

Activity and stereoselectivity of Ru-based catalyst bearing a fluorinated imidazolinium ligand

Research Article

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Abstract: Grubbs II generation catalyst (**3**), bearing a fluorinated imidazolinium ligand, was investigated in cross metathesis (CM), ring closing metathesis (RCM) and ring opening polymerization metathesis (ROMP) for a variety of substrates. Kinetic studies showed reduced stability of the catalyst in methylene chloride following the first 15 minutes of reaction preventing a higher efficiency despite the very high activity. Beneficial solvent effects on the catalyst stability were observed by performing RCM in C_6F_6 .

Keywords: Metathesis • Ruthenium-based catalyst • Kinetics

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1. Introduction

Olefin metathesis has emerged in past decades as one of the most useful methods for constructing C=C bonds [1]. The discovery of Ru alkylidene complexes able to catalyze olefin metathesis reactions (**1** in Chart 1) [2] inspired intensive research efforts toward the synthesis of more efficient catalytic precursors. In particular, after the first isolation in 1991 of a free N-heterocyclic carbene (NHC) by Arduengo *et al.* [3], this family of ligands came to the forefront of coordination chemistry and Ru-based catalysis leading to the substitution of one phosphine with an N-heterocyclic carbene (NHC) ligand (**2**) [4,5]. Recently, the introduction of fluorine atoms in the ortho-position of the NHC N-aryl groups (**3**) led to a rate acceleration in the ring closing metathesis (RCM) of diethyldiallylmalonate, probably due to a ruthenium-fluorine interaction [6]. Despite this interesting result, no more experimental data, relative to the behaviour of **3** toward other substrates, have been reported.

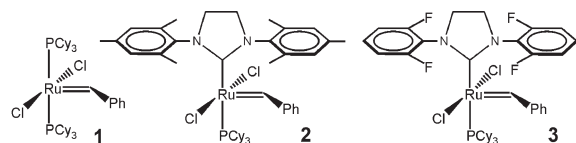


Chart 1

In order to depict a more comprehensive analysis of the behavior of this catalyst, the catalytic activity and stereoselectivity of **3** was tested in cross metathesis (CM), ring closing metathesis (RCM) and ring opening polymerization metathesis (ROMP) for a variety of substrates.

2. Experimental Procedure

All reactions involving metal complexes were conducted in oven-dried glassware under nitrogen atmosphere with anhydrous solvents, using standard Schlenk techniques and glove box techniques. Toluene was distilled from sodium/benzophenone. CH_2Cl_2 was dried on CaH_2 and freshly distilled before use. All chemical products were purchased from Sigma –Aldrich Company and were reagent quality. These products were used without further purification. The synthesis of substrates **8** and **10** were produced by reported procedures [7]. Flash column chromatography of organic compounds was performed using silica gel 60 (230-400 mesh). Silica gel for the purification of organometallic complexes was obtained from TSI Scientific, Cambridge, MA (60 Å, 230-400 mesh, pH 6.5-7.0). All procedures relative to RCM, ROMP and CM in the presence of **3** are described in the supporting information.

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Compound 4. Under inert atmosphere, tris(dibenzylideneacetone)dipalladium(0) (203.3 mg, 0.222 mmol), BINAP (450.2 mg, 0.723 mmol), sodium t-butoxide (2.129 g, 22.16 mmol), 2-bromo-1,3-difluorobenzene (3.036 g, 15.73 mmol) and ethylenediamine (455.5 mg, 7.48 mmol) were added to toluene (50 mL). The solution was heated at 110°C for 24 hours, then cooled to room temperature, diluted with 30 mL of hexanes and filtered through a plug of silica. The product was eluted with dichloromethane and purified by chromatography eluting with hexane:dichloromethane = 7:3. The solution was concentrated in vacuo to obtain a yellow oil of **4** (818.2 mg, 2.88 mmol, 38.5% yield). ^1H -NMR (400 MHz, CDCl_3) δ : 3.52 ppm (s, 4H), 6.68 ppm (m, 2H), 6.81 ppm (t, 4H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 46.8; 111.7; 118.1; 125.7; 152.6; 155.0. ^{19}F -NMR (376 MHz, CDCl_3) δ : 129.3 ppm (s) (see supporting information).

Compound 5. Compound **4** (403.3 mg, 1.42 mmol) was diluted with 2 mL of diethyl ether and acidified with $\text{HCl}/\text{Et}_2\text{O}$ 2 M. The white powder of diammonium salt was filtered and washed with $\text{HCl}/\text{Et}_2\text{O}$ 2M, then concentrated in vacuo. The salt was added to triethyl orthoformate (9.4 mL, 56.5 mmol) and the solution was heated at 135°C for 30 min. The solution was cooled, filtered and the solid was washed with diethyl ether to obtain a white solid of the tetrafluorodihydroimidazolium chloride **5** (390.3 mg, 1.18 mmol, 83% yield). NMR data matched with those reported in the literature [6] (see supporting information).

Compound 3. In a glove box, compound **5** (701.1 mg, 2.12 mmol), silver(I) oxide (280.4 mg, 1.21 mmol) and 5Å molecular sieves (822 mg) were added to dichloromethane (8.5 mL) and the solution stirred in the dark for 1 hour at room temperature. The grey suspension was filtered on a glass microfibre filter and the filter was washed with dichloromethane. The obtained solid and 1st generation Grubbs catalyst (**1**) (995.8 mg, 1.21 mmol) were dissolved in toluene (15 mL) and the solution was stirred in the dark at room temperature for 16 hours. The suspension was purified by chromatography in a column packed with

TSI Scientific gel dry eluting with pentane: Et_2O = 4:1, then 1:1, and finally 1:4. The solution was concentrated in vacuo to obtain a brown-red powder of **3** (468.7 mg, 0.56 mmol, 46.3% yield). NMR data matched with those reported in [6] (see supporting information).

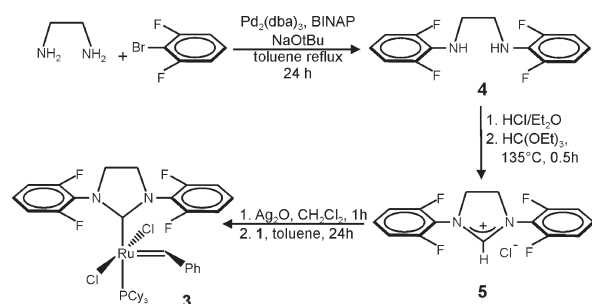
NMR spectra and catalytic test details have been reported in the supporting information.

3. Results and Discussion

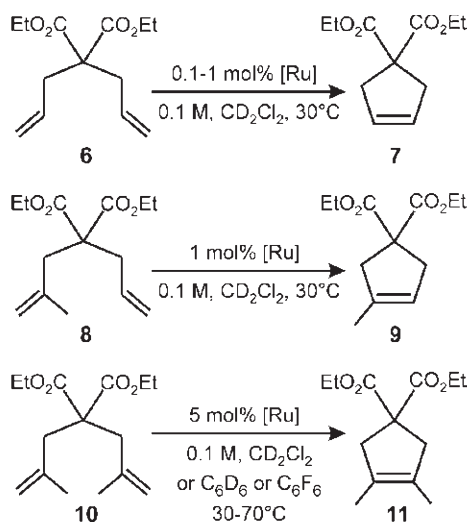
Synthesis of complex **3** is described in Scheme 1. Hartwig-Buchwald coupling of the first step [8], for the synthesis of **4**, requires harsh conditions, due to the strongly deactivated Br-C bond of the Br-aryl derivative [9]. In fact, the presence of an electron-withdrawing function on the aromatic moiety significantly reduces the yield with respect to other substrates. Despite the moderate yield (around 39%), the Hartwig-Buchwald coupling as a first step discloses the possibility of achieving analogue chiral ruthenium catalysts with a fluorine atom in the ortho-position of the NHC N-aryl groups. In fact, a chiral diamine could be used instead of ethylenediamine. Dihydroimidazolium salt **5** was obtained in high yields (83 %) by salification of **4** with HCl followed by condensation with triethyl orthoformate. The overall procedure to obtain **5** leads to lower yields (32%) with respect to the synthesis reported by Grubbs *et al.* [6] (54% yield), which involves the reaction of oxalyl chloride with 2,6-difluoroaniline. Nevertheless, the latter procedure does not allow for the production of chiral ligands. Compound **5** was treated with Ag_2O to afford the carbene transfer agent that was reacted with **1** to obtain the desired complex **3**, by transmetalation [10], in 47% yield.

The activity of **3** was tested in the RCM of **6**, **8** and **10** (Scheme 2). The course of reaction was monitored by ^1H NMR spectroscopy and the conversion of starting materials to products over time was measured as shown in Fig. 1. As for the kinetic profile of RCM of substrate **6**, the experimental data are in agreement with those reported in the literature [6]. The activity and the conversions in the RCM of **8** and **10**, which lead to a tri and a tetrasubstituted olefin, respectively, showed to be lower. Nevertheless, catalysts of Grubbs type reported in the literature, are generally unable to promote the RCM of all three kinds of substrates. Only a few of them, with particularly low steric hindrance, revealed to be active toward **6**, **8** and **10** [11,12].

RCM of substrate **6** was also performed in the presence of 0.1% of **3** as shown in the kinetic profile depicted in Fig. 2 and is compared with the analogue reaction in the presence of 1% of **3**. After the first



Scheme 1. Synthesis of **3**.



Scheme 2. RCM of **6**, **8** and **10**.

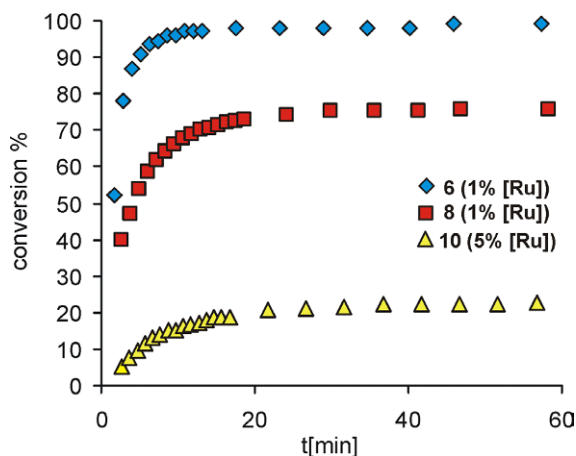


Figure 1. Kinetic profiles of RCM of **6**, **8**, **10** 0.1 M, conducted in CD_2Cl_2 at 30°C and monitored by ^1H NMR.

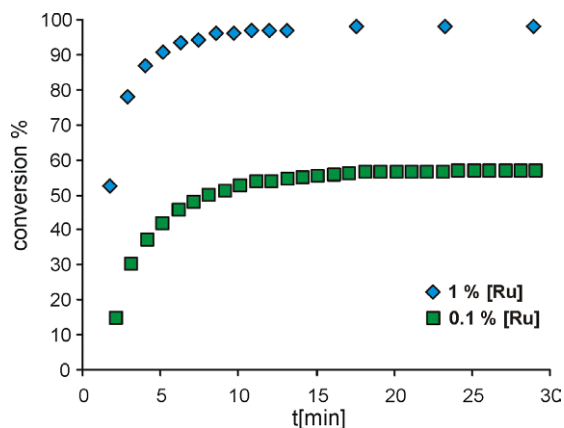


Figure 2. Kinetic profiles of RCM of **6** 0.1 M, conducted in CD_2Cl_2 at 30°C and monitored by ^1H NMR.

15-20 min, RCM in the presence of 0.1% of catalyst reaches a plateau, suggesting that after that time the catalyst decomposes. The lack of stability of **3** can be

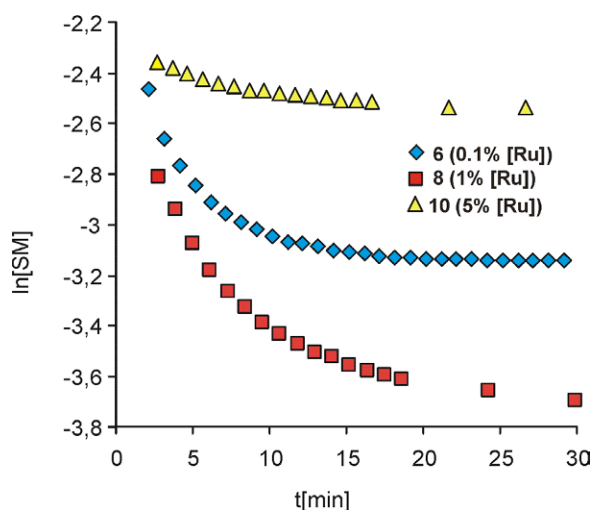


Figure 3. Log plots for **3** in the RCM of **6** (0.1% catalyst loading), **8** (1% catalyst loading) and **10** (5% catalyst loading).

illustrated by plotting $\ln([\text{starting material}])$ vs. time (Fig. 3). In fact, instead of a linear plot, which would indicate a pseudo-first kinetic rate over the course of the reaction, curved plots, consistent with catalyst decomposition, are observed for all substrates.

Kinetic profiles depicted in Fig. 4 revealed that no relevant yield improvement in the challenging RCM of hindered substrate **10** could be obtained in benzene (Fig. 4A), even at higher temperatures (60°C). The RCM of **10** was also conducted in C_6F_6 to reach higher conversions. In fact, fluorinated aromatic solvents have been reported to significantly enhance yields in the RCM of olefins promoted by Ru catalysts [13]. Significant beneficial solvent effects were, in this case, observed (Fig. 4B). Catalyst lifetime at 70°C increases up to 2 hours leading to an 81% yield and, at 30°C, the catalyst was still working after 40 hours reaching a 92% yield. The C_6F_6 can affect the catalyst lifetime either stabilizing the Ru species or, alternatively, decreasing the Ru complex solubility that would occur slowly during the reaction. Indeed, the poor solubility of **3** in C_6F_6 is directly observable from the undissolved Ru complex under the reaction conditions.

Afterward, complex **3** was tested in ROMP of **12**, **13** and **14**. Reactions are sketched in Scheme 3 and all results are reported in Table 1. The high activity of **3** toward **12** and **13** were confirmed by the good conversions achieved after 5 minutes in the presence of only 0.001% of catalyst [14]. As for **14**, longer times (30 minutes) and higher amounts of catalyst (0.01%) were required in order to obtain high conversions.

^1H and ^{13}C NMR spectroscopy allowed for the determination of the Z fraction of the newly formed double bond in the polymer chains. Poly(**12**) shows about 60%

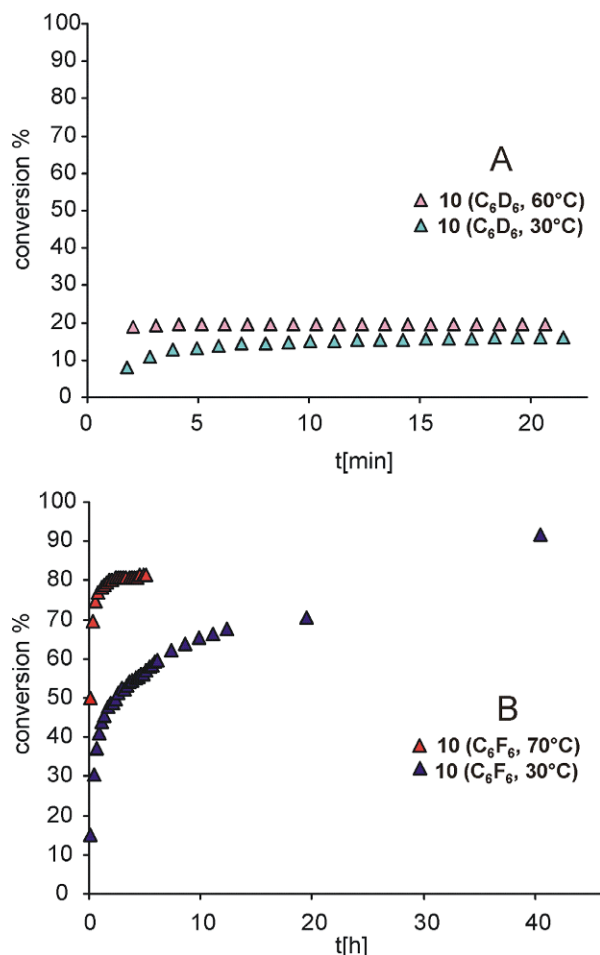
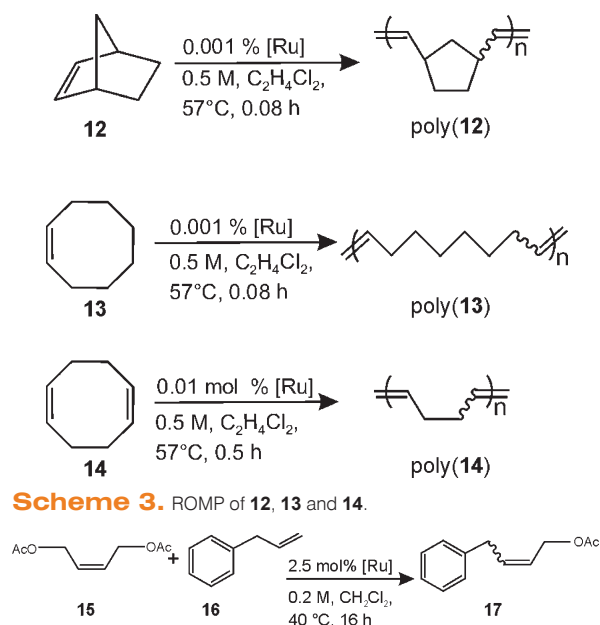


Figure 4. Kinetic profiles of RCM of 10 0.1 M and 5% catalyst loading, conducted in C_6D_6 (A) and in C_6F_6 (B) monitored by 1H NMR.



Scheme 3. ROMP of 12, 13 and 14.

Scheme 4. CM of 15 and 16.

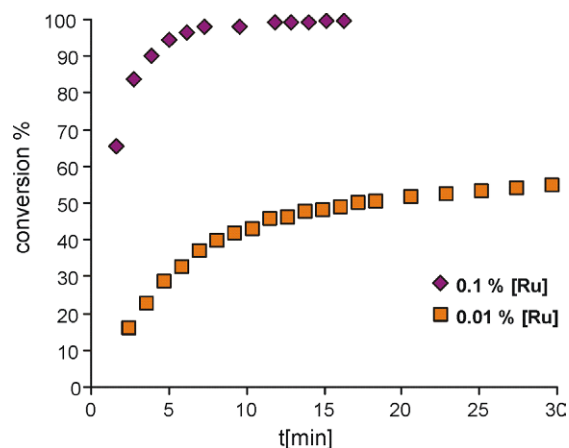


Figure 5. Kinetic profiles of ROMP of 14 0.5 M, conducted in CD_2Cl_2 at 30°C and monitored by 1H NMR.

Table 1. ROMP and CM conducted in the presence of 3.

Run	Cat% ^{a)}	Substrate	Product	t(h)	Yield% ^{b)}	E:Z ^{c)}
1 ^{d)}	0.001	12	poly(12)	0.08	68	1.5
2 ^{d)}	0.001	13	poly(13)	0.08	54	0.9
3 ^{d)}	0.001	14	poly(14)	1	traces	-
4 ^{d)}	0.01	14	poly(14)	0.5	88	0.5
5 ^{e)}	2.5	15-16	17	16	47	6.3

^{a)} Percentage of catalyst 3 with respect to the substrate.

^{b)} Yields from isolated products.

^{c)} Ratio based on data from 1H and ^{13}C NMR of isolated products.

^{d)} Reaction conducted in dichloroethane at 57°C, substrate 0.5 M.

^{e)} Reaction conducted in CH_2Cl_2 at 40°C, 15-16 0.2 M.

of *E* double bonds along the chain at 68 % of monomer conversion. The slight prevalence of *E* is probably related to an equilibrium-controlled polymerization in which secondary chain transfer occurs [15]. The ROMP of 13 and of 14 showed a lack of stereoselectivity as well. It is noteworthy that the 66% of *Z* double bonds in poly(14) is not indicative of a selectivity toward the formation of *cis* double bonds, which would be confirmed only by an amount of *Z* double bonds greater than 75%.

The ROMP of 14 in CD_2Cl_2 was also monitored by 1H NMR in the presence 0.1 and 0.01% of 3 (see Fig. 5). The comparison between the kinetic profile and the data reported in literature indicates that the activity of 3 is similar to that of catalyst 2 and much higher than the activity of 1 [15]. As in the case of RCM of 6, the kinetic profile of ROMP of 14, at lower concentrations of catalyst, underlines that the conversion slows down after 15-20 min.

We finally investigated the activity of 3 in the representative cross metathesis (CM) reaction of *cis*-1,4-diacetoxy-2-butene (15) and allyl benzene (16), depicted in Scheme 4 [16]. Conversion to desired heterocoupled product 17 (47%) showed to be lower than Grubbs first and second generation catalysts and *E*:*Z* ratio (6.3:1) comparable to that of Grubbs second generation catalyst (2).

4. Conclusions

The activity and stereoselectivity of Grubbs II generation catalyst **3**, bearing fluorinated imidazolium ligand, has been tested in RCM, ROMP and CM reactions. The catalyst showed to be highly active in methylene chloride, with respect to (SIMes)(Cl)₂Ru=CHPh(PCy)₃ (**2**), during the first 15–20 minutes of the reaction. Afterward, the reaction rate slowed down, independently from the type of substrate, due to the decomposition of the active species, as confirmed by kinetic studies. Catalyst lifetime can be significantly lengthened by performing RCM in C₆F₆, reaching over 90% yield in the challenging RCM of hindered olefins.

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The synthetic approach for **3**, presented in this paper, discloses the possibility to achieve analogue chiral ruthenium catalysts with fluorine atom in the ortho-position of the NHC N-aryl groups.

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