Synthetic Methods

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Synthesis of α-Aryl Esters and Nitriles: Deaminative Coupling of α-Aminoesters and α-Aminoacetonitriles with Arylboronic Acids**

*Guojiao Wu, Yifan Deng, Chaoqiang Wu, Yan Zhang, and Jianbo Wang**

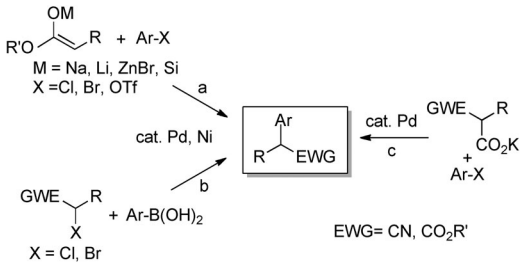
Abstract: *Transition-metal-free synthesis of α-aryl esters and nitriles using arylboronic acids with α-aminoesters and α-aminoacetonitriles, respectively, as the starting materials has been developed. The reaction represents a rare case of converting $C(sp^3)$–N bonds into $C(sp^3)$–$C(sp^2)$ bonds. The reaction conditions are mild, demonstrate good functional-group tolerance, and can be scaled up.*

Nitriles and α-aryl esters are versatile intermediates because of their easy conversion into amides, carboxylic acids, aldehydes, and primary amines, as well as their applications in the synthesis of heterocyles.[1] Additionally, α-aryl carboxylic acid derivatives are found as important moieties in various medicinal and natural products.[2] Because of their importance, the synthesis of α-aryl esters and nitriles have attracted attention over the past decades.[3] Traditional strategies for the synthesis of α-aryl nitriles include Friedel–Crafts reactions,[4] cyanation of benzylic alcohols or halides,[5] and dehydration of α-aryl amides and oximes.[6] These traditional methods generally suffer from drawbacks which include the need for toxic reagents, harsh reaction conditions, and multistep operations.[7]

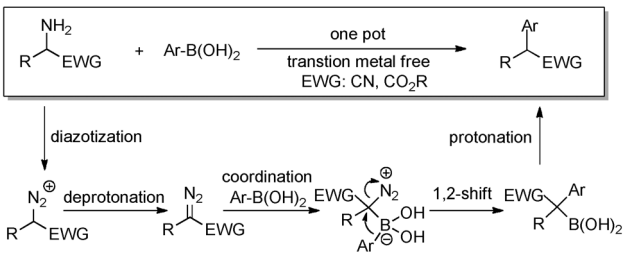
In 1997 the groups of Miura, Buchwald, and Hartwig reported the palladium-catalyzed arylation of ketones.[8] Subsequently, the synthesis of α-aryl esters and nitriles through palladium-catalyzed coupling reactions was developed (Scheme 1 a).[3,9] Such coupling reactions require strong base, such as LiHMDS or NaHMDS, to deprotonate the substrate to generate enolates. The use of strong base imposes some limits to the reaction, including the functional-group tolerance, side reactions from Claisen condensations, and diarylations. To obviate the need for a strong base, zinc enolates and silyl enol ethers,[10–12] and α-silyl nitriles and zinc cyanoalkyls[13] have been used as the enolate precursors to achieve arylation under mild reaction conditions.

Alternatively, the synthesis of α-aryl esters and nitriles can be achieved through a cross-coupling reaction of arylboron reagents with α-halocarbonyl compounds[14] and α-halonitriles,[15] respectively (Scheme 1 b). Recently, Liu and co-workers developed a palladium-catalyzed decarboxylative coupling to access α-aryl esters and nitriles,[16] and similar reactions have also been reported by the groups of Kwong[17] and Xu[18] (Scheme 1 c). Although significant progress has been made in transition-metal-catalyzed synthesis of α-aryl esters and nitriles, further development of alternative approaches toward these important compounds is still highly desirable.

Herein, we report a transtion-metal-free process to synthesize α-aryl esters and nitriles by deaminative coupling of α-aminoesters and α-aminoacetonitriles, respectively, with boronic acids (Scheme 2). α-Aminoesters and α-aminoacetonitriles attracted our attention because of their ready availability.[19] We previously reported the transtion-metal-free reaction of boronic acids with diazo compounds.[20,21] This type of transformation follows a simple process involving the coordination of electron-rich diazo carbon atoms to the electron-deficient boron center and subsequent 1,2-shift to form a carbon–carbon bond.[22] As shown in Scheme 2, with electron-withdrawing groups adjacent to the amino group, the α-aminoesters and α-aminonitriles can be converted into the



Scheme 1. Synthesis of α-aryl esters and nitriles through transition-metal-catalyzed coupling reactions. Tf = trifluoromethanesulfonyl.



Scheme 2. Transition-metal-free process for the synthesis of α-aryl esters and nitriles.

[*] G. Wu, Y. Deng,[+] C. Wu,[+] Dr. Y. Zhang, Prof. Dr. J. Wang
Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University
Beijing 100871 (China)
E-mail: wangjb@pku.edu.cn
Prof. Dr. J. Wang
The State Key Laboratory of Organometallic Chemistry
Chinese Academy of Sciences, Shanghai 200032 (China)
[+] These authors contributed equally to this work.
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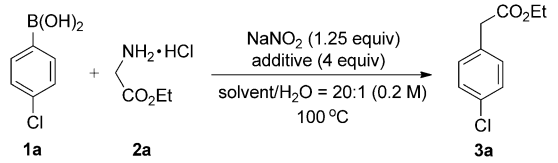
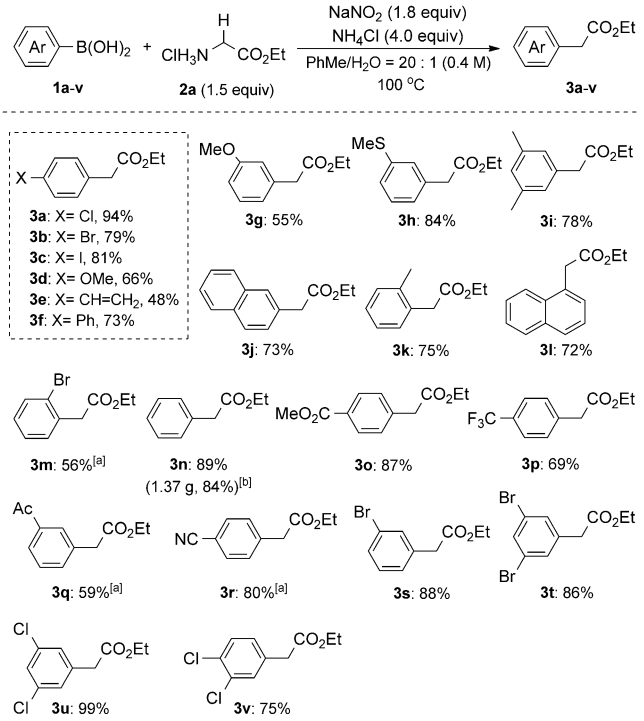
Table 1: Optimization of the reaction conditions.[a]



Eentry	Solvent	Additive	**1a**/**2a**	Yield [%][b]
1	toluene	–	1:2	< 15
2	toluene	NH_4F	1:2	< 20
3	toluene	NH_4Cl	1:2	80
4	toluene	HCO_2NH_4	1:2	74
5	PS[c]	NH_4Cl	1:2	0
6	DCE	NH_4Cl	1:2	66
7	toluene	NH_4Cl	1:1.5	88
8	toluene	NH_4Cl	1:1.25	79
9	toluene	NH_4Cl	1.25:1	73
10[d]	toluene	NH_4Cl	1:1.5	94

[a] Reaction was carried out with **1a** and **2a** in solvent (0.5 mmol, 0.2 M) at 100 °C for 24 h. [b] Yield of isolated product. [c] PS = polar solvents, including 1,4-dioxane, THF, DMF, and MeCN. [d] The reaction was carried out in toluene and water (0.4 M). DCE = 1,2-dichloroethane, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.



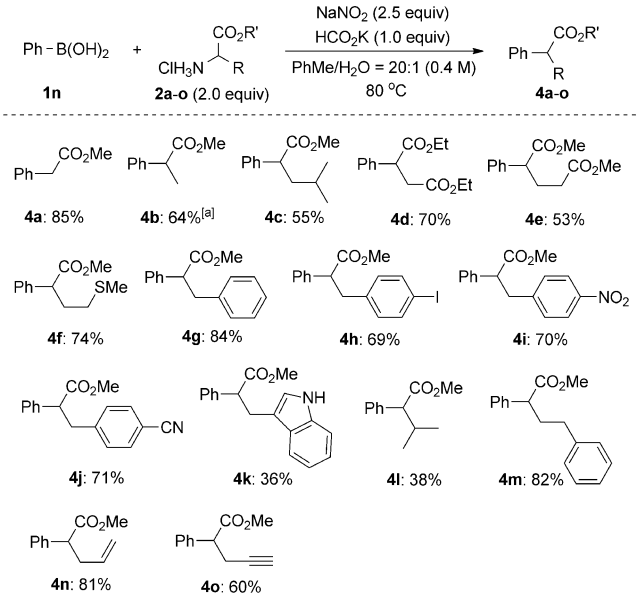
Scheme 3. Reaction of arylboronic acids with glycine ethyl ester hydrochloride. If not otherwise noted, the reaction was carried out with **1** (0.5 mmol) and **2a** (0.75 mmol) in PhMe/H_2O (20:1; 1.25 mL) at 100 °C. All the yields refer to those of the isolated products. [a] The reaction was carried out at 120 °C. [b] Reaction was scaled up to 10 mmol of **1n** and 15 mmol of **2a**.

corresponding diazo compounds through diazotization and subsquent deprotonation.[23] The in situ generated diazo compounds react with arylboronic acids to achieve transtion-metal-free synthesis of α-aryl esters and nitriles.

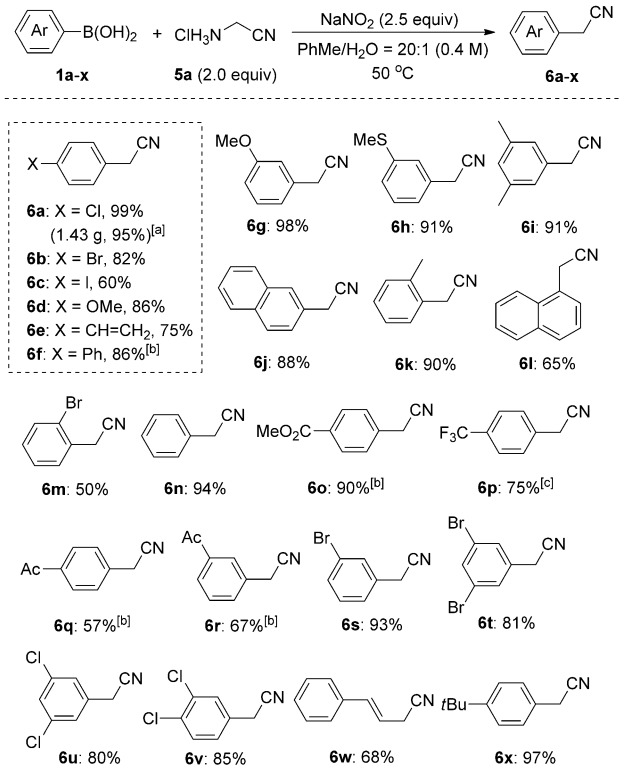
The original study was carried out with 4-chlorophenyl boronic acid (**1a**) and glycine ethyl ester hydrochloride (**2a**; Table 1). With toluene as the solvent, the desired product **3a** could be obtained, albeit in low yield (entry 1). Then a series of additives were investigated in the reaction (entries 2–4).[20b] The reaction was not significantly improved with NH_4F as an additive. To our delight, the yield was dramatically improved with NH_4Cl and HCO_2NH_4 as the additives, and the former gave a better result with an 80% yield upon isolation (entry 3). To further optimize the reaction, a series of solvents were screened. Polar solvents, such as 1,4-dioxane, MeCN, THF, and DMF, gave no desired product, whereas DCE resulted in a diminished yield as compared that obtained with toluene (entries 5 and 6). Finally, by tuning the ratio of **1a** to **2a** (entries 7–9) and increasing the reaction concentration, the optimal result was obtained with 94% yield upon isolation of **3a** (entry 10).

With the optimized reaction conditions in hand, we next carried out a study on the reaction scope with various arylboronic acids. As shown in Scheme 3, the arylboronic acids bearing both electron-rich and electron-poor substituents, such as methoxy, methylthio, olefin, ketone, ester, and cyano, all can be successfully converted into the desired products, thus indicating that the reaction is only marginally affected by electronic effects. The arylboronic acids bearing a halide group gave the desired α-aryl esters with moderate to excellent yields (**3a–c** and **3s–v**). Remarkably, the iodo substituent could tolerate the reaction (**3c**), and thus provides the possibility for additional transformations through transition-metal-catalyzed coupling reactions. It is also noteworthy that a base-sensitive ketone group can tolerate the reaction (**3q**). For arylboronic acids bearing electron-withdrawing substituents, high temperature is needed to promote the reaction (**3m**, **3q**, and **3r**). A gram-scale experiment was carried out with **1n**, thus affording **3n** in similar yield as a small scale experiment.

Furthermore, the scope with respect to the α-aminoesters was investigated by using phenylboronic acid (**1n**). However, with the same protocol, the deaminative coupling with alanine methyl ester hydrochloride afforded the desired product with only low yield (< 10%). We observed the α-chloro ester formation in the reaction.[23] Therefore, the additive was changed from NH_4Cl to HCO_2K to avoid the α-chloro ester formation. Under such reaction conditions, satisfactory results were obtained. With the modified protocol, a range of α-aminoesters were examined. The deaminative coupling proved to be effective and broadly applicable, as shown in Scheme 4. Substituted glycine ethyl ester hydrochlorides all showed good reactivity (**4b–g** and **4m**). The reaction was not affected by substituents such as iodo, nitro, and cyano on the aryl ring of phenylalanine methyl ester hydrochloride (**4h–j**). The tryptophan methyl ester hydrochloride bearing a heterocycle with a free NH also afforded the desired product **4k**, though with a lower yield. The diminished yield of **4l** may be attributed to steric hindrance of the α-aminoester. To our delight, the olefin and alkynyl moieties are compatible with the reaction (**4n** and **4o**).



Scheme 4. Reaction of phenylboronic acid (**1n**) with α-aminoester hydrochlorides. If not otherwise noted, the reaction was carried out with **1n** (0.5 mmol) and **2** (1.0 mmol) in $PhMe/H_2O$ (20:1; 1.25 mL) at 80 °C. All the yields refer to those of the isolated products. [a] The reaction was carried out in the absence of water.



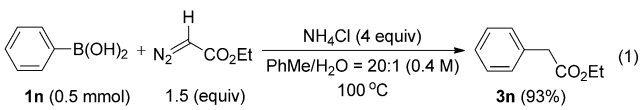
Scheme 5. Reaction of arylboronic acids with α-aminoacetonitrile hydrochloride (**5a**). If not otherwise noted, the reaction was carried out with **1** (0.5 mmol) and **5a** (1.0 mmol) in $PhMe/H_2O$ (20:1; 1.25 mL) at 50 °C. All the yields refer to those of the isolated products. [a] Reaction was scaled up to 10 mmol of **1a** and 20 mmol of **5a**. [b] The reaction was carried out at 100 °C with DCE as solvent instead of PhMe. [c] The reaction was carried out at 100 °C.

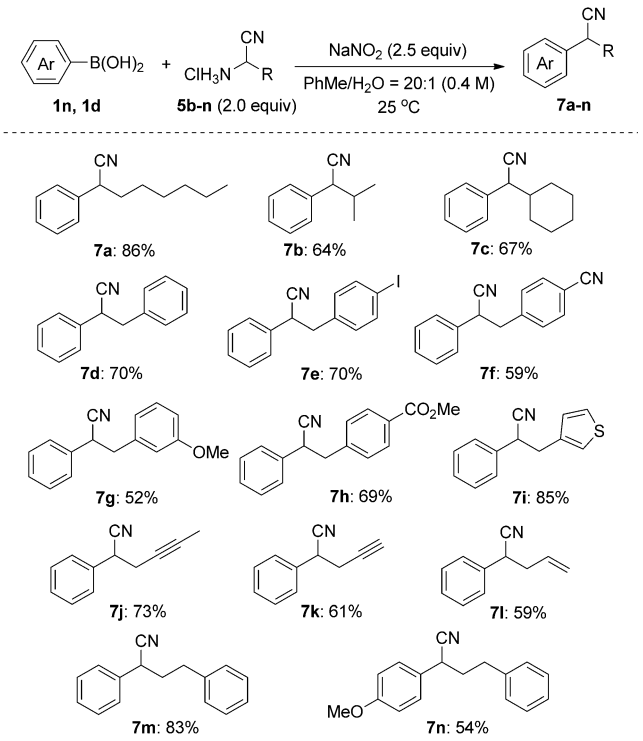
Having the synthetic protocol for α-aryl esters established, we next turned our attention to the synthesis of α-aryl nitriles with the same strategy of deaminative coupling. Gratefully, under the same reaction conditions employed for the synthesis of α-aryl esters, the reaction of **1a** with aminoacetonitrile hydrochloride (**5a**) afforded the expected product in 79% yield at 75 °C. A 93% yield of the isolated product could be obtained at a reaction temperature of 50 °C, while the yield was decreased to 66% at 30 °C. Interestingly, 99% yield could be obtained when carrying out the reaction without NH_4Cl.

With the modified reaction conditions, a series of substitued arylboronic acids were submitted to investigate the scope of this deaminative coupling for the synthesis of α-aryl nitriles. As demonstrated in Scheme 5, a series of arylboronic acids reacted smoothly to give moderate to excellent yields of the corresponding α-aryl nitriles. It was illustrated that halide substituents on the aryl ring of the boronic acid was compatible with this protocol (**6a–c**, **6m**, and **6s–v**). This transformation is not significantly affected by both electron-withdrawing and electron-donating substituents. The terminal alkenyl (**6e**), ester (**6o**), and ketone (**6q**,**r**) functional groups are also tolerated under the reaction conditions. Moreover, arylboronic acids with steric hindrance undergo successful transformation, although in some cases with diminished yields (**6k–m**). Notably, the reaction with vinylboronic acid afforded the desired product with a moderate yield (**6w**). Similarly, for the electron-poor arylboronic acids both a higher reaction temperature and DCE as the solvent enhance the yields (**6o–r**). A gram-scale experiment has also been carried out with **1a**, thus affording **6a** in similar yield.

Finally, the scope of α-aminoacetonitrile derivatives was explored. As summarized in Scheme 6, α-aminoacetonitrile derivatives with monoalkyl, dialkyl, cycloalkyl, and benzyl substituents all showed good reactivities under the same reaction conditions (**7a–d** and **7m–n**). The functional groups such as iodo, cyano, methoxyl, and ester attached to the benzyl group does not significantly affect the reaction (**7e–h**). The heterocyclic substituent is also compatible with the reaction conditions (**7i**). An alkynyl substituent, especially a terminal alkyne, and terminal alkene remain intact, thus giving moderate yields of the desired products (**7k**,**l**).

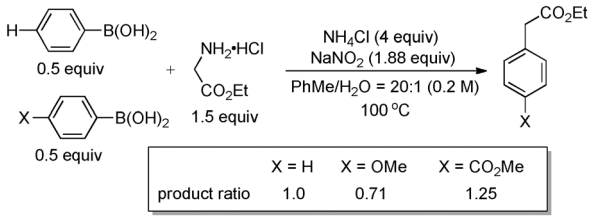
Experiments were carried out to gain some insight into the reaction mechanism. Since the diazo compound has been proposed as the intermediate in the reaction, ethyl diazoacetate (EDA), instead of glycine ethyl ester hydrochloride, was used as the substrate to react with phenylboronic acid under the standard reaction conditions in the absence of $NaNO_2$. The reaction gave **3n** in 93% yield [Eq. (1)]. This result is consistent with the mechanism shown in Scheme 2.





Scheme 6. Reaction of phenylboronic acids and aminoacetonitrile derivatives. The reaction was carried out with **1n** or **1d** (0.5 mmol) and **5b–n** (1.0 mmol) in PhMe/H_2O (20:1; 1.25 mL) at 25 °C. All the yields refer to those of the isolated products.

Next, the effect of the substituents on the phenyl ring of arylboronic acids was investigated, and the results are shown in Scheme 7. The resulting product ratios demonstrate that the electron-withdrawing group facilitates the reaction, while



Scheme 7. Studies on the effect of the substituents.

the electron-donating substituent slows the reaction. This outcome is also consistent with the mechanism shown in Scheme 2. The electron-withdrawing group will facilitate the coordination of the electron-rich diazo carbon atom to the electron-deficient boron center, thus increasing the rate of the overall transformation.

In summary, we have developed an effective access to α-aryl esters and nitriles by transition-metal-free deaminative coupling of α-aminoesters and α-aminoacetonitriles with boronic acids. This new synthetic method is operationally simple and uses readily accessible reactants. The reaction has wide substrate scope and excellent functional-group tolerance, and it can be scaled up easily. With these advantages, we expect that this method will find wide applications in organic synthesis.

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Keywords: arenes · boron · diazo compounds · nitriles · synthetic methods

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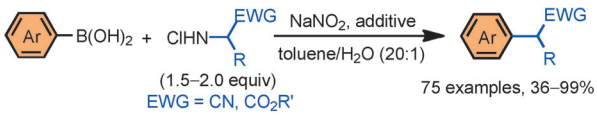
Communications

Synthetic Methods

G. Wu, Y. Deng, C. Wu, Y. Zhang, J. Wang* ——— ■■■■–■■■■

Synthesis of α-Aryl Esters and Nitriles: Deaminative Coupling of α-Aminoesters and α-Aminoacetonitriles with Arylboronic Acids



Touch base: A transition-metal-free protocol for the synthesis of α-aryl esters and nitriles by deaminative coupling is presented. Strong bases and transition-metal catalysts are not needed. The new synthetic method uses readily available starting materials and demonstrates wide substrate scope.

