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PALLADIUM-CATALYZED TANDEM ASSEMBLY OF NORBORNENE, VINYLIC HALIDES, AND CYANIDE NUCLEOPHILE LEADING TO *CIS-EXO*-2,3-DISUBSTITUTED NORBORNANES

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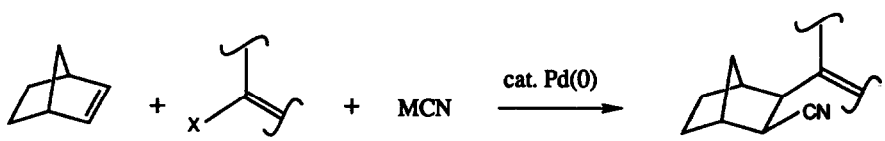
Summary : Three components, i.e., norbornene, 1-alkenyl or aryl halide, and cyanide nucleophile, were assembled with palladium catalyst ($Pd(OAc)_2/PPh_3$) in DMF at 80 °C to obtain stereoselectively *cis-exo*-2-cyano-3-alkenyl- or arylnorbornanes, which may be prominent intermediates for the currently attractive PGH analogues.

Recently, new prostaglandin H (PGH) analogues have been found to show a significant bioactivity and intensive research on these molecules have been accumulated.[1] Most of these compounds bear 2,3-disubstituted norbornane skeletons. In the context of our study directed toward the synthesis of PG and its analogues, we have paid our attention to the palladium-catalyzed introduction of a side chain onto a cyclic segment.[2] The frameworks of the newly developed PGH analogues encouraged us to examine the palladium-catalyzed direct connection of three components such as norbornene, 1-alkenyl moieties, and cyanide nucleophile. Larock has published a substitution of a norbornylpalladium complex with copper cyanide,[3] while Migita reported that the palladium-catalyzed coupling of the three components *i.e.* norbornene, bromobenzene, and tri-n-butyltin cyanide did not give the expected product.[4] Thus, the direct and catalytic coupling reaction of these three fragments has not been succeeded. Herein, we wish to disclose a palladium-catalyzed tandem three-component assembly as shown below.

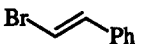
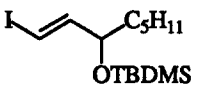
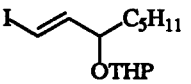
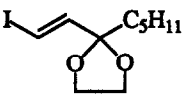
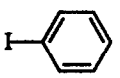
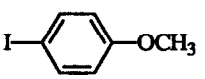
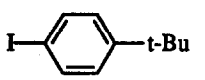
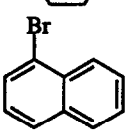


1 2 3

The representative results of the reaction using various 1-alkenyl and aryl halides are collected in Table 1. Copper cyanide was used for the direct three-component coupling process, because Larock reported that the copper cyanide can react with norbornylpalladium complex providing an excellent yield of 3 in a stoichiometric reaction.[3] However, copper cyanide gave the desired compound 3 in only 14% yield (Entry 1). On the other hand, the employment of sodium cyanide could improve the yield of 3 as shown

in Entry 2 and the more improved yield was obtained with potassium cyanide (Entry 3). Polar aprotic solvents gave better results. Among them, use of DMF as a solvent increased the yield of 3 up to 81% (Entry 4). The conditions composed of palladium acetate (5 mol%), triphenylphosphine (20 mol%), potassium cyanide (1 equiv.), and DMF were examined to a variety of 1-alkenyl and aryl halides.

Table 1. Tandem Three-Component Coupling with Cyanide [a]

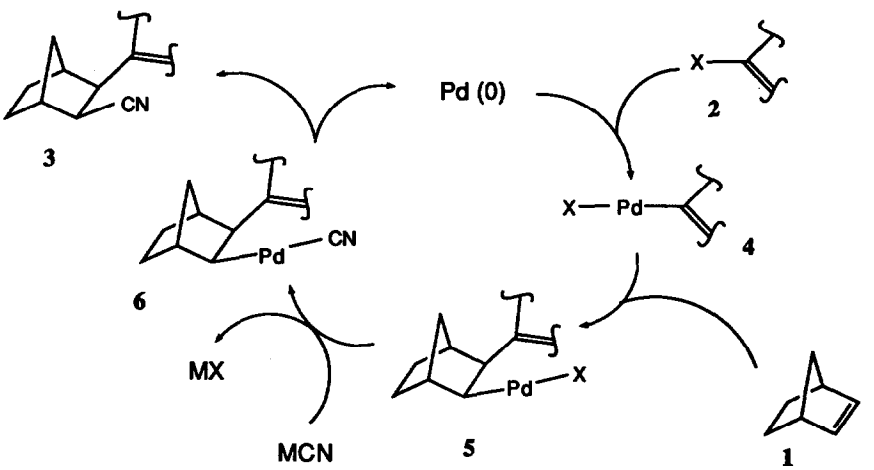
Entry	Halide	Solvent	Cyanide	Time (h)	Yield (%) [b]
1		THF	CuCN	12	14
2	"	THF	NaCN	12	65
3	"	THF	KCN	18	71
4	"	DMF	"	12.5	81
5		"	"	18	65
6		"	"	12.5	60
7		"	"	12	70
8		"	"	12	74
9		"	"	12	68
10		"	"	12	72
11		"	"	12	73
12		"	"	12.5	52

a) Conditions : **1** (2 mmol), **2** (1 mmol), cyanide salt (1 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol), 80 ^{o}C.

b) Satisfactory ^{1}H, ^{13}C NMR, and IR spectra were obtained for each product.

A general reaction procedure is as follows. A mixture of norbornene (1) (2 mmol), 1-alkenyl or aryl halide 2 (1 mmol), and potassium cyanide (1 mmol) in DMF (5 ml) containing palladium acetate (0.05 mmol) and triphenylphosphine (0.2 mmol) was stirred at 80 °C under argon atmosphere. The envisioned assembling reaction was completed in *ca.* 12 h. A usual workup followed by column chromatography on silica gel afforded the expected product 3 in high yields.

Entries 5 through 7 demonstrate that the common side chains for the prostaglandin synthesis can be combined to form the desired framework of the PGH analogues. The products arising from the iodides in Entries 5 and 6 were mixtures of two diastereomers in equal amounts respectively.[5] Thus, no diastereoselection took place in this tandem three-component assembly.[6] The reaction with aromatic iodides also proceeded to produce 3 in satisfactory yields. Bromonaphthalene gave the corresponding cyanide in 52% yield (Entry 12), although other aryl bromides did not react smoothly under these conditions.



Scheme I. Plausible Reaction Path

A plausible reaction path is illustrated in Scheme I.[7] Thus, oxidative addition of the halide 2 to Pd(0) produces alkenylpalladium complex 4, which then undergoes insertion of norbornene (1) to afford norbornylpalladium 5. Cyanation of 5 with metal cyanide gives the norbornylpalladium cyanide 6. Subsequent reductive elimination of the product 3 generates a Pd(0) species, which completes the catalytic cycle. Although a palladium-catalyzed substitution of aromatic and vinylic halides with cyanide anion is known for the formation of cyanoaromatic and α,β-unsaturated nitrile compounds, respectively,[8] the insertion of norbornene (1) into the alkenylpalladium complex 4 seems to be faster than the transmetalation with potassium cyanide.

Nitrile is known to be a versatile functional group for further elaborations. For example, cyano group can be readily converted to the other functionalities such as carboxylic acid, aldehyde, and amine. Thus, an extremely simple one-pot method to attain the prominent precursors for the synthesis of PGH analogues[1] has been achieved by using the palladium-catalyzed tandem three-component assembly. Since the reaction can be carried out under completely neutral conditions, this method may provide a novel approach to a variety of 2,3-disubstituted bicyclo[2.2.1]heptane skeletons besides PGH analogues.

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3) R. C. Larock, S. S. Herschberger, K. Takagi, and M. A. Mitchell, *J. Org. Chem.*, **51**, 2450 (1986).

4) M. Kosugi, H. Tamura, H. Sano, and T. Migita, *Tetrahedron*, **45**, 961 (1989).

5) Careful analysis of the ^{1}H NMR spectrum (500 MHz) of the products indicates that the relative stereochemistry of the substituents on the bicyclo[2.2.1]heptane skeleton is *cis-exo*. The reference 3 also described that cyanation product has *cis-exo* configuration.

6) The diastereoselective assembly is successfully in progress and it will be published in due course.

7) See references 3, 4, and literatures cited therein.

8) K. Takagi, T. Okamoto, Y. Sakakibara, and S. Oka, *Chem. Lett.*, **1973**, 471; A. Sekiya and N. Ishikawa, *Chem. Lett.*, **1975**, 277; K. Takagi, T. Okamoto, Y. Sakakibara, A. Ohno, S. Oka, and N. Hayama, *Bull. Chem. Soc. Jpn.*, **48**, 3298 (1975); K. Yamamura and S. Murahashi, *Tetrahedron Lett.*, **1977**, 4429.

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