Improved One-Pot Synthesis of Second-Generation Ruthenium Olefin Metathesis Catalysts

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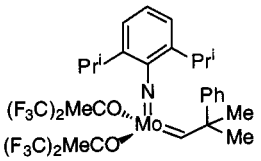
Summary: An improved one-pot synthesis of olefin metathesis catalysts $(PCy_3)(L)Ru{=}CHPhCl_2$ *(L = N-heterocyclic nucleophilic carbene: IMes,* ***3****; SIMes,* ***4****) employs potassium tert-amylate to deprotonate the imidazolium salt ligand precursor. Both of the reaction steps are carried out using a one-pot protocol in hexane with commercially available reagents under mild conditions, permitting the isolation of* ***3*** *and* ***4*** *by simple filtration.*

Introduction

Olefin metathesis has become a powerful assembly strategy and a widely used synthetic tool in the formation of C−C bonds.[1] This reawakened interest in olefin metathesis processes during the past decade is largely attributable to the discovery of highly active, well-defined molybdenum and ruthenium alkylidene catalysts **1**[2] and **2**.[3] Although the ruthenium complex **2** ("Grubbs' catalyst") possesses significant advantages over molybdenum complex **1** in terms of stability and ease of storage and handling, complex **1** displays higher reactivity toward a broad range of sterically and electronically varied substrates. However, neither of these complexes displays significant tolerance to thermal treatment.[1]



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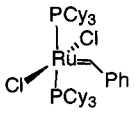

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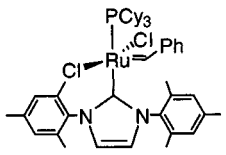
Second-generation ruthenium benzylidene complexes **3**[4] and **4**,[5] where one phosphine in complex **2** has been replaced by an unsaturated (1,3-dimesitylimidazol-2-ylidene, IMes) or saturated (1,3-dimesityl-4,5-dihydroimidazol-2-ylidene, SIMes) N-heterocyclic nucleophilic carbene bearing N-mesityl substituents, have recently been reported. These complexes possess greater thermal stability than the parent complex **2**[6] and exhibit activity comparable to that of the most active early transition metal systems while retaining the functional group tolerance of complex **2**. Complexes **3** and **4** have been successfully employed in a broad range of olefin metathesis reactions ranging from ring-closing metathesis (RCM)[7] to ring-opening metathesis polymerization (ROMP)[8] and cross-metathesis.[9]



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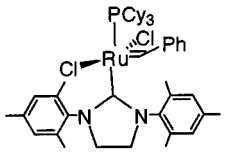

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Results and Discussion

The first preparations of complexes **3** and **4** employed the isolated free (by deprotonation of the imidazolium

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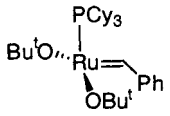
salt) carbene to replace one phosphine ligand in **2**. Subsequently, to avoid the independent isolation of the air- and moisture-sensitive carbene ligands, a one-pot synthetic procedure for **3** was developed in which the imidazolium salt (nucleophilic carbene precursor) is deprotonated in situ with a strong base such as $KOBu^t$ in a nonpolar solvent.[10] However, the insolubility of $KOBu^t$ in hexane called for longer reaction times and heating the reaction mixture. This resulted in lower than quantitative yields. In efforts to improve the yields of this reaction, we noted that the purity of commercially obtained $KOBu^t$ left something to be desired. Purification by sublimation (twice) improved reaction yields somewhat. The remaining issue was the thermal treatment of the reaction mixtures in view of the poor solubility of $KOBu^t$ in hexane. This was of some concern since the commercially available ruthenium complex **2** is also known to react with excess $KOBu^t$ to afford four-coordinate complex **5** upon extensive heating. Complex **5** proved to be inactive in the RCM of diethyl diallylmalonate (the standard test for catalytic activity in olefin metathesis).[11]



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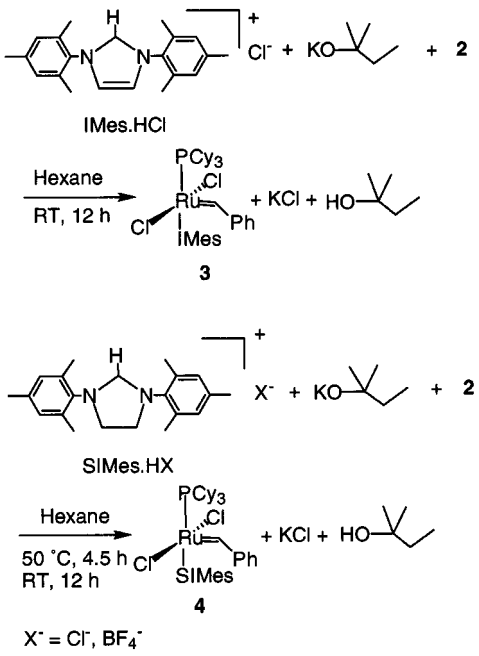
Similarly, the use of prolonged reaction times at elevated temperature in the one-pot preparation of **3** and **4** has been observed to yield products displaying lower RCM activity. This is believed to be due to the formation of inactive ruthenium alkoxide species.[12]

An alternative one-pot synthesis of **4**[5] also employs $KOBu^t$ as base. This method involves the use of solvents such as THF and benzene to render the starting material soluble. The workup of the reaction mixture consequently consists of the removal of solvents under high vacuum. We therefore sought an alternative, more soluble base for the ligand deprotonation step, which would permit the use of mild reaction conditions while maintaining the advantageous use of hexane as solvent. Potassium *tert*-amylate ($KOC(CH_3)_2CH_2CH_3$) seemed to be an ideal choice. It is somewhat more soluble than $KOBu^t$ in hexane but retains strongly basic character, ensuring the complete conversion of the imidazolium salt to the free carbene in a much shorter time. The procedure employed is shown in Scheme 1. Reaction between $KOC(CH_3)_2CH_2CH_3$ and IMes·HCl or SIMes·HCl in hexane at room temperature afforded a slightly turbid, pale yellow solution. After 1 h of stirring, addition of **2** followed by stirring at room temperature overnight (12 h for IMes·HCl and formation of **3**) or at 50 °C for 5 h followed by 12 h at room temperature (for SIMes·HCl and formation of **4**) afforded a pink-brown precipitate. This precipitate could be isolated by filtration on a collection frit, washed with methanol, and dried in vacuo to afford good yields of complex **3** or **4**. Alternatively, SIMes·HBF_4 could be employed as ligand

Scheme 1. Syntheses of Ruthenium Complexes 3 and 4



precursor, employing essentially the same reaction protocol, with two variations. The first was the reaction time: in a small-scale preparation, following initial deprotonation of SIMes·HBF_4 at room temperature and addition of **2**, 2 h of stirring at 60 °C was sufficient for the reaction to be complete. The second difference was that an additional purification step was necessary, namely, extraction of the filtered and washed product into benzene, owing to the lesser solubility of KBF_4 in methanol. In all cases the obtained products were pure by ^1H and ^{31}P NMR spectroscopies and displayed the expected activity in the RCM of diethyl diallylmalonate. The reaction was found to be equally successful in both large- (20 g) and small-scale (200 mg) procedures, giving product yields of 92% for **3** and 77% (SIMes·HCl) or 67% (SIMes·HBF_4) for **4**.

In conclusion, an improved protocol for the preparation of second-generation olefin metathesis catalysts has been developed. The imidazolium salt SIMes·HCl affords a higher reaction yield than SIMes·HBF_4. This is believed to be due to the more facile deprotonation of the imidazolium salt with the chloride counterion, borne out by independent deprotonation reactions in NMR experiments. This one-pot procedure makes use of hexane as solvent. Since the products **3** and **4** are insoluble in hexane, a simple filtration followed by a methanol wash affords the pure product in good yield.

Experimental Section

General Considerations. All reactions were carried out under an atmosphere of dry argon. IMes·HCl is available from Strem Chemicals. SIMes·HCl was synthesized following the literature procedure.[13] SIMes·HBF_4 was prepared by dissolving SIMes·HCl in water and adding aqueous HBF_4 (50% by weight from J. T. Baker Co.) followed by filtration and drying of the resulting white precipitate overnight under dynamic vacuum. Potassium *tert*-amylate in toluene (25 wt % solution) was

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purchased from Callery Chemical Co., and the solvent was removed in vacuo to afford a waxy, cream-white solid. Anhydrous solvents were purchased from Aldrich and degassed before use. Grubbs' catalyst $(PCy_3)_2Ru(=C(H)Ph)Cl_2$ was purchased from Strem Chemicals. NMR spectra were recorded using a Varian 400 MHz spectrometer. Gas chromatographic analyses were performed on a Hewlett-Packard HP 5890 II equipped with a FID and a HP-5 column.

General Procedure for Preparation of 3 and 4. In a glovebox, a 200 mL Schlenk flask was charged with IMes·HCl (3.1 g, 9.10 mmol) or SIMes·HCl (3.1 g, 9.10 mmol), potassium *tert*-amylate (1.26 g, 10.0 mmol), and hexane (40 mL). The reaction mixture, a slightly turbid, yellow solution, was stirred at room temperature for 1 h. $(PCy_3)_2Ru(=C(H)Ph)Cl_2$ (5.0 g, 6.1 mmol) was added to the reaction flask as a solid over 30 min. The flask was taken out of the glovebox, connected to a Schlenk line, and placed under 1 atm of argon. The reaction mixture was then stirred at room temperature for 12 h (in the case of the IMes·HCl reaction) or heated to 50 °C for 4.5 h, allowed to cool to room temperature, and stirred 12 h (in the case of the SIMes·HCl reaction). During this time the original purple color of the reaction mixture changed to brown-pink. The brown-pink precipitate was then filtered under argon with the help of a collection frit, and the collected solid was washed with methanol (3 × 10 mL) and dried in vacuo to afford the pure product (4.80 g, 92% (**3**) or 3.99 g, 77% (**4**)). (A similar protocol in the preparation of **4** could be followed with SIMes·HBF_4, employing SIMes·HBF_4 (100 mg, 0.3 mmol) and potassium *tert*-amylate (65 mg, 0.3 mmol) in 5 mL of hexane, stirring for 1.5 h, then adding $(PCy_3)_2Ru(=C(H)Ph)Cl_2$ (150 mg, 0.2 mmol) and heating the purple mixture to 60 °C for 2 h followed by workup. An additional step was required during workup, namely, extraction of the pink-brown product into benzene, following initial washing with small portions of hexane and methanol, evaporation of the benzene extracts, and drying of the residue in vacuo. A yield of 102 mg, 67%, was obtained.)

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Supporting Information Available: NMR spectra (^1H and ^{31}P) for product of reactions using IMesHCl, SIMesHCl, and SIMesHBF$_4$ are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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