

Available online at www.sciencedirect.com





Journal of Organometallic Chemistry 692 (2007) 3574-3576

www.elsevier.com/locate/jorganchem

Chloro-substituted Hoveyda–Grubbs ruthenium carbene: Investigation of electronic effects

Note

Roberta Ettari *, Nicola Micale

Dipartimento Farmaco-Chimico, University of Messina, Viale Annunziata, 98168 Messina, Italy

Received 12 March 2007; received in revised form 11 April 2007; accepted 11 April 2007 Available online 21 April 2007

Abstract

A series of applications of cross and ring-closing metathesis has been made to investigate the application profile of the chloro-substituted Hoveyda–Grubbs ruthenium carbene in order to evaluate electronic effects resulting from the introduction of a chlorine atom *para* to the isopropoxy moiety of its parent catalyst.

© 2007 Elsevier B.V. All rights reserved.

Keywords: Cross metathesis; Ring-closing metathesis; Electronic effects; Chloro-substituted Hoveyda-Grubbs catalyst

1. Introduction

Over the last decade, olefin metathesis reactions have emerged as a powerful tool for the formation of carbon– carbon bonds in chemistry [1].

The ruthenium carbene complexes introduced by Grubbs and co-workers are undoubtedly the most popular and versatile catalysts for these reactions. Despite its limited thermal stability, the first generation Grubbs alkylidene **1** proved to be an efficient catalyst in particular for metathesis of terminal olefins [2], whereas all second generation *N*-heterocyclic carbene (NHC) ruthenium complexes, e.g. **2–3**, showed higher reactivity towards a broad range of electron-deficient substrates (Fig. 1) [3]. These imidazolidinylidene-based systems possess greater electron density at the metal center as the imidazolidinylidene ligand acts as a strong σ donor and has almost no π acceptor properties.

The stability of bimetallic, bridged-chloride Ru-carbene complexes can be critically dependent on the presence of steric bulk in the ligand environment surrounding the metal center [4]. Despite the promising application profile observed in reactions of the phosphine-free catalyst 3,

introduced by Hoveyda [5], this catalyst proved to initialize slower than **2**, probably as a result of steric (large isopropoxy group) and electronic factors (*i*PrO \rightarrow Ru chelation) [6].

Several studies have been made by Blechert et al. [7] on the influence of various substituents other than hydrogen *ortho* or *para* to the isopropoxy group. Since the decrease of electron density at the oxygen atom of the *i*PrO group results in an increase of the catalytic activity [6,7], the introduction of an electron withdrawing group (EWG) could weaken the *i*PrO \rightarrow Ru chelation and thus facilitate the initiation of the catalytic cycle. With regard to the effect of the introduction of an halogen atom in *para* to the bulky group, the fluoro-analogue **4** (Fig. 1) was compared with its precursor **3** in a series of ring-closing metathesis (RCM) by showing that the introduction of a fluorine atom led to a less efficient catalyst but faster than **3** [7].

In order to evaluate the reactivity of the bromo-analogue 5 (Fig. 1), Grela et al. [8] tested metal-carbenes 3 and 5 in some model reactions showing that the reactivity patterns of complexes 3 and 5 were in general similar, with the latter system visibly less reactive.

The aim of our paper is to report an investigation on the application profile of the chloro-substituted complex 6 [9] (Fig. 1) in order to complete the studies on electronic effects

^{*} Corresponding author. Tel.: +39 090 6766466; fax: +39 090 355613. *E-mail address:* rettari@pharma.unime.it (R. Ettari).

⁰⁰²²⁻³²⁸X/\$ - see front matter @ 2007 Elsevier B.V. All rights reserved. doi:10.1016/j.jorganchem.2007.04.017

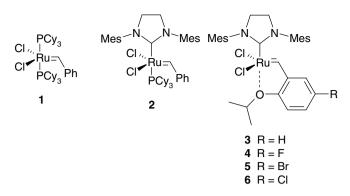


Fig. 1. Ruthenium carbene complexes for olefin metathesis (Cy = cyclohexyl and Mes = C_6H_2 -2,4,6-Me₃).

previously reported [7,8], with the purpose to give a final complete picture of the influence of all halogen atoms introduced in *para* to the *i*PrO group of Hoveyda–Grubbs second generation catalyst.

2. Results and discussion

The reactivity of the chloro-substituted complex 6 in cross metathesis (CM) reactions was compared with that of second generation Grubbs catalyst 2 and Hoveyda–Grubbs catalyst 3 in a series of CM with electron-deficient substrates.

Test reactions between allylbenzene (2.5 equiv.), olefins **7a–d** (1 equiv.) and ruthenium complexes **2**, **3** or **6** (2.5 mol%) were performed under argon, in refluxing dry CH_2Cl_2 for 5–12 h. Under these conditions, we observed the initial formation of a small amount of homodimer of allylbenzene which decreased significantly after prolonged

stirring. The corresponding CM products 8a-c were isolated, by flash column chromatography, exclusively as the E-isomers, whereas 8d was obtained as a mixture of isomers Z/E in a 3:1 ratio (Table 1). In these reactions catalyst 6 gave excellent yields with very reactive olefins 7a-b, as catalysts 2 and 3, whereas with less reactive olefins 7c-dit exhibited higher activity than that of complex 2, as expected, and slightly lower than that of complex 3.

For the coupling of styrene with olefins 7e–f, we sought to employ microwave (MW) irradiation as an energy source to promote CM. A few studies of microwave assisted metathesis have been reported, but most refer to RCM [10]. Therefore, a mixture of styrene (2.5 equiv.), olefin (7e or 7f) (1 equiv.) and metal-carbene complex (2, 3 or 6) in dry CH₂Cl₂ was stirred under MW irradiation at 100 °C for 30 min. The crude was purified by flash column chromatography to afford the CM product in good yields with excellent stereoselectivity towards the E-isomer for both compounds **8e** and **8f** (Table 1).

An identical cross-coupling, using 1.9 equiv. of styrene, 1 equiv. of CM partner 7e–f, 5 mol% of catalyst 2, in CH₂Cl₂ at 40 °C for 15 h, proceeds in 25% yield for 8e and 63% for 8f [11]. These data clearly demonstrate the potential of microwave irradiation to both improve the yields and reduce the reaction times of CM reactions.

The obtained results point out that the chloro-substituted complex 6 shows a catalytic efficiency towards CM undoubtedly better than that of Grubbs catalyst 2 and almost comparable, sometimes lower, than that of parent catalyst 3.

The activity of the complex 6 in RCM reactions has been briefly explored, as shown in Table 2.

Table 1 Cross metathesis reactions^a

Entry	Olefin	CM-partner 7	Product 8 ^b	Conditions	Catalyst	Yield % ^c	E/Z
a	Ph 🔨	COCH3		2.5 mol% of catalyst CH_2Cl_2 , Δ , 12 h	2	99	Е
u	Pn *	· 000113	111 000H ₃		3	99	
					6	99	
b	Ph	COOCH3	Ph COOCH,	2.5 mol% of catalyst CH_2Cl_2 , \varDelta , 12 h	2	99	Е
		3	3		3	99	
					6	99	
с	Ph	SO₂Ph	Ph SO ₂ Ph	2.5 mol% of catalyst CH_2Cl_2 , \varDelta , 12 h	2	43	Е
		2	2		3	71	
					6	62	
d	Ph 🔨	CN	Ph CN	2.5 mol% of catalyst CH_2Cl_2 , Δ , 5 h	2	51	Z/E
	1 11			•	3	67	3:1 ^d
		$\wedge \cdot 0$	<u>`</u> N∕		6	59	
e	Ph	// ¥-	. L	5 mol% of catalyst CH ₂ Cl ₂ , MW, 100 °C, 30 min	2	30	Е
		∠N ∖	Ph	•, , , ,	3	65	
					6	45	
f	Ph 🔨	Соон	Ph COOH	5 mol% of catalyst CH ₂ Cl ₂ , MW, 100 °C, 30 min	2	99	Е
		000011	PII ·		3	99	
					6	99	

^a All reactions were carried out by reacting 2.5 equiv. of allylbenzene or styrene and 1 equiv. of 7.

^b The analytical and spectroscopic data are in agreement with those reported in literature: 8a [13], 8b [14], 8c [6], 8d [15], 8e [16], 8f [17].

^c Isolated yields of analytically pure compounds.

^d Ratio determined by ¹H NMR spectroscopy.

Entry	Substrate 9	Product 10 ^a	Conditions	Yields % ^b	
				3	6
a	Ts I N		3 mol% of catalyst CH_2Cl_2 , rt, 2 h	99	99
b	Ts N N	N-Ts	5 mol% of catalyst CH_2Cl_2 , rt, 2 h	99	99
с	Ts N N	N-Ts	$5mol\%$ of catalyst $CH_2Cl_2,rt,2h$	85	49

Table 2		
Ring-closing	metathesis	reactions

^a The analytical and spectroscopic data are in agreement with those reported in literature: 10a [18], 10b [19], 10c [20].

^b Determined by ¹H NMR.

Metal-carbene complex (3 or 6) (3–5 mol%) was added to a 0.01 M solution of the diene 9 in dry CH_2Cl_2 and the reaction mixture was stirred under argon for 2 h at room temperature. After this time it was possible to appreciate the conversion of the substrate 9a-c into the cyclized product 10a-c in good yields (Table 2).

In these reactions catalysts **3** and **6** proved to be equipotent to promote cyclization of unsaturated amines 9a-b by RCM and only for RCM of 9c the parent catalyst **3** showed efficacy higher than the chloro-derivative **6**.

To sum up we can affirm that the chloro-analogue **6**, such as the fluoro and the bromo-substituted complexes **4–5** [7,8] are slightly less efficient than Hoveyda–Grubbs catalyst **3** in terms of yields, both in CM and RCM reactions. However, it has been reported [12] that the presence of both electron withdrawing (e.g. NO_2) and donating (e.g. OMe) groups exerts similar effects on the catalytic efficiency of the Hov-eyda-type chiral ruthenium carbene complexes showing that the effects of these electron modifications are actually far from being comprehensively clarified.

References

- (a) R.H. Grubbs (Ed.), Handbook of Metathesis, vol. 3, Wiley-VCH Verlag GmbH & Co., Weinheim, 2003;
 - (b) R.H. Grubbs, Tetrahedron 60 (2004) 7117;
 - (c) K.C. Nicolaou, P.G. Bulger, D. Sarlah, Angew. Chem., Int. Ed. 44 (2005) 4490.
- [2] (a) P. Schwab, R.H. Grubbs, J.W. Ziller, J. Am. Chem. Soc. 118 (1996) 100;
 - (b) A. Fürstner, Angew. Chem., Int. Ed. 39 (2000) 3012;
 - (c) T.M. Trnka, R.H. Grubbs, Acc. Chem. Res. 34 (2001) 18.

- [3] (a) M. Scholl, T.M. Trnka, J.P. Morgan, R.H. Grubbs, Tetrahedron Lett. 40 (1999) 2247;
- (b) C.W. Bielawsky, R.H. Grubbs, Angew. Chem. 112 (2000) 3025.
- [4] E.L. Dias, R.H. Grubbs, Organometallics 17 (1998) 2758.

Chem. 2 (2004) 1.

- [5] (a) S.B. Garber, J.S. Kingsbury, B.L. Gray, A.H. Hoveyda, J. Am. Chem. Soc. 122 (2000) 8168;
 (b) A.H. Hoveyda, D.G. Gillingham, J.J. Van Veldhuizen, O. Kataoka, S.B. Garber, J.S. Kingsbury, J.P.A. Harrity, Org. Biomol.
- [6] A. Michrowska, R. Bujok, S. Harutyunyan, V. Sashuk, G. Dolgonos, K. Grela, J. Am. Chem. Soc. 126 (2004) 9318.
- [7] M. Zaja, S.J. Connon, A.M. Dunne, M. Rivard, N. Buschmann, J. Jiricek, S. Blechert, Tetrahedron 59 (2003) 6545.
- [8] A. Michrowska, M. Bieniek, M. Kim, R. Klajn, K. Grela, Tetrahedron 59 (2003) 4525.
- [9] Chloro-substituted complex 6 has been purchased by Zannan Pharma Ltd., Shanghai, China; Zhan, Z.-Y. WO2007003135, 2007.
- [10] F.C. Bargiggia, W.V. Murray, J. Org. Chem. 70 (2005) 9636.
- [11] T.-L. Choi, A.K. Chatterjiee, R.H. Grubbs, Angew. Chem., Int. Ed. 40 (2001) 1277.
- [12] J.J. Van Veldhuizen, D.G. Gillinghan, S.B. Garber, O. Kataoka, A. Hoveyda, J. Am. Chem. Soc. 125 (2003) 12502.
- [13] S. Chang, J. Yoon, M. Brookhart, J. Am. Chem. Soc. 116 (1994) 1869.
- [14] P. Muller, P. Polleux, Helv. Chem. Acta 81 (1998) 317.
- [15] S. Inaba, H. Matsumoto, R.D. Rieke, J. Org. Chem. 49 (1984) 2093.
- [16] G.B. Gill, G. Pattenden, G.S.J. Reynolds, J. Chem. Soc., Perkin Trans. 1 (1994) 369.
- [17] T. Kim, C. Huh, B. Lee, I. Lee, J. Chem. Soc., Perkin. Trans. 2 (1995) 2257.
- [18] A. Fürstner, L.A. Ackermann, Chem. Commun. (1999) 95.
- [19] H. Clavier, N. Audic, J.-C. Guillemin, M. Mauduit, J. Organomet. Chem. 690 (2005) 3585.
- [20] M.S. Visser, N.M. Heron, M.T. Didiuk, J.F. Sagal, A.H. Hoveyda, J. Am. Chem. Soc. 118 (1996) 4291.