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Advanced Fine-Tuning of Grubbs/Hoveyda Olefin Metathesis Catalysts: A Further Step toward an Optimum Balance between Antinomic Properties

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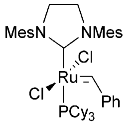
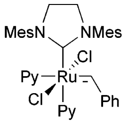
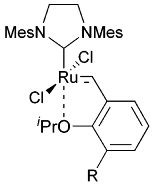
With the recognition of a major impact of olefin metathesis in modern organic synthesis,[1] recent years have witnessed a surge of productive research efforts in Ru catalyst design,[2−10] driven by the fascinating challenge to improve the already-impressive performances of Grubbs catalyst, $(PCy_3)_2Cl_2Ru{=}CHPh$,[2] and its upgraded second **1a**[2] and third **1b**[3] generations. Parallel significant progress was made with the advent of Grubbs-Hoveyda catalyst **1c** based on the "release/return" concept.[4] Enhanced versions of the latter[5−8] exhibiting a broader application profile[5,11] were obtained by modifying the chelating arm upon introduction of a bulky phenyl group (Blechert's catalyst **1d**)[5] or an electron-withdrawing substituent (our own "nitro" catalyst **1e**)[6] in such a way to destabilize the oxygen/metal interaction, thereby favoring a faster access to the key "propagating" 14 electron species.[12]



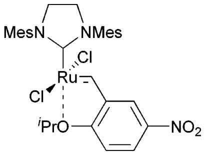
1a



1b



1c R = H
1d R = Ph



1e

Cy = cyclohexyl; Mes = 2,4,6-trimethylphenyl; Py = 3-bromopyridine

Also quite spectacular was the report by Piers[9] of an elegant direct access to a 14 electron catalyst based on a phosphonium alkylidene, obtained without liberation of any auxiliary ligand susceptible to be recaptured by the active species.

As recently mentioned by Fogg,[10] however, higher activity may come at the price of catalyst lifetime. So, in the context of green chemistry, there is still an obvious need to find the best compromise between desirable (but antinomic) properties such as the stability of the precatalyst, a high initiation rate, a high selectivity for challenging substrates, and the possibility of catalyst recycling.

In the present attempt to enhance the leaving group properties of the styrenyl ether, we were led to functionalize its aliphatic end group by attachment of an ester function, originally selected in account of its electron withdrawing properties.

The required ligand **3f** was prepared according to Scheme 1 and reacted with **1a** in the presence of CuCl,[5,13] to produce the air stable green complex **1f**. The molecular structure of **1f**, established by X-ray diffraction (Figure 1), revealed the occurrence of an additional coordination of the carbonyl oxygen of the ester function to the metal (2.54 Å).

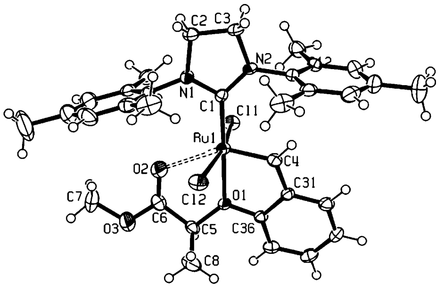
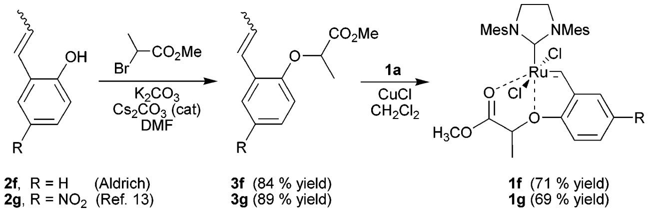


Figure 1. Molecular structure of the catalyst **1f** (see ESI for details).

Scheme 1. Two-Step Preparation of Catalysts **1f** and **1g**



The new complex **1f** was subject to a series of comparative catalytic ring-closing metathesis (RCM) reactions (at 0 °C) and cross-metathesis (CM) with methyl acrylate (at 25−26 °C) with a set of benchmark catalysts **1c**−**e** (Table 1). Interestingly, in the more challenging CM reaction, the **1f** catalyst's performance was matching that recorded with Blechert's catalyst (Table 1, entry 2). The ester catalyst **1f** appeared to be particularly insensitive to impurities, as established by a selected CM reaction deliberately carried out in an opened tube and in commercial grade dichloromethane (entry 2). Significantly, **1f** catalyses the cross metathesis of a model olefin, **4c**,[6a,b] with acrylonitrile (95% yield after 5 h at 25 °C with 3 mol % of catalyst loading), or methacrylonitrile (56% yield after 16 h at 40 °C with 5 mol % of catalyst loading).[14]

In a logical extension of this approach, we also prepared the closely related complex **1g**, incorporating both the electron-withdrawing NO_2 group[6,13] and the ester. An interesting point is that the combined independent effects of the coordinating ester and the electron-withdrawing groups are additive. This is particularly obvious in the RCM of **4a** at 0 °C, where 99% is achieved within 1 h with only 1 mol % of catalyst **1g** (Table 1, entry 1), and in the RCM of diethyldiallylmalonate **4b** (Figure 2).

Particularly appealing are the high turnover numbers recorded with **1g** in the RCM of dienes **4f** (TON = 1367), **4g** (TON = 3200), and in enyne **4h** cycloisomerization (TON = 560). Selectivity, a further advantage of the catalyst, can be appraised in the synthesis of **5i**, a pheromone of the Leopard moth (*Zeuzera pyrina*), obtained in good yield without homo-dimerization product, and requiring

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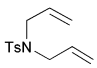
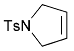
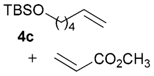
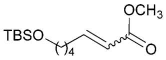
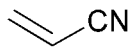
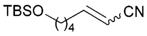
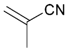
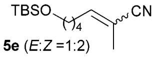
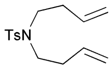
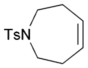
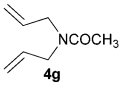
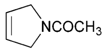
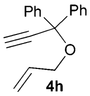
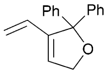
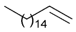
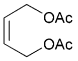
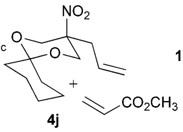
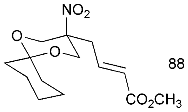
Table 1. Screening of **1f** and **1g** in Model Metathesis Reactions[a]

Entry	Substrate **4**	Catalyst **1** ([mol %])	Conditions Temp [°C], *t* [h]	Product **5**	yield [%][b]
1	 **4a**	**1c** 1.00% **1d** 1.00% **1e** 1.00% **1f** 1.00% **1g** 1.00%	0°C 1h 0°C 1h 0°C 1h 0°C 1h 0°C 1h	 **5a**	(10) (95) (78) (55) (99)
2[c]		**1d** 2.50% **1e** 1.00% **1f** 1.00% **1f** 1.00% **1g** 1.00%	20°C 0.3h 25°C 16h 25°C 2h 25°C 16h 25°C 1h	 **5c** (*E*:*Z* = 97:3)	91[d] (95) (90) 89[e] (80)
3[f]	**4c** + 	**1f** 3.00%	25°C 5h	 **5d** (*E*:*Z* =1:2.7)	(95) 70
4[g]	**4c** + 	**1f** 5.00%	40°C 16h	 **5e** (*E*:*Z* =1:2)	56
5	 **4f**	**1g** 0.03% **1g** 0.06%	25°C 0.5h 25°C 0.6h	 **5f**	(41) (65)
6	 **4g**	**1g** 0.03%	25°C 0.5h	 **5g**	(96) 90
7	 **4h**	**1g** 0.20% **1g** 0.05%	25°C 1.5h 25°C 1h	 **5h**	85 (28)
8[h]	 **4i** + 	**1e** 3.00% **1g** 1.00% **1g** 0.30%	28°C 3h 25°C 2h 25°C 0.5h	 **5i** (*E*:*Z* = 88:12)	85 97 (80)73
9[c]	 **4j**	**1f** 2.00%	26°C 5h	 **5j** (*E*:*Z* = 100:0)	88

[a] Conditions: 0.03−3.00 mol % catalyst, 0−28 °C, dry CH_2Cl_2, argon. [b] Isolated yields after silica gel chromatography. In parentheses are yields determined by GC. [c] Reaction with 2 equiv of methyl acrylate. [d] Reference 5a. [e] Reaction in commercially grade CH_2Cl_2, in air. [f] Reaction with 2 equiv of acrylonitrile. [g] Reaction with 4 equiv of methacrylonitrile. [h] Reaction with 2 equiv of (*Z*)-4-(acetoxy)-2-butenyl acetate.

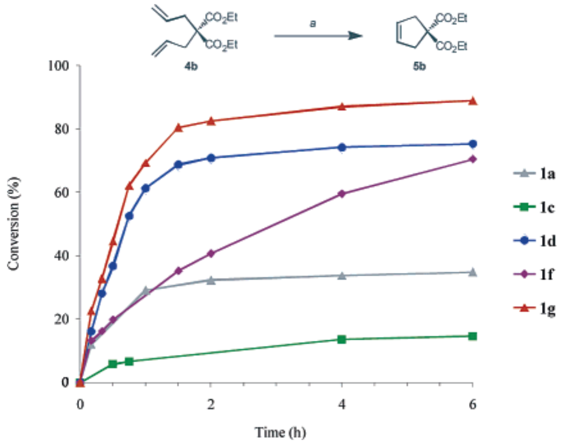


Figure 2. Relative conversion rates for RCM of **4b**, by **1a** (Grubbs), **1c** (Hoveyda), **1d** (Blechert), **1f**, and **1g** (this work) using 1 mol % catalyst in CH_2Cl_2 at 0 °C. See ref 15 and ESI for more details.

only a very low catalyst loading (0.3 mol % of **1g**), just *ten times less* than required with already very active[6] **1e** to obtain the same result. This highlights the fact that apparently "minor" changes in the structure of Hoveyda-Grubbs type catalysts can dramatically improve their performances and also broaden the scope of their applications, which can be taken as a rewarding justification of relevant research efforts in this direction.

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Supporting Information Available: Experimental details for the preparation of the reported compounds and crystallographic data for **1f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) This is much better than **1a**, which gives 30% conversion for methacrylonitrile under the same conditions (for a similar reaction in toluene, see ref 6a). Interestingly, **1b** and analogues were reported to give very good results with acrylonitrile, see: ref 3b and (b) Bai, C.-X.; Zhang, W.-Z.; He, R.; Lua, X.-B.; Zhang, Z.-Q. *Tetrahedron Lett.* **2005**, *46*, 7225. (c) Bai, C.-X.; Lu, X.-B.; He, R.; Zhang, W.-Z.; Feng, X.-J. *Org. Biomol. Chem.* **2005**, *3*, 4139.
(15) The same benchmark reaction of **4b** has recently been used by Piers et al. (ref 9) for comparison of selected active catalysts, leading in general to similar conclusions. According to this experiment the Grubbs 2nd generation catalyst **1a** is poor initiator at 0 °C and only reaches 25% of conversion after 4 h. The 3rd generation ruthenium **1b** and Schrock's molybdenum alkylidene Mo(N-2,6-$Me_2-C_6H_3$)($CHCMe_2Ph$) ($OCMe(CF_3)_2)_2$ are much more active than **1a**, providing 60 and 90% of conversion respectively, after 6 h (ref 9).

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