Journal of Organometallic Chemistry 696 (2011) 1556–1564

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Zirconium-catalyzed chemoselective methylalumination of ethers, amines, and sulfides bearing two terminal alkenyl groups

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ARTICLE INFO

Article history:
Received 28 October 2010
Received in revised form
11 December 2010
Accepted 24 December 2010

Keywords:
Zr-catalyzed methylalumination
Chemoselectivity
Heteroatom

ABSTRACT

Chemoselectivity in the methylalumination reaction of unsymmetrical ethers, amines, and sulfides bearing two different terminal alkenyl groups, a 13-tetradecenyl group and an allyl, 4-pentenyl or 6-heptenyl group was examined. The methylalumination of the allyl derivatives proceeded with complete chemoselectivity to afford only the 13-tetradecenyl-monomethylated products. In the methylalumination reactions of the 4-pentenyl and the 6-heptenyl derivatives, in addition to the 13-tetradecenyl-monomethylated products, and dimethylated products were also obtained. However, as in the case of the allyl derivatives, monomethylation to the shorter 4-pentenyl or 6-heptenyl group was not observed, except in the case of 6-heptenyl 13-tetradecenyl amine. The unique selectivity was rationalized upon how readily the intramolecular ligand exchange reaction between intermediate zirconocenium–alkene and zirconocenium–heteroatom complexes could occur.

1. Introduction

Zirconium-catalyzed carboalumination of terminal alkynes was first reported in 1978 by Negishi and co-workers [1]. Owing to the versatility of the reaction, extensive attempts for the carboalumination of alkenes were carried out, and asymmetric versions of the reaction were developed [2]. Notable improvements to this reaction were reported by Wipf and co-workers who have disclosed that reactivity is significantly increased by either adding a small amount of H_2O or using MAO in the place of Me_3Al [3], and by Lipshutz and co-workers who have found that the use of Cp modified catalysts improves regioselectivity [4]. Since the reaction can simultaneously introduce two functional groups to terminal alkynes and alkenes, it has been widely applied to the synthesis of natural products and related bioactive compounds [5]. The zirconium-catalyzed carboalumination of terminal alkenes is also an important reaction in olefin polymerization [6].

It has been reported that the presence of polar heterofunctional groups, such as hydroxy groups, ethers, esters, and ketones, in alkynes and alkenes sometimes leads to the deactivation of the catalyst and the decrease in stereoselectivity [2a,5j,7,8]. This stems largely from the strong Lewis acidity of the zirconocenium cation, which causes the metal to become extremely susceptible to coordination by the polar heterofunctional group. Some NMR experiments have indicated that the oxygen atom of ethoxy ethers coordinate to $[Cp_2ZrMe]^+$, which was generated in situ from $Cp_2ZrMe(\mu\text{-}Me)B(C_6F_5)_3$ and methylaluminoxane (MAO) [9]. Therefore, in order to maintain catalyst reactivity in the carboalumination reaction, coordination to the heterofunctional group has to be inhibited by masking it with additives such as additional alkylaluminium [10]. Although the presence of heterofunctional groups is sometime problematic, Hou and co-workers have developed regio- and stereoselective scandium-catalyzed methylalumination reaction of silyloxy/alkoxy-substituted alkynes and alkenes that takes advantage of heterofunctional group–metal interaction [11]. This success indicates the possibility of the use of heterofunctional groups as directing groups in zirconium-catalyzed methylalumination. In this study, we have investigated chemoselectivity in the zirconium-catalyzed methylalumination of ethers, amines, and sulfides bearing two terminal alkenyl groups with different lengths and have found that reaction at the longer alkenyl group is preferred.

2. Results and discussion

2.1. Zirconium-catalyzed methylalumination of TBS ethers of 5-hexen-1-ol and 12-tridecen-1-ol

In relation with another ongoing project, we examined the Negishi carboalumination reaction on *tert*-butyldimethylsilyl (TBS) ethers of 5-hexen-1-ol and 12-tridecen-1-ol (Table 1). Commonly

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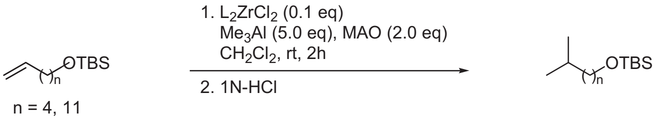
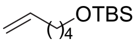
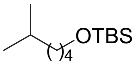
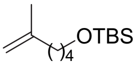
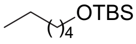
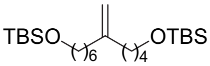
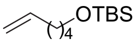
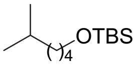
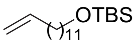
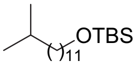
doi:10.1016/j.jorganchem.2010.12.031

Table 1
Zirconium-catalyzed methylalumination of TBS ethers of 5-hexen-1-ol and 12-tridecen-1-ol.



Entry	Substrate	L_2ZrCl_2	Product[a]
1		Cp_2ZrCl_2	 9%  28%  41%  5%
2		$Et(Ind)_2ZrCl_2$	 57%
3		$Et(Ind)_2ZrCl_2$	 100%

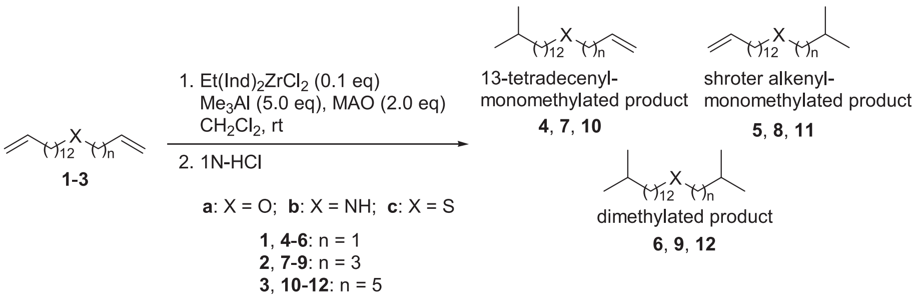
[a] Isolated yield. The remainder was starting material for entry 2.

used Cp_2ZrCl_2 was first applied as the catalyst in the methylalumination reaction of the hexenyl ether with Me_3Al and MAO. As a result, a large amount of undesired products, generated via β-elimination from the methylaluminated intermediate, were obtained (Table 1, entry 1). β-Elimination could be avoided by the application of a zirconium catalyst bearing the sterically hindered 1,2-ethylene-1,1′-bis(η^5-indenyl) [$Et(Ind)_2$] group (Table 1, entries 2,3) [2a,12]. In the examination of the two alkenes, we incidentally found that the substrate having a longer alkenyl group reacted faster. Thus, while the reaction of the silyl ether of 12-tridecen-1-ol was complete within 2 h, nearly half of the starting material remained in the reaction of the silyl ether of 5-hexen-1-ol after the same amount of time.

In order to determine the generality of this phenomenon, we decided to survey chemoselectivity in the reaction of ethers, secondary amines, and sulfides (**1**–**3**) bearing a 13-tetradecenyl as the long length terminal alkenyl group along with a shorter alkenyl group (Scheme 1).

*2.2. Zirconium-catalyzed methylalumination of 13-tetradecenyl allyl ether **1a**, amine **1b**, and sulfide **1c***

The methylalumination reactions of allyl ether **1a**, amine **1b**, and sulfide **1c** were first examined with Me_3Al (5.0 eq) and MAO (2.0 eq) in CH_2Cl_2 in the presence of [$Et(Ind)_2$]$ZrCl_2$ (Table 2). In the reaction of allyl ether **1a**, the methyl group was exclusively introduced to the terminal alkenyl group of the 13-tetradecenyl group and the monomethylated product **4a** was obtained in 76% isolated yield (Table 2, entry 1). It has previously been revealed that when heteroatom-containing alkynes and alkenes, such as alcohols and amines, were used as substrates for the methylalumination reaction, pretreatment of the substrate with Me_3Al was necessary in order to mask the heteroatom [2a,10]. To determine whether this would have a bearing on the outcome, ether **1a** was pretreated with Me_3Al before the addition of $Et(Ind)_2ZrCl_2$ and MAO (Table 2, entry 2). However, the high chemoselectivity was not affected by the pretreatment and 13-tetradecenyl-monomethylated product **4a** was obtained as the



Scheme 1. Zirocnium-catalyzed methylalumination of ω-alkenyl ω-tetradecenyl ethers, amines, and sulfides **1-3**.