

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

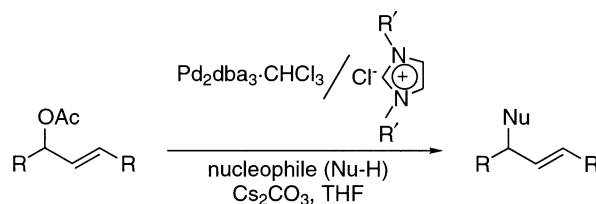
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ABSTRACT



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 PdCl₂ with BuLi in the presence of imidazolium salts (**2a–d**)¹¹ (Table 1). To

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

a THF suspension of PdCl₂ (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).

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(11) Recently, we have reported a preparation of Ni–carbene complexes from NiCl₂ and imidazolium salts by treatment with BuLi; see: Sato, Y.; Sawaki, R.; Mori, M. *Organometallics* **2001**, *20*, 5510.

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 Cs₂CO₃ 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 Pd₂dba₃·CHCl₃ and imidazolium salt **2d** in the presence of Cs₂CO₃ (Table 2).

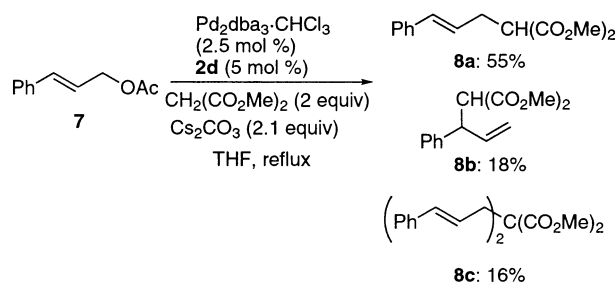
Table 2. Reaction of **1** with Dimethyl Malonate Using Pd₂dba₃ and Imidazolium Salt **2d**

run	base	time (h)	yield (%)
1	NaH	2	98
2	Cs ₂ CO 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 Pd₂dba₃·CHCl₃ (2.5 mol %), imidazolium salt **2d** (5.0 mol %), and Cs₂CO₃ (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 Pd₂dba₃·CHCl₃ and imidazolium salt **2d** in the presence of an excess amount of Cs₂CO₃ 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 Pd₂dba₃·CHCl₃, **2d**, and Cs₂CO₃ is more reactive than the above-mentioned Pd–carbene catalyst prepared from PdCl₂, **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 Cs₂CO₃, operates as a ligand in this reaction. The reaction of **1** and sodio dimethyl malonate (**4**) with Pd₂dba₃·CHCl₃ (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.

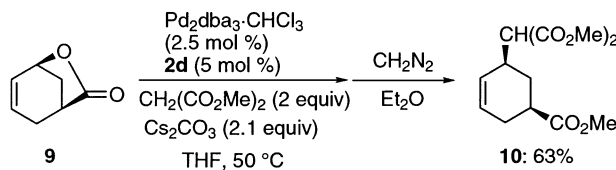
To evaluate the scope of this reaction, allylic substitution of various substrates using a Pd₂dba₃–imidazolium salt **2d**–Cs₂CO₃ system was investigated. The reaction of **7** and dimethyl malonate required heating to reflux, and allylation products were produced in a total yield of 89% (α-adduct **8a**, 55%; γ-adduct **8b**, 18%; double allylation product **8c**, 16%) (Scheme 1). In the case of cyclic lactone **9**, the reaction

Scheme 1



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

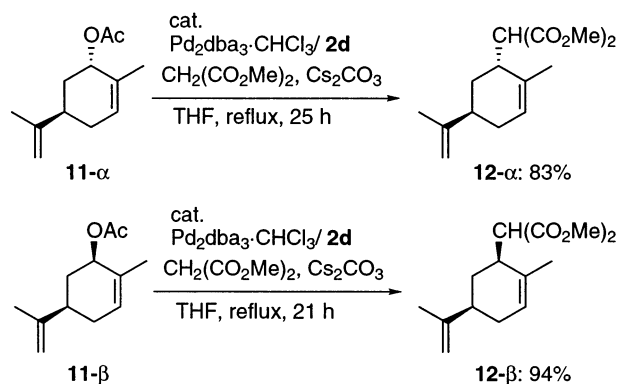
Scheme 2



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 substitu-

Scheme 3



tion 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_2dba_3 -imidazolium salt **2d**- Cs_2CO_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.

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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>.

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