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Palladium-Catalyzed Aminoallylation of Activated Olefins with Allylic Halides and Phthalimide

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The three-component aminoallylation reaction of the activated olefins **2** with the phthalimide **1a** and allyl chloride proceeded very smoothly in the presence of Pd_2dba_3·$CHCl_3$ (5 mol %)/P(4-$FC_6H_4)_3$ (40 mol %) and Cs_2CO_3 (3 equiv against **2**) in dichloromethane at room temperature to give the corresponding aminoallylated products, *N*-pent-4-enylphthalimides **3**, in 58−99% yields. The reaction of oxazolidinone **1b** also proceeded very smoothly to give *N*-(2,2-dicyano-1-phenylpent-4-enyl)-oxazolidinone in a quantitative yield; however, the Tsuji−Trost-type allylation products **4** were obtained in the case of dibenzylamine, *N*-tosylaniline, and pyrrolidin-2-one. Further, **2** underwent cycloaddition with *N*-tosylvinylaziridine **9a** in the presence of Pd_2dba_3·$CHCl_3$ (5 mol %)/P(4-$FC_6H_4)_3$ (40 mol %) in THF at room temperature, giving the corresponding pyrrolidines **11** in 69−99% yields.

Introduction

The transition-metal-catalyzed addition of amines across C−C multiple bonds is an efficient process for the introduction of a nitrogen functionality into unsaturated organic molecules and also in the synthesis of physiologically active substances.[1] Hydroamination of alkenes, alkynes, allenes, dienes, and enynes has been developed using transition-metal,[2,3] lanthanide,[4] and/or actinide[5] catalysts for this purpose (eq 1). A three-component coupling reaction of amines (>N−H), C−C multiple bonds, and organic halides (R−X) must be a more powerful strategy for the multifunctionalization of unsaturated organic molecules;[6] however, it is not an easy task since the production of ammonium salts (>NH^+RX^-) is a competitive process, and in general, this reaction takes place more readily than the three-component coupling reaction (eq 2). We recently found that the three-component coupling reactions between certain nucleophiles, allylic halides, and activated alkenes occurs unexpectedly easily in the presence of Pd catalysts (eq 3). As nucleophiles, allylic stannanes,[7] allyl acetoacetate,[8] alcohols,[9,10] and trimethyl cyanide[11] could be utilized. Interestingly, in these previous cases, the direct reaction between Nu^- and allylic halides was not observed, and the three-component coupling reaction proceeded well. Our next interest was focused on a nitrogen nucleophile. Can similar three component coupling reactions be

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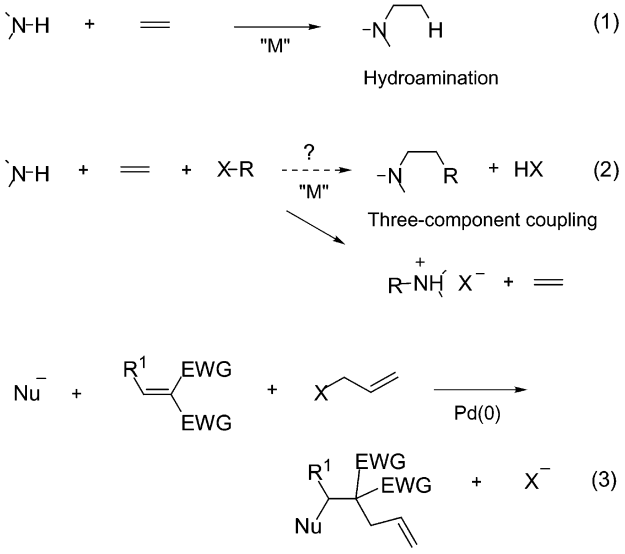
carried out with amines? As mentioned in eq 2, amines are stronger nucleophiles, in general, than the oxygen and carbon nucleophiles shown in eq 3, and therefore, there was a possibility for the formation of ammonium salts. Herein we report the aminoallylation of the activated olefins **2** with the amines **1**, *bearing an EWG group*, and allyl chloride takes place efficiently in the presence of palladium(0) catalyst (eq 4). The present transition-metal-catalyzed three-component coupling reaction enables us to perform the traditional two-step organic transformation, Michael addition of Nu^- to activated alkenes followed by trapping the resulting carbanion with allylic halides, in one pot without producing the allylamine **4**, which is an expected product via the ordinary Tsuji-Trost type nucleophilic allylation.[12]

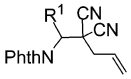
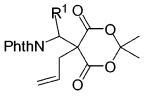
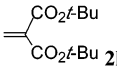
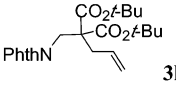


Nu = allyl amphiphilic bisallylation
= CH_2Ac β-acetonation-α-allylation
= OR alkoxyallylation
= CN cyanoallylation

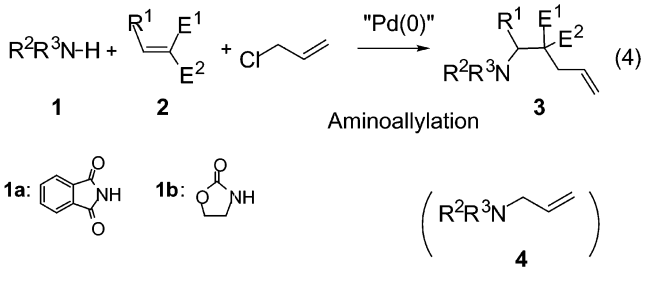
Results and Discussion

Intermolecular Amphiphilic Aminoallylation Reaction. Benzylidenemalononitrile **2a** underwent the facile aminoallylation with phthalimide **1a** and allyl chloride in the presence of $Pd_2dba_3{\cdot}CHCl_3$ (5 mol %)/P(4-$FC_6H_4)_3$ (40 mol %), and Cs_2CO_3 (3 equiv against **2a**) in dichloromethane at room temperature to give the corresponding three-component coupling product **3a** in a quantitative yield (eq 4). The reaction of oxazolidinone **1b** also proceeded very smoothly to give *N*-(2,2-dicyano-1-phenylpent-4-enyl)oxazolidinone in a quantitative yield, however, the Tsuji−Trost-type allylation products **4** were obtained in the case of dibenzylamine, *N*-tosylaniline, and pyrrolidin-2-one. Accordingly, it is essential to use the amines **1a** and **1b**, having an EWG, to avoid the direct reaction between the nucleophiles **1** and allyl chloride. Since *N*-substituted phthalimides can be easily converted to the corresponding primary amines, **1a** was used as an amine source for further investigation of the three component coupling reactions. The results are summarized in Table 1. The various activated olefins **2a**−**f** having aromatic substituents underwent the aminoallylation with **1a** and allyl chloride to give the corresponding *β*-amino-α-allylated adducts **3a**−**f** in 85−99% yields (entries 1−6). The reaction of *tert*-butyl-substituted olefin **2g** also proceeded very smoothly to give **3g** in 89% yield (entry 7). Not only the activated olefins derived from malononitrile (**2a**−**g**) but also those from Meldrum's acid (**2h**−**k**) underwent the three-component aminoallylation, giving the corresponding adducts **3h**−**k** in good to high yields (entries 8−11), and di-*tert*-butyl ethylidenemalonate **2l** afforded **3l** in 58% yield under the same condition (entry 12).

TABLE 1. Palladium(0)-Catalyzed Three-Component Aminoallylation of the Activated Olefins 2 with Phthalimide 1a and Allyl Chloride

entry	olefin, **2**	product, **3**	yield, (%)[a]
			
1	**2a**, R^1 = Ph	**3a**	>99
2	**2b**, R^1 = 4-$NO_2C_6H_4$	**3b**	>99
3	**2c**, R^1 = 4-FC_6H_4	**3c**	>99
4	**2d**, R^1 = 4-$CO_2MeC_6H_4$	**3d**	>99
5	**2e**, R^1 = 4-MeC_6H_4	**3e**	96
6	**2f**, R^1 = 4-$MeOC_6H_4$	**3f**	85
7	**2g**, R^1 = *t*-Bu	**3g**	89
			
8	**2h**, R^1 = Ph	**3h**	71
9	**2i**, R^1 = 4-$NO_2C_6H_4$	**3i**	86
10	**2j**, R^1 = 4-MeC_6H_4	**3j**	72
11	**2k**, R^1 = *t*-Bu	**3k**	91
12	 **2l**	 **3l**	58

[a] Isolated yields based on **2**.



Various allylic halides were also examined in the palladium-catalyzed three-component aminoallylation reaction, and the results are summarized in eq 5 and Table 2. As shown in Table 1, in the case of simple allylation, the use of allyl chloride gave very high yields of the desired products. However, in the case of substi-

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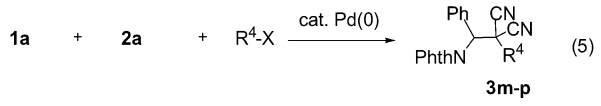
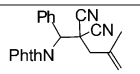
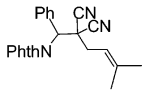
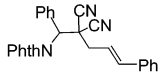
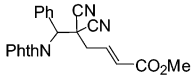
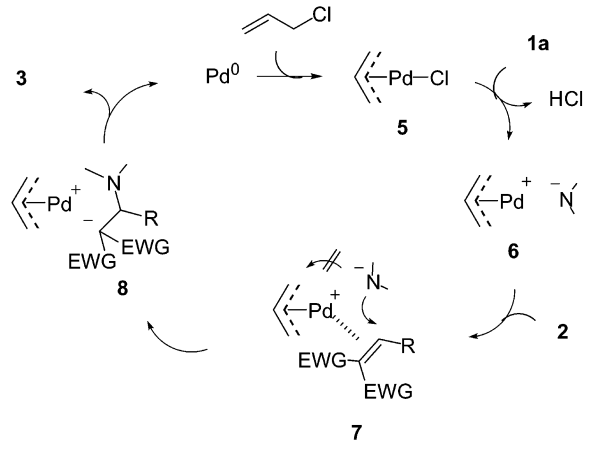
TABLE 2. Palladium-Catalyzed Aminoallylation of the Activated Olefins 2a with Phthalimide 1a and Various Allyl Halides[a]



entry	R^4-X	product **3**		yield, (%)[b]
1	CH_2=C(CH_3)CH_2Br		**3m**	76
2	CH_3(CH_3)C=$CHCH_2$Br		**3n**	72
3	PhCH=$CHCH_2$Br		**3o**	99
4	MeO_2CCH=$CHCH_2$Br		**3p**	71

[a] The reactions were carried out in the presence of Pd_2dba_3·CH_3Cl catalyst (5 mol %), P(4-FC_6H_4)$_3$ ligand (40 mol %), and Cs_2CO_3 (3.0 equiv) in CH_2Cl_2 at room temperature. [b] Isolated yields based on **2**.

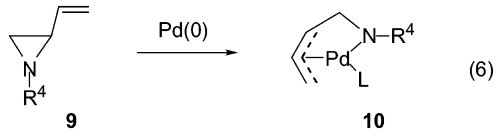
SCHEME 1



tuted allylic derivatives, the use of allylic bromides gave higher yields in comparison to the corresponding allylic chlorides. The reaction of **1a**, **2a**, and methallyl bromide produced the corresponding aminoallylation product **3m** in 76% yield (entry 1). The three-component coupling reaction also proceeded with prenyl and cinnamyl bromide and methyl 4-bromo-2-butenoate to give **3n**−**p** in 71−99% yields (entries 2−4). It should be noted that the allylation with the substituted allylic bromides took place exclusively at the α-position, and no C−C bond forming products at the γ-position were obtained.

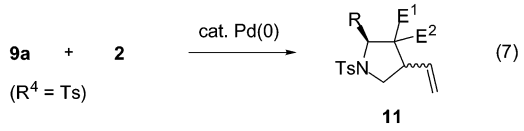
Mechanism. A plausible mechanism for the three-component aminoallylation is shown in Scheme 1. The π-allylpalladium complex **5** generated from Pd(0) and allyl chloride would react with **1a** to afford the π-allylpalladium amide **6**. The Michael addition of the nitrogen nucleophile of **6** to the activated olefin **2** would give the C−N bond-forming product **8** through the intermediate **7**. It is interesting that no direct coupling between the nitrogen nucleophile, such as phthalimide and oxazolidinone, and π-allyl group takes place in the intermediate **7**, although the direct allylation were observed in the case of other nitrogen nucleophiles, such as dibenzylamine, *N*-tosylaniline, and pyrrolidin-2-one. The nucleophilic carbon of **8** attacks the π-allylpalladium complex resulting in the formation of the aminoallylation adducts **3**. We examined the simple Michael addition between **1a** and **2a**, but no reaction took place even at elevated temperatures and the starting materials were recovered. Next, the reaction of potassium phthalimide with **2a** was examined, but again no reaction occurred. It is considered that there would be equilibrium between **7** and **8**, and the reductive elimination from **8** would promote the catalytic cycle. The key for the palladium-catalyzed three-component aminoallylation is a choice of the nitrogen nucleophiles. The less electron density on the nitrogen atom may avoid the direct attack of the nitrogen nucleophiles to π-allyl group on the palladium(II) complex **7**. The palladium(II) of **7** would act as a Lewis acid to activate the Michael acceptor at this step. This thought is supported by the need for a poor donor ligand, such as P(4-FC_6H_4)$_3$, which makes the metal more electrophilic.[13]

Intramolecular Version of the Aminoallylation. Formation of Pyrrolidine Derivatives. It was envisioned from the mechanism that the nitrogen-containing heterocycles would be readily prepared if the π-allyl group in **6** is connected to the amide through a carbon chain. Since it is known that vinylaziridines **9** react with palladium(0) to form π-allylpalladium amides **10** as shown in eq 6,[14] we examined the cycloaddition of *N*-tosylvinylaziridine **9a**[15] with activated olefins in the presence of the palladium catalyst (eq 7). The results are



shown in Table 3. The reaction of **2a** proceeded very

TABLE 3. Cycloaddition of the Activated Olefins 2 with *N*-Tosylvinylaziridine 9a



entry	olefin, **2**	product, **3**	yield[a] (%)	ratio (cis/trans)
1	**2a**	**11a**	>99	55/45
2	**2c**	**11b**	84	54/46
3	**2d**	**11c**	88	52/48
4	**2e**	**11d**	92	52/48
5	**2g**	**11e**	69	35/65
6	**2h**	**11f**	84	23/77
7	**2m**[b]	**11g**	78	

[a] Isolated yields based on **2**. [b] CH_2=C(SO_2Ph)$_2$.

smoothly in the presence of Pd_2dba_3·$CHCl_3$ (5 mol %)/P(4-FC_6H_4)$_3$ (40 mol %) catalyst in THF at room temper-

(13) We thank a reviewer who pointed out the possibility that the Lewis acidity of the palladium(II) catalyst may activate the reactivity of the Michael acceptor in **7**.

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(15) Ali, I. S.; Nikalje, D. M.; Sudalai, A. *Org. Lett.* **1999**, *1*, 705.

ature to give 3,3-dicyano-2-phenyl-*N*-tosyl-4-vinylpyrrolidine **11a** in a quantitative yield as a 55/45 mixture of cis and trans isomers (entry 1). The various activated olefins (**2c**−**e** and **2g**-**h**) underwent the cycloaddition reaction similarly, giving the corresponding pyrrolidines (**11b**-**f**) in 69−92% yields (entries 2−6). Unfortunately, the diastereoselectivities of the cycloaddition reactions were low. The reaction of 1,1-bis(phenylsulfonyl)ethylene **2m** also afforded 3,3-bis-phenylsulfonyl-*N*-tosyl-4-vinylpyrrolidine **11g** in 78% yield (entry 7).

Conclusion

The current palladium-catalyzed three-component aminoallylation reaction proceeded smoothly by using phthalimide **1a** and oxazolidinone **1b** as an amine source. The use of cyclic amines having an electron-withdrawing group is essential for the reaction, since higher electron density on a nitrogen atom induces the direct allylation to the π-allylpalldium complex **5**, and the palladium(II) complex promotes the Michael addition of the nitrogen nucleophiles to the activated olefins **2** at the stage of **7** in the catalytic cycle. The present finding enables us to conduct the one-pot multifunctionalization of carbon−carbon unsaturated compounds.

Experimental Section

General Procedure for the Intermolecular Aminoallylation. To a solution of $Pd_2dba_3{\cdot}CHCl_3$ (0.025 mmol), $(4\text{-}FC_6H_4)_3P$ (0.20 mmol), **2** (0.50 mmol), phthalimide **1a** (0.60 mmol), and Cs_2CO_3 (1.50 mmol) in CH_2Cl_2 (4 mL) was added allyl chloride (0.60 mmol) under Ar atmosphere. The reaction mixture was stirred at room temperature, and the reaction progress was monitored by TLC. When **2** was consumed completely (6−24 h), the reaction mixture was filtered through a short florisil column chromatography to remove the catalysts. Purification by a silica gel column chromatography (hexane/ethyl acetate = 10:1) gave **3**.

General Procedure for the Cycloaddition of *N*-Tosylvinylaziridine 9a with the Activated Olefins 2. To a solution of $Pd_2dba_3{\cdot}CHCl_3$ (0.025 mmol), $(4\text{-}C_6H_4F)_3P$ (0.20 mmol), and **2** (0.50 mmol) in THF (5 mL) was added *N*-tosylvinylaziridine **9a** (0.60 mmol) under Ar atmosphere. The reaction mixture was stirred at room temperature and the reaction progress was monitored by TLC. When **2** was consumed completely (∼1 d), the reaction mixture was filtered through a short florisil column chromatography to remove the catalysts. Purification by a silica gel column chromatography (hexane/ethyl acetate = 6:1) gave **11**.

Supporting Information Available: Characterization date for new compounds **3a**−**p** and **11a**−**g** (PDF). This material is available free charge via the Internet at http://pubs.acs.org.

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