# The Nitrile Functionality as a Directing Group in the Palladium-Catalysed Addition of Aryl Boronic Acids to Alkynes

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**Abstract:** The nitrile group is shown to direct the palladium-catalysed hydroarylation of internal alkynes bearing a pendant nitrile with boronic acids.

**Keywords:** Palladium, catalysis, nitrile, directing-group, hydroarylation.

The nitrile group is a useful functional group because of its ease of installation, its inertness to many nucleophiles at low temperature, and its ready transformation into other functionalities such as a primary amine and a carboxylic acid. The nitrile group is very small and linear with a bond length of 1.14 Å and it is well known for its ability to coordinate to metals [1]. Surprisingly, there is only one report in the chemistry literature of a metal-catalysed process that is directed by this interaction – the ruthenium-catalysed *ortho*-olefination of aromatic nitriles [2]. Examples of the use of nitriles as directing groups in non-catalysed reactions are also few but this phenomenon has been proposed in an intramolecular thermal [6+4] cycloaddition [3], Lewis acid mediated intramolecular Diels-Alder cycloadditions [4], a thermal Diels-Alder cycloaddition [5], an 8π-electro-cyclisation [6] and the oxymercuration of cyclohex-3-enecarbonitrile [7].

As part of our research programme, we were interested in developing transition-metal catalysed cycloaddition and cycloisomerisation reactions of alkynyl nitrile substrates. Unfortunately, the nitrile group proved to be remarkably stable to most of the conditions investigated. However, we came across an interesting effect whereby the pendant nitrile group can be seen to direct the palladium-catalysed addition of aryl boronic acids to alkynes.

The transition-metal catalysed cross-coupling reaction of organoboron derivatives with organic halides has been the subject of considerable research over many years [8]. The transition-metal catalysed addition of heteroatom-hydrogen bonds to alkynes, including hydroboration, has also been widely studied [9] while the transition-metal catalysed hydroarylation of alkynes though direct functionalisation of carbon-hydrogen bonds has gained interest in recent years [10]. In contrast, little attention has been devoted to the transition-metal catalysed addition of boronic acids to alkynes [11].

The rhodium-catalysed addition of arylboronic acids to alkynes was reported in 2001 by Hayashi [12] and they extended this to the arylative cyclisation of alkyne tethered alkenes and aldehydes [13]. In 2003, Oh and co-workers published their work on the palladium-catalysed addition of arylboronic acids and alkenylboronic acids to alkynes in the presence of acetic acid [14]. Zeng and Hua reported the hydrophenylation of alkynes under conditions similar to those of Oh but with sodium tetraphenylborate instead of boronic acids [15]. These reactions suffer from low regioselectivity when unsymmetrical alkynes are used, unless one of the substituents is an ester or phosphonate group for the rhodium chemistry, or a hydrogen atom for the palladium chemistry. A further report from Oh described their efforts to improve the regioselectivity of their process with alcohol directing groups; however they found that regioselectivity was hugely dependent on the alkyne substituents at both ends of the alkyne [16]. Cheng and co-workers recently reported the cobalt(II)-catalysed hydroarylation of alkynes with organoboronic acids [17].

We discovered that the hydroarylation of prop-1-ynylbenzene (**1a**) with phenylboronic acid occurred with palladium acetate, triphenylphosphine and two equivalents of potassium carbonate in refluxing dioxane to afford a 1:1.5 mixture of regioisomeric alkene products (**2a** and **3a**) (Table **1**, entry 1). The major product was that with the two phenyl groups *trans* to each other. Under the same conditions, 3-phenylprop-2-yn-1-ol (**1b**) preferentially formed the other regioisomer in a 4:1 ratio (entry 2). This result suggests a directing effect akin to that reported by Oh *et al*. Unsurprisingly, converting the alcohol into a benzyl ether and repeating the reaction led to lower regioselectivity being observed (entry 3). The presence of a pendant ester group was expected to lead to higher regioselectivity, but this was not the case and a 2:1 mixture was obtained (entry 4). However, the presence of a pendant nitrile group led to an increase in regioselectivity (3:1) and chemical yield (entry 5) [18]. Clearly, the nitrile substituent has a positive effect on the selectivity observed in this reaction.

The differences in regioselectivity for the but-2-yne-1-ol derivatives were investigated next (Scheme **1**). With an ester substituent a moderate yield of a 3:1 mixture of regioisomeric products (**5a** and **6a**) was obtained, whereas with the nitrile substrate (**4b**) the selectivity was increased to 4:1 and the yield was almost doubled to 77%.

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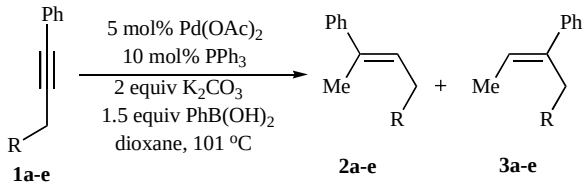
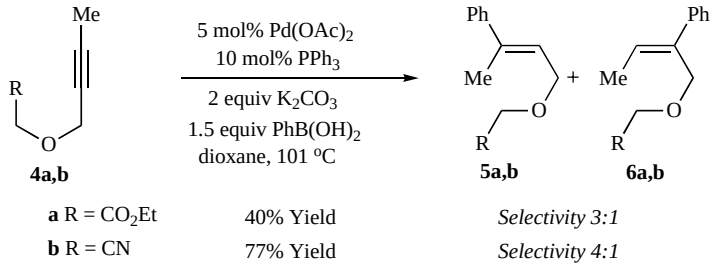
**Table 1. Differences in Regioselectivity Caused by Alkyne Substituents**

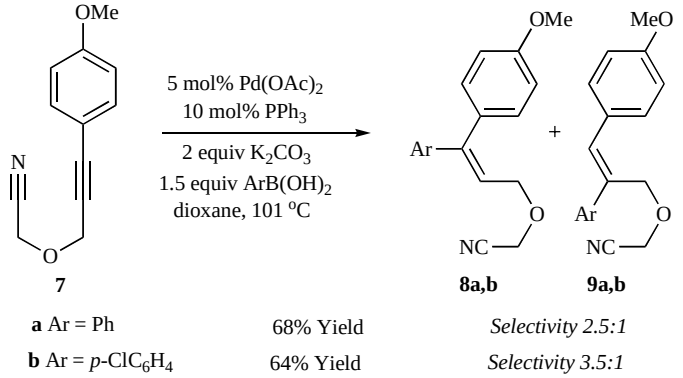



| Entry | Substrate | R | Product | Yield/%[a] | Selectivity 2 : 3[b] |
|---|---|---|---|---|---|
| 1 | **1a** | H | **2a + 3a** | 54 | 1:1.5 |
| 2 | **1b** | OH | **2b + 3b** | 50 | 4:1 |
| 3 | **1c** | OBn | **2c + 3c** | 59 | 2:1 |
| 4 | **1d** | $OCH_2CO_2Et$ | **2d + 3d** | 45 | 2:1 |
| 5 | **1e** | $OCH_2CN$ | **2e + 3e** | 72 | 3:1 |

[a]Yield of isolated product. [b]Determined by $^1$H NMR analysis.




**Scheme 1.** Directing effects of ester and nitrile groups.




**Scheme 2.** Electronic effects on selectivity.

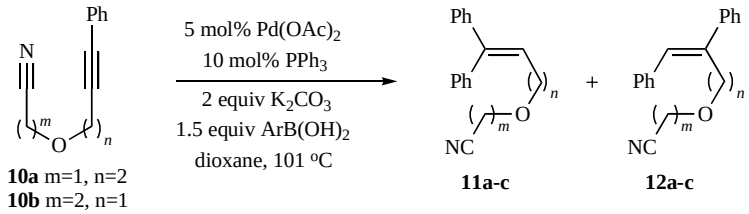
The electronic effects of the aryl substituents on the reaction outcome, if any, were investigated in turn (Scheme **2**). Accordingly, the *p*-methoxyphenyl alkynyl nitrile (**7**) was synthesised and under the reaction conditions a diminished regioselectivity of 2.5:1 (**8a** and **9a**) was observed with phenyl boronic acid, compared with 3:1 for the parent phenyl alkynyl nitrile (**1e**). However, with *p*-chlorophenylboronic acid a superior 3.5:1 ratio of (**8b** and **9b**) was obtained. These results indicate that the electronics of the substrate and the boronic acid both play roles in determining the regioselectivity of the reaction.

Increasing the tether length by a methylene unit between the alkyne and the ether or between the nitrile and the ether led to a drop in regioselectivity from 3:1 to 2.5:1 in each case (Table **1**, entry 5 *versus* Table **2**, entries 1 and 2), but again *p*-chlorophenyl boronic acid resulted in higher selectivity being observed (Table **2**, entry 3).

The mechanism of this transformation is not fully understood, however, the nitrile is envisaged to coordinate to the palladium centre during the addition of the aryl group to the alkyne Fig. (**1**). Oh *et al.* reported acidic conditions for their hydroarylation reaction [14] whereas here we describe a basic reaction medium. It is reasonable to assume that these processes proceed by different mechanisms.

In conclusion, the presence of a pendant nitrile group has been shown to improve the regioselectivity of the palladium-catalysed addition of arylboronic acids to alkynes. This is a

**Table 2. Effects of Tether Length on Regioselectivity**




**10a** m=1, n=2
**10b** m=2, n=1

**11a-c** **12a-c**

| Entry | Substrate | Ar | Product | Yield/%[a] | Selectivity 11: 12[b] |
|---|---|---|---|---|---|
| 1 | 10a | Ph | 11a + 12a | 73 | 2.5:1 |
| 2 | 10b | Ph | 11b + 12b | 72 | 2.5:1 |
| 3 | 10b | *p*-$ClC_6H_4$ | 11c + 12c | 75 | 3:1 |

[a]Yield of isolated product. [b]Determined by $^1$H NMR analysis.

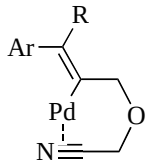



**Fig. (1).** Proposed coordination of the nitrile to the palladium centre.

little investigated phenomenon in organic synthesis and hopefully this report will inspire further studies.

## ACKNOWLEDGEMENTS

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[18] Representative procedure for the addition of phenylboronic acid to 2-(3-phenylprop-2-ynyloxy)acetonitrile 1e: A flask was charged with 2-(3-phenylprop-2-ynyloxy)acetonitrile 1e (50 mg, 0.29

mmol, 1 equiv), phenylboronic acid (53 mg, 0.44 mmol, 1.5 equiv), potassium carbonate (80 mg, 0.58 mmol, 2 equiv), palladium acetate (3.3 mg, 0.15 mmol, 0.05 equiv) and triphenylphosphine (7.6 mg, 0.029 mmol, 0.1 equiv). A reflux condenser was fitted to the flask and a nitrogen atmosphere was introduced. Dry 1,4-dioxane ( 1 mL) was added and the reaction mixture was heated at 100 $^{o}$C. After 15 hours the volatiles were removed under reduced pressure and the residue was purified by flash chromatography (9:1 petroleum ether 40-60/ethyl acetate). An inseparable 3:1 mixture of 2-(3,3-diphenylallyloxy)acetonitrile **2e** and (*E*)-2-(2,3-diphenyl-allyloxy)acetonitrile **3e** was isolated as a yellow solid (52 mg, 72%). **2e** $^{1}$H NMR (400 MHz, $CDCl_3$): δ 4.19 (2H, d, *J* = 7.0 Hz), 4.21 (2H, s), 6.18 (1H, t, *J* = 7.0 Hz), 7.12-7.44 (10H, m). **2e** $^{13}$C NMR (100 MHz, $CDCl_3$): δ 54.6, 68.5, 115.4, 121.8, 127.0, 127.3, 127.4, 127.6, 127.7, 129.0, 137.8, 140.6, 146.6. **3e** $^{1}$H NMR (400 MHz, $CDCl_3$): δ 4.26 (2H, s), 4.65 (2H, s), 7.12-7.44 (10H, m), 7.57 (1H, d, *J* = 7.9 Hz). **3e** $^{13}$C NMR (100 MHz, $CDCl_3$): δ 54.8, 68.3, 125.6, 127.2 (2C), 127.9, 128.0 (2C), 128.2, 129.0, 135.2, 135.8, 139.7. IR (neat): 1088 (m), 1456 (w), 2858 (w), 2921 (w) $cm^{-1}$. HRMS: m/z calc'd for $C_{17}H_{15}NNaO$ 272.1046, found 272.1046.