Development of Thiourea-Based Ligands for the Palladium-Catalyzed Bis(methoxycarbonylation) of Terminal Olefins

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Thiourea-based ligands were evaluated for the palladium-catalyzed bis(methoxycarbonylation) of terminal olefins. The usefulness of these ligands for this reaction is demonstrated by their stability to oxidizing agents, and their superiority in preventing palladium precipitation and double-bond isomerization.

Introduction

The Pd^{II}-catalyzed carbonylation of olefins is a useful methodfor integrating CO into substrates, to form aldehyde, ketone, ester, amide, and other carbonyl functionalities.[1−3] Although a variety of metal-catalyzed carbonylations have been documented,[4−10] the ligand-accelerated Pd^{II}-catalyzed bis-carbonylation of nonfunctionalized olefins has been much less studied. The following reasons might explain the lack of progress in this area: (a) To maintain a catalytic cycle, the Pd^0 formed after one catalytic cycle must be re-oxidized to Pd^{II} by an oxidizing agent[11,12] such as $CuCl_2$ and O_2. These oxidants are generally required in large amounts and this excess usually interferes with phosphane- or nitrogen-based ligands, (b) Pd^{II} often catalyzes double-bond polymerization and isomerization, which can become a serious problem when the reaction is carried out under harsh conditions (e.g. high temperature or high CO pressure),[13−16] (c) Oxidation of CO to carbonic acid derivatives by Pd^{II} may compete with the carbonylation of olefins in the presence of water or alcohols, causing palladium aggregation.[17−20]

However, the ligand-accelerated Pd^{II}-catalyzed bis(methoxycarbonylation) of olefins has relied principally on nitrogen- and phosphorus-based auxiliaries,[21−23] and no other types of ligands have been described in the literature. Recently, we have witnessed the increased application of thiourea derivatives as ligands and catalysts in organic synthesis;[24−31] the palladium−thiourea catalyzed carbonylation of terminal alkynes and allylic alcohols by Chiusoli is particularly attractive.[32,33] Our own experience in using $[Pd(tu)_4]I_2$ (tu = thiourea) as an effective catalyst in the palladium-catalyzed carbonylative annulation illustrated that thiourea is stable under a variety of oxidative conditions, and that no palladium precipitation occurred.[34,35] These distinguishing features led us to investigate whether $[Pd(tu)_4]I_2$ could be applied to the palladium-catalyzed bis(methoxycarbonylation) of styrene. To the best of our knowledge, no study has so far been reported that uses thiourea as a ligand in this type of reaction.

Our original results using $[Pd(tu)_4]I_2$ under the reported reaction conditions[21−23,34−35] for the bis(methoxycarbonylation) of styrene were discouraging. The reaction did not generate the expected product and, in fact, extensive styrene polymerization was observed.[15,16]

We reasoned that the failure of $[Pd(tu)_4]I_2$ in this reaction might have resulted from its tetradentate nature, which restricts the available coordinative space for the olefin,[36] since the palladium is tightly surronded by thiourea. We therefore employed the monodentate palladium complex $[Pd(tmtu)]Cl_2$ [37,38] (tmtu = tetramethyl thiourea) as a catalyst in this reaction. Fortunately, the desired product **1a** (Scheme 1) was indeed obtained, albeit in a yield of less than 30%. After a systematic evaluation of the effects of various reaction parameters (palladium halide, oxidizing agent, solvent, temperature, and CO pressure) on this reaction, the yield was eventually improved to over 60% using the conditions indicated in Scheme 1 (see Supporting Information for more details, for Supporting Information see also the footnote on the first page of this article).

Recently, there has been significant progress reported in the development of low-coordinate palladium

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Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

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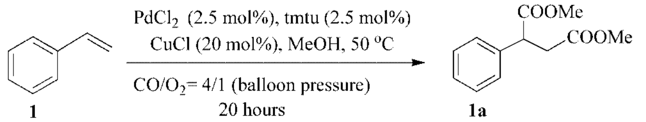
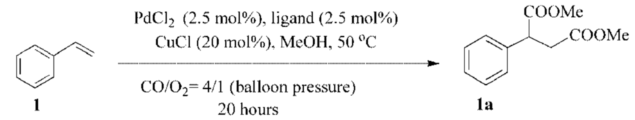


Scheme 1. The $[Pd(tmtu)]Cl_2$-catalyzed bis(methoxycarbonylation) of styrene

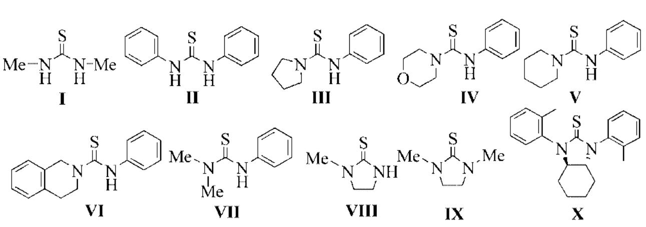
complexes.[39–42] Based on the available structural information for $PtCl_2$–tmtu,[37,38,43] we deduced that it might exist as its low-coordinate palladium complex. The good result that we obtained for the bis(methoxycarbonylation) of styrene might therefore be attributed to tmtu's capability to facilitate the generation of the low-coordinate palladium complexes, from which the catalytic elementary steps proceed.

To provide evidence for our hypothesis, ten additional thioruea derivatives **I**–**X** (Table 1) were used to investigate the substituent effect on this reaction. The easily polymerizable styrene[15,16] was used as the substrate, and the reactions were carried out under the same conditions as those used for the conversion of **1** to **1a** (see Scheme 1). The thioureas **I**, **II** and **VIII** are commercially available, **III**–**VII** were made by reaction of the corresponding secondary amine with phenyl isothiocyanate,[44–45] **IX** was synthesized by thionation of its corresponding urea with Lawesson's reagent,[46–48] and the ligand **X** was generated by the palladium-catalyzed coupling of 1,2-diaminocyclohexane with *o*-methyl bromobenzene, followed by condensation with thiophosgene.[49]

Table 1. Carbonylation of styrene with thioureas **I**–**X**



Ligand	I	II	III	IV	V	VI	VII	VIII	IX	X
Yield	33%	35%	69%	78%	79%	71%	66%	40%	69%	90%

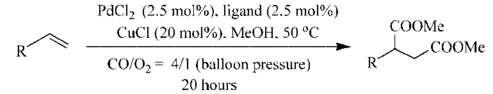


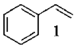
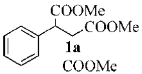
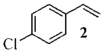
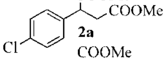
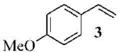
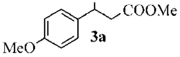
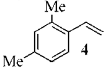
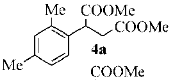
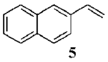
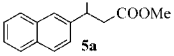
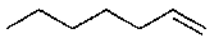
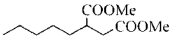
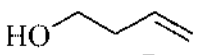
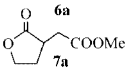
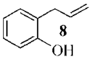
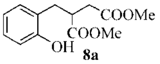
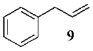
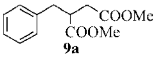
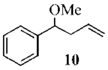
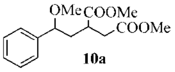
I **II** **III** **IV** **V** **VI** **VII** **VIII** **IX** **X**

Table 1 lists the results of the carbonylation of styrene with these diverse thioureas. We then made the following observations: (1) In comparison to disubstituted thioureas (**I**, **II**), trisubstituted thioureas (**III**–**VIII**) and tetrasubstituted thioureas (**IX**, **X**) give higher yields of carbonylated product, (2) Considering the steric effect of tetrasubstituted thioureas on the outcome of the carbonylation reaction, we observed that the hindered ligand **X** gives a better result than ligand **IX**. This result is in agreement with our notion that the more hindered thiourea ligand would be more effective at generating the low-coordinate palladium complex.

To assess the general applicability of these thioureas to the carbonylation of olefins, five ligands (**V**, **VII**, **IX** and **X**) and nine additional terminal olefins (**2**–**10**) were selected for use in this reaction. The results are listed in Table 2.

Table 2. Carbonylation of different olefins with thioureas **V**, **VII**, **IX** and **X**



Entry	Terminal olefins	Product	Yield[a] Ligand V	Yield[a] Ligand VII	Yield[a] Ligand IX	Yield[a] Ligand X
1	 **1**	 **1a**	78%	66%	69%	90%
2	 **2**	 **2a**	41%	22%	38%	84%
3	 **3**	 **3a**	61%	48%	60%	80%
4	 **4**	 **4a**	34%	43%	62%	67%
5	 **5**	 **5a**	36%	78%	74%	86%
6	 **6**	 **6a**	77%	56%	66%	75%
7	 **7**	 **7a**	44%	67%	59%	78%
8	 **8**	 **8a**	78%	67%	70%	79%
9	 **9**	 **9a**	67%	51%	64%	81%
10	 **10**	 **10a**	62%	68%	48%	78%

[a] Isolated yield after silica gel chromatography.

From these results, we can see that the thioureas **IX** and **X** gave better results than **V** and **VII**, which indicates that tetra-substituted thioureas might hold greater potential in the search for more effective ligands in the future. It is important to note that no palladium precipitation was observed in any of these reactions, and even the easily isomerizable substrates **8** and **9** gave the desired products **8a** and **9a** in satisfactory yields. In addition, no other regioisomers were observed, indicating that double-bond isomerization was prevented.

In summary, this report describes for the first time the use of substituted thioureas as effective ligands for the palladium-catalyzed bis(methoxycarbonylation) of terminal olefins. The chemistry described above demonstrates their capability in this respect, as well as their stability to oxidizing agents, and their superiority in preventing palladium precipitation and double-bond isomerization. Further evaluation of thiourea-based ligands in the asymmetric palladium-catalyzed bis(carbonylation) of olefins is currently under way in our laboratory.

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