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Simple Ruthenium Precatalyst for the Synthesis of Stilbene Derivatives and Ring-Closing Metathesis in the Presence of Styrene Initiators

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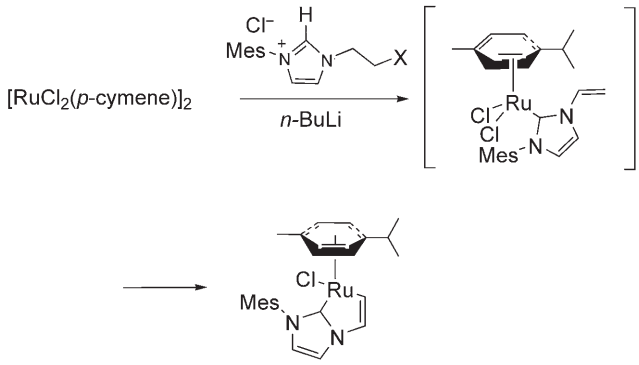
This paper is dedicated to Professor Masakatsu Shibasaki on the occasion of his 60th birthday.

Abstract: The ruthenium complex $RuCl_2$(*p*-cymene)(IMes) was found to be an efficient precatalyst, with styrene as an initiating species, for the alkene metathesis of various styrenes into symmetrical and unsymmetrical stilbene derivatives and for the ring-closing metathesis reaction of a sterically hindered olefin leading to a tetrasubstituted cycloolefin.

Keywords: alkene metathesis; N-heterocyclic carbenes; ring-closing metathesis; ruthenium; stilbenes; styrenes

Stilbene derivatives, in particular hydroxy- or alkoxy-subtituted ones are gaining importance due to their biological activities for the prevention of cancer or cardiovascular diseases.[1] They are also an important family of building blocks for the design of conjugated materials with optical properties.[2] Wittig or Wittig–Horner reactions[3] constitute a priviledged approach for the synthesis of stilbene derivatives but they generate stoichiometric amounts of phosphine oxides hence requiring fastidious purification. Catalytic reactions such as Heck or Suzuki couplings can be used as more efficient ways to synthesize stilbene derivatives.[4] More recently catalytic olefin metathesis[5] appeared as a tool of choice for the efficient and stereoselective synthesis of stilbene derivatives thanks to the emergence of very active catalysts for cross-metathesis.[6] In particular, the ruthenium-based second generation Grubbs catalyst has been shown to efficiently promote the self- and cross-metathesis of styrene derivatives.[7] Other complexes based on molybdenum[8] or osmium[9] have also been described as efficient catalysts for this transformation.

We recently reported the intramolecular vinyl C–H bond activation of an *N*-vinyl-N-heterocyclic carbene-ruthenium(II) intermediate leading to a bidentate NHC-alkenyl ruthenium complex (Scheme 1).[10]



Scheme 1. Intramolecular vinyl C–H bond activation.

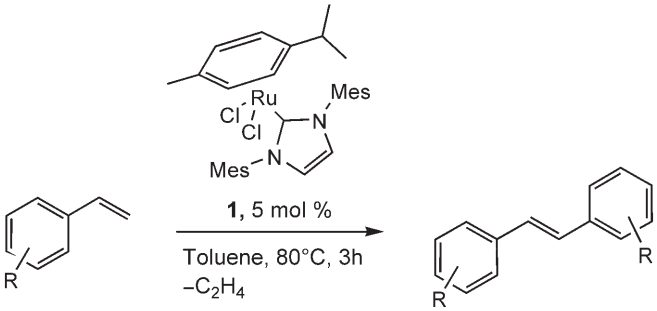
In an attempt to explore the intermolecular version of this transformation, styrene was reacted with the readily available ruthenium complex $RuCl_2$(*p*-cymene)(IMes) **1**[11] [IMes = 1,3bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]. This reaction resulted in the stereoselective formation of *E*-stilbene in very good yield, thus suggesting a self-metathesis reaction. Here we describe several aspects of $RuCl_2$(*p*-cymene)-(IMes) as catalyst precursor for alkene metathesis reactions. In the absence of an alkene metathesis carbene initiator, complex **1** acts as a pre-catalyst for the metathesis transformation of various styrene derivatives into the corresponding stilbenes including unsymmetrical ones. We show the dual ring-closing metathesis (RCM) *vs.* cycloisomerisation activity of **1** and that, *in the presence of styrene as an activator,* complex **1** is effective for the RCM of a sterically hindered diene.

There were some indications that complex **1** could promote catalytic alkene metathesis: Nolan reported one example of RCM activity of complex **1** with diethyl diallylmalonate[11] and Noels pointed out the activity of complex **1** for the ROMP of cyclic olefins with or without addition of a diazo compound ($N_2CHSiMe_3$) as a carbene initiator[12] and for the ATRP of acrylate derivatives and styrene.[13]

The formation of stilbene was first revealed by the stoichiometric reaction of complex **1** with styrene at 80 °C in toluene. The catalytic synthesis of symmetrical stilbenes by self-metathesis was then screened with a series of styrene derivatives bearing electron-donating and electron-withdrawing substituents (Table 1). Typically, the reactions were carried out for 3 h at 80 °C in toluene and afforded only stilbene derivatives with the *E*-configuration.[14] The results show that a strong electron-withdrawing substituent totally inhibits the reaction (entries 7 and 8) in contrast to a strong-donating one (entry 6). The weak electron-withdrawing bromide substituent does not prevent the reaction, except for the *meta*-derivative (entry 3).

The effect of light was found to be determining for the outcome of the reaction since no conversion of styrene was observed when the reaction was performed in total darkness.[15] However, the combination of daylight and long distance artificial lighting ensured good activity as well as reproductibility. Light is expected to promote the arene decoordination to afford an active, coordinatively unsaturated ruthenium(II) species. The self-metathesis of the sterically hindered α-methylstyrene was attempted but no conversion was observed suggesting that this substrate is not suitable to either activate the precatalyst **1** or to react with the generated catalyst. The synthesis of unsymmetrical stilbene derivatives was then investigated (Scheme 2).

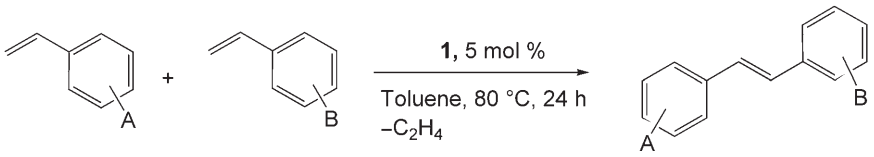
Table 1. Self-metathesis of styrene derivatives.[a]



Entry	R	Conversion [%][b]	Isolated yield [%]
1	H	93	84
2	2-bromo	78	76
3	3-bromo	0	-
4	4-bromo	82	77
5	2,4-dimethyl	89	87
6	4-methoxy	80	76
7	4-nitro	0	-
8	4-cyano	0	-

[a] 5 mol % of **1**, toluene, 80 °C, 3 h.
[b] Determined by GC after 3 h.

Various substitution patterns have been obtained with very good conversions of substrates and with a selectivity always in favour of the unsymmetrical stilbene derivative (Table 2). When α-methylstyrene was used in combination with styrene, the only product obtained was stilbene hence showing that the steric



Scheme 2. Synthesis of unsymmetrical stilbenes.

Table 2. Synthesis of unsymmetrical stilbene derivatives.[a]

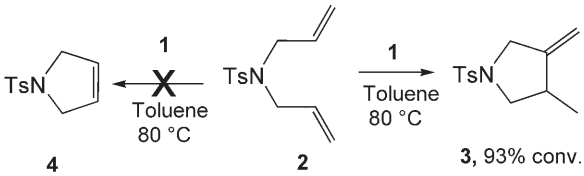
Entry	A (1 equiv)	B (1 equiv)	Conv. A [%][b]	Conv. B [%][b]	AA[c]	AB[c]	BB[c]
1	styrene	4-methoxystyrene	91	92	30	49(38)	21
2	styrene	4-bromostyrene	92	92	34	46[d]	20
3	styrene	2,4-dimethylstyrene	91	92	13	45[d]	42
4	styrene	α-methylstyrene	92	-	100	-	-
5	4-bromostyrene	4-methoxystyrene	86	86	27	38(33)	25
6	4-bromostyrene	2-bromostyrene	92	88	28	58(51)	14
7	4-bromostyrene	2,4-dimethylstyrene	91	93	24	52[d]	24

[a] *Reaction conditions:* **1**, 5 mol %, toluene, 80 °C, 24 h.
[b] Determined by GC.
[c] Product distribution determined by GC, (isolated yield).
[d] Products could not be separated by column chromatography.

hindrance of α-methylstyrene prevents its transformation by metathesis. Indeed, in the present case an alkene metathesis catalyst is generated as shown by the conversion of styrene into stilbene (entry 4).

The cross-metathesis of 4-bromostyrene and 4-methoxystyrene was repeated with a ten-fold excess of styrene in order to improve the selectivity toward the unsymmetrical product.[6,7,16] These conditions efficiently and selectively produced the unsymmetrical products (AB) with high conversions along with the formation of stilbene (BB) *and almost no self-metathesis (AA) of the reagent used in default was observed* (Table 3).

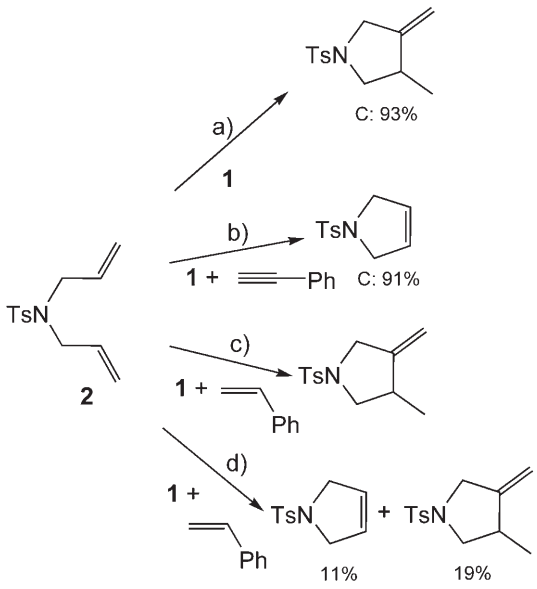
Complex **1** was evaluated in the RCM of the benchmark substrate *N,N*-diallyl-4-methylbenzenesulfonamide **2**. In that case the expected RCM product was not obtained but an *exo*-methylene 5-membered ring product **3** resulting from a cycloisomerisation reaction was obtained instead (Scheme 3). It is thus evidenced



Scheme 3. Cycloisomerisation of diallyl-*N*-tosylamine.

that the nature of the olefin is responsible for the transformation of **1** into an olefin metathesis catalysts.[17] When such a transformation is not possible or not favoured, cycloisomerisation takes place, very likely by oxidative coupling of the diene to the ruthenium centre.[18]

This type of reactivity was already observed with the *in situ* generated catalyst $[RuCl_2(p\text{-cymene})]_2$/$ImesH_2Cl$/$Cs_2CO_3$ (molar ratio 1/2/4).[18a] It was also shown that the RCM activity *vs.* cycloisomerisation could be restored by adding an alkyne derivative to promote the formation of a ruthenium vinylidene [Ru=C=CHR] initiating species.[18a] With this in mind we considered the possibility to use a terminal alkyne or styrene as activator to perform the RCM of the diallyl-*N*-tosylamine **2** (Scheme 4).



Scheme 4. RCM *vs.* cycloisomerisation. *Reaction conditions:* a) 5 mol% of **1**, toluene, 80°C, 3 h. b) Same as a) + 10 mol% of phenylacetylene, toluene, 80°C, 3 h. c) Same as a) + 25 mol% of styrene, toluene, 80°C, 3 h. d) Same as a) + 25 mol% of styrene, 30 min at 90°C before addition of **2**.

When phenylacetylene (10 mol%) was added to **2** in the presence of precatalyst **1** the reaction produced only the ring-closing metathesis product, thus likely *via* a ruthenium-vinylidene complex. On the other hand, an attempt with styrene (25 mol%, reaction c, Scheme 4) failed to provide the RCM product but again the cycloisomerisation product was obtained. Hence, we performed an activation step reacting **1** (5 mol%) and styrene (25 mol%) at 80°C for 30 min before **2** was added (reaction d, Scheme 4). A gas chromatographic analysis of the reaction mixture after 3 h showed the presence of both the RCM and cycloisomerisation products in approximatively the same amounts. It seems clear that two reactions are in competition, the cycloisomerisation one being favoured very likely because of the slow transformation of **1** into an olefin metathesis catalyst.

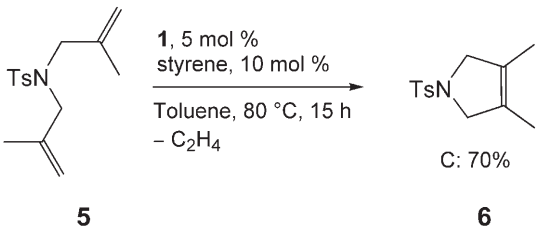
It was thus necessary to attempt the transformation of a substrate for which the cycloisomerisation is not possible. The more sterically demanding diene **5** was reacted with **1** in the presence of styrene to furnish

Table 3. Synthesis of unsymmetrical stilbene derivatives.[a]

Entry	A (1 equiv.)	B (10 equivs.)	Conv. A [%][b]	AB[c]	AA[c]
1	4-bromostyrene	styrene	91	98	2
2	4-methoxystyrene	styrene	93	100	0

[a] *Reaction conditions:* **1**, 5 mol%, toluene, 80°C, 24 h.
[b] Determined by GC.
[c] Product distribution determined by GC.

exclusively the RCM product **6** with a conversion of 70% (Scheme 5).



Scheme 5. RCM of a sterically hindered substrate.

This result reveals the potential of this catalyst precursor **1** since the RCM of a sterically hindered diene is still a challenging reaction. Indeed, this transformation performed with well defined ruthenium-alkylidene catalysts (Grubbs, Hoveyda, Grela) provided the RCM product in a maximum 52% yield (cat: 5 mol%, CH_2Cl_2, reflux, 20 h).[19]

The activity of our system reaches that of these reference catalysts while being more easily prepared since complex **1** is readily obtained from the commercially available $[RuCl_2(p\text{-cymene})]_2$ and 1,3-bis(2,4,6-trimethylphenyl)imidazolidinium chloride (IMesHCl) compounds. Although it is not possible at this stage to define the nature of the catalytic species, it is clear that the formation of an alkene metathesis catalyst from **1** requires the presence of styrene. There are a few examples of alkene metathesis catalysts *in situ* generated from metal complexes and olefins as in the polymerisation of norbornene with $RuCl_3$ in ethanol[20] or $Ru(H_2O)_6^{2+}$ in water.[21]

In conclusion, we have performed the synthesis of a series of symmetrical and unsymmetrical stilbene derivatives by olefin metathesis using a ruthenium catalyst *in situ* generated from an easily available complex $RuCl_2$(NHC)(arene) and styrene derivatives. We have also demonstrated that complex **1** with styrene as an initiator efficiently promotes the RCM of a sterically hindered diene.

Developments in this domain are underway and will be reported in due course.

Experimental Section

All the reactions were performed under an argon atmosphere using Schlenck tubes techniques and freshly dried and distillated solvents.

Synthesis of Complex 1

IMesHCl[22] (1.21 g, 3.56 mmol, 1 equiv.) and *t*-BuOK (0.98 g, 8.9 mmol, 2.5 equivs.) in 25 mL of freshly distilled THF were stirred at room temperature for 40 min. The resulting orange solution was concentrated to 3 mL and transferred *via* a filter cannula into a Schlenk tube containing 1.06 g (1.78 mmol, 0.5 equivs.) of $[RuCl_2(p\text{-cymene})]_2$ in 25 mL of freshly distilled toluene. The reaction mixture was stirred for 2 h at room temperature and the solvent evaporated. The resulting brown product was washed sequentially by 10 mL of diethyl ether and 10 mL of pentane. The complex was purified by flash column chromatography on a short plug of neutral activated alumina using dichloromethane as the eluent to furnish after solvent evaporation **1** as an orange-brown powder; yield: 1.61 g (76%). HR-MS: $m/z = 575.1773$, calcd. for $[M-Cl]^+$: 575.1767; ^{1}H NMR (200.131 MHz; $CDCl_3$): $\delta = 1.11$ [d, 6H, $^3J_{H,H} = 6.95$ Hz, CH-(CH_3)$_2$], 1.82 (s, 3H, CH_3), 2.26 (s, 12H, Mes-2,6-CH_3), 2.37 (s, 6H, Mes-4-CH_3), 2.56 [m, 1H, $CH(CH_3)_2$)], 4,66 (d, 2H, $^3J_{H,H} = 5.86$ Hz, C_6H_4), 5.07 (d, 2H, $^3J_{H,H} = 5.86$ Hz, C_6H_4), 6.93 (s, 2H, NC*H*C*H*N), 6.97 (s, 4H, Mes-3-C*H*); ^{13}C NMR (50.329 MHz; $CDCl_3$): $\delta = 18.5$ (CH_3), 19.5 (CH_3), 21.6 (CH_3), 22.9 (CH_3), 30.6 (CH), 86.1 (CH), 86.2 (CH), 96.2 (Cq), 103.3 (Cq), 125.6 (CH), 129.1 (CH), 136.6 (Cq), 139.1 (Cq), 139.2 (Cq), 172.2 (Cq).

Crystallographic data (excluding structure factors) for the structure of complex **1** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-602393. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) +44–1223/336–033; e-mail: mailto:deposit@ccdc.cam.ac.uk].

General Procedure for the Synthesis of Stilbene Derivatives

Complex **1** (17.5 mg, 0.03 mmol, 0.05 equivs.) and 0.6 mmol of styrene derivative in 2 mL of toluene were stirred at 80 °C. Conversions were determined by gas chromatography by measuring area ratios assuming identical response factors for all the compounds. Some reactions have been repeated with good reproducibility. The stilbene derivatives were isolated by column chromatography on silica gel using a mixture of heptane/dichloromethane as the eluent. ^{1}H NMR data of the following isolated stilbenes were in agreement with reported values: 1,1′-(*E*)-ethene-1,2-diylbis(2-bromobenzene)[23] (Table 1, entry 2), 1,1′-(*E*)-ethene-1,2-diylbis(4-bromobenzene)[24] (Table 1, entry 4), 1,1′-(*E*)-ethene-1,2-diylbis(2,4-dimethylbenzene)[25] (Table 1, entry 5), 1,1′-(*E*)-ethene-1,2-diylbis(4-methoxybenzene)[7b] (Table 1, entry 6), 1-methoxy-4-[(*E*)-2-phenylvinyl]benzene[26] (Table 2, entry 1), 1-bromo-4-[(*E*)-2-(4-methoxyphenyl)vinyl]benzene[27] (Table 2, entry 5), 1-bromo-2-[(*E*)-2-(4-bromophenyl)vinyl]benzene[28] (Table 2, entry 6).

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