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# Palladium-catalyzed bisfunctionalization of active alkenes by β-acetonitrile-α-allyl addition: application to the synthesis of unsymmetric 1,4-di(organo)fullerene derivatives

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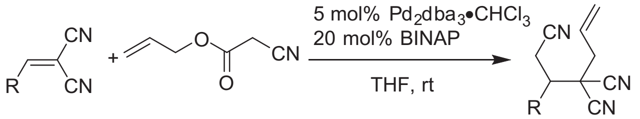
ABSTRACT

A new, efficient palladium-catalyzed bisfunctionalization of ethylidene malononitriles by addition of acetonitrile and allyl groups is developed for the construction of all-carbon quaternary and tertiary centers simultaneously. This methodology is successfully applied to the synthesis of unsymmetric 1,4-disubstituted $C_{60}$.

Palladium-catalyzed β-nucleophilic-α-allyl addition of active olefins through π-allyl-palladium intermediates has emerged as a mild and efficient multiple bond-forming method for the simultaneous construction of all-carbon quaternary and tertiary centers,[1,2] which are important structural units in a wide range of bioactive substances and natural products.[3] Over the past decade, we and other groups have been interested in developing new palladium-catalyzed β-nucleophilic-α-allyl addition reactions toward active alkenes through various π-allyl palladium intermediates, including heteroatom- and carbon-nucleophile addition/allylation,[2e–k] bis-allylation,[2a–d] acetonation/allylation,[2l,m] amidoallylation,[2n] and iminoallylation (Fig. 1).[2o] The palladium-catalyzed decarboxylative reaction for the formation of π-allyl palladium species is an environmentally friendly and economical process[1c,4,5]; the reaction proceeds under essentially neutral conditions with high atom economy. Based on this concept, we envisioned that the bis-π-allylpalladium[2a] analogue acetonitrile-(π-allyl)palladium complex should be formed by the reaction of cyanoacetic acid allyl ester with a palladium catalyst, which will undergo acetonitrile/allyl addition to the active alkenes (Fig. 1). Furthermore, in continuation of our interest in transition metal catalyzed functionalization of [60]fullerene ($C_{60}$),[6] we reasoned that if successful, this methodology would be applicable to the selective bisfunctionalization of $C_{60}$ because of its electrophilic nature and specialized alkene component. Transition metal catalyzed functionalization of $C_{60}$ has emerged as a promising method for preparing functionalized $C_{60}$ derivatives with high selectivity and high functional group compatibility under mild reaction conditions.[7] However, investigations on the synthesis of unsymmetric 1,4-di(organo)fullerenes have been seldom studied,[8] in particular, a one-step catalytic method has not been reported.

Herein, we report a new Pd-catalyzed bisfunctionalization of various malononitriles **1** with cyanoacetic acid allyl ester (**2**), that affords the β-acetonitrile-α-allyl addition products **3** in good to high yields (Eq. 1). Moreover, we have successfully applied this method to the synthesis of unsymmetric 1-acetonitrile-4-allyl-[60]fullerene **4a** in good yield in one step.



**1** **2** **3**

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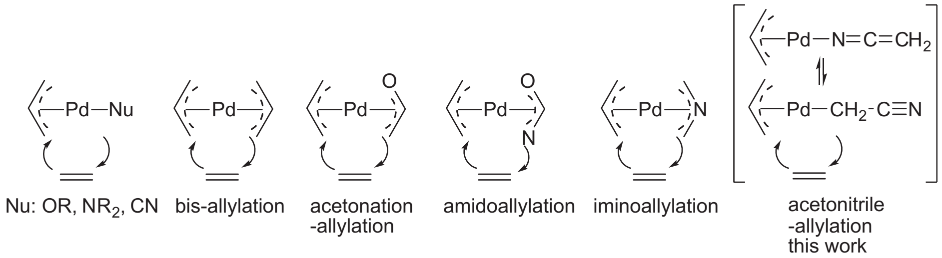
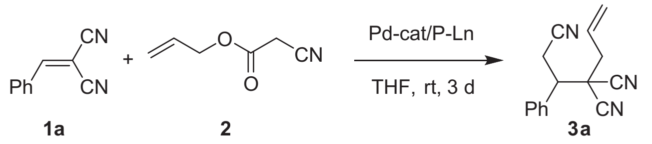


**Figure 1.** Bisfunctionalization of active alkenes with various π-allylpalladium species.

Initially, according to our previous results,[1b] we focused on screening transition metal catalysts and ligands for the efficient formation of bisfunctionalized product **3a** via the reaction of malononitrile **1a** and cyanoacetic acid allyl ester (**2a**) under an Ar atmosphere at room temperature in THF as the solvent (Table 1). The use of the typical catalyst, $Pd(PPh_3)_4$ (10 mol %), afforded the corresponding product **3a** in 40% isolated yield (entry 1). The use of $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %) combined with $PPh_3$ (40 mol %) ligand gave a slightly increased yield, although without the phosphine ligand, the reaction did not proceed at all (entries 2 and 3). These results indicated that the use of a phosphine ligand was crucial, and implied that a change of phosphine ligand species would increase the efficiency of the present transformation. We investigated various phosphine ligands using $Pd_2(dba)_3{\cdot}CHCl_3$ as the catalyst (5 mol %). The electronic characteristics of monodentate triarylphosphine ligands (40 mol %), such as $PPh_2(2\text{-MeO-}C_6H_4)$ (63%), $PPh_2(4\text{-F-}C_6H_4)$ (47%), and $P(4\text{-F-}C_6H_4)_3$ (50%) did not exhibit any obvious influence on the catalytic activity (entries 4–6). The use of the triheteroarylphosphine ligand, $P(2\text{-furyl})_3$ gave only a trace amount of **3a** (entry 7). The bulky monodentate trialkylphosphine ligand $P(t\text{-Bu})_3$ showed lower reactivity compared to that of triarylphosphine ligands (entry 8). Bidentate phosphine ligands, such as dppf, dppe, and dppp showed comparable catalytic activity (entries 9–11), and finally racemic BINAP gave **3a** in 79% isolated yield (entry 12). It is noted that the use of a 1:1 Pd-BINAP ratio decreased the yield of **3a**.[5]

**Table 1**
Screening of the reaction conditions for the formation of **3a**[a]



| Entry | Pd-catalyst/P-ligand (10/40 mol %) | Yield[b] (%) |
|---|---|---|
| 1 | $Pd(PPh_3)_4$ | 45 (40) |
| 2 | $Pd_2(dba)_3{\cdot}CHCl_3$ | 0 |
| 3 | $Pd_2(dba)_3{\cdot}CHCl_3/PPh_3$ | 50 |
| 4 | $Pd_2(dba)_3{\cdot}CHCl_3/PPh_2(2\text{-MeO-}C_6H_4)$ | 63 |
| 5 | $Pd_2(dba)_3{\cdot}CHCl_3/PPh_2(4\text{-F-}C_6H_4)$ | 47 |
| 6 | $Pd_2(dba)_3{\cdot}CHCl_3/P(4\text{-F-}C_6H_4)_3$ | 50 |
| 7 | $Pd_2(dba)_3{\cdot}CHCl_3/P(2\text{-furyl})_3$ | Trace |
| 8 | $Pd_2(dba)_3{\cdot}CHCl_3/P(t\text{-Bu})_3$ | 36 |
| 9 | $Pd_2(dba)_3{\cdot}CHCl_3$/dppf | 57 |
| 10 | $Pd_2(dba)_3{\cdot}CHCl_3$/dppe | 58 |
| 11 | $Pd_2(dba)_3{\cdot}CHCl_3$/dppp | 78 |
| 12 | $Pd_2(dba)_3{\cdot}CHCl_3$/BINAP | 84 (79) |

dba = *trans*, *trans*-dibenzylideneacetone, *t*-Bu = *tert*-butyl, dppf = bis(diphenylphosphino)ferrocene, dppe = bis(diphenylphosphino)ethane, dppp = bis(diphenylphosphino)propane, BINAP = (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl).

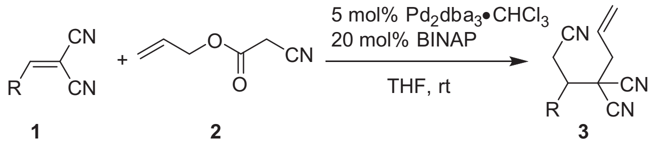
[a] To a mixture of palladium catalyst (10 mol %), phosphine ligand (40 mol %) and phenylethylidene malononitrile (**1a**) (0.2 mmol) in THF (0.2 M) was added cyanoacetic acid allyl ester (**2**) (0.24 mmol). The mixture was stirred at room temperature for 3 days.

[b] $^1H$ NMR yields determined by using dichloroethane as an internal standard. Isolated yields are shown in parentheses.

Various ethylidene malononitriles were examined under the optimized reaction conditions: 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 20 mol % BINAP, cyanoacetic acid allyl ester (**2**) (1.2 equiv), and THF (0.2 M) at room temperature (Table 2). The reactions of **1b–d**, substituted with an electron-donating group on the benzene ring at *meta* or *para* positions, gave the corresponding products in good to high yields (entries 1–3). In contrast, the use of phenylethylidene malononitrile **1e** having an electron-withdrawing group (–Cl) on the benzene ring decreased the yield of **3e** dramatically even after longer reaction times (6 days) (entry 4). The electronic characteristics of the aromatic ring of **1** exert a significant influence on the yields of products **3**. Not only naphthyl-substituted alkene **1f**, but also the heteroaromatic 2-thienyl (**1g**) substituted alkene afforded the corresponding β-acetonitrile-α-allyl addition products **3f** and **3g** in high yields (entries 5 and 6). The reaction with ethylidene malononitriles bearing an alkyl group at R, such as cyclopropyl (**1h**) or *n*-octyl (**1i**), occurred smoothly, giving the corresponding products **3h** and **3i** in 75% and 74% yields, respectively (entries 7 and 8). Ethylidene malononitriles bearing a bulky cyclohexyl (**1j**) or *t*-butyl (**1k**) group at R showed a lower reactivity, giving the corresponding addition products **3j** and **3k** in 64% and 40% yields, respectively (entries 9 and 10). It should be noted that in the case of lower yields of **3** (entries 4, 9, and 10), the major side-product was the decarboxylative self-coupling product 2-allylpent-4-enenitrile.[4c]

A plausible reaction mechanism is shown in Scheme 1. Initially, the reaction of cyanoacetic acid allyl ester (**2**) with the Pd(0) catalyst

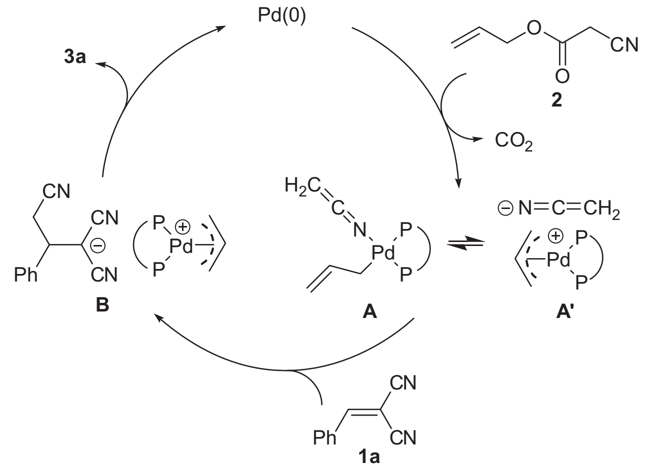
**Table 2**
Nucleophilic addition of various activated alkenes[a]



| Entry | R | 1 | Time (d) | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $3\text{-Me-}C_6H_4$ | **1b** | 3.5 | **3b** | 72 |
| 2 | $4\text{-Me-}C_6H_4$ | **1c** | 3.5 | **3c** | 76 |
| 3 | $3\text{-MeO-}C_6H_4$ | **1d** | 4 | **3d** | 68 |
| 4 | $4\text{-Cl-}C_6H_4$ | **1e** | 6 | **3e** | 35 |
| 5 | 2-Naphthyl | **1f** | 3 | **3f** | 83 |
| 6 | 2-Thienyl | **1g** | 4.5 | **3g** | 70 |
| 7 | Cyclopropyl | **1h** | 4.5 | **3h** | 75 |
| 8 | *n*-Octyl | **1i** | 3 | **3i** | 74 |
| 9 | Cyclohexyl | **1j** | 4.5 | **3j** | 64 |
| 10 | *t*-Butyl | **1k** | 6 | **3k** | 40 |

[a] To a THF (0.2 M) solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %) and BINAP (20 mol %) were added ethylidene malononitrile **1** (0.2 mmol) and cyanoacetic acid allyl ester (**2**) (0.24 mmol). The mixture was stirred at room temperature under Ar for the time shown in the table.

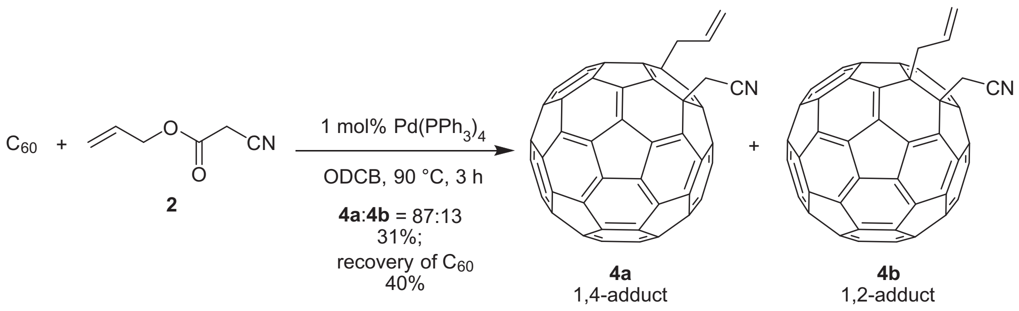
[b] Isolated yield.



**Scheme 1.** A plausible reaction mechanism.

forms π-allylpalladium complex **A′**, which should be in equilibrium with σ-allylpalladium complex **A**, along with the exclusion of $CO_2$ gas. The β-nucleophilic addition of acetonitrile to ethylidene malononitrile **1a** gives the ion-paired (π-allyl)palladium intermediate **B**. Reductive elimination of **B** produces the β-acetonitrile-α-allyl adduct **3a**.

Next, the present methodology was successfully applied to the regioselective synthesis of a 1,4-di(organo)fullerene which has attracted much attention as potentially useful n-type materials in organic photovoltaic applications.[9] Unfortunately, the reaction of $C_{60}$ with cyanoacetic acid allyl ester (**2**) in the presence of the $Pd_2(dba)_3 \cdot CHCl_3$/BINAP catalyst system in *ortho*-dichlorobenzene (ODCB) afforded only a trace amount of the corresponding products **4a** and **4b**, and $C_{60}$ was recovered mainly. After a brief optimization of the palladium catalyst, we found that the reaction proceeded smoothly in the presence of $Pd(PPh_3)_4$ (1 mol %) to give an 87:13 mixture of the 1,4-disubstituted product **4a** and 1,2-disubstituted product **4b** in 31% yield along with the recovery of $C_{60}$ in 40% yield (**4a** was obtained as the major product) (Eq. 2). It should be noted that in contrast to the present acetonitrile/allylation, our previously reported acetonation/allylation method[2l] was not applicable for the functionalization of $C_{60}$: Under similar conditions to Eq. 2, the reaction of $C_{60}$ with allyl acetoacetate gave a mixture of multi-adducts and a small amount of recovered $C_{60}$.



In conclusion, we have developed a novel palladium-catalyzed β-acetonitrile-α-allyl addition reaction of active alkenes with cyanoacetic acid allyl ester. This method has provided a new approach for the construction of an all-carbon quarternary carbon adjacent to a tertiary carbon. The present methodology was successfully applied to the unsymmetric bisfunctionalization of $C_{60}$ through the selective 1,4-addition of two different organic functional groups in one step. Further extension of this method to the synthesis of various functionalized fullerenes and application to photovoltaic cells are in progress.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.075.

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