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Reactivity of Grubbs' Catalysts with Urea- and Amide-Substituted Olefins. Metathesis and Isomerization

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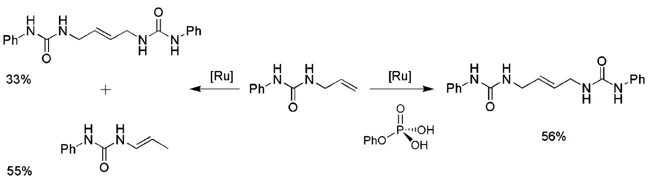
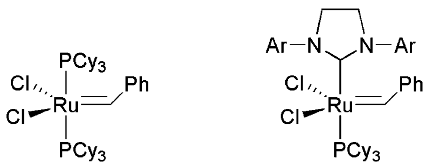
Received June 3, 2005



The reactions of a series of urea- and amide-substituted olefins with Grubbs' catalysts are presented. Depending on the substrate's nature, the formation of either cross-metathesis or isomerization products is observed. To favor the cross-metathesis products, the reactions have been carried out using a wide range of experimental conditions. Upon addition of monophenyl phosphoester to these reactions, the isomerization of the olefins is completely suppressed and the cross-metathesis products are obtained in up to 60% yield.

Metal-catalyzed olefin metathesis has become one of the most widely used organometallic transformations for carbon−carbon bond formation.[1] Although it has now been several years since the first catalysts for this type of reaction were developed,[2] the initial scope of metathesis reactions was limited by the low functional group tolerance that the catalysts had.[3] However, over the past decade, a series of ruthenium-based catalysts have been developed (see Scheme 1) which combine high reactivity with very good tolerance to a wide range of functional groups.[4] Several of these ruthenium complexes and their derivatives have been shown to also catalyze other nonmetathetic reactions such as olefin isomerization and hydrogenation.[5] Although these reactions broaden the synthetic scope of the ruthenium−alkylidene catalysts, they can be troublesome if the metathesis products are the ones required.[6]

SCHEME 1



1 **2**

We have a particular interest in using olefin metathesis to generate dynamic combinatorial libraries (DCL)[7] of species containing hydrogen-bonding groups which can potentially act as molecular receptors (in particular for anionic species). Consequently, we have carried out a systematic study of the products obtained when a series of urea- and amide-substituted olefins are treated with Grubbs' catalysts. In particular, we have found that complexes **1** and **2** under previously reported "standard" experimental conditions catalyze mainly the isomerization of the urea- and amide-substituted olefins. Since for our goals, this is an unwanted reaction, we investigated the conditions under which the reaction would mainly give the metathesis products. Herein, we report that upon addition of monophenyl phosphoester $P(=O)(OPh)(OH)_2$ to the reaction mixture the course of the reaction changes favoring the formation of the metathesis products and suppressing completely the isomerization process. To the best of our knowledge, this is the first time that a phosphoester has been used to suppress *completely* the isomerization reaction in favor of the metathesis process.

Since ureas have been widely used as building blocks to generate molecular receptors with hydrogen-bonding capabilities,[8] we first investigated the reaction between phenyl allyl urea **3** (which was prepared from allylamine and PhNCO) and Grubbs' catalyst **1**. The aim of this reaction was to obtain the metathesis product **4** (see the reaction scheme in Table 1). This reaction was carried out using conditions similar to those employed previously for allylic substrates (CH_2Cl_2, at 40 °C and using 5 or 10 mol % of the catalyst). However, instead of the expected

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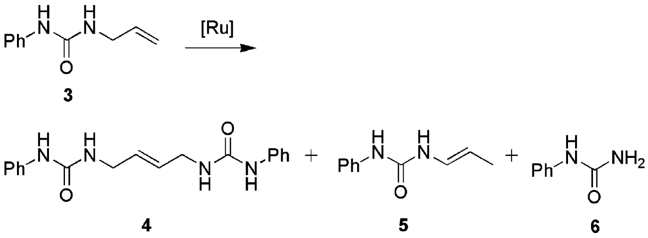
10.1021/jo051120y CCC: $30.25

TABLE 1. Summary of the Conditions Employed and the Results Obtained for the Different Ruthenium-Catalyzed Reactions of Phenylallyl Urea 3



entry[a]	cat.	additive	products[e,f] (%)			
			4 (*E*/*Z*)	5 (*E*/*Z*)	6	3 (%)
1	1[b]	–	–	–	57	–
2	1[b]	–	–	40 (1:2)	20	25
3	1[c]	–	–	58 (1:1)	–	25
4	1[c]	$P(=O)(Cy)_3$	7	50 (1:2)	–	22
5	2[b]	–	10	21 (1:1)	–	32
6	2[b,d]	–	15	18 (*Z*)	–	42
7	2[c]	–	33	55 (1:1)	–	10
8	2[b]	$P(=O)(Cy)_3$	4	42 (1:5)	–	32
9	2[b]	$P(=O)(OPh)(OH)_2$	31	–	–	53
10	2[c]	$P(=O)(OPh)(OH)_2$	56	–	–	30

[a] The solvent and temperature used for entry 1 were 1,2-dichloroethane and 80 °C; for entry 2 they were 1,2-dichloroethane and 50 °C; for entries 3–10 they were dichloromethane and 40 °C. [b] The catalyst was added at 5 mol %. [c] The catalyst was added 10 mol %. [d] The catalyst was purified by column chromatography prior to its utilization. [e] In most cases, a mixture of ***E*/*Z*** isomers was obtained for the isomerization product **5**. The proportions of each isomer (assigned according to ref 6) are indicated in parentheses next to the overall yield of **5**. In all cases, only one isomer was obtained for the metathesis product **4**. [f] The yields reported for all products are after 16 h of reaction.

metathesis product **4**, this reaction yielded the isomerization product **5** (in 60% yield) and left some unreacted allyl urea. Isomerization reactions of allyl amides catalyzed by Grubbs' catalyst have been previously reported.[9] In these reactions, the nature and purity of the catalyst, the reaction conditions (solvent, temperature, concentration of catalyst), and the presence of certain additives to the reaction mixture (such as $O{=}PCy_3$ or styrene) have an important influence on the distribution of the final products. Consequently, the reactions of allyl urea and Grubbs' catalysts **1** and **2** were investigated using different experimental conditions to determine under which of these conditions would isomerization be inhibited and metathesis favored. The results are summarized in Table 1.

From these results, it is clear that complex **1** is not a good catalyst for the metathesis of the allylurea substrate **3**. As shown in entry 3 of Table 1, when the reaction was performed at 40 °C, in CH_2Cl_2 using 10 mol % of catalyst **1**, no metathesis was observed. Instead, the isomerization product **5** was formed in 58% yield. The influence of the solvent in the catalytic performance of **1** was then investigated by carrying out the reactions in dichloroethane. In this case, the major product (when performing the reaction at 80 °C) was phenylurea **6** while at 50 °C a mixture of **5** and **6** was obtained. It has been previously observed that an allylic amide can undergo isomerization of the double bond followed by cleavage of the amide–allyl bond.[10] The results presented here suggest that a similar reaction is taking place with allylurea **3,** especially at high temperatures.

Previous studies have shown that some of the nonmetathetical reactions observed when using Grubbs' catalysts can be suppressed when the reaction is carried out in the presence of certain additives such as cyclohexylphosphine oxide.[11] As is shown in entry 4 of Table 1, in the presence of this additive, the course of the reaction using catalyst **1** yielded a small amount (7%) of the expected metathesis product **4**, although a large amount of isomerization product was still observed.

Considering the problems of substrate isomerization and cleavage when using **1** as a catalyst, we decided to investigate if the more active Grubbs' catalyst **2** would lead to the formation of the metathesis products in higher yields. As can be seen in entries 5–10, the reactions performed with this catalyst yielded various amounts of the metathesis product **4**. Since under the initial conditions (i.e., in CH_2Cl_2, at 40 °C and 5 mol % of catalyst) only 10% of **4** was obtained, various parameters were studied to improve the yield of this product. We first investigated if purification of the catalyst (by column chromatography as has been reported elsewhere[12]) would stop the isomerization reaction. However, as can be seen by comparing entries 5 and 6 in Table 1, purification of the catalyst did not lead to a significant improvement in the yield of compound **4**. On the other hand, the addition of cyclohexyl phosphine oxide (10 mol % in respect to the catalyst) to the reaction mixture (entry 8), had a detrimental effect on the performance of the catalyst since only 4% of the metathesis product was obtained.

Considering that the urea group of the olefin under study has hydrogen-bonding capabilities,[13] we decided to explore whether the addition of phenyl phosphoester (a species that hydrogen bonds to ureas) would have an effect on the course of the reaction. As can be seen by comparing entries 5 and 9, addition of the phosphoester led to the complete suppression of the isomerization process and the formation of **4** in 31% yield (in comparison to the 10% previously obtained). The yield of **4** can be increased to 56% (still with no traces of the isomerization product detected) if the reaction is performed with 10 mol % loading of the catalyst. Although the reactions were consistently left for 16 h to ensure full conversion, monitoring this reaction by ^{1}H NMR spectroscopy showed that all the metathesis product obtained (ca. 56%) forms within the first 2 h of reaction.

With these encouraging results, we decided to expand our studies to a series of allyl amides. Catalyst **2** has been recently shown to catalyze the isomerization of allylic amides in favor to the corresponding metathesis process.[6] As is shown in Scheme 2, we also observed that the reaction between phenyl amide (**7**) and 5 mol % of **2**

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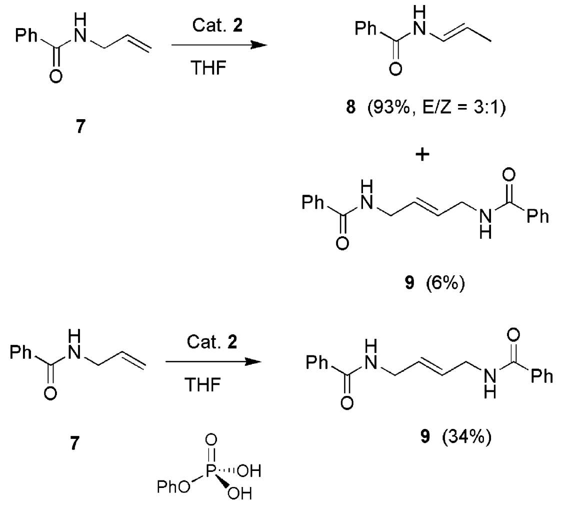
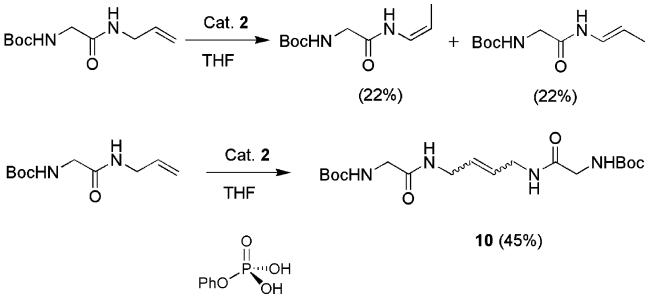
SCHEME 2



yielded mainly the isomerization product **8**. However, when the same reaction was repeated in the presence of the phenyl phosphoester additive the isomerization process was completely inhibited and the metathesis product **9** was obtained and isolated in 34% yield (leaving 53% of unreacted starting material).

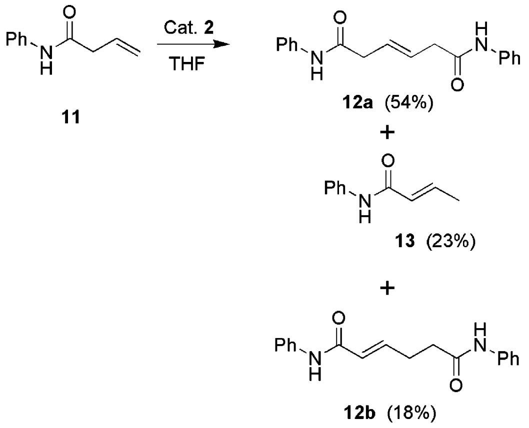
Once it was established that the phosphoester inhibits the ruthenium-catalyzed isomerization of **3** and **7**, the scope of the reaction was further investigated by studying a previously reported system. Miller has recently shown[6] that a series of protected allyl amide derivatives of Boc-protected amino acids are easily isomerized in the presence of Grubbs' catalyst **1**. In particular, it has been reported that for the allyl amide derivative of Boc-protected glycine the isomerization product is formed in 48% yield while the metathesis product **10** is not obtained (although isomers of the metathesis product are obtained in ca. 14% yield). We repeated this reaction using Grubbs' catalyst **2**, and as shown in Scheme 3, the isomerization product was obtained in 44% yield (the *E* and *Z* products in roughly 1:1 ratio). Interestingly, when the reaction was carried out using catalyst **2** but this time in the presence of the phenyl phosphoester additive, the isomerization reaction was completely suppressed and the metathesis product **10** was obtained in 45% yield (see Scheme 3). These results broaden the scope of the methodology here presented to suppress the isomerization of the alkenes in favor of the metathesis product.

SCHEME 3



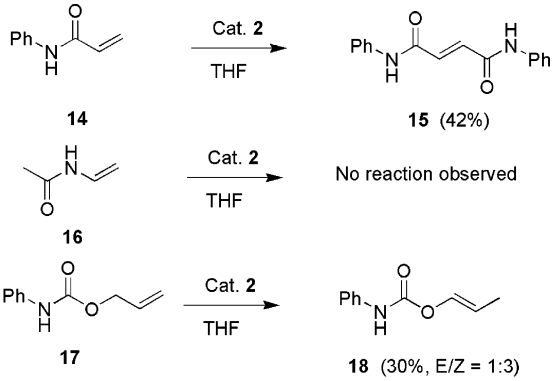
To gain more insight into the structural aspects of the urea- and amide-substituted olefins that give rise to the isomerization process (in the absence of phenyl phosphoester), the reactions between **2** and several substituted olefins were investigated. As can be seen in Scheme 4, the reaction between **2** and amide **11** favors the metathesis process (**12a** and **12b**), although some isomerization product (**13**) is also observed.

SCHEME 4



On the other hand, when amide **14** (with the alkene directly linked to the carbonyl of the amide) was employed, no isomerization was observed (as would be expected considering the structure of the olefin) the metathesis product **15** being the only one observed (see Scheme 5). Repeating the reaction using amide **16** (where the olefin is directly attached to the nitrogen of the amide) no transformation of the starting material was observed. Finally, the reaction was carried out using **17** as substrate where the allyl group is linked to an oxygen atom. In this case, isomerization product **18** is the only one observed in around 30% yield (see Scheme 5).

SCHEME 5



The results summarized in Table 1 and Schemes 2−5 suggest that when the alkene is part of an allylic moiety where the $-CH_2CH{=}CH_2$ group is linked to an electronegative atom the allylic CH_2 protons become more acidic favoring the isomerization of the substrate. However, the presence of monophenyl phosphoester inhibits completely the isomerization of the alkene and favors the metathesis process. To the best of our knowledge, this is the first time that a hydrogen-bonding phosphoester additive has been used to suppress unwanted isomerization reactions when using Grubbs' catalysts. The detailed mechanism of action by which this additive suppresses the isomerization of the alkenes is not immediately obvious. One possibility is that it acts as a template by hydrogen bonding to the NHs of the urea and amide substrates modifying the course of their reactions. Another possibility is that the phosphoester reacts with ruthenium–hydride complexes that might be formed in the reaction mixture. Since these type of complexes have been previously invoked as intermediates in ruthenium-mediated isomerization processes, their reaction with the phosphoester would suppress the isomerization of the alkenes. Further studies will be required to determine the molecular mode of action by which the phosphoester suppresses isomerization in favor of the desired cross-metathesis pathway.

Experimental Details

Cross-Metathesis of Allylphenylurea. The following general procedure was employed for the metathesis of the allylurea (in Table 1, further details regarding some of the experimental conditions are provided): To a solution of allylphenylurea (61.50 mg, 0.4 mmol) in dry and degassed CH_2Cl_2 (or 1,2-dichloroethane in some of the experiments, see Table 1), Grubbs' catalyst (5 or 10 mol % corresponding to a concentration of catalyst ranging between 1 and 2 mM) in the same solvent was added under nitrogen. The resulting mixture was heated overnight under N_2 to either 40, 50, or 80 °C depending on the solvent used (see Table 1). When the reactions were performed in CH_2Cl_2, the formation of a white precipitate (corresponding to the metathesis product **4**) was observed in the course of the reactions. This solid was isolated by filtration and washed several times with hexane. The solvent from the remaining filtrate was evaporated under reduced pressure to yield a brown oil. This crude was purified by silica gel column chromatography using CH_2Cl_2/ethyl acetate (9:1 (v/v)) as eluent.

For those reactions carried out in the presence of an additive (namely $P(=O)Cy_3$ or $P(=O)(OPh)(OH)O^-$), the following conditions were used: (a) tricyclohexylphosphine oxide (10 mol % relative to the catalyst) was mixed with the allyl urea in CH_2Cl_2. The catalyst was then added to the mixture. (b) The phenyl phosphoester was mixed with the allyl urea (1 equiv of phosphoester per 2 equiv of urea) in CH_2Cl_2. The catalyst was then added to the mixture.

Cross-Metathesis of Amides and Urethanes. The following general procedure was employed: To a 0.05 M solution of the corresponding amide or urethane in dry and degassed THF, a THF solution of Grubbs' catalyst **2** (5 mol % corresponding to a concentration of catalyst of ca. 2 mM) was added under N_2. The resulting mixture was heated to 65 °C overnight under N_2. After removal of the solvent, the residue (brown oil) was passed through a silica gel column to yield the different pure products generated in the reaction.

Acknowledgment. We are grateful to the EU for a Marie Curie Fellowship (P.F.), to the Spanish "Ministerio de Educación y Ciencia", and to the ICIQ Foundation for financial support.

Supporting Information Available: Spectroscopic and analytical data for all the products obtained in the metathesis/isomerization reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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