Synthesis of α-keto esters by the rhodium-catalysed reaction of cyanoformate with arylboronic acids†

Hiroshi Shimizu and Masahiro Murakami*

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An arylrhodium(I) species selectively reacts with the cyano group of ethyl cyanoformate to afford the corresponding α-keto ester in good yield.

The rhodium-catalysed reaction of organoboron species with unsaturated organic compounds has emerged as a powerful method for carbon–carbon bond formation.[1] The reaction generally proceeds by transmetallation to generate an intermediate organorhodium species, which then undergoes 1,2-addition to alkynes,[2] alkenes,[3] aldehydes,[4] imines,[5] esters,[6] acid anhydrides,[7] 1,2-dicarbonyl compounds[6,8] and nitriles[5h,9] in an intermolecular fashion. We have developed cascade reactions, in which an organorhodium intermediate adds intramolecularly to a cyano group,[10] and found that, in some cases, the organorhodium species exhibits a higher propensity to react with a cyano group than with an ester group. Ethyl cyanoformate is an interesting electrophilic substrate for comparing the reactivities of its cyano and ester groups toward nucleophiles (Fig. 1). Since both functionalities are electron-withdrawing, their electrophilic reactivities are enhanced relative to isolated ester and nitrile groups. Nucleophiles, such as organomagnesium[11] and organolithium[12] compounds, lithium enolates,[13] lithiated amides,[14] alcohols[15] and amines,[16] selectively attack the ester carbonyl group of ethyl cyanoformate, with the cyano group acting as a leaving group to afford the corresponding ethoxycarbonylated products. On the other hand, selective addition to the cyano group proceeds when ethyl cyanoformate is reacted under acidic conditions with softer nucleophilic species, such as active methylene compounds,[17] electron-rich benzenes[18] and organocadmium compounds.[19] Our previous studies on rhodium-catalysed cascade reactions[10] led us to examine the reaction of ethyl cyanoformate with phenylboronic acid in the presence of a rhodium catalyst in order to determine which functionality is more vulnerable to intermolecular attack by a phenylrhodium species. Thus, a mixture of ethyl cyanoformate (**1**), phenylboronic acid (**2a**, 1.2 equiv.) and $[Rh(OH)(cod)]_2$ (2.5 mol%, 5% of Rh) in dioxane was heated at 80 °C for 3 h. Aqueous work-up, followed by chromatographic isolation, afforded ethyl benzoylformate (**3a**) in 37% yield (Table 1, entry 1). No ethyl benzoate was detected in the ^{1}H NMR spectrum of the crude reaction mixture. The selective formation of **3a** suggests that the phenylrhodium intermediate generated by transmetallation undergoes 1,2-addition to the cyano group in preference to the ester group. Addition of boric acid (H_3BO_3, 1.0 equiv.) improved the yield to 62% yield (Table 1, entry 2). The best yield, of 83%, was obtained in a reaction at 60 °C using 1.2 equiv. of phenylboronic acid (**2a**) and 2.0 equiv. of boric acid (Table 1, entry 4).

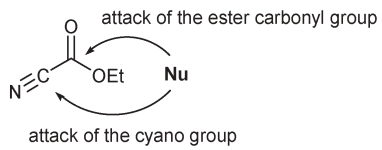
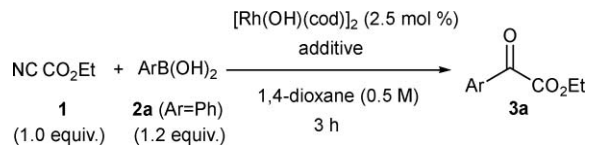


Fig. 1 Ambivalent electrophilicity of cyanoformate.

The results obtained with other arylboronic acids are summarized in Table 2.‡ The corresponding α-keto esters were produced in yields ranging from 46 to 87%. Good yields were obtained with arylboronic acids having a methoxy substituent at either the *ortho*, *meta* or *para* positions of the phenyl ring (Table 2, entries 2–4). Although *ortho*-tolylboronic acid was a suitable substrate (Table 2, entry 9), *ortho*-biphenylboronic acid gave only a moderate yield (Table 2, entry 10). Electron-withdrawing groups at *ortho* and *para* positions decreased the yield (Table 2, entries 8 and 11). Of note is that a formyl group remained intact under the reaction conditions (Table 2, entry 12). Formation of considerable quantities of arenes by protonolysis of arylboronic acids was observed in cases where the desired products **3** were obtained in moderate yield (Table 2, entries 10–12).

The mechanism depicted in Scheme 1 is assumed for the formation of **3**. Arylrhodium(I) **4** is generated by transmetallation, and then undergoes selective 1,2-addition to the cyano group. The resultant iminorhodium(I) species, **5**, is protonated with boric acid (or **2**) to afford imine **6** and rhodium(I) boronate (**7**), which is then transmetalated with arylboronic acid **2** to regenerate

Table 1 The effect of boric acid as an additive



1 (1.0 equiv.) **2a** (Ar=Ph) (1.2 equiv.) **3a**

Entry	Additive	Temperature/°C	Yield (%)[a]
1	—	80	37
2	H_3BO_3 (1.0 equiv.)	80	62
3	H_3BO_3 (2.0 equiv.)	80	78
4	H_3BO_3 (2.0 equiv.)	60	83
5	H_3BO_3 (2.0 equiv.)	40	53

[a] Isolated yields.

Department of Synthetic Chemistry and Biological Chemistry, Kyoto University, Katsura, Kyoto 615-8510, Japan.
E-mail: murakami@sbchem.kyoto-u.ac.jp; Fax: +81 75 383 2748; Tel: +81 75 383 2747

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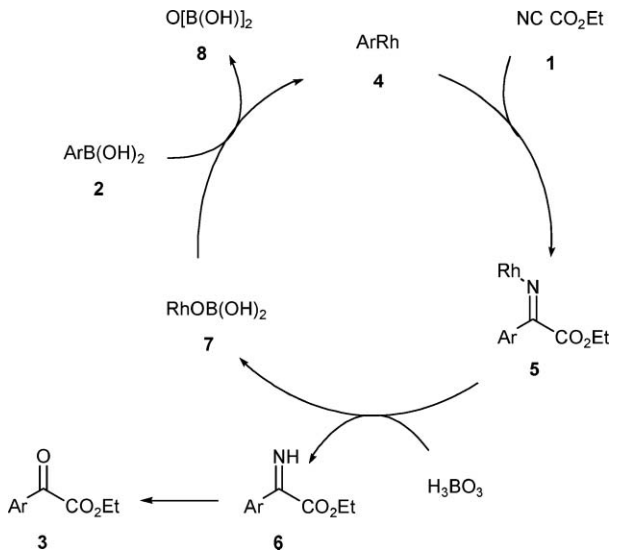
Table 2 Reaction of ethyl cyanoformate (**1**) with arylboronic acids **2**

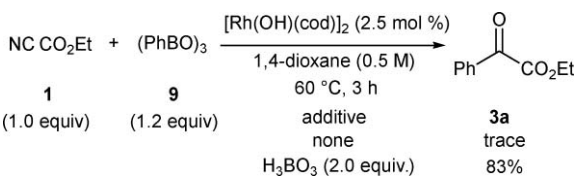
Entry	2	Ar	Product 3	Yield (%)[a]
1	**2a**	Ph	**3a**	83
2	**2b**	4-MeO–C_6H_4	**3b**	80
3	**2c**	3-MeO–C_6H_4	**3c**	74
4	**2d**	2-MeO–C_6H_4	**3d**	87
5	**2e**	4-Br–C_6H_4	**3e**	82
6	**2f**	4-F–C_6H_4	**3f**	73
7	**2g**	3-Cl–C_6H_4	**3g**	81
8	**2h**	2-Cl–C_6H_4	**3h**	46
9	**2i**	2-Me–C_6H_4	**3i**	83
10	**2j**	2-Ph–C_6H_4	**3j**	50
11	**2k**	4-MeO_2C–C_6H_4	**3k**	58
12	**2l**	3-CHO–C_6H_4	**3l**	50

[a] Isolated yields.



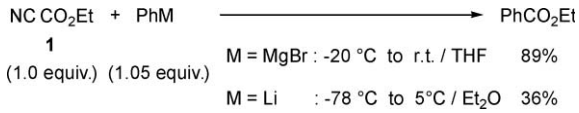
Scheme 1 Proposed mechanism for the formation of **3** from **1** and **2**.

arylrhodium(I) **4**. α-Keto ester **3** is formed by the hydrolysis of **6**. Boric acid is presumed to facilitate the release of rhodium from the iminorhodium(I) intermediate **5** by protonolysis. The effect of the acidic proton of boric acid is apparent from the contrasting results of the reaction of **1** with phenylboroxine (**9**), both with and without boric acid (eqn. 1).



(1)

The selective reaction of the cyano group of **1** with organometallic reagents is rare. The reaction of **1** with phenylcadmium bromide in the presence of zinc dichloride has been reported to give **3** in 31% yield.[19] For comparison, we carried out reactions of **1** with phenylmagnesium bromide and phenyllithium. When **1** was reacted with phenylmagnesium bromide (1.05 equiv.) in THF, with the reaction temperature being raised from –20 °C to room temperature, ethyl benzoate was obtained in 89% yield, and no **3a** was observed. The reaction of **1** with phenyllithium in ether afforded ethyl benzoate in 36% yield, together with various other compounds, including triphenylmethanol and benzophenone (eqn. 2). The selective formation of α-keto esters in the present reaction is in sharp contrast to the results obtained with phenylmagnesium bromide and phenyllithium.



(2)

In conclusion, the rhodium-catalysed reaction of ethyl cyanoformate with arylboronic acids provides a convenient method for the synthesis of arylated α-keto esters. It has been demonstrated that arylrhodium(I) species preferentially add to the cyano group of **1** rather than to the ester carbonyl group.

Notes and references

‡ **General procedure**: A mixture of arylboronic acid **2** (0.6 mmol, 1.2 equiv.), H_3BO_3 (1.0 mmol, 2.0 equiv.), $[Rh(OH)(cod)]_2$ (0.0125 mmol, 2.5 mol%) and ethyl cyanoformate (**1**, 0.5 mmol, 1.0 equiv.) in 1,4-dioxane (1 ml) was stirred for 30 min at room temperature, and then at 60 °C for 3 h under an Ar atmosphere. The reaction mixture was cooled and diluted with AcOEt (10 ml) and citric acid (10% aq., 5 ml). The organic layer was separated, and the aqueous layer was extracted with AcOEt (3 × 5 ml). The combined extracts were washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by preparative thin layer chromatography (hexane : AcOEt) to give the product **3**, which was characterized by ^1H and ^{13}C NMR, and/or HRMS (see ESI†).

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