ORGANIC LETTERS
2004
Vol. 6, No. 20
3597−3599

A New Ketone Synthesis by Palladium-Catalyzed Cross-Coupling Reactions of Esters with Organoboron Compounds

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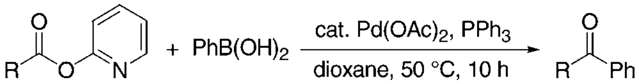
Received July 29, 2004

ABSTRACT



The palladium-catalyzed coupling reaction of 2-pyridyl esters with organoboron compounds is described. The reaction is compatible with various functional groups and proceeds under mild reaction conditions. The coordination of the nitrogen atom to Pd is a key step for efficient reaction.

Recently, palladium-catalyzed cross-coupling reactions have become one of the most powerful and reliable methods for C−C bond formation and a variety of coupling reactions have been developed.[1] It is no exaggeration to say that complicated molecules cannot be constructed without the use of coupling reactions. Among coupling reactions, the Suzuki−Miyaura reaction is widely used in the laboratory or industrial scale because of its reliability, high functional group compatibility, the nontoxicity of organoboron compounds, easy handling, and mild reaction conditions.[2] The carbonylative Miyaura−Suzuki reaction was also accomplished in the presence of carbon monoxide to give ketones.[3] The use of carboxylic acid derivatives as the substrates represents an attractive alternative route to ketones instead of the carbonylative coupling reaction of halides. In fact, acid chlorides have already been applied to the Suzuki−Miyaura reaction.[4] In recent years, the progress of palladium-catalyzed coupling reactions of carboxylic acid derivatives has been remarkable, and various carboxylic acid derivatives have been used by several groups.[5] The reaction of acid anhydrides was reported by Goossen[6] and Yamamoto[7] independently, and they showed that carboxylic acids could be directly used as starting material by being converted to acid anhydrides in situ. It was found that thioesters are also suitable substrates for coupling reactions, as reported by Terfort[8] and Liebeskind.[9] Yamamoto also reported a coupling reaction of esters with organoboron compounds.[10] However, the reaction was limited to electronically activated esters, such as perfluoroaliphatic carboxylic esters. Recently, we demonstrated that even esters which are not activated by electron-withdrawing

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[1] For recent reviews on cross-coupling, see: Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, U.K., 1995; pp 290−422. *Metal-catalyzed Cross-coupling Reactions*; Diedrich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

[2] For recent reviews on the Suzuki−Miyaura coupling, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. Miyaura, N. *J. Organomet. Chem.* **2002**, *653*, 54. Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83. Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11.

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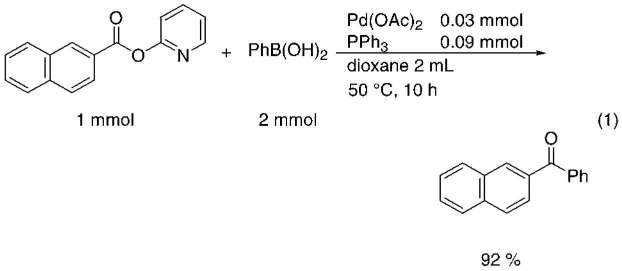
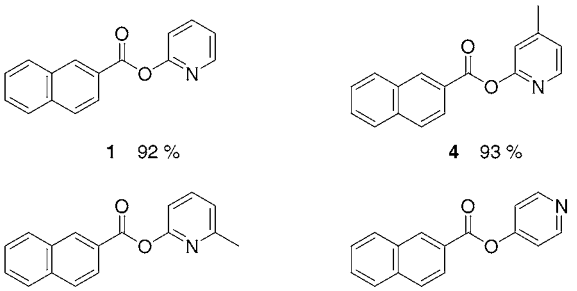
10.1021/ol048513o CCC: $27.50

groups can be used for the coupling reaction with the aid of chelation assistance.[11] However, the ruthenium-catalyzed reaction is limited in that the reaction requires harsh reaction conditions and isomerization leading to branched ketones takes place in the reaction of normal aliphatic esters. Now we wish to describe an efficient palladium-catalyzed coupling reaction of 2-pyridyl esters with organoboron compounds under mild conditions.

We tested various combinations of catalysts and esters derived from alcohols having heteroatoms which can coordinate to the catalyst. Finally, we found that the reaction of 2-pyridyl ester with phenylboronic acid efficiently proceeded in the presence of a catalytic amount of a palladium complex. Treatment of 2-pyridinol-2-naphthoate (**1**, 1 mmol) with phenylboronic acid (**2**, 2 mmol) in the presence of $Pd(OAc)_2$ (0.03 mmol) and PPh_3 (0.09 mmol) in dioxane (2 mL) at 50 °C for 10 h led to complete consumption of **1** and gave 2-naphthalenylphenyl methanone (**3**) in 92% isolated yield (eq 1).



2-Pyridyl esters are known to be useful substrates for ketone[12] and peptide[13] synthesis because of their high reactivity toward the nucleophiles, such as organometallics and amino group in the amino acids. This high reactivity of pyridyl esters is attributed to the fact that the 2-pyridyloxy group is a very good leaving group. Control experiments were carried out to investigate the role of the pyridyl group and whether it works only as a good leaving group or also functions as a directing group. We compared the reactivity of 4-methyl-2-pyridyl ester **4** and 6-methyl-2-pyridyl ester **5**. They are nearly equal in electronic nature as a leaving group but extremely different in coordination ability of the nitrogen atom. The results shown in Figure 1 obviously exhibit the importance of the coordination of the nitrogen atom to the palladium. The use of **6** as a substrate resulted in low yield. The corresponding phenyl ester gave no product. These results clearly show that the pyridyl group serves as a directing group. These two factors, good leaving group and good coordinating group, might be key for the reaction to proceed.



1 92 %

4 93 %

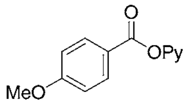
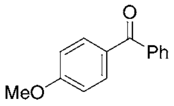
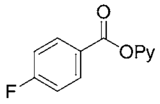
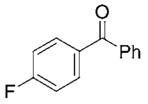
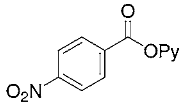
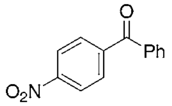
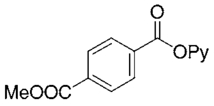
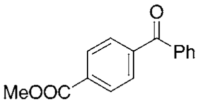
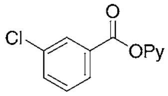
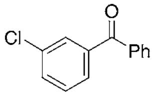
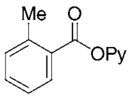
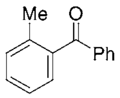
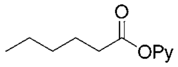
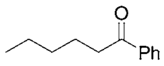
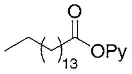
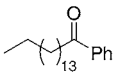
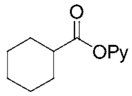
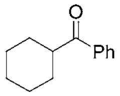
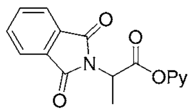
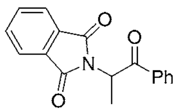
5 23 %

6 22 %

Figure 1. Comparison between esters endowed with various coordination styles.

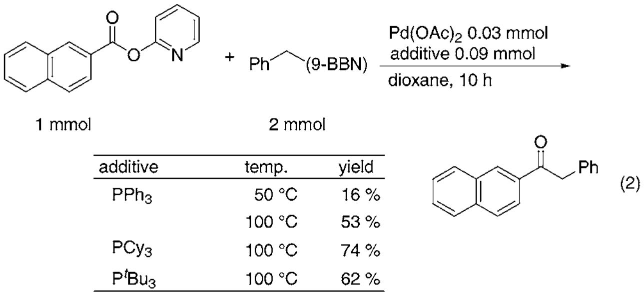
No other byproducts such as decarbonylated product, phenylnaphthalene, or a naphthyldiphenylmethanol were detected in eq 1. Other palladium complexes also could catalyze the reaction ($Pd(PPh_3)_4$, 87%; $Pd_2(dba)_3{\cdot}CHCl_3/3PPh_3$, 71%; $Pd(OAc)_2$; 84%), while palladium complexes possessing a chloro ligand ($PdCl_2$, $PdCl_2/PPh_3$, $PdCl_2(PPh_3)_2$) did not show catalytic activity. Rh(acac)(coe)$_2$ was also active (45% at 100 °C). Other representative results are listed in Table 1. The electronic nature of the substituents on the benzene ring of

Table 1. Coupling Reaction of Pyridyl Esters with Phenylboronic Acid Catalyzed by the Palladium Complex[a]

entry	ester	ketone	isolated yield
1			97%
2			93%
3			94%
4			90%
5			89%
6			90%
7			75%
8			72%
9			71%
10			68%

[a] Reaction conditions: pyridyl ester (1 mmol), phenylboronic acid (2 mmol), $Pd(OAc)_2$ (0.03 mmol), PPh_3 (0.09 mmol), 1,4-dioxane (2 mL), 50 °C, 10 h. Py = 2-pyridyl.

the benzoate esters did not affect the efficiency of the reaction, and the corresponding benzophenone derivatives were obtained in excellent yields (entries 1−4). It should be noted that only the pyridyl ester group converted to ketone and a methyl ester group remained intact although an excess amount of phenylboronic acid was used (entry 4). This clearly indicates that the presence of a pyridyl group is essential for the reaction to proceed. Sterically hindered 2-methylbenzoate also underwent a coupling reaction (entry 6), but no reaction took place in the case of more hindered 2,4,6-trimethylbenzoate (not shown). The reaction was applicable to aliphatic carboxylic acid esters, though product yields were slightly lower. It is noteworthy that 2-pyridyl hexanoate yielded only pentylphenyl ketone and no branched isomer was observed, in contrast to the ruthenium-catalyzed reaction we reported previously (entry 7).[11] It was anticipated that in the case of aliphatic ester they might undergo decarbonylation and formation of alkene. However, when we examined the possibility of the formation of alkenes by using palmitate, no pentadecene was observed in the reaction mixture (entry 8). α-Amino acid derivative could be used as a substrate, and N-protected-α-aminoketone was obtained (entry 10).



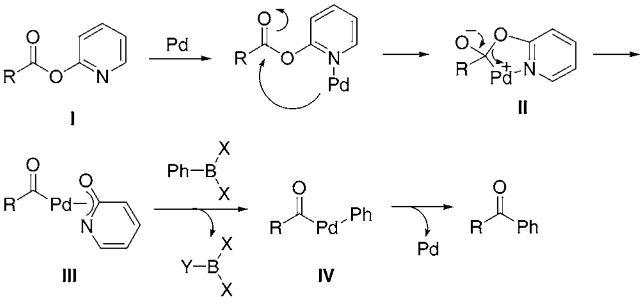
additive	temp.	yield
PPh$_3$	50 °C	16 %
	100 °C	53 %
PCy$_3$	100 °C	74 %
P^{t}Bu$_3$	100 °C	62 %

(2)

In sharp contrast to arylboron compounds, alkylboron compounds can rarely be used for coupling reactions since they are reluctant to transfer the alkyl groups on the boron atom. In fact, there are few reports on the coupling reaction in which alkylboron compounds were used as carbon nucleophile,[4e,9c,11] although many coupling reaction of carbonyl compounds with arylboron compounds were already reported. We first tried to introduce a benzyl group using 9-benzyl-(9-BBN) because it is known that 9-alkyl-(9-BBN), which can be easily prepared by hydroboration of alkenes, is superior to alkylboronic acids with respect to transmetalation. Under the same reaction conditions, benzylnaphthyl ketone was obtained in only 16% yield. Higher temperature (100 °C) improved the product yield to 53%. When a bulky and electron-rich phosphine, PCy$_3$, which was found to be especially effective for the alkyl−alkyl Suzuki−Miyaura coupling by Fu,[14] was used in place of PPh$_3$, the yield of the benzyl ketone was increased up to a 74% yield. On the other hand, other ligands, such as dppp, P(OEt)$_3$, 2-(di-*tert*-butylphosphino)biphenyl, and imidazolium carbene, were ineffective, and complicated reaction mixtures were obtained. Other 9-alkyl-(9-BBN) reagents prepared by the hydroboration gave complex reaction mixtures, probably due to *β*-hydride elimination.

A proposed mechanism is shown in Scheme 1. The nitrogen atom in **I** coordinates to Pd, and then Pd attacks the carbonyl carbon to give tetrahedral intermediate **II**. This nucleophilic attack is in accord with the fact that sterically hindered ester carbonyls did not give the product. C−O bond cleavage takes place with re-formation of the carbonyl group and acylpalladium **III** is generated. Transmetalation between **III** and organoboron compounds affords **IV**.[15] Finally, reductive elimination from **IV** yields ketone with regeneration of active Pd(0).[16]

Scheme 1. Proposed Mechanism



In summary, a new ketone synthesis by the palladium-catalyzed coupling reaction of 2-pyridyl esters with organoboron compounds is described. The reaction is compatible with various functional groups and proceeds under mild reaction conditions. Benzylboron compounds can be used as a nucleophile, which have been rarely used in coupling reactions of carbonyl compounds. It is also shown that the coordination of the nitrogen to the catalyst is essential for the efficient reaction. This reaction involves the catalytic generation of acylpalladium intermediates from esters, and its application to ketone synthesis is achieved.

Acknowledgment. H.T. acknowledges Research Fellowships from J.S.P.S. for Young Scientists.

Supporting Information Available: Experimental procedure and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Mukaiyama reported the nickel-catalyzed coupling reaction of pyridyl ester with diethylzinc. They proposed the nucleophilic attack of ethylnickel spiecies derived from diethylzinc and nickel catalyst. See ref 12c.