

Note

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

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].

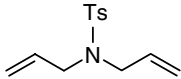
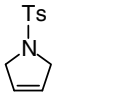
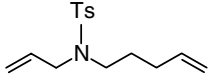
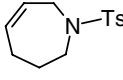
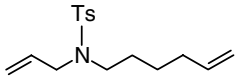
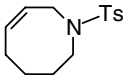
Several studies have been made by Blechert et al. [7] on the influence of various substituents other than hydrogen *ortho* or *para* to the isopropoxy group. Since the decrease of electron density at the oxygen atom of the *i*PrO group results in an increase of the catalytic activity [6,7], the introduction 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 a 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).

Table 2
Ring-closing metathesis reactions

Entry	Substrate 9	Product 10 ^a	Conditions	Yields % ^b	
				3	6
a			3 mol% of catalyst CH ₂ Cl ₂ , rt, 2 h	99	99
b			5 mol% of catalyst CH ₂ Cl ₂ , rt, 2 h	99	99
c			5 mol% of catalyst CH ₂ Cl ₂ , rt, 2 h	85	49

^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 CH₂Cl₂ 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. NO₂) and donating (e.g. OMe) groups exerts similar effects on the catalytic efficiency of the Hoveyda-type chiral ruthenium carbene complexes showing that the effects of these electron modifications are actually far from being comprehensively clarified.

References

- [1] (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.
- [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. Chem. 2 (2004) 1.
- [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. Chatterjee, R.H. Grubbs, Angew. Chem., Int. Ed. 40 (2001) 1277.
- [12] J.J. Van Veldhuizen, D.G. Gillingham, 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.