ORGANIC
LETTERS

2003
Vol. 5, No. 1
31−33

Pd-Catalyzed Allylic Substitution Using Nucleophilic N-Heterocyclic Carbene as a Ligand

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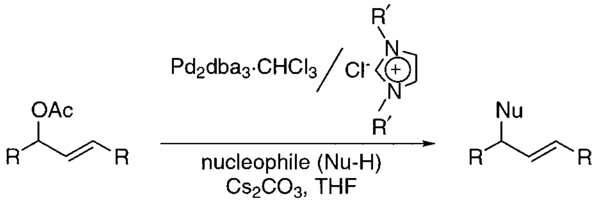
Received September 25, 2002

ABSTRACT



A nucleophilic N-heterocyclic carbene has been successfully used in a Pd(0)-catalyzed allylic substitution for the first time. It was found that allylic substitution with a soft nucleophile using a Pd–carbene catalyst proceeds via retention of configuration, the stereochemical reaction pathway being the same as that of the reaction using a Pd–phosphine complex.

Since the first isolation and X-ray crystallographical characterization of nucleophilic N-heterocyclic carbenes,[1] these compounds have attracted considerable attention not only as a stable isolable carbene species but also as molecules for coordination to various transition metals.[2] Nucleophilic carbenes are regarded as strong σ-donor ligands and have reactivities similar to tertiary phosphines. In recent palladium chemistry, high catalytic efficiency has been found in a variety of reactions, including Suzuki−Miyaura coupling,[3] Kumada−Tamao−Corriu-type coupling,[4] Mizoroki−Heck reaction,[5] amination of aryl halide,[6] and Sonogashira coupling,[7] using nucleophilic carbenes as ligands. A palladium-mediated allylic substitution was reported for the first time as a stoichiometric reaction by Tsuji in 1965.[8] Later, this reaction was expanded to a catalytic reaction by Hata and Atkins in 1970,[9] independently. At present, this reaction has been recognized as one of the most synthetically useful C−C bond-forming reactions.[10] However, there have been no reports on Pd(0)-catalyzed allylic substitution using a nu-

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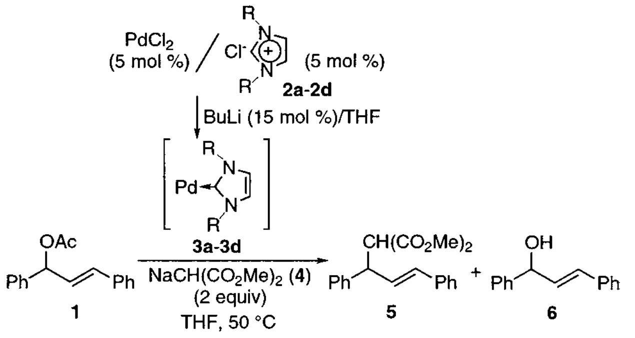
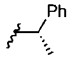
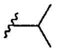
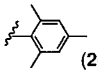
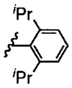
cleophilic carbene as a ligand. Herein we report the first application of a nucleophilic carbene as a ligand to this reaction.

Initially, reactions of acetate **1** with sodio dimethyl malonate (**4**) were investigated using various Pd−carbene catalysts (**3a**−**d**) formed by treatment of $PdCl_2$ with BuLi in the presence of imidazolium salts (**2a**−**d**)[11] (Table 1). To a THF suspension of $PdCl_2$ (5 mol %) and imidazolium salt **2a** (5 mol %) was added a solution of BuLi−hexane (15 mol %) at 0 °C, and the mixture was stirred for about 1 h at the same temperature. To the mixture of Pd−carbene catalyst (**3a**) was added a THF solution of **1** followed by addition of a solution of **4** at 0 °C, and the mixture was heated at 50 °C for 24 h. As a result, the desired substitution product **5** was afforded in only 6% yield, and starting material **1** was recovered in 76% yield along with alcohol **6**, which would be derived from **1**, in 13% yield (Table 1, run 1). It was found that the reaction of **1** and **4** with Pd−carbene catalyst **3c** or **3d**, having aromatic rings on nitrogens in the imidazol-2-ylidene skeleton, improved the yield of desired product. The use of **3d**, having a sterically bulky substituent on the aromatic ring, showed the best reactivity in this reaction, giving **5** in 77% yield (run 4).

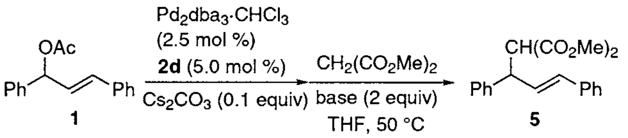
Table 1. Allylic Substitution of **1** with **4** Using a Pd−Carbene Complex



run	imidazolium salt (-R)	time (h)	yield (%)		recovery of **1** (%)
			5	6	
1	 (**2a**)	24	6	13	76
2	 (**2b**)	15	—	11	79
3	 (**2c**)	18	25	16	30
4	 (**2d**)	37	77	—	16

It has recently been reported that Pd−carbene species can be formed in situ from a palladium complex and imidazolium salts in the presence of Cs_2CO_3 as a base, and this Pd−carbene catalyst has been used in various C−C coupling reactions.[3c] Thus, reactions of **1** with dimethyl malonate were again investigated using a Pd−carbene catalyst formed from $Pd_2dba_3{\cdot}CHCl_3$ and imidazolium salt **2d** in the presence of Cs_2CO_3 (Table 2).

Table 2. Reaction of **1** with Dimethyl Malonate Using Pd_2dba_3 and Imidazolium Salt **2d**



run	base	time (h)	yield (%)
1	NaH	2	98
2	Cs_2CO_3	10	100

Surprisingly, when a THF solution of acetate **1** and sodio dimethyl malonate (**4**) was treated with a Pd−carbene catalyst formed from $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol %), imidazolium salt **2d** (5.0 mol %), and Cs_2CO_3 (10 mol %), the reaction was completed in 2 h to give the desired product **5** in excellent yield (98%) (Table 2, run 1). In addition, the reaction of **1** and dimethyl malonate using $Pd_2dba_3{\cdot}CHCl_3$ and imidazolium salt **2d** in the presence of an excess amount of Cs_2CO_3 at 50 °C gave the desired product **5** in quantitative yield, although the reaction time was slightly prolonged (run 2). These results indicate that the Pd−carbene species generated from $Pd_2dba_3{\cdot}CHCl_3$, **2d**, and Cs_2CO_3 is more reactive than the above-mentioned Pd−carbene catalyst prepared from $PdCl_2$, **2d**, and BuLi and that prior preparation of sodio dimethyl malonate (**4**) from dimethyl malonate and NaH is unnecessary in this catalyst system. Next, a control experiment without imidazolium salt **2d** was carried out in order to confirm whether a nucleophilic carbene, generated from imidazolium salt **2d** and Cs_2CO_3, operates as a ligand in this reaction. The reaction of **1** and sodio dimethyl malonate (**4**) with $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol %) in the absence of imidazolium salt **2d** in THF at 50 °C produced a trace amount of desired product **5** in 3% yield, and the starting material **1** was recovered in 97% yield. This result indicates that the addition of imidazolium salt **2d** is necessary in this reaction and that a nucleophilic carbene formed from **2d** plays an important role as a ligand to afford the product **5** in good yield.

To evaluate the scope of this reaction, allylic substitution of various substrates using a Pd_2dba_3-imidazolium salt **2d**-Cs_2CO_3 system was investigated. The reaction of **7** and dimethyl malonate required heating to reflux, and allylation products were produced in a total yield of 89% (α-adduct **8a**, 55%; γ-adduct **8b**, 18%; double allylation product **8c**, 16%) (Scheme 1). In the case of cyclic lactone **9**, the reaction

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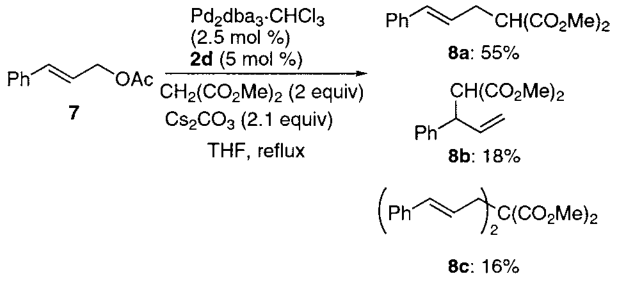
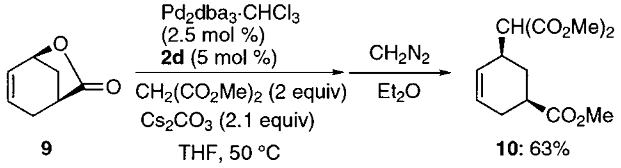
(11) Recently, we have reported a preparation of Ni−carbene complexes from $NiCl_2$ and imidazolium salts by treatment with BuLi; see: Sato, Y.; Sawaki, R.; Mori, M. *Organometallics* **2001**, *20*, 5510.

Scheme 1



with dimethyl malonate proceeded at 50 °C to give the product **10** in 63% yield as a single diastereomer (Scheme 2).

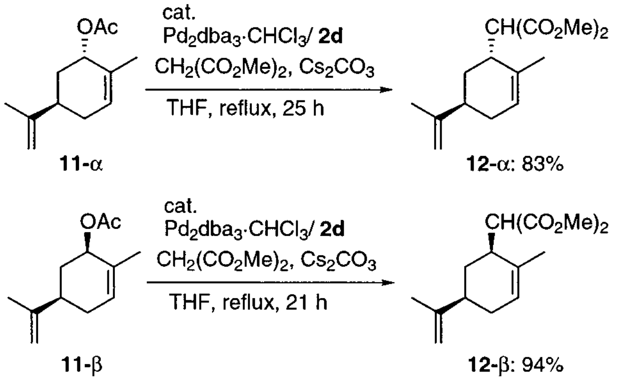
Scheme 2



To examine the stereochemical reaction course in the allylic substitution using a Pd−carbene catalyst, reactions of **11**-α and **11**-*β* were investigated (Scheme 3). In the reactions of **11**-α and **11**-*β* under similar conditions, **12**-α and **12**-*β* were stereospecifically produced in 83 and 94% yields, respectively. These results indicate that allylic substitution using a Pd−carbene catalyst proceeds via an overall retention mode in a manner similar to that using a Pd−phosphine complex.

In summary, a nucleophilic N-heterocyclic carbene has been successfully applied to Pd(0)-catalyzed allylic substitution for the first time. It has been proven that an imidazolium salt **2d** having the bulky aromatic rings attached to the nitrogens in its imidazol-2-ylidene skeleton is suitable as a ligand and that a Pd$_2$dba$_3$-imidazolium salt **2d**-Cs$_2$CO$_3$ system is highly efficient for producing Pd−carbene catalyst in this reaction. It has also been found that allylic substitution with a soft nucleophile such as dimethyl malonate using a Pd−carbene catalyst proceeds via overall retention to give the product in a stereospecific manner, the stereochemical reaction course obviously being the same as that of the reaction using a Pd−phosphine complex. Further studies to expand the scope of this reaction and to apply this method to asymmetric synthesis are ongoing.

Scheme 3



Acknowledgment. This work was financially supported by a Grand-in-Aid for Scientific Research from the Japan Society of the Promotion of Science (No. 14703031).

Supporting Information Available: Typical experimental procedures for allylic substitution of **1** with **4** and spectral data for **12**-α. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026961V