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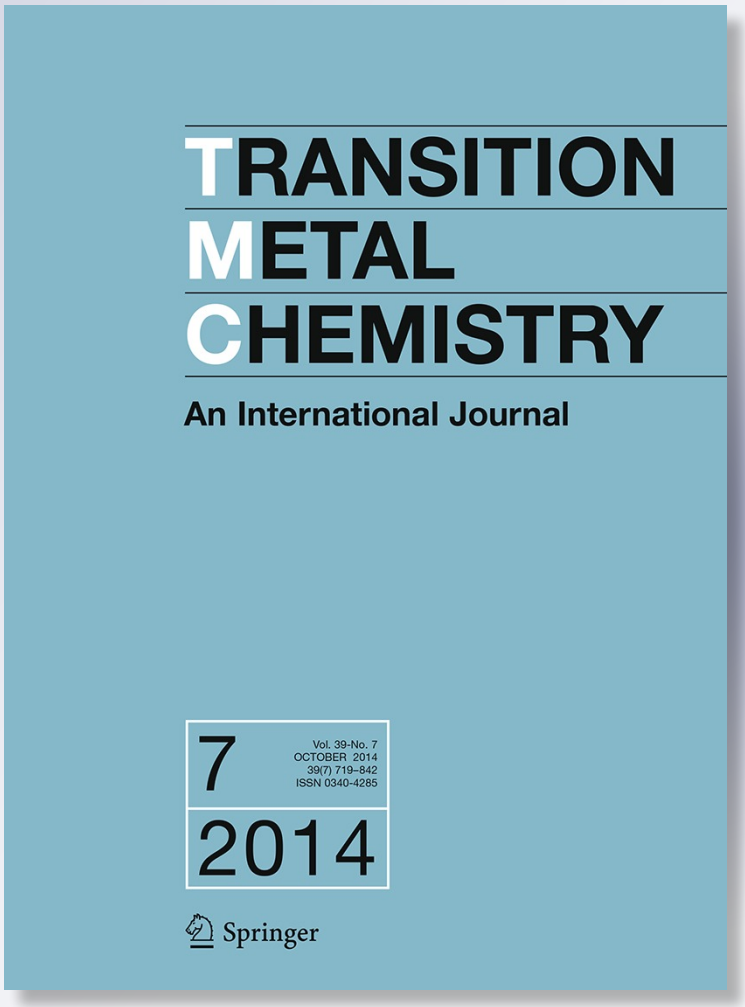

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Copper(I) halides inhibit olefin isomerized by-products from phosphine-based Grubbs' metathesis catalysts in polar protic solvents

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Abstract Copper(I) halides are employed as 'phosphine sponges' to sequester phosphor-ylides when using phosphine-based Grubb's metathesis catalysis in polar protic solvents and under heat. These cuprous halides are hypothesized to significantly slow the formation of the ruthenium hydride olefin isomerization catalyst. We demonstrate their use in both cross metathesis and ring-closing metathesis.

Introduction

Olefin metathesis is one of the most important reactions in C–C bond formation, and its importance has been highlighted by the number of catalysts developed [1–12]. Applications of olefin metathesis range from small molecule synthesis to living polymerization [13–23]. One of the more versatile metathesis catalysts is the ruthenium-based Grubbs' catalysts [1–12]. The use of these catalysts in polar media or elevated temperatures, however, is limited by degradation to the undesired olefin isomerization catalysts [24–28]. Scheme 1 shows two examples of olefin isomerization reactions from literature when Grubbs' catalyst was used in polar protic solvents [20]. Attempts to improve the Grubbs' metathesis catalysts for use in polar protic media include: use of solid supports [16], ligand modification occlusion/encapsulation in polymeric materials [13–15, 17–21], and use of quinone additives [22, 23].

Olefin isomerization during metathesis has been attributed to degradation of the Grubbs' catalysts to ruthenium hydrides (Scheme 2). This degradation is induced by heat or polar protic solvents [20, 24–28]. The mechanism of degradation depends on the structure of the catalyst, with the carbene-based second-generation catalyst, **2**, being more resistant to degradation than catalyst **1** (Fig. 1) [25, 26]. Grubbs and co-workers isolated the dinuclear hydrido complex, **10**, when catalyst **2** was thermally degraded in benzene (Scheme 2) [26, 28]. Grubbs and others also showed that rutheno hydrides like, **10**, caused olefin isomerization [26, 28]. Labeling experiments by Wagener and co-workers also showed that olefin isomerization was catalyzed by a metal hydride via an addition elimination mechanism rather than via a π-allyl, η^3-ruthenium mediated rearrangement as previously proposed [29]. A key intermediate in the formation of the rutheno hydride, however, is the dissociated phosphine ligand, without which degradation would only lead to catalyst depreciation without the undesired olefin isomerization (Scheme 2) [26, 27]. We therefore hypothesized that removal of the dissociated phosphine would exclusively lead to olefin metathesis without any isomerization.

Copper(I) has been regarded as a 'phosphine sponge' [30, 31]. In principle, the addition of Cu(I) halides during metathesis reactions is appealing because: (1) it would inhibit formation of unwanted metal hydrides and therefore

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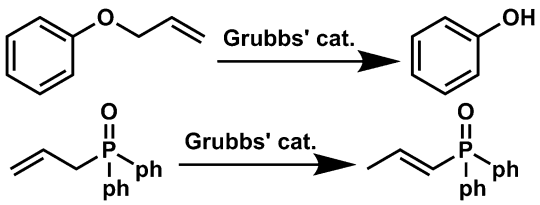


Scheme 1 Examples of two products reported in literature generated through isomerization of olefins by Grubbs' metathesis catalysts when used in polar protic media. The first reaction leads to deprotection of alcohols while the second reaction gives an isomerized olefin

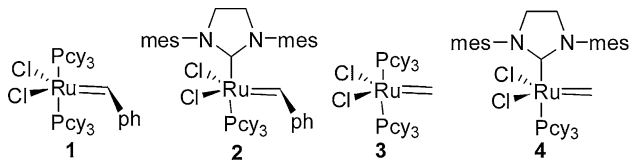


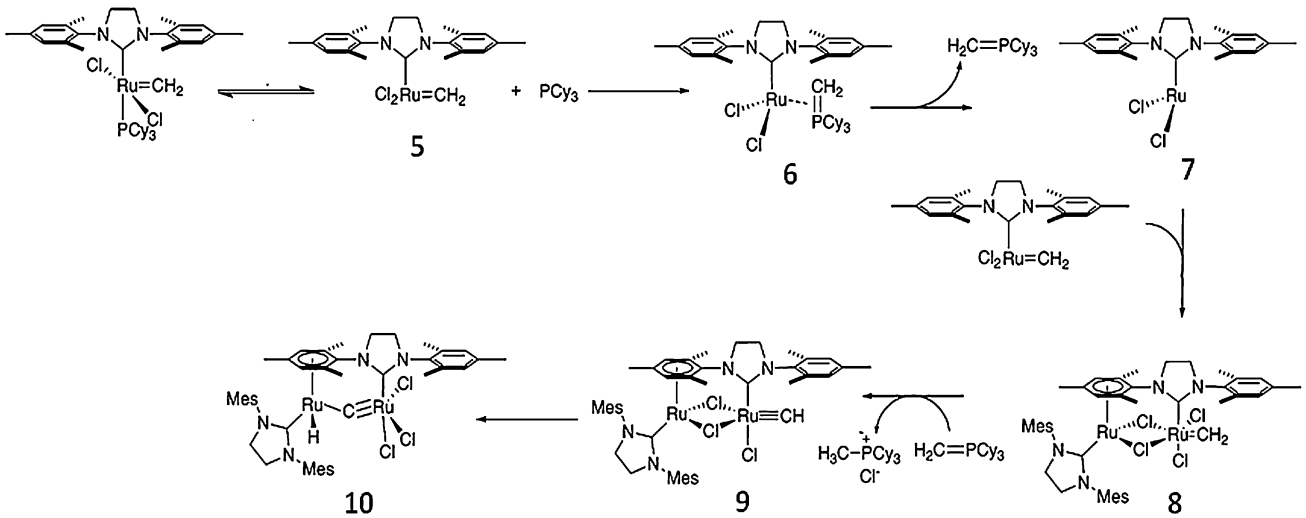
Fig. 1 Examples of the ruthenium-based Grubbs' metathesis pre-catalysts (**1** and **2**) with the corresponding metathesis-active methylidene catalysts (**3** and **4**)

minimize olefin isomerization, (2) the inorganic salts are readily removed, alongside the catalyst by-products, from the final product(s), (3) Cu(I) salts are cheap and readily available, and (4) only small quantities of Cu(I) are needed ($\sim$1:1 Cu(I):catalyst). In this paper, we discuss our findings on the effectiveness of Cu(I) halides as inhibitors of olefin isomerization while performing olefin metathesis under conditions in which isomerization is favored. We chose to perform our study under heat (50 °C) and in polar protic media (MeOH/ethylene glycol), conditions that are known to readily decompose Grubbs' catalysts to give high or exclusively isomerized olefins [20]. We show that the addition of Cu(I) halides inhibits olefin isomerization.

Efforts to prevent olefin isomerization include two main approaches: (1) Hydride traps can be introduced to eliminate any isomerization catalysts formed [29]. This approach was, for example, reported by Grubbs and co-workers when they employed benzoquinones [32]. (2) The application of hydride formation inhibitor(s) that may entail an additive that competes for the hydride formation pathway with the ruthenium species, or a reagent that prevents degradation of the Grubbs' catalyst to the unwanted hydrides. This latter approach would seek to inhibit, degrade, or re-route one or several of various intermediates (Scheme 2, complexes **5**–**9**) or fragments thereof. We desired to apply the second approach by sequestering the dissociated phosphine ligand using Cu(I).

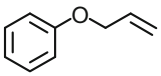
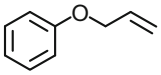
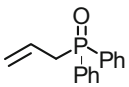
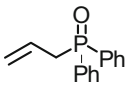
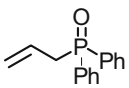
Experimental

To ensure that the catalyst was well dissolved, we initially dissolved it in 1 mL of CH_2Cl_2. The MeOH/ethylene glycol was then added followed by an additive of choice and finally the olefin. The reaction mixture was heated to 50 °C. The highly metathesis-active diethyl diallyl malonate, allyl phosphine oxide, and an allyl ether were used to study the effects of inorganic additives on the metathesis reaction in polar protic solvent. All solvents were degassed, and experiments performed under inert atmosphere. For all the reactions, Grubbs' first-generation metathesis catalyst was used unless otherwise stated. We monitored the reactions by periodically taking aliquots and running ^{1}H NMR



Scheme 2 The proposed degradation pathway for Grubbs'-type olefin metathesis catalysts. The dissociated phosphine ligand (PCy_3) is important in the degradation of the activated Grubbs' second-generation catalyst to the isomerizing dinuclear ruthenium hydride (**10**). Sequestering this phosphine ligand would, subsequently, inhibit formation of the hydride isomerization catalyst

Table 1 A comparison of adding copper halide versus alkali metals to the metathesis reactions of substrates that readily isomerizes in presence of MeOH

Entry	Substrate	Additive[a]	Time (h)	Metathesis product (%)[b]	Isomerization product (%)[b]
1		CuBr	39	0	0[e]
2		NaCl	39	0	100
3		KI	72	66[d]	25
4		NaCl	39	63	37
5		CuBr	72	81[c]	0

All reactions were performed at 50 °C

[a] 0.08 Equivalents relative to the olefin

[b] Determined by ^{1}H NMR

[c] 19 % Starting olefin

[d] 9 % Starting olefin

[e] Only allyl phenyl ether was recovered and no phenols were observed

in $CDCl_3$ (with TMS as an internal standard). The metathesis reaction products were differentiated from isomerization products by their unique ^{1}H NMR signals (for general procedure[1]).

Results and discussion

Cross metathesis reactions

To demonstrate the potential for Cu(I) halides to inhibit isomerization, we employed substrates that have been reported to preferentially isomerize instead of undergoing olefin metathesis when subjected to the Grubbs-type metathesis catalysts in presence of MeOH at 50 °C (Scheme 1) [20]. We compared the reaction of these substrates under the more readily degraded Grubbs' first-generation catalyst in presence of Cu(I). Alkali metal halides were employed as negative controls (Table 1). For the allyl phenyl ether, no isomerization (no phenol) was

Table 2 The effect of adding copper halides to the metathesis reaction in MeOH/ethylene glycol mixture

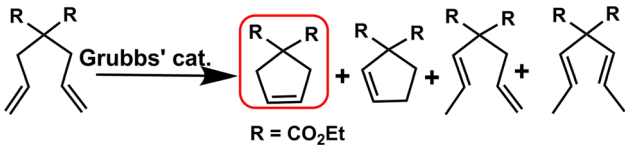
Entry	Catalyst (%)	Additive	Time (h)	Isomerization[a] (%)[b]
1	4	–	10	22
2	4	KI	3	33
3	4	KI	16	51
4	4	NaI	22	50
5	4	HCl	12	0
6	4	CuBr	2	0
7	4	CuBr	14	0
8	4	CuBr	24	0
9	4	CuCl	22	0
10	4	CuI	22	0

All reactions were performed at 50 °C

[a] Obtained as a mixture of the isomerized starting material and the isomerized product

[b] Relative to the metathesis product

[1] *General experimental procedure:* To a clean flask was added Grubbs' first-generation catalyst (17 mg, 21 μmol, 1 mol %) dissolved in 1 mL dichloromethane under inert atmosphere. To the flask was then added 5 mL of 1:1 MeOH:Ethylene glycol followed by NaI (3.2 mg, 21 μmol, 1 mol %). To the flask was added 1-propenyldiphenylphosphine oxide (509 mg, 2.1 mmol), and the reaction mixture was maintained at 50 °C using a temperature controlled oil-bath for 22 h. For analysis, an aliquot was drawn, dissolved in $CDCl_3$ (containing 1 % TMS internal standard), and sample analyzed by ^{1}H NMR. The ratio of peaks occurring at 6.69 ppm (isomerization product) and 5.70 ppm (metathesis product) was taken to calculate the ratio of the isomerization *versus* metathesis reactions—keeping in mind that the ratio of the peak at 5.70 ppm represents twice as many protons. ^{1}H NMR ($CDCl_3$) data: 1.20 (m, 3H, isomerized CH_3), 2.62 (m 4H, metathesis CH_2), 5.65 (m, 2H, metathesis CH), 6.28 (m, 1H, isomerized CH), 6.70 (m, 1H, isomerized CH), 7.49 (m, 12H, Ph), 7.70 (m, 8H, Ph). Isomerized: metathesis ratio = 1:1. All other reactions were performed following this procedure.



Scheme 3 Schematic representation of possible products generated from diallyl malonate in the presence of Grubbs' metathesis catalyst **1** in a polar protic media. The desired ring-closing metathesis product is highlighted in a box, but when polar protic solvents are used, olefin isomerization products are observed

observed in presence of the CuBr, but in presence of NaCl, only the isomerized product was obtained (Table 1 entry 1 and 2). Similarly, when allyl phosphine oxide was the substrate, both NaCl and KI failed to inhibit olefin isomerization (Table 2 entry 3 and 4) while CuBr gave no isomerization products (Table 2 entry 4). Although the copper bromide gave no isomerization products, the olefin metathesis reaction did not go to completion even after 72 h. We hypothesized that although the CuBr inhibits isomerization, it does not inhibit thermal decomposition of the catalyst, and therefore, the catalyst could be lost through a non-hydride forming pathway.

Ring-closing metathesis reactions

To demonstrate the efficiency of Cu(I) to inhibit isomerization of the starting material and/or the product, we examined the effect of Cu(I) with a highly active metathesis substrate. Scheme 3 shows our reaction under isomerization-prone conditions [13–15, 21]. Reaction of the diallyl malonate with **1** goes to 100 % conversions to the ring-closing metathesis product in minutes when CH_2Cl_2 is the reaction medium. When the reaction was performed at 50 °C in presence of polar protic solvents, however, 22 % of the olefin isomerized while only 10 % was converted to the desired metathesis product even after prolonged reaction times (Table 2, entry 1). This suggests that there was no olefin metathesis catalyst left in solution. When potassium iodide was added to the reaction 33 % of the olefin isomerized in 3 h (Table 2 entry 2). On extended reaction times, about 50 % of the starting material underwent olefin isomerization when either an alkali metal halide (Na^+ or K^+) was added with <25 % converting to the olefin metathesis product (Table 2, entry 3–4). When aqueous HCl was added to the reaction, however, no isomerization was observed, indicating that it is not the anion that is important to inhibit the degradation to the isomerization catalyst. The presence of an acid would prevent any degradation to the hydride through in situ inhibition of the formation of a phosphor-ylide or through halide chelation to the metathesis catalyst preventing further degradation. Unfortunately, the presence of acids and polar solvents like MeOH can lead to unwanted addition reactions across the olefin(s).

Inspired by the inhibition of olefin isomerization observed in the first reaction and the acidic conditions, we studied the effect of Cu(I) halides on isomerization of this highly metathesis-active substrate. As expected, when copper(I) halide (Cl, Br or I) was added to the reaction mixture, no isomerization products were observed even on extended reaction times (Table 2 entry 6–8). We observed >99 % conversion to the ring-closing metathesis product for all the reactions without any isomerization of the metathesis product. The nature of the halide anion had no effect on the inhibition of olefin isomerization (Table 2 entry 8–10). We attribute the lack of isomerization to the Cu(I) additives acting as 'phosphine sponge' and sequestering the dissociated phosphor ligand out of the solution. According to the mechanism proposed by Grubbs and coworkers, without the phosphor-ylide, the dinuclear rutheno complex, **8**, cannot proceed to the requisite hydride **10**. A lack of hydrides in solution implies that no olefin isomerization will be observed. The Grubbs metathesis catalyst (and the corresponding methylidenes **3** and **4**) is known to decompose in ≤7 h when left at >50 °C in absence of polar protic solvent [20, 26–28]. This degradation is expected to accelerate in the presence of polar protic solvent, and this is what we observed in cases where we used the diallyl malonate in absence of Cu(I).

Conclusions

In summary, we have demonstrated that by targeting the dissociated phosphine ligands during metathesis reactions, and therefore inhibiting formation of ruthenium hydrides, we can avert olefin isomerization while using Grubbs'-type catalysts in polar protic solvents and elevated temperatures. We have demonstrated our approach to inhibit isomerization with both cross metathesis and ring-closing metathesis substrates. Although presence of copper halides promotes rapid initiation of the metathesis reaction and inhibits olefin isomerization [26–28], they do not prevent thermal decomposition of the catalyst as witnessed by failure of the catalysts to convert all the allyl phosphine oxide to the cross metathesis products. Our results show that by simply adding copper(I) halides, the formation of ruthenium hydrides can be readily controlled, and thus, olefin isomerization controlled when Grubbs' catalysts are employed.

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