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Synthesis of Allyl Cyanamides and *N*-Cyanoindoles via the Palladium-Catalyzed Three-Component Coupling Reaction

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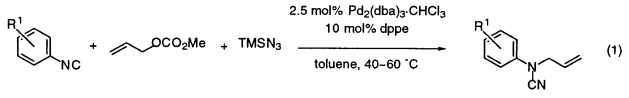
Abstract: The palladium-catalyzed three-component coupling reaction (TCCR) of aryl isocyanides, allyl methyl carbonate, and trimethylsilyl azide was conducted in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %) and dppe (1,2-bis(diphenylphosphino)ethane) (10 mol %). Allyl aryl cyanamides with a wide variety of functional groups were obtained in excellent yields. This palladium-catalyzed TCCR was further utilized for the synthesis of *N*-cyanoindoles. The reaction of 2-alkynylisocyanobenzenes, allyl methyl carbonate, and trimethylsilyl azide in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %) and tri(2-furyl)phosphine (10 mol %) at higher temperatures afforded *N*-cyanoindoles in good to allowable yields. (η^3-Allyl)(η^3-cyanamido)palladium complex, an analogue of the bis-π-allylpalladium complex, is a key intermediate in the TCCR, and a π-allylpalladium mimic of the Curtius rearrangement is involved to generate the (η^3-allyl)(η^3-cyanamido)-palladium intermediate.

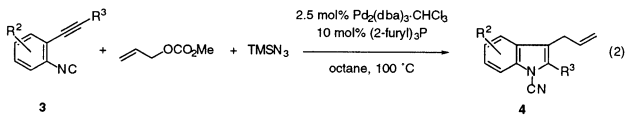
Introduction

Cyanamides have been attracting many chemists because of their unique structure and reactivity. They have been used not only as a building block for heterocyclic compounds in the fields of organic chemistry[1] but also as a ligand for various metals in those of inorganic chemistry and material science.[2] Some cyanamides are found in natural products[3] and are known to exhibit biological activities.[4] Although cyanamides are one of the important classes of chemicals, their synthetic routes are quite limited. The major approaches to the cyanamides are as follows:[1,5] (i) alkylation of cyanamide under basic conditions, (ii) cyanation of amines by using cyanogen bromide, and (iii) condensation of cyanamide with carbonyl compounds. Our recent work has focused on the synthesis of allyl cyanamides via the palladium-catalyzed three-component coupling reaction (TCCR) of isocyanides, allyl carbonate, and trimethylsilyl azide (eq 1).[6] We anticipated that this new palladium-catalyzed transformation of the allyl cyanamides could be applied for the synthesis of *N*-cyanoindoles by the proper design of the starting isocyanides.

Formation of allyl aryl cyanamides



Formation of *N*-cyanoindoles



Great attention has been paid to the synthesis of indoles because these structural frameworks are often seen in many

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natural products which exhibit unique biological activities. Although many methodologies have been developed for the construction of indoles, a new *catalytic* procedure compatible with a wide variety of functional groups is still needed.[7] Recent advances of transition metal chemistry in organic synthesis have provided new *catalytic* methodologies for the synthesis of indoles.[8] Various approaches utilizing *isocyanides* as a precursor of indole have been developed, and they are categorized under the following three types: (i) lithiation of 2-alkylisocyanobenzenes,[9,10] (ii) radical cyclization of 2-alkenylisocyanobenzenes,[11] and (iii) transition-metal-catalyzed[12a,13c] or -mediated[12,13] reaction of arylisocyanides. Although many useful procedures for the synthesis of indoles from isocyanides have been reported, the use of a stoichiometric amount of metal salts and organometallics or even more is needed in most cases. To the best of our knowledge, there have been no reports for the *palladium-catalyzed* synthesis of indoles from *isocyanides* as a starting material.[13c] We now report a new strategy for the synthesis of *N*-cyanoindoles (eq 2) together with a full account on the formation of allyl cyanamides, via the palladium-catalyzed TCCR of isocyanides, allyl carbonate, and trimethylsilyl azide.

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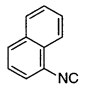
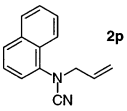
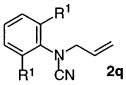
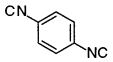
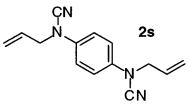
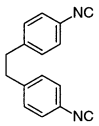
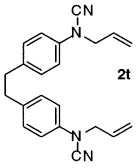
Table 1. Palladium-Catalyzed Formation of Allyl Cyanamides[a]

entry	isocyanide	R^1	temperature °C	time, h	cyanamide	yield, %[b]
1	**1a**	4-MeO	60	1	**2a**	99
2	**1b**	3-MeO	60	1	**2b**	98
3	**1c**	2-MeO	60	1	**2c**	94
4[c]	**1d**	4-TBSO$(CH_2)_2$	60	1	**2d**	79
5	**1e**	4-AcO$(CH_2)_2$	60	1	**2e**	85
6	**1f**	4-MOMO$(CH_2)_2$	60	1	**2f**	80
7	**1g**	4-MsO$(CH_2)_2$	60	1	**2g**	77
8	**1h**	4-CN	40	1	**2h**	80
9	**1i**	4-CO_2Me	40	1	**2i**	95
10	**1j**	4-Cl	40	2	**2j**	85
11	**1k**	2-Br	60	1	**2k**	76
12	**1l**	4-vinyl	60	1	**2l**	88
13	**1m**	4-Me_3SiC≡C	60	0.5	**2m**	97
14	**1n**	2-Me_3SiC≡C	40	1	**2n**	84
15	**1o**	2-Ph_3SiC≡C	40	1	**2o**	91
16	**1p**		60	0.5	**2p** 	69
17	**1q**	 R^1 = Me	60	1	**2q** 	84
18	**1r**	R^1 = ^{i}Pr	60	1	**2r**	65
19[d]	**1s**		60	1	**2s** 	93
20[d]	**1t**		60	1	**2t** 	55

[a] To a mixture of **1** (0.5 mmol), allyl methyl carbonate (1 mmol), and $TMSN_3$ (1 mmol) were added $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %) and dppe (10 mol %) in toluene (1 mL). The mixture was stirred at room temperature for 10 min and then at the indicated temperature for the time shown in Table 1. [b] Isolated yield. [c] $Pd(acac)_2$ (5 mol %) was used instead of $Pd_2(dba)_3$·$CHCl_3$.[14] [d] The reaction of **1** (0.5 mmol) was conducted with allyl methyl carbonate (2 mmol) and $TMSN_3$ (2 mmol) under $Pd_2(dba)_3$·$CHCl_3$ (5 mol %) and dppe (20 mol %) in toluene.

Results and Discussion

The Palladium-Catalyzed Synthesis of Allyl Cyanamides.[6] The results are summarized in Table 1. Allyl methyl carbonate and trimethylsilyl azide were added to a solution of 4-methoxy-1-isocyanobenzene **1a**, $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %), and dppe (10 mol %) in toluene. The mixture was stirred at room temperature for 10 min and then heated at 60 °C for 1 h to afford *N*-allyl-*N*-(4-methoxyphenyl)cyanamide **2a** in 99% yield (entry 1). Only a limited number of phosphine ligands, such as dppe, tri(2-furyl)phosphine, and dppp (1,3-bis(diphenylphosphino)propane), showed catalytic activity, whereas the use of the other phosphine ligands, such as PPh_3, (*o*-tolyl)$_3$P, ^{n}Bu$_3$P, and dppb (1,4-bis(diphenylphosphino)butane), did not give the desired product. Among the palladium sources we tested, $Pd_2(dba)_3$·$CHCl_3$ showed the best catalytic activity. $Pd(acac)_2$ was also effective; however, $Pd(OAc)_2$ and $[(\eta^3\text{-}C_3H_5)PdCl]_2$ were ineffective. As for the solvent, less polar solvents such as toluene and octane gave the desired product. Polar solvents such as CH_3-CN, THF, and 1,2-dichloroethane did not give the allyl cyanamide **2a**. In the absence of the palladium catalyst, no reaction took place even after heating at 60 °C for 1 h.

A wide applicability for the synthesis of allyl cyanamides **2** via the palladium-catalyzed three-component coupling reaction is shown in Table 1. The reaction proceeds regardless of the substitution pattern on the aromatic ring of isocyanides (entries 1−3). Representative protective groups for the alcohol, such as silyl, acetyl, methoxylmethyl, and mesyl groups, can be tolerated under the reaction conditions (entries 4−7). The reactions of the isocyanobenzenes with electron-withdrawing groups **1h**−**k** proceeded even at 40 °C to give the corresponding products **2h**−**k** (entries 8−11). The results indicate that the isocyanobenzenes with electron-withdrawing groups are more reactive than those with electron-donating groups. The isocyanobenzenes conjugated with vinyl **1l** and alkynyl groups **1m**−**o** afforded the corresponding products **2l**−**o** (entries 12−15). In the case of *ortho*-alkynyl isocyanobenzenes, it is important to *run reactions at 40* °C to obtain the desired allyl cyanamides as a sole product. Naphthyl isocyanide **1p** also gave the cyanamide **2p** (entry 16). Even sterically hindered 2,6-disubstituted isocyanobenzenes **1q** and **1r** gave the corresponding products **2q** and **2r** (entries 17 and 18). The reaction can be applicable for the sterically congested isocyanides. The substrates having two isonitrile groups in the same molecule **1s** and **1t** also afforded the corresponding dicyanamides **2s** and **2t** (entries 19 and 20). The reaction is applicable for the substrates having plural reaction sites.

The structures of the products were determined by spectroscopic data and elemental analysis. Furthermore, the structure of **2o** was unambiguously confirmed by X-ray crystallographic analysis (see Supporting Information). It is clear that the obtained product **2o** is an allyl cyanamide and not an allyl carbodiimide.

The Palladium-Catalyzed Synthesis of *N*-Cyanoindoles. In the course of the allyl cyanamide synthesis with 2-(trimethylsilylethynyl)-1-isocyanobenzene **1n**, we found that the cyclized product, 3-allyl-*N*-cyano-2-(trimethylsilyl)indole **4n**, was obtained as a very minor byproduct along with the desired allyl cyanamide **2n**. Further investigation revealed that the three-component coupling reaction of the *ortho*-alkynylisocyanobenzenes **3a**−**y** under the palladium catalyst at 100 °C gave the *N*-cyanoindoles **4a**−**y** in good to allowable yields (eq 2). It is essential to *carry out the reaction at 100* °C to obtain the desired *N*-cyanoindole as a sole product.

The results are summarized in Table 2. Allyl methyl carbonate and trimethylsilyl azide were added to a solution of 2-(trimethylsilylethynyl)-1-isocyanobenzene **1n**, $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), and tri(2-furyl)phosphine (10 mol %)[15] in octane. The mixture was stirred at room temperature for 10 min and then heated at 100 °C for 1 h. 3-Allyl-*N*-cyano-2-(trimethylsilyl)-indole **4n** was obtained in 59% yield (entry 1). Under these conditions, the allyl cyanamide **2n** was not obtained at all. Among the phosphine ligand we tested, tri(2-furyl)phosphine showed the best catalytic activity when combined with the $Pd_2(dba)_3{\cdot}CHCl_3$ complex. Other monodentate phosphine ligands such as PPh_3, $(o\text{-tolyl})_3P$, and tri(*p*-fluorophenyl)phosphine were also effective, whereas bidentate phosphine ligands such as dppe (1,2-bis(diphenylphosphino)ethane), dppp (1,3-bis(diphenylphosphino)propane), and dppb (1,4-bis(diphenylphosphino)butane) were ineffective. The reaction proceeded even without the addition of a phosphine ligand, but the yield of the desired indole was low. As for the palladium complexes, $Pd_2(dba)_3{\cdot}CHCl_3$ showed the best catalytic activity. $Pd(PPh_3)_4$ and $Pd(acac)_2$ also showed catalytic activity, while the use of $PdCl_2(PPh_3)_2$ resulted in the formation of complex mixtures. Less polar solvents such as octane and toluene gave the desired product in good yields. THF was also usable, although a slight decrease of the yield was observed. Polar solvents such as 1,2-dichloroethane, CH_3CN, and DMF afforded only small amounts of the indole **4n**.

We carried out the reactions with the isocyanides which have an electron-donating group at the position *para* to the isonitrile group. The isocyanobenzenes having alkyl substituents such as methyl **3a** and isopropyl group **3b** gave the corresponding indoles **4a** and **4b** in good yields (entries 2 and 3). The reaction of isocyanobenzenes having heteroatom containing electron-donating substituents such as methoxy **3c**, methylthio group **3d**, and phenylazo group **3e** also proceeded smoothly to give the corresponding indoles **4c**−**e** in good yields (entries 4−6). We next investigated the reactivity of isocyanides which have an electron-withdrawing group at the position *para* to the isonitrile group. The isocyanobenzenes having halogen **3f**−**h**, trifluoromethyl group **3i**, methoxycarbonyl group **3j**, nitro group **3k**, cyano group **3l**, and acetyl group **3m** afforded the corresponding indoles **4f**−**m** in moderate yields (entries 7−14). In the case of **3i**, the addition of 5 equiv of allyl methyl carbonate and 5 equiv of trimethylsilyl azide was needed to obtain the desired indole **4i** in high yield.[16] The isocyanide **3o** conjugated with the alkynyl group at the position *para* to the isonitrile group also proceeded

Table 2. Palladium-Catalyzed Formation of *N*-Cyanoindoles[a]

entry	isocyanide	R^2	indole	yield, %[b]
1	**1n**	H	**4n**	59
2	**3a**	4-Me	**4a**	68
3	**3b**	4-^{i}Pr	**4b**	77
4	**3c**	4-MeO	**4c**	69
5	**3d**	4-MeS	**4d**	67
6	**3e**	4-Ph−N═N	**4e**	45
7[c]	**3f**	4-F	**4f**	56
8[c]	**3g**	4-Cl	**4g**	54
9	**3h**	4-Br	**4h**	47[e]
10[d]	**3i**	4-CF_3	**4i**	65
11[c]	**3j**	4-CO_2Me	**4j**	53
12[c]	**3k**	4-NO_2	**4k**	34
13[c]	**3l**	4-CN	**4l**	30
14[c]	**3m**	4-CH_3CO	**4m**	37
15	**3o**	4-$Me_3SiC{\equiv}C$	**4o**	58
16	**3p**	5-Me	**4p**	65
17	**3q**	5-MeO	**4q**	57
18	**3r**	5-Cl	**4r**	47
19[c]	**3s**	5-NO_2	**4s**	59
20[c]	**3t**	5-CH_3CO	**4t**	45
21[c]	**3u**	5-$Me_3SiC{\equiv}C$	**4u**	61
22	**3v**	3-MeO	**4v**	62
23	**3w**	6-MeO	**4w**	63

[a] To a mixture of **1** (0.5 mmol), allyl methyl carbonate (1 mmol), and $TMSN_3$ (1 mmol) were added $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %) and $(2\text{-furyl})_3P$ (10 mol %) in octane (1 mL), and the mixture was stirred at room temperature for 10 min and then at 100 °C for 1 h. [b] Isolated yield. [c] THF was used instead of octane. [d] Five equivalents of allyl methyl carbonate and five equivalents of $TMSN_3$ were used. [e] Allyl cyanamide was obtained in ∼17% yield.

(14) It is difficult to separate the cyanamide **2d** and dibenzylideneacetone derived from $Pd_2(dba)_3{\cdot}CHCl_3$.

(15) (a) Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997−1030. (b) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434−5444. (c) Amatore, C.; Jutand, A.; Meyer, G.; Atmani, H.; Khalil, F.; Chahdi, F. O. *Organometallics* **1998**, *17*, 2958−2964.

(16) The reaction with 2 equiv of allyl methyl carbonate and 2 equiv of trimethylsilyl azide gave **4i** only in 37% yield.

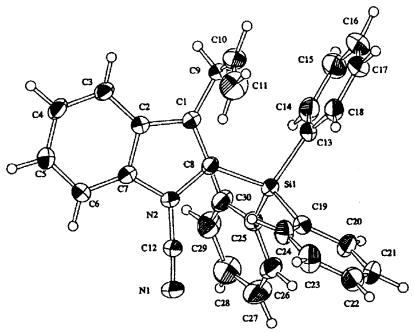
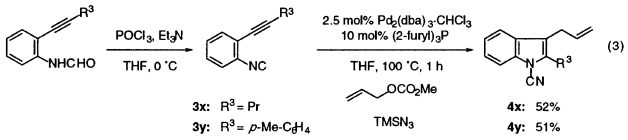


Figure 1. X-ray structure of **4z**.

to give the corresponding indole **4o** in 58% yield (entry 15). We further carried out the reactions with the isocyanides which have a substituent at the position *para* to the alkynyl group. The isocyanobenzenes with electron-donating substituents such as methyl **3p** and methoxy group **3q** gave the corresponding indoles **4p** and **4q** in 65 and 57% yields, respectively (entries 16 and 17). The isocyanobenzene having chloro **3r**, nitro group **3s**, and acetyl group **3t** also afforded the corresponding indoles **3r**−**t** in moderate yields (entries 18−20). The isocyanobenzene **3u** conjugated with the alkynyl group at the position *para* to the trimethylsilylethynyl group gave the corresponding indole **4u** in 61% yield (entry 21). Even 3- and 6-substituted methoxyisocyanobenzenes **3v** and **3w** gave the corresponding indoles **4v** and **4w** in 62 and 63% yields, respectively (entries 22 and 23). It is clear that the indole forming reaction proceeds smoothly irrespective of the substitution site and the electronic nature of the substituents on aromatic ring. A wide variety of functional groups are tolerated under the reaction conditions.



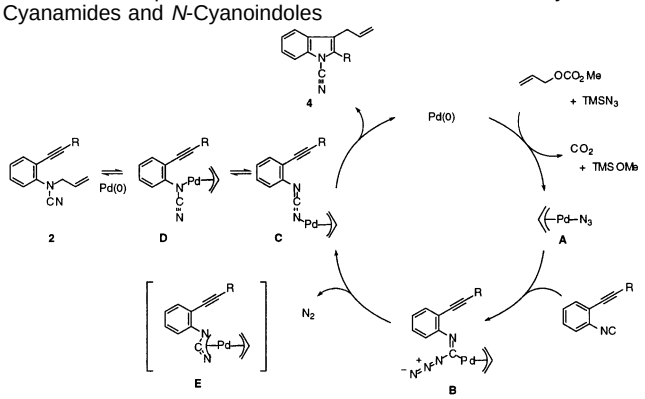
(3)

We next examined the isocyanobenzenes having alkyl and aryl groups at the end of the alkynyl substituent (eq 3). The reactions were conducted in a sequential procedure. The isocyanides were derived from the corresponding formanilides and used without purification, because they were unstable at room temperature and decomposed during the isolation step.[17] Both propyl **3x** and *p*-methylphenyl substituted isocyanobenzenes **3y** afforded the corresponding indoles **4x** and **4y** in moderate yields.

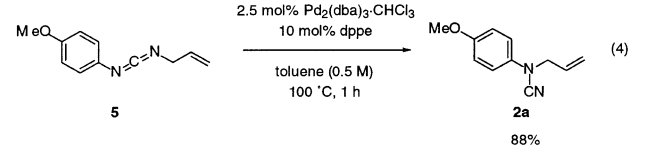
The structures of the products were determined by spectroscopic data and elemental analysis. Furthermore, the structure of **4z**, which was obtained in a manner similar to those shown in Table 2, was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).

A proposed mechanism is shown in Scheme 1. First, Pd(0) reacts with allyl methyl carbonate and $TMSN_3$ to give the π-allylpalladium azide **A**;[18] CO_2 and TMSOMe would be generated at this stage. The insertion of the isocyanide between the Pd−N_3 bond in the π-allylpalladium azide **A** would then give the π-allylpalladium intermediate **B**. Elimination of N_2

Scheme 1. Proposed Mechanism for the Formation of Allyl Cyanamides and *N*-Cyanoindoles



followed by the 1,2-migration of π-allylpalladium moiety from the carbon atom to the α-nitrogen atom in **B** would give the palladium-carbodiimide complex **C**.[19] It should be noted that the conversion from **B** to **C** is a *π-allylpalladium mimic of the Curtius rearrangement*. The palladium-carbodiimide complex **C** could be in equilibrium with the palladium-cyanamide complex **D**, or more probably could be represented as a heteroatom containing bis-π-allylpalladium analogue **E**.[20] The allyl cyanamides **2** are formed as a final product after the reductive elimination of Pd(0) from the intermediate **D** at lower temperature (up to 40 °C), whereas at elevated temperature (100 °C), the *N*-cyanoindoles **4** are formed via the insertion of the alkyne moiety into the Pd−N bond in intermediate **D**[21] followed by the reductive elimination of Pd(0).

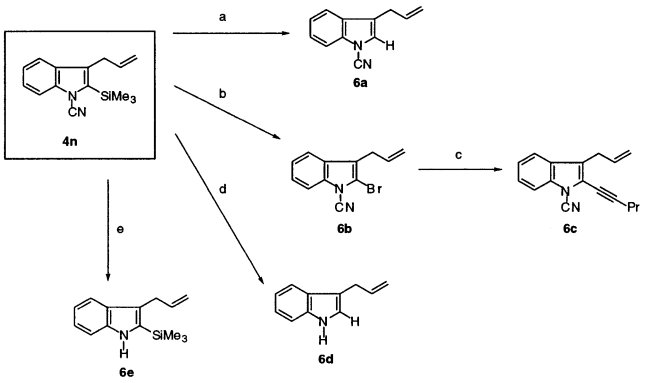


(4)

One of the key steps for the proposed mechanism is the formation of π-allylpalladium carbodiimide complex **C** and its isomerization to π-allylpalladium cyanamide complex **D**. To obtain a strong support for this interesting isomerization, we synthesized the allyl carbodiimide **5**[22] and examined the isomerization under the palladium catalyst (eq 4). As expected, the allyl cyanamide **2a** was obtained in 88% yield.[23] When **5**

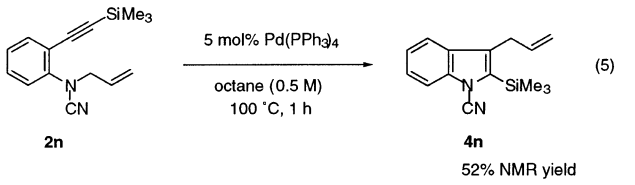
(17) These isocyanides were especially unstable in concentrated pure form. Thus, careful handling is needed. See Experimental Section.
(18) (a) Busetto, L.; Palazzi, A. *Inorg. Chim. Acta* **1975**, *13*, 233−238. (b) Shaw, B. L.; Shaw, G. *J. Chem. Soc. A* **1971**, 3533−3535.
(19) Stoichiometric reaction of palladium-azido complexes with isocyanides, see: (a) Kim, Y.-J.; Kwak, Y.-S.; Lee, S.-W. *J. Organomet. Chem.* **2000**, *603*, 152−160. (b) Kim. Y.-J.; Kwak, Y.-S.; Joo, Y.-S.; Lee, S.-W. *J. Chem. Soc., Dalton Trans.* **2002**, 144−151. (c) Beck, W.; Burger, K.; Fehlhammer, W. P. *Chem. Ber.* **1971**, *104*, 1816−1825.
(20) For the chemistry on bis-π-allylpalladium, see: (a) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641−6647. (b) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242−4243. (c) Nakamura, H.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8113−8114. (d) Shim, J.-G.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 8470−8474. (e) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 729−731. (f) Nakamura, H.; Aoyagi, K.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372−377. (g) Kamijo, S.; Jin, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9453−9454. (h) Szabó, K. J. *Chem.-Eur. J.* **2000**, *6*, 4413−4421. (i) Solin, N.; Narayan, S.; Szabó, K. J. *Org. Lett.* **2001**, *3*, 909−912. (j) Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2002**, *4*, 1563−1566.
(21) Two palladium atoms might participate in this step.
(22) Shi, C.; Zhang, Q.; Wang, K. K. *J. Org. Chem.* **1999**, *64*, 925−932.
(23) It is well known that a π-allylpalladium complex is formed by the oxidative addition of Pd(0) to CH_2═$CHCH_2Y$ (Y: halide, OCO_2R, OAc, OP(O)$(OR)_2$, NR_2, etc.). However, to the best of our knowledge, there is no report for the oxidative addition of Pd(0) to allyl carbodiimide (Y: N═C═NR). See: Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley: New York, 2000; Chapter 4.

Scheme 2. Transformations of **4n**[a]



[a] Reagents and Conditions: (a) HCl, CH_3CN, 100 °C, 75%; (b) NBS, CH_3CN, 100 °C, 85%; (c) $Pd(PPh_3)_4$ (5 mol %), CuI (10 mol %), 1-pentyne, Et_3N, 78%; (d) TBAF, THF, 50 °C, 70%; (e) MeMgBr, THF, 0 °C to room temperature, 93%.

was heated in toluene with 10 mol % dppe at 100 °C for 1 h, no reaction took place, and **5** was recovered.[24] Accordingly, it is very probable that the π-allylpalladium complexes **C**−**E** intervene in the catalytic cycle of the three-component coupling process.



Another interesting step in the proposed mechanism is that the insertion of the alkyne moiety to the π-allylpalladium intermediates **C**−**E** takes place in *trans manner* to afford the *N*-cyanoindoles **4**. To obtain detailed information for the unique cyclization, we examined the reaction of the allyl cyanamide **2n** at 100 °C under the palladium catalyst (eq 5). As expected, the *N*-cyanoindole **4n** was obtained in 52% NMR yield.[25] When **2n** was heated in the absence of the palladium catalyst in octane at 100 °C for 1 h, no reaction took place, and **2n** was recovered quantitatively. This result indicates the existence of an equilibrium between the π-allylpalladium intermediates **C**−**E** and the allyl cyanamide **2**. High temperature is needed for the insertion of the alkyne moiety to the Pd−N bond in the π-allylpalladium intermediate **D**.

We also investigated further transformations of 3-allyl-2-trimethylsilyl-*N*-cyanoindole **4n** obtained through the three-component coupling reaction (Scheme 2). Selective removal of the trimethylsilyl group was achieved by treatment with hydrogen chloride.[26] Complete protodesilylation was attained in CH_3CN at 100 °C to give the *N*-cyanoindole **6a** in 75% yield. The reaction with *N*-bromosuccinimide (NBS) in CH_3CN at 100 °C afforded the 2-bromoindole **6b** in 85% yield.[8d,26] The treatment of the obtained 2-bromoindole with 1-pentyne under a catalytic amount of $Pd(PPh_3)_4$ and CuI afforded the 2-alkynylindole **6c** in 78% yield. Both the trimethylsilyl group and the cyano group could be removed all at once by the treatment with tetrabutylammonium fluoride (TBAF) at 50 °C. 3-Allylindole **6d** was obtained in 70% yield. Selective deprotection of the cyano group was achieved by treatment with MeMgBr. 3-Allyl-2-(trimethylsilyl)indole **6e** was obtained in 93% yield.[27]

Conclusions

A novel synthetic route to the allyl aryl cyanamides **2** and *N*-cyanoindoles **4** has been developed. The allyl aryl cyanamides are synthesized through the palladium-catalyzed three-component coupling reaction (TCCR) between arylisocyanides **1**, allyl carbonate, and trimethylsilyl azide. *N*-Cyanoindoles are synthesized by the use of the arylisocyanides **3**, substituted by *ortho*-alkynyl groups, at higher reaction temperatures under a modified catalyst system. Mechanistically, a very interesting step is involved in the three-component coupling reaction, that is to say, a π-allylpalladium mimic of the Curtius rearrangement. Perhaps one of the most useful and powerful aspects of the present TCCR is that a wide range of functional groups are tolerated at the *p*-, *m*-, and even *o*-positions of the aromatic ring. Further manipulation of *N*-cyanoindoles can provide a wide range of indole derivatives.

Experimental Section

Typical Procedure for the Palladium-Catalyzed Synthesis of Allyl Cyanamides.[6] To a toluene solution (1.0 mL) of 4-methoxy-1-isocyanobenzene **1a** (66.6 mg, 0.5 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (13.0 mg, 0.0125 mmol), and dppe (20.0 mg, 0.05 mmol) were added allyl methyl carbonate (0.11 mL, 1 mmol) and trimethylsilyl azide (0.13 mL, 1 mmol) under an argon atmosphere. The solution was stirred at room temperature for 10 min and then at 60 °C for 1 h. The reaction mixture was cooled to room temperature and filtered through a short Florisil pad and concentrated. The residue was purified by column chromatography (silica gel, hexane−ether 10/1 to 1/1) to afford *N*-allyl-*N*-(4-methoxyphenyl)cyanamide **2a** in 99% yield (93.3 mg).

Typical Procedure for the Palladium-Catalyzed Synthesis of *N*-Cyanoindoles. To an octane solution (1.0 mL) of 2-(trimethylsilylethynyl)-1-isocyanobenzene **1n** (99.7 mg, 0.5 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (13.0 mg, 0.0125 mmol), and tri(2-furyl)phosphine (11.6 mg, 0.05 mmol) were added trimethylsilyl azide (0.13 mL, 1 mmol) and allyl methyl carbonate (0.11 mL, 1 mmol) under an argon atmosphere. The solution was stirred at room temperature for 10 min and then at 100 °C for 1 h. The reaction mixture was cooled to room temperature and filtered through a short Florisil pad and concentrated. The residue was purified by column chromatography (silica gel, hexane−ether 50/1 to 10/1) to afford 3-allyl-2-(trimethylsilyl)-*N*-cyanoindole **2n** in 59% yield (74.6 mg).

Typical Procedure for the Sequential Reaction. Synthesis of 3-Allyl-2-propyl-*N*-cyanoindole (4x). A THF solution (2 mL) of 2-(1-pentynyl)-1-formanilide (187.3 mg, 1 mmol) and Et_3N (0.42 mL, 3 mmol) was cooled at 0 °C; then phosphorus oxychloride (0.11 mL, 1.2 mmol) was added dropwise. After the reaction was completed, saturated $NaHCO_3$ aqueous solution (∼1 mL) was added at 0 °C to quench the reaction, and the product was extracted with ether (∼10 mL). The extract was dried with Na_2SO_4, and the solvent was removed under vacuum at 0 °C (ice bath). THF (0.5 mL) was added immediately to dissolve 2-(1-pentynyl)-1-isocyanobenzene **3x**, and the resulting solution was kept at 0 °C. To a THF solution (0.5 mL) of $Pd_2(dba)_3{\cdot}CHCl_3$ (25.9 mg, 0.025 mmol) and tri(2-furyl)phosphine (23.3 mg, 0.1 mmol) was added a THF solution of 2-(1-pentynyl)-1-isocyanobenzene **3x** under an argon atmosphere, and the mixture was stirred for 5 min at room temperature. Trimethylsilyl azide (0.27 mL, 2 mmol) and allyl

(24) Yamamoto, N.; Isobe, M. *Chem. Lett.* **1994**, 2299−2302.
(25) Palladium-catalyzed synthesis of 3-allylindoles, see: (a) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001−1011. (b) Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799−1802.
(26) Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525−4542.
(27) Wu, Y.-q.; Limburg, D. C.; Wilkinson, D. E.; Hamilton, G. S. *Org. Lett.* **2000**, *2*, 795−797.

methyl carbonate (0.23 mL, 2 mmol) were then added to the reaction mixture, and the mixture was stirred at room temperature for 10 min and at 100 °C for 1 h. The reaction mixture was cooled to room temperature and filtered through a short Florisil pad and concentrated. The residue was purified by column chromatography (silica gel, hexane−ether 50/1 to 10/1) to afford 3-allyl-2-propyl-*N*-cyanoindole **4x** in 52% yield (116.4 mg).

Acknowledgment. We thank faculties in the Instrumental Analysis Center for Chemistry at Tohoku University for measurements of X-ray crystallography, NMR spectra, mass spectra, and elemental analyses.

Supporting Information Available: Characterization data and ^{1}H NMR spectra of compounds **2k**, **2n**, **2p**, **2t**, **4a**−**z**, **5**, **6a**−**e** (PDF) and X-ray crystallographic data for **2o**, **4z** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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