ORGANIC LETTERS

2005
Vol. 7, No. 25
5693−5696

Ligand-Induced Acceleration of the Intramolecular [3 + 2] Cycloaddition between Alkynes and Alkylidenecyclopropanes

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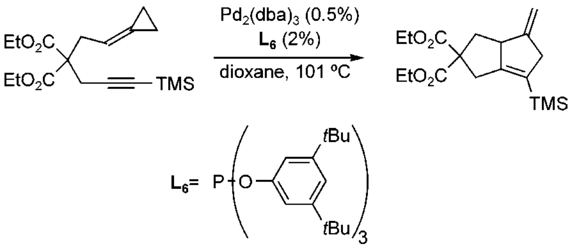
Received October 5, 2005

ABSTRACT



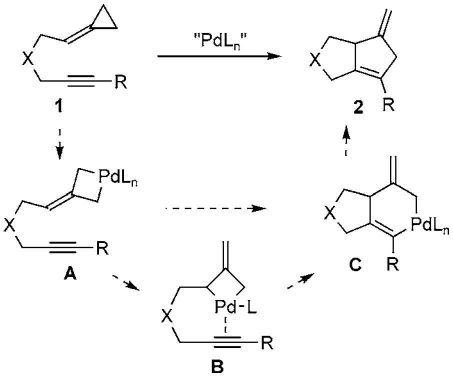
Bulky phosphite L_6 and several sterically robust phosphoramidites are excellent ligands for promoting the Pd-catalyzed [3 + 2] intramolecular cycloaddition between alkylidenecyclopropanes and alkynes. The use of these ligands allows for low catalyst loadings and facilitates the otherwise sluggish cycloaddition of hept-6-ynylidenecyclopropane systems.

Metal-catalyzed cycloadditions are of great relevance in modern organic synthesis since they usually convey a substantial increase in complexity at a relatively low economical and ecological cost.[1] For this reason, there is ongoing interest in developing new types of cycloadditions that allow the transformation of readily available substrates into target-relevant products using minimal amounts of the metal catalyst.[2]

We recently reported that alk-5-ynylidenecyclopropanes such as **1**, which can be easily assembled by addition of appropriate nucleophiles to allylcyclopropyltosylate, undergo an efficient palladium-catalyzed intramolecular [3 + 2] cycloaddition to give bicyclo[3.3.0]octenes (Scheme 1).[3,4]

The cycloisomerization reaction has been carried out by heating the substrate in dioxane in the presence of $Pd_2(dba)_3$ (6 mol %) and $P(i\text{-}PrO)_3$ (20 mol %) and is tolerant to a variety of substituents at the alkyne terminus. From a mechanistic point of view, the reaction could involve the

Scheme 1



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[1] For a review on transition metal-catalyzed cycloadditions, see: Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92.

[2] For reviews discussing important parameters of modern organic synthesis, see: (a) Wender, P. A.; Miller B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, p 27. (b) Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind.* **1997**, *19*, 765−769. (c) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (d) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281. (e) Fürstner, A. *Chem. Eng. News* **2001**, March 26, 180.

10.1021/ol0524095 CCC: $30.25

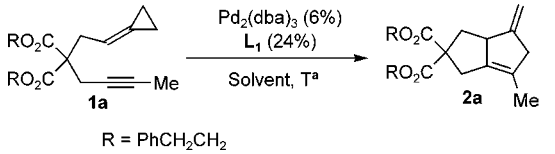
initial insertion of the metal complex into the distal bond of the alkylidenecyclopropane to give palladacyclobutane **A** followed by rearrangement to the intermediate **C**. Reductive elimination of this compound would provide the cycloadduct **2**. The rearrangement **A**−**C** could occur either directly or through the intermediacy of isomer **B**.[5]

Given that the cycloaddition reaction involves the generation of a stereocenter, it appeared reasonable to investigate the prospect of inducing asymmetry by using an appropriate chiral ligand. The electronic similarity between phosphites and phophoramidites, coupled to the increasing demonstration of the utility of this latter type of ligands in several catalytic asymmetric transformations,[6] prompted us to investigate their behavior in our reaction system.

This investigation has led to the discovery of new ligands that accelerate the cycloaddition process to the extent that it can be carried out in a truly practical and efficient manner using low catalyst loadings.

The initial assays were carried out with the well-known binaphthyl-containing phosphoramidite $\mathbf{L}_1$, which has been shown to give interesting results in several metal-catalyzed asymmetric C−C bond-forming reactions.[6g−k] Although the asymmetric induction results obtained in the cycloaddition of **1a** were poor (Table 1), we were surprised to observe a substantial acceleration of the cycloaddition process with respect to reaction rate achieved using the standard P(i-PrO)$_3$. We therefore decided to further analyze this accelerating effect by examining the performance of different phosphoramidites (Figure 1).

Table 1. Enantioselectivity Observed in the Pd-Catalyzed Cycloaddition Using Phosphoramidite Ligand L_1



entry	solvent	time (min)^a	T (°C)	ee^b (%)
1	dioxane	15	101	8
2	toluene	180	80	26

^{a} Time required for complete consumption of the starting material. ^{b} Analyzed by chiral HPLC (Chiralcel OJ, i-PrOH/Hex 1:9, 0.5 mL/min).

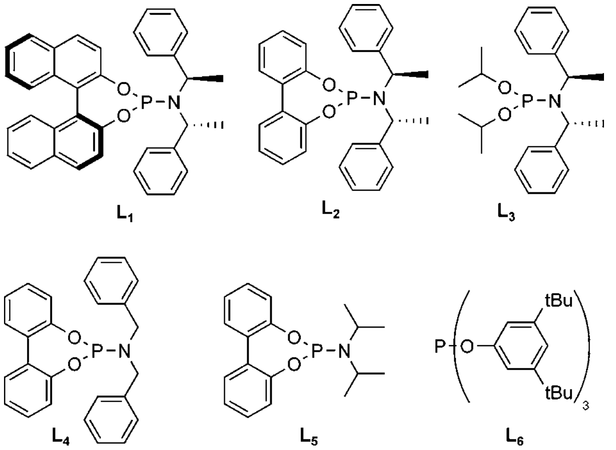


Figure 1. Ligands used in the study.

The synthesis of ligands $\mathbf{L}_2$, $\mathbf{L}_3$, and $\mathbf{L}_4$ was accomplished according to published procedures by heating the required amine with a stoichiometric amount of phosphorus trichloride in toluene (70 °C) followed by room-temperature treatment with the appropriate diol in the presence of Et_3N.[7a] Ligand $\mathbf{L}_5$ was better prepared in two steps by refluxing the diol in neat phosphorus trichloride and, after removal of the remaining phosphorus trichloride, addition of diisopropylamide (see the Supporting Information).[7b,c]

The acceleration effects were studied on substrate **1b** because it is easily distinguishable from the product **2b** by gas chromatography (GC). The reactions were performed in refluxing dioxane (50 mM) using 1 mol % of $Pd_2(dba)_3$ and 4 mol % of the ligand. The conversion results are represented in Figure 2. It can be observed that the reaction rate with ligands $\mathbf{L}_1$ and $\mathbf{L}_2$ is quite similar and considerably higher than that observed with P(i-PrO)$_3$, which apparently requires an induction period. Replacement of the biphenol by two 2-propanol groups generates a ligand ($\mathbf{L}_3$) that performs considerably worse. Remarkably, removal of the branching methyl groups from the benzylamino moieties of $\mathbf{L}_2$ leads to a marked decrease in the accelerating power of the ligand (ligand $\mathbf{L}_4$). On the other hand, the use of $\mathbf{L}_5$, which features a bis(isopropyl)amine instead of the bis(1-phenylethyl)amine of $\mathbf{L}_2$, produces a less dramatic but still significant decrease in the reaction rate. We also observed that in toluene the rate differences between the best ligands and P(i-PrO)$_3$ are even greater than those observed in dioxane.

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(5) Ongoing theoretical calculations from our group support these pathways. The results will be published in due course.

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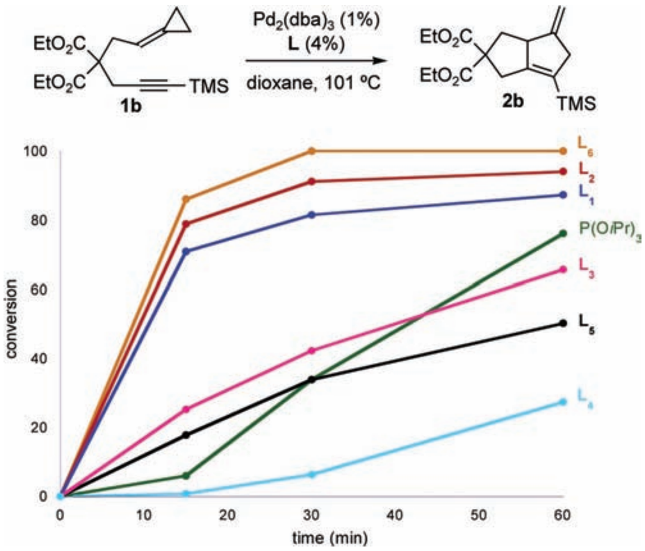


Figure 2. Plot showing the kinetics for the cycloaddition of **1b** in the presence of different ligands. Reaction aliquots were filtered through Florisil and injected into the GC−MS without further purification. Significant peaks due to byproducts were not found. The data represent results from an average of three experiments.

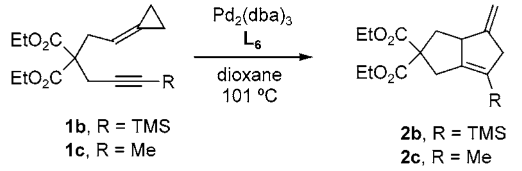
From these results, it can be inferred that the steric characteristics of the ligand rather than the electronic properties of the substituents on the phosphorus are the factors that most influence the reaction rate.

In the search for alternative bulky achiral ligands with similar efficiency to that of chiral ligands $\mathbf{L}_1$ or $\mathbf{L}_2$, we discovered that commercially available tris-(3,5-di-*tert*-butylphenyl)phosphite (ligand $\mathbf{L}_6$) promotes the reaction at even higher rates (complete conversion in less than 30 min, Table 2).[8] The observation that the use of triphenyl phosphite as a ligand leads to a marked decrease in the reaction efficiency (less than 10% of conversion after 2 h) corroborates the steric origin of the acceleration effect promoted by $\mathbf{L_6}$. This acceleration was also observed for substrates with other substituents at the alkyne terminus, such as **1c** (Table 2, entry 2). On the other hand, we observed that the reaction also worked efficiently on using a 1:1 rather than a 1:2 Pd/ligand ratio (entry 4, Table 2), which suggests the intermediacy of monoligated Pd species.[8c]

With ligand $\mathbf{L}_6$ it is possible to reduce the loading of the catalyst, meaning that the cycloaddition reaction of **1b** can be efficiently carried out using only 0.5% of the Pd source (entry 5, Table 2).

The discovery of the efficiency of ligand $\mathbf{L}_6$ prompted us to investigate whether it could induce the cycloaddition of hept-6-ynylidenecyclopropanes such as **3**, a compound that reacts sluggishly under standard conditions (25% conversion after 5 h in the presence of 2 mol % $Pd_2(dba)_3$ and 8 mol % of P(*i*-PrO)$_3$). Satisfyingly, heating a dioxane solution of **3** in the presence of 2% of $Pd_2(dba)_3$ and 8% of $\mathbf{L_6}$ gave the expected cycloadduct **4** in 80% yield (Scheme 2).

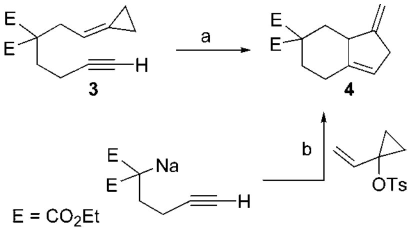
Table 2. Cycloaddition in the Presence of L_6



entry	**1**	$Pd_2(dba)_3$ (%)	L_6 (%)	time[a] (h)	**2** (yield, %)[b]
1	**1b**	1	4	0.5	**2b** (93)
2	**1c**	1	4	0.5	**2c** (97)
3	**1b**	1	3	0.5	**2b** (96)
4	**1b**	1	2	0.5	**2b** (90)[c]
5	**1b**	1	2	1	**2b** (96)
6	**1b**	0.5	2	12	**2b** (91)[d]

[a] Time required for complete consumption of the starting material. [b] Isolated yield. [c] 95% conversion. [d] 1.1 mmol scale.

Scheme 2 [a]



[a] Key: (a) $Pd_2(dba)_3$ (2%), $\mathbf{L_6}$ (8%), dioxane, reflux, 3 h, 80%; (b) $Pd_2(dba)_3$ (3%), $\mathbf{L_6}$ (8%), dppe (1%), dioxane, 1 h, rt, and reflux for 4 h, 78%.

Particularly interesting was the finding that the product **4** can be immediately assembled from the sodium carbanion of diethyl 2-(but-3-ynyl)malonate in a tandem, one-step process involving the Pd-catalyzed coupling of the anion with allylcyclopropyltosylate followed by in situ cycloaddition of the resulting enyne **3**. The tandem reaction did not proceed on using $\mathbf{L_6}$ as the only ligand, as this phosphite is ineffective in the coupling reaction. However, it can be efficiently achieved by adding a suitable proportion of dppe to the reaction mixture, given that this bidentate ligand facilitates the first step without interfering in the cycloaddition (second step).[9]

The simplicity of this tandem process allows for ranking the approach among those most competitive and practical to construct bicyclo[4.3.0]nonane systems, a type of bicarbocycle that constitutes the main structural framework of a large number of natural products.[10]

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(8) For references on accelerating effects of related bulky phosphite ligands on other type of metal-catalyzed reactions, see: (a) van Rooy, A.; Orij, E. N.; Kamer, P. C. J.; van den Aardweg, F.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Chem. Commun.* **1991**, 1096−1097. (b) van Strijdonck, G. P. F.; Boele, M. D. K.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **1999**, *1073*, 3−1076. (c) For a review on palladium species monoligated to bulky ligands, see: Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366−374.

(9) The cycloaddition reaction does not proceed if dppe is used as the only ligand.

In conclusion, we have discovered an important accelerating effect in the palladium-catalyzed [3 + 2] intramolecular cycloaddition of ynylidenecyclopropanes. The effect is associated to the use of bulky phosphoramidite ligands or tris(3,5-di-*ter*-butylphenyl) phosphite, a very convenient and accessible phosphite. As a consequence, the cycloaddition of several enyne precursors can be carried out with high efficiency and with low catalyst loadings. Mechanistic studies to explain the underlying reasons for such acceleration and synthetic applications of this methodology are ongoing and will be reported in due course.

Acknowledgment. This work was supported by the E.R.D.F and the Spanish Ministry of Education and Science (SAF2004-01044). We acknowledge Johnson Matthey for the generous loan of the palladium source. J.D. and M.G. thank the Spanish Ministry of Education and Science and the Galician Government for their respective predoctoral fellowships.

Supporting Information Available: Experimental procedures, including the preparation of **1a**, **3,** and phosphoramidites $\mathbf{L}_3$, $\mathbf{L}_4$, and $\mathbf{L}_5$, and spectroscopic data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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