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Activation of olefin metathesis complexes containing unsymmetrical unsaturated N-heterocyclic carbenes by copper and gold transmetalation

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The activation of ruthenium-indenylidene complexes containing two unsymmetrical unsaturated N-heterocyclic carbenes (u2-NHCs) by a transmetalation process is reported. The use of copper(I) or gold(I) chlorides promotes the rapid trapping of one NHC ligand that releases the catalytic active Ru-species. Impressive initiation rates with full-conversions are observed within one minute. This practical protocol demonstrates excellent catalytic performances in various ring-closing metathesis (RCM) and self-metathesis (SM).

In a few decades, olefin metathesis has rapidly become one of the most efficient synthetic tools in organic chemistry. This attractiveness was mainly due to the development of efficient, well-defined, air stable and easy to handle ruthenium-arylidene complexes with high tolerance towards many organic functions.¹ Since the pioneer works describing the phosphine-based Grubbs first-generation catalyst in early 1990s,² the research efforts to furnish more robust and powerful complexes have drastically increased.^{1,3} The development of catalysts containing a N-Heterocyclic Carbene (NHC) ligand that demonstrated higher stability and activity, known as Grubbs second generation catalysts, represents certainly the most successful achievement in this field.⁴ While numerous catalysts bearing one NHC unit have been intensively developed,⁵ the class of Ru-complexes featuring two NHCs has scarcely been investigated. Historically, the first members of this class were reported in 1998 by the Herrmann group prior to the Grubbs second generation catalyst.⁶ Unfortunately, due to a stronger coordination of the NHC ligand, a significant thermal stimulus was needed to observe satisfactory activities in olefin metathesis. In recent years, a renewed interest has taken place for these catalysts, notably in materials science, in which a full-control of the catalytic initiation of the metathesis polymerisation is strongly

required.⁷ Several strategies were reported to improve their catalytic performances by facilitating the decoordination of one NHC ligand with noteworthy successes.⁸ Notably, the introduction of electron-deficient NHC ligands⁹ or small NHC units¹⁰ could enhance the activity of the related complexes with catalyst loadings as low as 0.05 mol% (Figure 1, a). In 2011, Grubbs and Bertrand successfully reported the use of a Brønsted acid as external stimulus to promote the protonolysis of a mesoionic carbene (MIC).¹¹ The resulting 14e⁻ catalytic species proved to be extremely active, surpassing current commercial Ru-catalysts (Figure 1, b-left). More recently, our group synthesised new complexes **Ru-1** containing two unsymmetrical unsaturated N-cycloalkyl-NHCs (u2NHCs) that were activated by anhydrous HCl (Figure 1, b-right).¹² These catalysts were quite efficient in various metathesis transformations, notably in macrocyclic ring-closing metathesis (RCM) yielding various macrocyclic odorant molecules of remarkable >99% purity. Nevertheless, the use of anhydrous HCl remained difficult to handle.¹³

Fig. 1 Previously reported activation of Ru-complexes containing two NHC ligands (a and b) and the proposed transmetalation protocol (c, this work)

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We would like now to report an efficient activation of Ru-indenylidene complexes **Ru-1** containing two u2-NHCs by a transmetalation process involving copper(I) or gold(I) chlorides. The rapid release of the active catalytic Ru-species in the reaction media led to impressive initiation rates with full conversions that occur within a few minutes. Through this practical protocol, excellent catalytic performances were observed in various RCM and SM.

In 1997, Grubbs and co-workers were the first to report the beneficial use of copper(I) chloride to enhance the initiation rates of well-defined $(\text{PR}_3)_2\text{X}_2\text{Ru}=\text{CH}-\text{CH}=\text{Ph}_2$ precatalysts during RCM transformations.^{14a} Albeit the nature of the resulting species was unknown, the authors suspected that CuCl could act as a phosphine scavenger. Later, Blechert and co-workers used this protocol to enhance the turnover number (TON) of Grubbs 2nd generation precatalyst in cross-metathesis of reluctant acrylonitrile.^{14b} It is worth to underline that the phosphine-scavenging effect was also successfully employed to improve the synthesis of phosphine-free styrenylether Ru-catalysts (i.e. Hoveyda type precatalyst).¹⁵ More recently, Thuo and co-workers reported that copper(I) halides limited drastically the formation of isomerized by-product when metathesis reaction occurred in polar protic solvents with phosphine-based Grubbs catalysts.¹⁶ Based on these reports, we decided to examine the ability of copper(I) or gold(I) salts to activate our bis-u2NHC **Ru-1** by sequestering one NHC ligand (Figure 1, c). First, the transmetalation process was investigated by reacting **Ru-1a** complex with stoichiometric amounts of CuCl and 1-isopropoxy-2-vinylbenzene **L1** in CH_2Cl_2 at 50 °C (Scheme 1). We were delighted to observe remarkable conversions for expected Hoveyda-type catalyst **Ru-2a** and copper-u2NHC **Cu-1a** after 5 h of reaction (>95%, see ESI for details).

Scheme 1 Transmetalation process involving Cu(I) and Au(I) salts with bis-u2NHC **Ru-1a** complex. ^a Determined by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. ^b Isolated yield

Moreover, thanks to their robustness toward silica gel, **Ru-2a** and **Cu-1a** were isolated in excellent 91 and 86% yields after purification. Interestingly, the transmetalation process also succeed with gold(I) chloride but required higher reaction time (24 h) to reach 69% conversion. **Ru-2a** and gold-u2NHC **Au-1a** were isolated in respectively 45 and 39% yield after purification. Additionally, X-ray diffraction analysis unambiguously confirmed the structure of **Ru-2a** and **Au-1a** (Scheme 1). Unfortunately, all attempts to isolate suitable single crystals of **Cu-1a** remained unsuccessful.

With this efficient protocol of activation in hands, the catalytic activity profile of **Ru-1a** was studied for the RCM of diethyldiallylmalonate (DEDAM) **S1** under standard conditions (1 mol%, 0.1 M).^{17a} As depicted in figure 2, the critical role of CuCl and AuCl appeared quite prominent. At 30 °C, as expected for a bis-NHC catalyst, **Ru-1a** showed a very slow reactivity toward diene **S1** with only 10% conv. after two hours (67% at 24 h, Fig. S5, ESI). Addition of CuCl (5 mol%) led to a fast initiation of the metathesis reaction, reaching up to 80% conv. after only 20 min. and a full conversion after 40 min.^{17b} With gold activator, an impressive initiation rate occurred converting up to 80% of **S1** within 5 min., however the catalytic system became rapidly less productive as a very slow consumption was observed after 2 hours (84% conv.).

Fig. 2 Catalytic activity profile of **Ru-1a** catalyst for RCM of DEDAM **S1** at 30 °C (a) and 80 °C (b) without (black line) or with activators: CuCl (red line); AuCl (blue line). Conversions were monitored by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard.

At 80 °C, while Ru-**1a** became productive reaching 73% conv. over 2 hours (and >99% after 6 h, Fig. S7, ESI), the copper-activation drastically enhanced the reaction rate with a full conversion within 4 minutes. Remarkably, a similar trend also occurred with only 0.1 mol% of catalyst loading (and 0.5 mol% of CuCl) as >99% conv. were reached after 30 min. (see Fig. S6, ESI). Regarding AuCl, the catalytic activation was also impressive with a full consumption of **S1** after 30 min. Encouraged by this, the transmetalation activation for other bis-NHC Ru-complexes was next investigated. To this end, we synthesized Ru-**1b**, Ru-**1c** and Ru-**1d** complexes (Figure 3). Precatalyst Ru-**1b** containing mixed NHCs, i.e. one SIMes and one cyclooctylIMes ligands, was isolated in 55% yield from commercially available **M2** (see Scheme S1, ESI). Furthermore, complexes Ru-**1c** and Ru-**1d** containing two u2NHC featuring halogeno-*N*-aryl substituents were synthesized in good yields following our protocol developed for Ru-**1a** (57%, see Scheme S2, ESI). Moreover, the structure of complex Ru-**1b** was confirmed by single crystal X-ray diffraction studies (Figure 3).

Fig. 3 Newly synthesized bis-NHC containing Ru-complexes **1b**, **1c** and **1d** and solid-state structure of Ru-**1b** from single crystal X-ray diffraction (N in blue, C in grey, Cl in green and Ru in pink).

The catalytic profile of Ru-**1b-d** towards the benchmark RCM was then examined (Table 1). First, the transmetalation with copper or gold drastically doped the catalytic activity of Ru-**1b** by completing the metathesis within 5 min. at 80 °C (entries 2 and 4). Again, at 30 °C, the copper activation was more pronounced with a full conversion occurring over 20 min. while only 68% were reached in presence of AuCl (entries 1 and 3). Interestingly, Ru-**1c** and Ru-**1d** surpassed their Ru-**1a-b** congeners with full conversions within a few minutes in presence of CuCl, whatever the temperature of the reaction (entries 5-6 and 9-10). With AuCl, similar trends were observed at 80 °C (entries 8 and 12) but at 30°C, despite a rapid initiation rate (70% for Ru-**1c** and 86% for Ru-**1d**, entries 7 and 11), catalytic systems became rapidly less productive with a slower evolution of the metathesis. To illustrate this new and efficient activation protocol towards u2-NHC Ru-precatalysts, we turned our attention to other valuable olefin metathesis reactions (Scheme 2). Depending of the targeted transformation, CuCl or AuCl were chosen. To our delight, moderate to excellent yields were observed in short times (10

to 30 min.) for RCM, excepted for reluctant substrate **P11**¹⁸ that remained totally inert, even at 120 °C. Regarding the self-metathesis of terminal olefins performed in neat condition at 60 °C, CuCl was inappropriate as many isomerized by-products and related secondary metathesis products were also produced (see Fig. S15 and S16, ESI).

Table 1 Catalytic activity of Ru-**1b**, **1c**, **1d** catalysts in RCM of DEDAM **S1** with activator^a

Entry	Ru-cat	activator	Temp. (°C)	Time	Yield (%) ^b
1	Ru- 1b	CuCl	30	20 min.	>99
2	Ru- 1b	CuCl	80	1 min.	>99
3	Ru- 1b	AuCl	30	20 min.	68(76) ^c
4	Ru- 1b	AuCl	80	4 min.	>99
5	Ru- 1c	CuCl	30	6 min.	>99
6	Ru- 1c	CuCl	80	<1 min.	>99
7	Ru- 1c	AuCl	30	2 min.	70(78) ^d
8	Ru- 1c	AuCl	80	<1 min.	>99
9	Ru- 1d	CuCl	30	6 min.	>99
10	Ru- 1d	CuCl	80	<1 min.	>99
11	Ru- 1d	AuCl	30	2 min.	86(92) ^e
12	Ru- 1d	AuCl	80	<1 min.	>99

^a Reaction conditions: DEDAM **S1** (1 mmol), catalyst (0.01 mmol), activator (0.05 mmol), toluene (1 mL), under Ar. ^b NMR yield using 1,3,5-trimethoxybenzene as an internal standard. ^c Conversion after 7 h. ^d Conversion after 2 h. ^e Conversion after 4 h.

Fortunately, when Ru-**1c** or Ru-**1d** (0.1 mol%) were activated by 0.1 mol% of AuCl, expected internal olefins **P12** and **P13** were produced in good yields and excellent purity (95->97%) after 20 min. of reaction. It is noteworthy that the mixed SIMes/cyclooctylIMes indenylidene complex Ru-**1b** led to a significant alteration of the purity for **P13** (87%), similarly to usual SIMes-based Ru-catalyst (Grubbs 2nd generation).^{12a} We surmised that the SIMes(Cl)₂Ru-methylidene *versus* cyclooctylIMes(Cl)₂Ru-methylidene active species was formed in the reactive media. In order to confirm this behavior, the stoichiometric transmetalation of Ru-**1b** with CuCl in presence of **L1** was thus attempted. As depicted in Scheme 3, SIMes-Hoveyda catalyst Ru-**2b** and the related cyclooctylIMes-CuCl complex Cu-**1a** were produced in respectively 95 and 75% yields, evidencing unambiguously that cyclooctylIMes acts as the labile ligand.

Conclusions

A practical protocol allowing an efficient activation of robust ruthenium olefin metathesis complexes featuring unsymmetrical unsaturated u2-NHCs was developed. By adding copper(I) or gold(I) chloride salts, a transmetalation process occurred to trap the labile u2-NHC ligand and to form well-defined CuCl- and AuCl-NHC complexes in the reactive media. An impressive catalytic initiation rates was achieved with full-conversions reached within a few minutes, even at 30 °C. The resulting Ru-active species demonstrated remarkable

catalytic performances towards a range of RCM and SM transformations. Taking the opportunity that Au- or Cu-NHC complexes are cleanly formed in the media, further investigations on the development of dual catalytic reactions are currently underway in our laboratory.¹⁹

Scheme 2 Scope of metathesis transformations catalyzed by Ru-**1c**, **1d**/CuCl or AuCl^a

^aReaction conditions: Substrate **S** (1 mmol), catalyst (0.01 mmol), activator (0.05 mmol), toluene (1 mL), under Ar. ^bDetermined by ¹H NMR spectroscopy. ^cNMR yield using 1,3,5-trimethoxybenzene as an internal standard. ^d30 min. of reaction. ^e20 min. of reaction. ^fPerformed in neat with 0.1 mol% of catalyst and 0.1 mol% of AuCl. ^gYield, purity and *E/Z* ratio were determined by GC (see ESI for details).

Scheme 3 Transmetalation process between Cu(I)Cl and mixed NHC Ru-**1b** complex

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Conflicts of interest

The authors declare no conflict of interest

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