Intramolecular nucleophilic addition of an organorhodium(I) to a nitrile†

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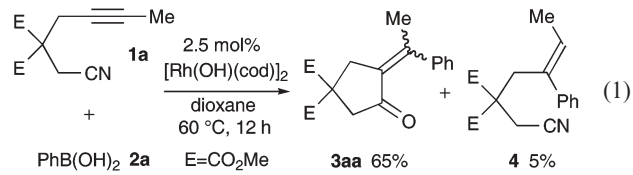
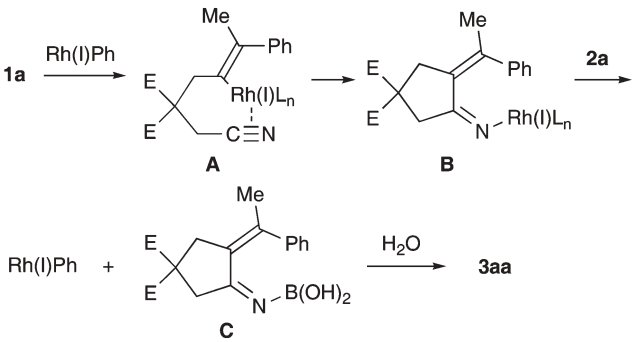
Nucleophilic addition of an organorhodium(I) to a cyano group has been observed for the first time in the rhodium-catalysed reaction of cyano-substituted alkynes with arylboronic acids. The higher reactivity of a cyano group relative to an alkoxycarbonyl group toward an organorhodium(I) species is demonstrated by an intramolecular example.

The nucleophilic addition of main group organometallics such as organolithium and organomagnesium compounds to carbon–heteroatom multiple bonds provides a facile method for forming carbon–carbon bonds. On the other hand, the organometallic compounds of late transition metals are typically less polar, and hence less nucleophilic than other organometallics. Therefore, their synthetic potential as nucleophiles toward polar electrophilic multiple bonds[1] have been overshadowed compared to their addition to non-polar carbon–carbon multiple bonds.[2] Recently, it has been reported that organorhodium(I) species undergo nucleophilic addition to aldehydes,[3] ketones,[4] esters,[3i,5] acid anhydrides[6] and imines.[7] For example, the rhodium-catalysed reaction of 4-cyanobenzaldehyde with phenylboronic acid produces the corresponding secondary alcohol, in which the cyano group remains intact.[3a] This result suggests that a cyano group is significantly less reactive than an aldehydic carbonyl group. In fact, there have been no reports of the addition of organorhodium(I) species to nitriles, although this reaction has been documented for organopalladium nucleophiles.[8] Our previous studies on the rhodium(I)-catalysed intramolecular acylation of esters[5] inspired us to examine the equivalent reactions with nitriles. In this communication we report a new cyclisation reaction of cyano-substituted alkynes—the first examples of a nucleophilic addition of an organorhodium(I) species to a cyano group.

When alkynyl nitrile **1a** was treated with phenylboronic acid (**2a**, 3.0 equiv.) in the presence of $[Rh(OH)(cod)]_2$ (0.05 equiv. of Rh) (cod = cycloocta-1,5-diene) in 1,4-dioxane at 60 °C under a nitrogen atmosphere for 12 h, arylative cyclisation product **3aa** was obtained in 65% yield as a mixture of *E* and *Z* isomers (36 : 64) together with the 1,2-addition product **4** (5% yield) (eqn. 1). The proposed reaction pathway is depicted in Scheme 1. Initially, a phenylrhodium(I) species is generated by the transmetalation of hydroxorhodium(I) with phenylboronic acid (**2a**). This undergoes *cis*-1,2-addition onto the alkyne giving the alkenylrhodium(I) intermediate **A**. The minor product **4** was formed by 1,2-addition of the phenylrhodium(I) species with the opposite regiochemistry



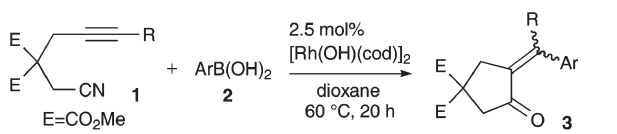
(1)



Scheme 1

and its subsequent hydrolysis. From **A**, intramolecular nucleophilic addition to the nitrile occurs in a 5-*exo*-dig mode to obtain the corresponding *N*-rhodium imine **B**. Subsequent transmetalation with **2a** produces *N*-boron imine **C**, along with regeneration of a phenylrhodium(I) species. The *N*-boron imine **C** is a good conjugate acceptor and therefore undergoes geometrical isomerisation of the *exo*-olefin moiety through a 1,4-addition/elimination process.[9] Finally, hydrolysis produces the ketone **3aa** and ammonia.

Table 1 Rhodium-catalysed arylative cyclisation of alkynyl nitriles **1**



Entry	**1** substrate	**2** Ar	**3** product	Yield (%) (*E* : *Z*)
1	**1a** R = Me	**2b** 4-NO_2-C_6H_4	**3ab**	77 (45 : 55)
2	**1a**	**2c** 3-Cl-C_6H_4	**3ac**	63 (52 : 48)
3	**1a**	**2d** 3-MeO-C_6H_4	**3ad**	51 (45 : 55)
4	**1a**	**2e** 1-naphthyl	**3ae**	53 (55 : 45)
5	**1b** R = Et	**2a** Ph	**3ba**	44 (1 : 99)

† Electronic Supplementary Information (ESI) available: Experimental details and selected spectral data for the new compounds. See http://www.rsc.org/suppdata/cc/b5/b503686k/

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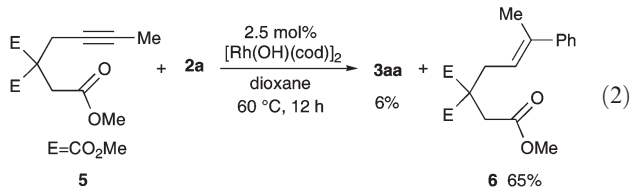
The results obtained with other arylboronic acids **2** and alkynyl nitriles **1** are summarised in Table 1.‡ The corresponding alkylidenecyclopentanones **3ab–3ba** were obtained in yields ranging from 44–77%. A small amount of 1,2-addition product **4** (~3–5%) was obtained in the cases of entries 1 and 3.

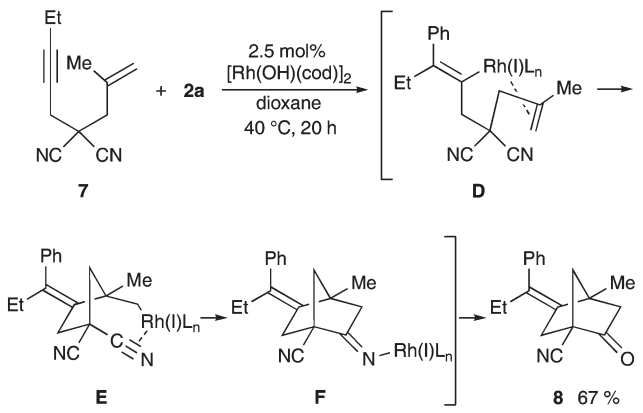
Next, the reactivity of the cyano group of a type **1** compound was compared to that of the alkoxycarbonyl group of substrate **5**, possessing an analogous structure. When alkynyl ester **5** was subjected to reaction conditions identical to those used for **1a**, the cyclisation product **3aa** was obtained in only 6% yield. The major product **6**, isolated in 65% yield, resulted from protonation of the intermediate alkenylrhodium(I) species (eqn. 2). This demonstrates that the cyano group of **1a** is more reactive toward the alkenylrhodium(I) intermediate than the methoxycarbonyl group of **5**, even when the carbonyl is positioned precisely for undergoing nucleophilic attack.[10] It is noteworthy that the reactivity order of the cyano and alkoxycarbonyl groups observed in these intramolecular reactions is opposite of that for organolithium[11] and organomagnesium[12] reagents.



(2)

As reported previously,[3i,5] the rhodium(I)-catalysed reaction of arylboronic acids with 1,6-enynes, whose alkene and alkyne moieties were tethered through a methyl malonate group, produced a bicyclic product *via* 1,2-addition, 5-*exo*-trig cyclisation and acylation with the methoxycarbonyl group. This result prompted us to examine the reaction of 1,6-enyne, **7**, tethered through a malononitrile group. Compound **7** underwent an analogous domino cyclisation reaction to afford the bicyclic product **8** in 67% yield through intramolecular nucleophilic addition of the alkylrhodium(I) intermediate **E** onto the nitrile (Scheme 2).

In summary, new cyclisation reactions forming cyclic ketones were developed in which an intermediate alkenyl or alkylrhodium(I) species underwent intramolecular, nucleophilic addition to a nitrile. The higher reactivity of the cyano group relative to the alkoxycarbonyl group toward organorhodium(I) species has been demonstrated by an intramolecular example.[13]



Scheme 2

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Notes and references

‡ To an oven dried, N_2-purged flask were added a solution of substrate **1** (0.2 mmol, 1.0 equiv.) in 1,4-dioxane (2.0 mL), arylboronic acid **2** (0.6 mmol, 3.0 equiv.) and $[Rh(OH)(cod)]_2$ (2.28 mg, 0.5 μmol, 0.05 equiv. of Rh). The reaction mixture was stirred at 60 °C. After complete consumption of the substrate and imine intermediate, monitored by GC, water was added. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by preparative thin-layer chromatography (hexane : ethyl acetate) to give the product **3**.

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