waste. The ruthenium contamination in the crude products was determined to be <3500 ppm which is not an excellent value but



mol% Ru-cat	**6**[a]	**14**[b]
2	97%	quant.
1	9%	quant.
0.5	< 2%	quant.
0.34		95%
0.25		72%
0.17		11%
0.08	0%	3%

Scheme 3. Comparison of Grubbs II catalyst **6** with immobilized Hoveyda-type catalyst **14**. Reagents and conditions: [a]**2**/alkene 1:2, CH_2Cl_2, 40 °C, 2.5 h; [b]**2**/alkene 1:2, CH_2Cl_2, 40 °C, 8 h (only *E*-isomer).

still is dramatically lower than typically determined for homogeneous Ru-catalysts. Here, ruthenium contaminations are in the range between 11,000 and 22,000 ppm. As previously described by us, reuse is easily possible through reloading of the active catalyst by simple washing steps typical for ion exchange resins,[14] which creates an additional advantage during a planned scale-up of this process.[21] In essence, we showed that our Hoveyda-type olefin metathesis precatalyst **14**, immobilized by ion exchange, is a highly reactive species for cross- olefin metathesis with improved properties over common homogeneous Ru-complexes as it allows facile purification and regeneration without substantial loss of activity. The attractive conceptual feature of complex **14** is the activation by immobilization.

Currently, work is in progress for utilizing immobilized catalyst **14** for the large scale, continuous production of 17βHSD1 inhibitors.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.134.

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21. Prolonged heating times and low amount of catalyst lead to complete deactivation of **14** after the first run.
22. *General procedure for cross-metathesis reaction.* Estrone derivative **2** (30 mg, 75 μmol) and 150 μmol of the olefin (entries 1–8; Table 1 and Supplementary data) were dissolved in 10 ml CH_2Cl_2 under nitrogen. Ru-catalyst (3–5 mol %) was added and the mixture was stirred at 40 °C (80 °C in ethylene dichloride for catalyst **13**) for 1–5 h (depends on catalyst, substrate and solvent employed). The products were isolated by flash column chromatography using a mixture of cyclohexane/ethyl acetate as eluent.