
9 Olefin Metathesis Reactions

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9.1 HIGHLY ACTIVE RUTHENIUM (PRE)CATALYSTS FOR METATHESIS REACTIONS

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The development of stable and active well-defined ruthenium carbene complex $\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}$ and its “second-generation” successors (**1a**) and (**1b**) (Figure 9.1) has meant that olefin metathesis reactions have become valuable tools in synthetic organic chemistry.^[1] Among them the ring-closing (RCM), en-yne and cross-metathesis (CM) reactions have received much attention as they

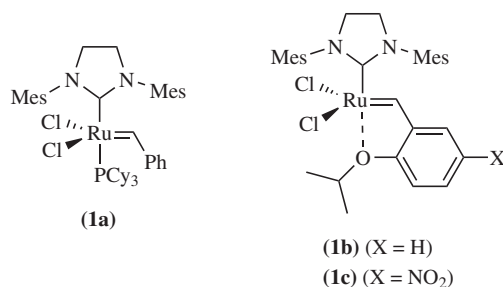
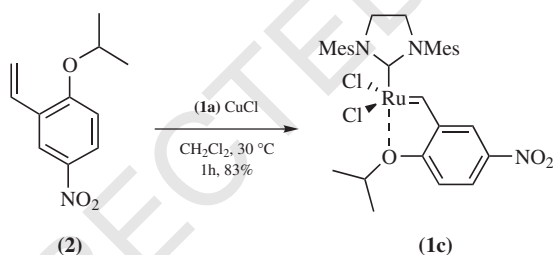


Figure 9.1 Second generation ruthenium carbene complexes for metathesis reactions.

offer great potential for an intra- and intermolecular C=C bond construction.^[1] Recently, the stable and easy-to-use nitro-substituted catalyst (**1c**) has been developed; it possesses a dramatically enhanced reactivity, e.g. promoting metathesis even at 0 °C.^[2a-b]

9.1.1 SYNTHESIS OF THE RUTHENIUM (PRE)CATALYST (1C)



Materials and equipment

- Copper(I) chloride (anhydrous), 18 mg, 0.18 mmol
 - Grubbs' II-generation ruthenium catalyst, 153 mg, 0.18 mmol
 - Dichloromethane (dry, desoxygenated), 14 mL
 - 2-Isopropoxy-5-nitrostyrene, 38 mg, 0.18 mmol
 - *c*-Hexane (HPLC grade), 300 mL
 - Ethyl acetate (HPLC grade), 120 mL
 - *n*-Pentane (dry, deoxygenated)
-
- Silica gel (Merk 60, 230-400 mesh), 15 g
 - TLC plates, Polygram® SIL G/UV₂₅₄
 - 30-ml Schlenk flask with magnetic stirrer bar
 - Magnetic stirrer plate
 - One glass column, diameter 3 cm
 - Ten 50-mL Erlenmeyer flasks
 - Rotary evaporator

Procedure

1. Grubbs' II-generation ruthenium catalyst (**1a**) (153 mg, 0.18 mmol), copper(I) chloride (18 mg, 0.18 mmol) and dichloromethane (10 mL) were placed in a Schlenk flask. A solution of 2-isopropoxy-5-nitrostyrene (**2**) (38 mg, 0.18 mmol) in dichloromethane (4 mL) was then added and the resulting solution was stirred under argon at 30 °C for 1 hour. From this point forth, all manipulations were carried out in air with reagent-grade solvents.
2. The reaction mixture was concentrated *in vacuo* and the resulting material was purified by column chromatography on silica. Elution with c-hexane:EtOAc (5:2) removes ruthenium complex (pre)catalysts containing a nitro group in *para*-position to the isopropoxy group as a green band (*R_f* = 0.30, c-hexane:EtOAc 8:2). Removal of solvent, washing with cold n-pentane and drying under vacuum afforded ruthenium (**1c**) as a green microcrystalline solid (100 mg, 83% yield).

¹H NMR (500 MHz, CD₂Cl₂) δ 16.42 (1H, s), 8.46 (1H, dd, *J* 9.1, 2.5 Hz), 7.80 (1H, d, *J* 2.5 Hz), 7.10 (4H, s), 6.94 (1H, d *J* 9.1 Hz), 5.01 (1H, sept, *J* 6.1 Hz), 4.22 (4H, s), 2.47 (18H, 2s), 1.30 (6H, d, *J* 6.1 Hz).

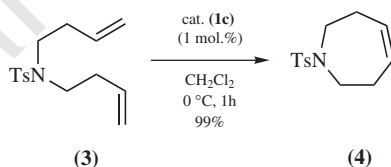
¹³C NMR (125 MHz, CD₂Cl₂) δ 289.1, 208.2, 156.8, 150.3, 145.0, 143.5, 139.6, 139.3, 129.8, 124.5, 117.2, 113.3, 78.2, 52.0, 21.3, 21.2, 19.4

IR (KBr) 2924, 2850, 1606, 1521, 1480, 1262, 1093, 918, 745 cm⁻¹.

HRMS (IE) *m/z* calcd for C₃₁H₃₇N₃O₃³⁵Cl₂¹⁰²Ru: [M]⁺. 671.1255, found 671.1229.

Elemental analysis calcd (%) for C₃₁H₃₇Cl₂N₃O₃Ru (671.63): C 55.44, H 5.55, N 6.26; found: C 55.35; H 5.70, N 6.09.

9.1.2 SYNTHESIS OF 1-[(4-METHYLPHENYL)SULFONYL]-2,3,6,7-TETRAHYDRO-1H-AZEPINE 4



Materials and equipment

- *N,N*-Dibut-3-enylbenzenesulfonamide, 210 mg, 0.75 mmol
- Ruthenium (pre)catalysts (**1c**), 5 mg, 1 mol %
- Dichloromethane (dry, deoxygenated), 37 mL
- c-Hexane (HPLC grade), 240 mL
- Ethyl acetate (HPLC grade), 60 mL
- Silica gel (Merk 60, 230-400 mesh), 10 g
- TLC plates, SIL G-60 UV₂₅₄

- 30-ml Schlenk flask with magnetic stirrer bar
- Magnetic stirrer plate
- One glass column, diameter 4 cm
- Twenty 25-mL Erlenmeyer flasks
- Rotary evaporator

Procedure

1. To a solution of *N,N*-dibut-3-enylbenzenesulfonamide (**3**) (210 mg, 0.75 mmol) in dichloromethane (35 ml) a solution of ruthenium (**1c**) (5 mg, 1 mol %) in dichloromethane (2 ml) was added at 0°C. The resulting solution was stirred at the same temperature for 1 hour.
2. Solvent was then removed under vacuum and the residue was purified using silica gel column chromatography with *c*-hexane: EtOAc 8:2 to give 1-[(4-methylphenyl)sulfonyl]-2,3,6,7-tetrahydro-1H-azepine (186 mg, 99% yield) as colorless solid.

¹H NMR (200 MHz, CDCl₃) δ 2.28 (4H, m), 2.39 (3H, s), 3.25 (4H, m), 5.72 (2H, m), 7.25 (2H, d, *J* 8.2 Hz), 7.64 (2H, d, *J* 8.2 Hz).

¹³C NMR (50MHz, CDCl₃) δ 21.5, 29.948.2, 126.9, 129.5, 130.1, 136.2, 142.9.

MS (EI) *m/z* 251 (5, [M]⁺), 223 (2), 184 (6), 155 (4), 105 (2), 91 (19), 96 (16), 77 (1), 65 (13), 42 (100).

IR (KBr) 3030, 2942, 2899, 2855, 1657, 1596, 1450, 1332, 1286, 1162, 910, 816, 712 cm⁻¹.

HRMS (EI) calculated for [M]⁺ (C₁₃H₁₇O₂NS): 251.0980; found 2251.0979.

CONCLUSION

Although the second-generation ruthenium complex (**1a**) possesses in general very good application profile, the phosphine-free catalyst (**1b**), recently introduced by Hoveyda *et al.*,^[3] displays even higher reactivity toward some electron-deficient substrates, such as acrylonitrile, fluorinated olefins and vinyl sulfones. Excellent air-stability, ease of storage and handling and possibility of a catalyst reuse render additional advantages of this system.

The Hoveyda-type catalysts has been shown that it can be significantly improved by changing electronic situation in the ruthenium-chelating isopropoxy-fragment. Namely, introduction of the strong electron-withdrawing group to the 2-isopropoxybenzylidene ligand leads to ruthenium complex (**1c**), which is similarly stable but dramatically more reactive than the Hoveyda-type catalyst. The active and easy to obtain (pre)catalyst (**1c**) is attractive from a practical point of view. This catalyst operates in very mild conditions (0 to 40 °C) and can be successfully applied in various types of metathesis (Table 9.1).^[2]

Table 9.1 Metathesis reactions promoted by ruthenium complex **1c**.

Substrate	Product	Yield [%] (1c , temp., time)
		98% (1 mol.%, 0 °C, 1 h)
		99% (1 mol.%, 0 °C, 1 h)
		78% (2.5 mol.%, 0 °C, 8 h)
		99% (2.5 mol.%, RT, 4 h)
		82% (2.5 mol.%, RT, 30 min)
		95% (1 mol.%, RT, 30 min)
		90% (2.5 mol.%, RT, 16 h)
		82% (5 mol.%, 40 °C, 16 h)
		83% (5 mol.%, 40 °C, 2 h)

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Materials and equipment

- Styrene derivative (**1**), 0.025 g, 0.087 mmol
 - 2-Hydroxymethyl-(7-oxabicyclo[2.2.1]hept-5-enyl)benzoate (**2**), 0.060 g, 0.261 mmol
 - Copper(I) chloride, 0.001g, 0.101 mmol
 - 1,3-(Bis-(mesityl)-2-imidazolinylidene)dichloro(phenylmethylene)tricyclohexylphosphaneruthenium, 0.0074g, 0.0087 mmol
 - Dry dichloromethane
 - *n*-Hexane, dichloromethane, diethyl ether
-
- One two-necked 10-mL round-bottomed flask
 - One 2-mL syringe
 - One 25-mL round-bottomed flask
 - Pre-washed cotton wool
 - One Pasteur pipette
 - Magnetic heater/stirrer plate, stirring bar and silicone oil bath
 - One reflux condenser
 - One rotary evaporator
 - Nitrogen gas line

Procedure

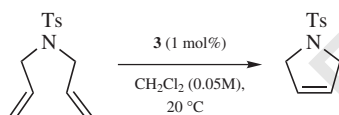
1. To a solution of styrene (**1**)^[1] (0.025 g, 0.087 mmol) and ester (**2**)^[1] (0.060 g, 0.261 mmol) in dichloromethane (3 mL) under a nitrogen atmosphere in a 10-mL round-bottomed flask was added (**2**) (0.0074 g, 0.0087 mmol) in *dry* dichloromethane (2 mL) *via* syringe with vigorous stirring at room temperature. After 10 minutes ¹H NMR analysis of the red solution indicated complete consumption of both (**1**) and (**2**) as seen by the complete disappearance of the norbornene signals at δ 6.2–6.5 ppm. Copper(I) chloride (0.001 g, 0.101 mmol) was added in one portion, the flask was fitted with a condenser and the resulting solution heated under nitrogen at 45 °C for 1 hour, affording a light green solution.
2. After cooling, the reaction mixture was concentrated to dryness *in vacuo* (rotary evaporator) and taken up in (1:1) *n*-hexane:dichloromethane. The insoluble copper-phosphane salts were removed by passing the resulting suspension through a plug of pre-washed cotton wool in a Pasteur pipette into a 25-mL round-bottomed flask. The clear green solution was then evaporated to dryness *in vacuo* (rotary evaporator) and the solid washed successively with *n*-hexane (10 mL) and diethyl ether (10 mL) followed by drying under high vacuum to give catalyst (**3**) (0.0745 g, 93% yield) as a light green solid which readily adheres to surfaces such as glass or metal.

¹H NMR (500 MHz, CDCl₃): δ (ppm) 16.67 (1 H, bs, Ru = $\underline{\text{CH}}$), 7.99 (60 H, bs, *o*-Ar-ester), 7.50 (31 H, bs), 7.38 (62 H, bs), 7.04 (18 H, bs), 6.91 (9 H bs), 6.74 (9 H, bs), 5.7–5.6 (90 H, bs) 5.21 (10 H, bs), 4.7–3.7 (180 H, m), 2.78 (20 H, bs), 2.37 (61 H, bs), 2.01 (50 H, bs) 1.23 (60 H, bs).

The loading of the catalyst can be determined by comparison of the relative integration of the δ 16.67 (Ru alkylidene) and 7.99 (benzoate) ppm signals. A 1:60 ratio indicates quantitative loading of the catalyst. Typical catalyst loadings using this procedure are between 0.08 and 0.10 mmol g⁻¹.

Note: Due to overlapping and very broad signals some of the highfield signal integrals are approximate, but nevertheless consistent between polymer batches.

9.2.2 RING-CLOSING METATHESIS OF AN ACYCLIC DIENE AND SUBSEQUENT CATALYST RECOVERY/REUSE



Materials and equipment

- *N*-Tosylallylamine, 0.0302 g, 0.12 mmol
- Catalyst (**3**), 0.0012 mmol (mass depends on catalyst loading determined by ¹H NMR)
- Dry dichloromethane
- *n*-Hexane, diethyl ether
- One 5-mL round-bottomed flask
- One 2-mL syringe
- Pre-washed cotton wool
- One Pasteur pipette
- Magnetic stirrer plate and stirring bar
 - One reflux condenser
 - One rotary evaporator
 - Nitrogen gas line

Procedure

1. To a solution of catalyst (**3**) (0.012 g, based on a loading of 0.1 mmol g⁻¹, 0.0012 mmol) in *dry* dichloromethane (1 mL) under nitrogen *N*-tosylallylamine^[2,3] (0.0302 g, 0.12 mmol) in dichloromethane (1.4 mL) was added *via* syringe at room temperature. The resulting light-yellow/green solution was stirred under nitrogen until ¹H NMR or TLC analysis indicated quantitative conversion of the starting material (60 minutes). After reaction the catalyst was recovered by the addition of cold diethyl ether (10 mL), which precipitates the

catalyst as a green gum that adheres to the flask, allowing removal of the reaction mixture by Pasteur pipette. The flask was further rinsed with 1:1 diethyl ether:*n*-hexane (2×7 mL) and the colourless organic extracts combined. Removal of the solvent *in vacuo* (rotary evaporator) furnished the pure white product in quantitative yield (26.3 mg).

2. Alternatively addition of cold *n*-hexane or *n*-hexane-diethyl ether (1:1) gives complete precipitation of the catalyst as a light green solid. The product can then be separated by a filtration/evaporation sequence.
3. Re-use of the catalyst: The flask containing the catalyst was subjected to high vacuum for 20 minutes, placed under a nitrogen atmosphere and a second charge of *N*-tosyldiallylamine (0.0302 g, 0.12 mmol) in dichloromethane (1.6 mL) was added *via* syringe at room temperature. After quantitative conversion was observed, the above procedure was repeated to isolate the product and catalyst respectively. Under these conditions it was possible to recycle the catalyst 7 times with quantitative conversion of the starting material in each cycle (*extended reaction times were required after cycle 5*). TXRF analysis of the products from the first 4 cycles indicated a maximum of 0.004% ruthenium (wt%) was present in the ring-closed products.^[4]

Note: While the catalyst itself is stable indefinitely in air, when wet/dissolved in solvent it decomposes slowly to give a brown solid/solution. Therefore, for best results every precaution should be taken to minimise the time taken to recover the catalyst from the reaction once it has been exposed to air.

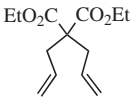
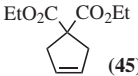
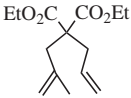
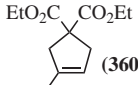
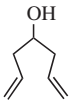

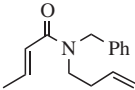
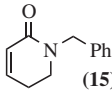

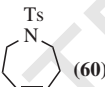
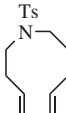
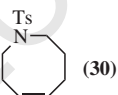
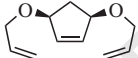
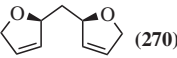
CONCLUSION

The procedure reported above represents a facile and reproducible method for the execution of various olefin metathesis reactions using a highly active and recoverable catalyst. Table 9.2 gives a list of representative substrates compatible with the technology and the time taken for quantitative conversion of the substrate using the ring-closing metathesis procedure.

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3. The procedure can be used to perform ring-closing metathesis, ring-rearrangement metathesis and ring-opening cross-metathesis reactions involving a variety of substrates.
4. TXRF analysis performed by Prof. Dr. B. O. Kolbesen, Institut für Anorganische Chemie, Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany.

Table 9.2 Activity of (3) in various metathesis reactions using the above procedure (Reaction times (minutes) in parentheses).

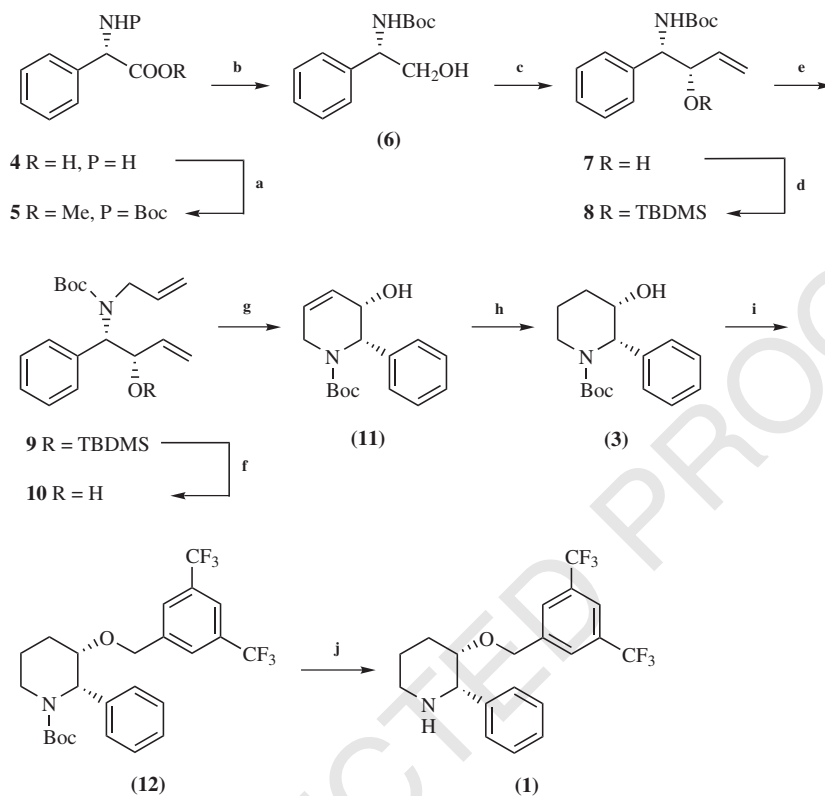
Substrate	Product	Conversion (%)
	 (45)	>98
	 (360)	>98
	 (60)	>98
	 (15)	>98
	 (60)	>98
	 (30)	>98
	 (270)	>98

9.3 STEREOSELECTIVE SYNTHESIS OF L-733,060

G. BHASKAR and B. VENKATESWARA RAO*

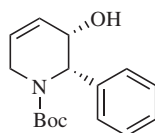
Organic Division III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

The non-peptidic neurokinin NK1 receptor antagonist (**1**) (L-733,060) is known to have a variety of biological activities including neurogenic inflammation,^[1] pain transmission and regulation of the immune response.^[2] It has been implicated in a variety of disorders including migraine,^[3] rheumatoid arthritis⁴ and pain.⁵ A stereoselective synthesis of L-733,060 using ring closing metathesis as key step, starting from L-phenylglycine has recently been reported.^[6]



- a) AcCl, MeOH then (Boc)₂O, Et₃N, THF, 0 °C-rt, 8 h, 97%;
 b) LiCl, NaBH₄, EtOH, THF, 0 °C-rt, 12 h, 87%;
 c) DMSO, (COCl)₂, DCM, *i*-Pr₂NEt then CH₂=CHMgBr, THF, 2 h, rt, 61%;
 d) TBDMS-Cl, imidazole, DCM, 0 °C-rt, 24 h, 90%;
 e) CH₂=CHCH₂Br, NaH, DMF, 0 °C-rt, 24 h, 90%;
 f) TBAF-AcOH, THF, 0 °C-rt, 24 h, 85%;
 g) Grubbs' catalyst, DCM, rt, 6 h, 82%;
 h) Pd/C, H₂, EtOH, 4 h, rt, 65%;
 i) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 80 °C, 13 h, 80%;
 j) trifluoroacetic acid, rt, 1 h, 79%.

9.3.1 SYNTHESIS OF (2S,3S)-N-tert-BUTOXYCARBONYL-2-PHENYL 1,2,3,6-TETRAHYDRO-3-PYRIDINOL



(11)

Materials and equipment

- Dry dichloromethane, 400 mL
- Grubb's Catalyst, 0.163 g
- Diolefin (**10**) 0.6 g

- One 1-L round-bottomed flask
- One magnetic stirrer bar
- Nitrogen atmosphere

Procedure

To a solution of diolefinic compound (**10**) (0.6 g, 1.98 mmol) in dry dichloromethane (400ml) at room temperature Grubbs' catalyst (0.163 g, 10 mol %) was added. The reaction mixture was stirred for 6 hours under nitrogen atmosphere at the same temperature. Reaction was monitored by TLC (30% ethyl acetate in hexane). After completion of reaction, solvent was removed under reduced pressure using rotary evaporator. Then purified by silica gel (60–120 mesh) column chromatography using ethyl acetate: hexane (1: 4) to give pure product (**11**) (0.45 g, 82%).

$^1\text{H NMR}$ (200 MHz, CDCl_3): δ 1.44 (s, 9H), 3.54 (ddd, 1H, $j = 1.4, 3.9, 19.0$ Hz), 4.16 (ddd, 1H, $j = 3.2, 5.6, 19.0$ Hz), 4.66 (br s, 1H), 5.53 (d, 1H, $j = 6.7$ Hz), 5.70–5.98 (m, 2H), 7.14–7.48 (m, 5H). $[\alpha]_{\text{D}}^{25} = +64.10$ (c 1.05, CHCl_3).

IR (neat, cm^{-1}): 3415, 2984, 1676, 1400, 1350, 1150.

CONCLUSION

The synthesis of L-733,060 (**1**) using ring closing metathesis starting from L-phenylglycine has been accomplished.

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