

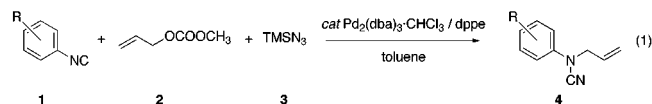
## Novel Synthetic Route to Allyl Cyanamides: Palladium-Catalyzed Coupling of Isocyanides, Allyl Carbonate, and Trimethylsilyl Azide

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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<sup>1</sup> but also as a ligand for various metals in the fields of inorganic chemistry and material science.<sup>2</sup> Some cyanamides are found in natural products<sup>3</sup> and known to exhibit biological activities.<sup>4</sup> Although cyanamides are one of the important classes of chemicals, their synthetic routes are quite limited. The major approaches are as follows:<sup>1–5</sup> (1) alkylation of cyanamide under basic conditions, (2) cyanation of amines by using cyanogen bromide, and (3) condensation of cyanamide with carbonyl compounds. We now report a novel synthetic route to cyanamides via palladium-catalyzed three component coupling of the isocyanides **1**, allyl carbonate **2**, and trimethylsilyl azide **3** to give the allyl cyanamides **4** in good to excellent yields (eq 1).



The results are summarized in Table 1. When a mixture of 4-methoxy-1-isocyanobenzene **1a**, allyl methyl carbonate **2**, and trimethylsilyl azide **3** in toluene was stirred at room temperature for 10 min and then heated at 60 °C for 1 h in the presence of 2.5 mol % of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> and 10 mol % of 1,2-bis-(diphenylphosphino)ethane, *N*-allyl-*N*-(4-methoxyphenyl)cyanamide **4a** was formed in 99% yield (entry 1). In the absence of the palladium catalyst, no reaction took place even after heating at 60 °C for 1 h. The regioisomers **1b** and **1c** also gave the corresponding products **4b** and **4c** in excellent yields (entries 2

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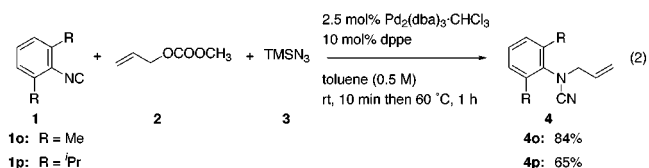
(5) Palladium-catalyzed reactions, see: (a) Cerezo, S.; Cortés, J.; Moreno-Mañas, M.; Pleixats, R.; Roglans, A. *Tetrahedron* **1998**, *54*, 14869–14884. (b) Cerezo, S.; Cortés, J.; López-Romero, J.-M.; Moreno-Mañas, M.; Parella, T.; Pleixats, R.; Roglans, A. *Tetrahedron* **1998**, *54*, 14885–14904.

Table 1. Palladium-Catalyzed Formation of Cyanamides **4**<sup>a</sup>

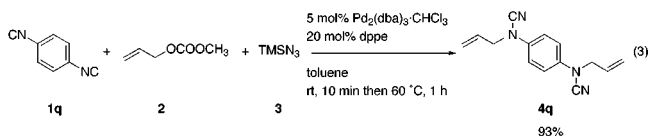
entry	<b>1</b>	R	temperature, °C	time, h	<b>4</b>	Yield, % <sup>b</sup>
1	<b>1a</b>	4-MeO	60	1	<b>4a</b>	99
2	<b>1b</b>	3-MeO	60	1	<b>4b</b>	98
3	<b>1c</b>	2-MeO	60	1	<b>4c</b>	94
4	<b>1d</b>	4-TBSO(CH <sub>2</sub> ) <sub>2</sub> <sup>c</sup>	60	1	<b>4d</b>	79
5	<b>1e</b>	4-AcO(CH <sub>2</sub> ) <sub>2</sub>	60	1	<b>4e</b>	85
6	<b>1f</b>	4-MOMO(CH <sub>2</sub> ) <sub>2</sub>	60	1	<b>4f</b>	80
7	<b>1g</b>	4-MsO(CH <sub>2</sub> ) <sub>2</sub>	60	1	<b>4g</b>	77
8	<b>1h</b>	4-CN	40	1	<b>4h</b>	80
9	<b>1i</b>	4-CO <sub>2</sub> Me	40	1	<b>4i</b>	95
10	<b>1j</b>	4-Cl	40	2	<b>4j</b>	85
11	<b>1k</b>	4-vinyl	60	1	<b>4k</b>	88
12	<b>1l</b>	4-Me <sub>3</sub> SiCC	60	0.5	<b>4l</b>	97
13	<b>1m</b>	2-Me <sub>3</sub> SiCC	40	1	<b>4m</b>	84
14	<b>1n</b>	2-Ph <sub>3</sub> SiCC	40	1	<b>4n</b>	91

<sup>a</sup> To a mixture of **1** (0.5 mmol), **2** (1 mmol), and **3** (1 mmol) were added Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (2.5 mol%) and dppe (10 mol%) in toluene (1 ml). The mixture was stirred at rt for 10 min and then at indicated temperature for the time shown in table 1. <sup>b</sup> Isolated yield. <sup>c</sup> Pd(acac)<sub>2</sub> (5 mol%) was used instead of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>.

and **3**). The isocyanobenzenes having a *tert*-butyldimethylsilyl-protecting group **1d**, acetyl group **1e**, methoxymethyl group **1f**, and mesyl group **1g** proceeded smoothly to give the corresponding cyanamides **4d–g**, respectively, in good yields (entries 4–7). In the case of silyl-protected isocyanide **1d**, Pd(acac)<sub>2</sub> was used instead of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> for the ease of separation of the product **4d**.<sup>6</sup> The isocyanobenzenes with electron-withdrawing groups **1h–j** reacted even at 40 °C to give the corresponding products **4h–j** in high to good yields (entries 8–10). The isocyanobenzenes conjugated with vinyl **1k** and alkynyl groups **1l–n** afforded the cyanamides **4k** and **4l–n**, respectively, in good to excellent yields (entries 11–14). Even sterically hindered isocyanides **1o** and **1p** underwent the three-component coupling reaction to give the corresponding cyanamides **4o** and **4p** in 84 and 65% yields (eq 2).



corresponding dicyanamide **4q** in 93% yield (eq 3). The structures of the products **4** were determined by spectroscopic data and elemental analysis. Furthermore, the structure of **4n** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1). It is clear that the obtained product **4n** is an allyl cyanamide and not an allyl carbodiimide.



A proposed mechanism is shown in Scheme 1. First, Pd(0) reacts with allyl carbonate **2** and TMSN<sub>3</sub> **3** to give π-allylpalladium azide along with CO<sub>2</sub> and TMSOMe. Then the reaction of isocyanide **1** with the π-allylpalladium azide would give the π-allylpalladium intermediate A. Elimination of N<sub>2</sub> followed by the 1,2-migration of π-allylpalladium group from the carbon to

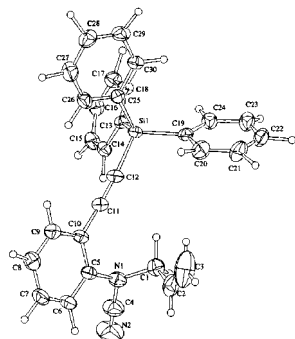
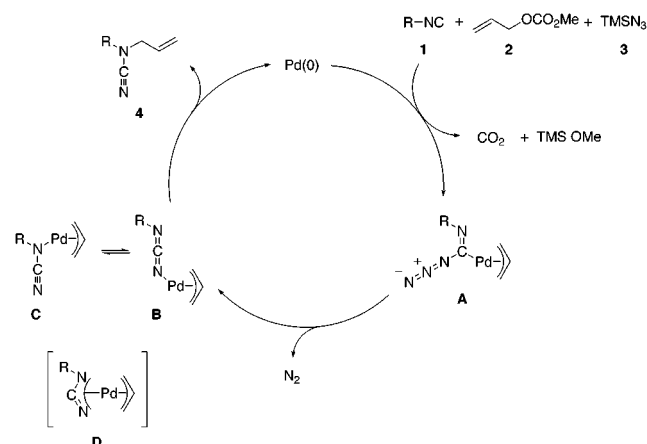


Figure 1. X-ray structure of **4n**

**Scheme 1.** Proposed Mechanism for the Formation of Allyl Cyanamides **4**

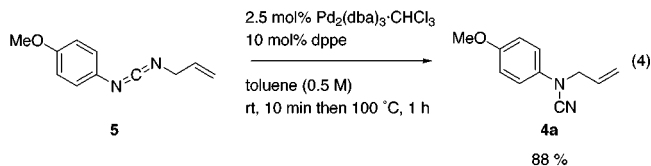


$\alpha$ -nitrogen atom in **A** would afford the palladium–carbodiimide complex **B**.<sup>7</sup> It should be noted that the conversion from **A** to **B** is a  $\pi$ -allylpalladium mimic of the Curtius rearrangement. The palladium–carbodiimide complex **B** could be in equilibrium with the palladium–cyanamide complex **C**, or more probably could be represented as a heteroatom containing bis- $\pi$ -allylpalladium analogue **D**.<sup>8</sup> Reductive elimination of Pd(0) from the palladium–cyanamide intermediate **C** gives the corresponding allyl cyana-

(6) It is difficult to separate the cyanamide **4d** and dibenzylideneacetone derived from Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>.

(7) Stoichiometric reaction of palladium–azido complexes with isocyanides, see: (a) Kim, Y.-S.; Kwak, Y.-S.; Lee, S.-W. *J. Organomet. Chem.* **2000**, *603*, 152–160. (b) Beck, W.; Burger, K.; Fehlhammer, W. P. *Chem. Ber.* **1971**, *104*, 1816–1825.

amide **4**. A key step for the proposed mechanism is the formation of  $\pi$ -allylpalladium carbodiimide complex and its isomerization to  $\pi$ -allylpalladium cyanamide complex. To obtain strong support for this interesting isomerization, we synthesized the allyl carbodiimide **5**<sup>9</sup> and examined the isomerization under the conditions similar to those of Table 1 (eq 4). As expected, the



allyl cyanamide **4a** was obtained in 88% yield.<sup>10</sup> When **5** was heated in toluene (0.5 M)/10 mol % dppe at 100 °C for 1 h, no reaction took place, and **5** was recovered.<sup>11</sup> Accordingly, it is very probable that the  $\pi$ -allylpalladium complexes **B–D** intervene in the catalytic cycle of the three-component coupling process.

We are now in a position to synthesize allyl aryl cyanamides in very high to good yields through the palladium-catalyzed three-component coupling reaction between isocyanides **1**, allyl carbonate **2**, and trimethylsilyl azide **3**. In addition, we pointed out that a  $\pi$ -allylpalladium mimic of the Curtius rearrangement intervenes in the catalytic cycle. Further studies on the synthetic application of this novel reaction and on the mechanistic detail are in progress in our laboratory.

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**Supporting Information Available:** Experimental procedures and spectroscopic and analytical data for relevant compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) It is well-known that a  $\pi$ -allylpalladium complex is formed by the oxidative addition of Pd(0) to CH<sub>2</sub>=CHCH<sub>2</sub>Y (Y: halide, OCO<sub>2</sub>R, OAc, OP(O)(OR)<sub>2</sub>, NR<sub>2</sub>, 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.

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