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Divergent Palladium-Catalyzed Tandem Reaction of Cyanomethyl Benzoates with Arylboronic Acids: Synthesis of Oxazoles and Isocoumarins

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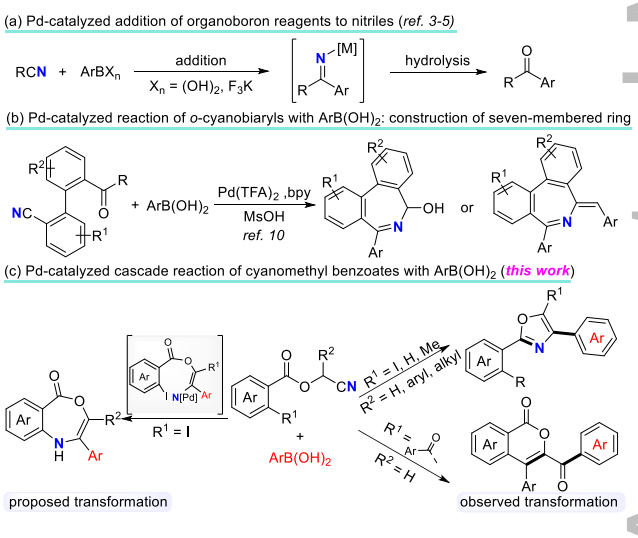
Abstract: A palladium-catalyzed tandem reaction of cyanomethyl benzoates with arylboronic acids has been achieved. Substitution at the 2-position of cyanomethyl benzoates was found to be crucial for the selective synthesis of oxazoles and isocoumarins. Cyanomethyl benzoates afforded 2,4-diaryloxazoles as products, while 2-benzoyl-substituted cyanomethyl benzoates delivered 3-benzoyl-4-aryl-isocoumarins selectively. Furthermore, a possible mechanism for the selective reaction of cyanomethyl benzoates with arylboronic acids was discussed.

Keywords: palladium-catalyzed; tandem reaction; oxazoles; isocoumarins; nitriles

Introduction

Owing to the ubiquity of heterocyclic compounds in both organic chemistry and medicinal chemistry,[1] the discovery of new transition-metal-catalyzed transformations for the construction of heterocycles in a selective manner from readily available starting materials is an active research area. Nitriles are an important class of molecular building blocks in organic synthesis.[2] Significant progress toward understanding the carbopalladation of nitriles[3] has promoted the development of transition-metal-catalyzed transformations of various nitrile-containing functional groups by our group[4] and others[5] (Scheme 1a). The scope of this chemistry has been successfully extended to sodium aryl sulfinates or arylsulfinic acids,[6] aryl halides,[7] benzoic acids,[8] and arylhydrazines[9] as coupling partners in the last decade. Inspired by our recent studies on palladium-catalyzed tandem reactions of *o*-cyanobiaryls with arylboronic acids for the synthesis of seven-membered 5*H*-dibenzo[*c*,*e*]azepines (Scheme 1b),[10] we envisaged that the palladium-catalyzed addition of arylboronic acids to cyanomethyl 2-halogenated benzoates and sequential intramolecular Buchwald–Hartwig coupling cyclization would offer a new strategy for the synthesis of 2-arylbenzo[*e*][1,4]oxazepin-5-ones (Scheme 1c, proposed transformation). To our surprise, substitution at the 2-position of cyanomethyl benzoates was found to be crucial for the selective synthesis of five-membered oxazoles[11] and six-membered isocoumarins[12] (Scheme 1c, observed transformation). Herein, we report the unexpected discovery using this novel protocol that cyanomethyl benzoates afford 2,4-diaryloxazoles as the sole products, while 2-benzoyl-substituted cyanomethyl benzoates deliver a new class of 3-benzoyl-4-aryl-isocoumarins that are often difficult to prepare using traditional routes.



Scheme 1. Reactions associated with this study.

Our initial investigation commenced with an examination of the reaction of cyanomethyl 2-iodobenzoate with phenylboronic acid for reaction condition optimization (Table S1, see SI for details). We found that 2-(2-iodophenyl)-4-phenyloxazole was isolated in 19% yield in the presence of $Pd(OAc)_2$, 2,2'-bipyridine (**L1**), and methanesulfonic acid (MsOH) at 95 °C in THF for 24 h, along with small amounts of deiodinated product 2,4-diphenyloxazole.

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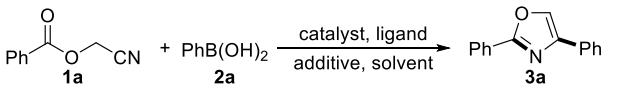
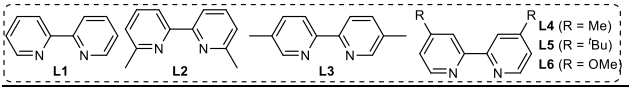
Therefore, we tested the reaction of readily available cyanomethyl benzoate (**1a**) with phenylboronic acid to screen reaction conditions (Table 1). 2,4-Diphenyloxazole (**3a**) was obtained in 25% yield when using a combination of $Pd(OAc)_2$, **L1**, and MsOH in THF (entry 1). Among other additives used, including trifluoroacetic acid (TFA), D-camphorsulfonic acid (D-CSA), heptafluorobutyric acid (HFBA), sulfuric acid, and trifluoromethanesulfonic acid (TfOH) (entries 2–6), TfOH exhibited the highest reactivity, affording **3a** in 43% yield (entry 6). A brief survey of solvents indicated that THF was the optimal choice (entries 6–9). Other palladium catalysts were evaluated (entries 10–12), with $Pd(acac)_2$ as catalyst improving the yield of **3a** to 58% (entry 12). The use of a ligand was crucial for accelerating this tandem reaction. A number of other bidentate pyridine-based ligands, including 6,6'-dimethyl-2,2'-bipyridine (**L2**), 5,5'-dimethyl-2,2'-bipyridine (**L3**), 4,4'-dimethyl-2,2'-bipyridine (**L4**), 4,4'-di-tert-butyl-2,2'-bipyridine (**L5**), and 4,4'-dimethoxy-2,2'-bipyridine (**L6**), were screened (entries 13–17), with significantly improved results observed were screened (entries 13–17), with significant reaction improvements observed with **L4** (81% yield, entry 15). Other reaction conditions, including the amount of catalyst, additive, and ligand, were also screened (Table S2, see SI for details).

Table 1. Optimization of reaction conditions.[a]



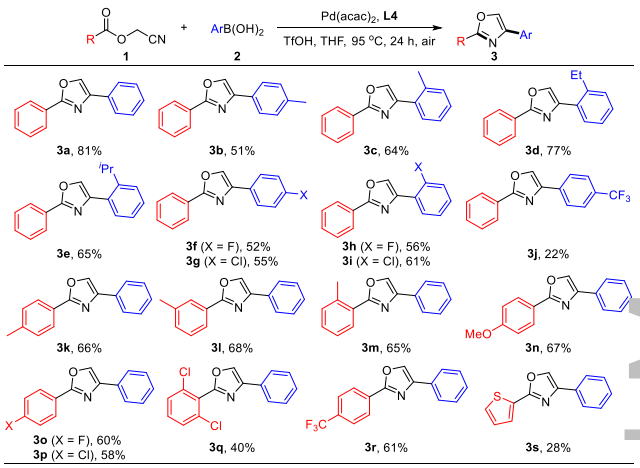
Entry	Pd catalyst	Ligand	Additive	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	**L1**	MsOH	THF	25
2	$Pd(OAc)_2$	**L1**	TFA	THF	35
3	$Pd(OAc)_2$	**L1**	D-CSA	THF	30
4	$Pd(OAc)_2$	**L1**	HFBA	THF	32
5	$Pd(OAc)_2$	**L1**	H_2SO_4	THF	23
6	$Pd(OAc)_2$	**L1**	TfOH	THF	43
7	$Pd(OAc)_2$	**L1**	TfOH	dioxane	30
8	$Pd(OAc)_2$	**L1**	TfOH	toluene	27
9	$Pd(OAc)_2$	**L1**	TfOH	NMP	36
10	$Pd(MeCN)_2Cl_2$	**L1**	TfOH	THF	35
11	$Pd_2(dba)_3$	**L1**	TfOH	THF	21
12	$Pd(acac)_2$	**L1**	TfOH	THF	58
13	$Pd(acac)_2$	**L2**	TfOH	THF	67
14	$Pd(acac)_2$	**L3**	TfOH	THF	71
15	$Pd(acac)_2$	**L4**	TfOH	THF	81
16	$Pd(acac)_2$	**L5**	TfOH	THF	70
17	$Pd(acac)_2$	**L6**	TfOH	THF	78



[a] Conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), Pd catalyst (5 mol %), ligand (10 mol %), additive (2 equiv.), solvent (2 mL), 95 °C, 24 h, air.
[b] Isolated yield.

To examine the scope of this tandem reaction, we first tested the reaction of cyanomethyl benzoate (**1a**) with arylboronic acids for the synthesis of 2,4-diaryl oxazoles (Table 2, **3a**–**3j**). Pleasingly, electron-donating groups, including methyl, ethyl, and isopropyl groups, were tolerated in this transformation (**3a**–**3e**). Notably, with an *ortho*-substituent present on the phenyl ring, desired products **3c**–**3e** were obtained in 64–77% yields, indicating that steric hindrance around the imine moiety prevented further hydrolysis. Electron-withdrawing groups, such as fluoro and chloro groups, were also tolerated in this transformation, providing corresponding products **3f**–**3i** in 52–61% yields. The tandem reaction with a strongly electron-withdrawing trifluoromethyl group attached to the phenyl ring also proceeded, albeit affording desired product **3j** in 22% yield. The scope of the cyanomethyl benzoates was also examined (Table 2, **3k**–**3s**). Both electron-rich substituents (such as Me and OMe) (**3k**–**3n**) and electron-deficient substituents (such as F, Cl, and CF_3) (**3o**–**3q**) were compatible with this transformation. Notably, substrate cyanomethyl thiophene-2-carboxylate also reacted successfully, providing **3s** in a low yield.

Table 2. Synthesis of 2,4-diaryl oxazoles.[a]



[a] Conditions: **1a** (0.3 mmol), **2** (0.45 mmol), $Pd(acac)_2$ (5 mol%), **L4** (10 mol%), TfOH (2 equiv.), THF (2 mL), 95 °C, 24 h, air, isolated yield.

We next investigated the tandem reaction of a wide range of readily available cyano(phenyl)methyl benzoates with phenylboronic acid to give the corresponding 2,4,5-triaryloxazoles (Table 3). We found that cyano(phenyl)methyl benzoates bearing substituents (such as OMe, Cl, CF_3, and NO_2) on the aryl ring were compatible with this tandem reaction, affording desired products **3t**–**3x** in 68–91% yields. Importantly, substrates with R^1 substituents, such as naphthyl (**3y**), pyridyl (**3z**), furyl (**3za**), and thienyl (**3zb**) groups, delivered the corresponding products in good to excellent yields. Alkyl-substituted substrates, such as cyano(phenyl)methyl 3-phenylpropanoate (**3zc**) and cyano(phenyl)methyl acetate (**3zd**), were also tolerated in this transformation. Pleasingly, substituents attached to the α-position of the cyano group (R^2), including aryl substituents (such as *p*-tolyl, *p*-methoxyphenyl, *p*-chlorophenyl, and *p*-fluorophenyl), heterocyclic substituents (such as pyridyl, furyl, and thienyl), and alkyl substituents (such as phenethyl, propyl, and cyclohexyl),

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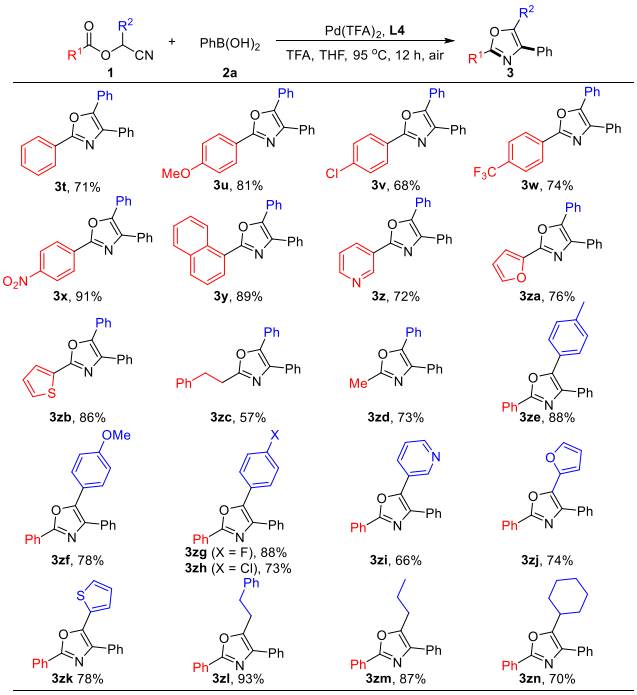
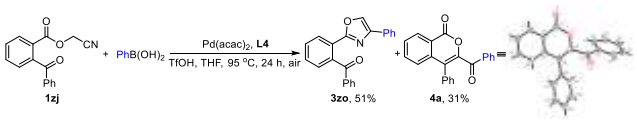
delivered the corresponding products (**3ze**–**3zn**) in 66–93% yields.

Table 3. Synthesis of 2,4,5-triaryl oxazoles.[a]



[a] Conditions: **1** (0.3 mmol), **2** (0.45 mmol), $Pd(TFA)_2$ (5 mol%), **L4** (10 mol%), TFA (2 equiv.), THF (2 mL), 95 °C, 12 h, air, isolated yield.

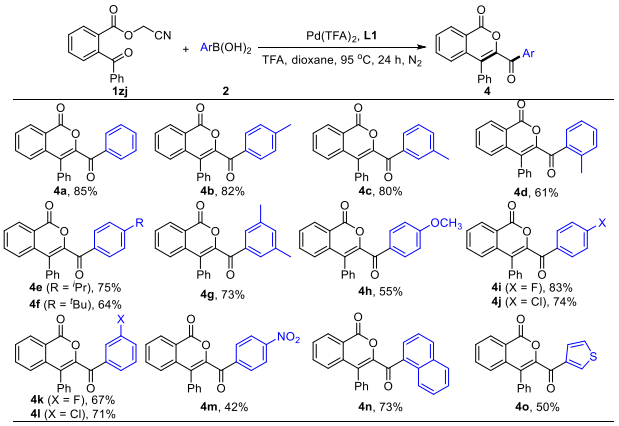
Interestingly, when cyanomethyl 2-benzoylbenzoate (**1zj**) was used, desired product phenyl(2-(4-phenyloxazol-2-yl)phenyl)methanone (**3zo**) was obtained in 51% yield, accompanied with byproduct 3-benzoyl-4-phenyl-1*H*-isochromen-1-one (**4a**) in 31% yield from hydrolysis of the imine intermediate followed by cyclization (Scheme 2). The structure of compound **4a** was determined by X-ray diffraction analysis.[13]



Scheme 2. Reaction of **1zj** with phenylboronic acid.

The importance of isocoumarins[12] in organic and medicinal chemistry attracted our attention to the development of a new tandem reaction for the synthesis of 3-benzoyl-4-aryl-isocoumarins. We investigated the tandem reaction of cyanomethyl 2-benzoylbenzoate (**1zj**) with phenylboronic acid to optimize the reaction conditions (Table S3, see SI for details). We found that desired product **4a** was isolated in 85% yield using a combination of $Pd(TFA)_2$, **L1**, and TFA for 24 h in dioxane at 95 °C under N_2.

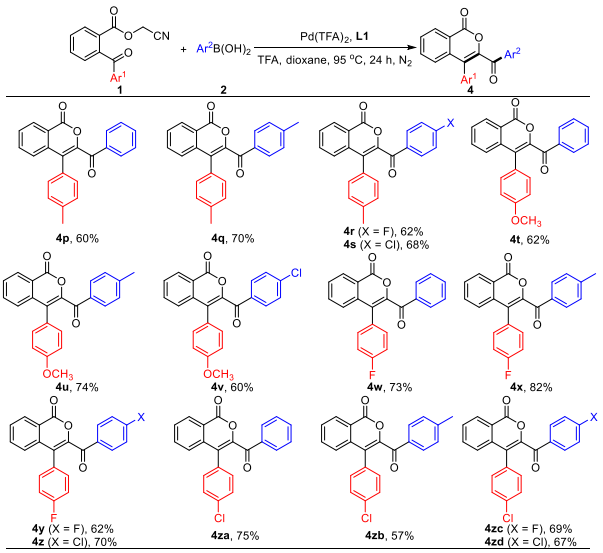
Table 4. Scope of arylboronic acids.[a]



[a] Conditions: **1** (0.3 mmol), **2** (0.6 mmol), $Pd(TFA)_2$ (5 mol%), **L1** (10 mol%), TFA (2 equiv.), dioxane (2 mL), 95 °C, 24 h, N_2, isolated yield.

We next examined the scope of arylboronic acids (Table 4). The tandem reaction of **1zj** with *p*- and *m*-tolylboronic acids gave **4b** and **4c** in 82% and 80% yields, respectively, while *o*-tolylboronic acid afforded **4d** in 61% yield. Moderately electron-donating groups, such as ^{i}Pr (**4e**), ^{t}Bu (**4f**), and dimethyl (**4g**) groups, were compatible with this reaction, affording the corresponding products in 64–75% yields. However, the substrate bearing strongly electron-donating group OMe did not retard the reaction, affording **4h** in 55% yield. Substrates bearing moderately electron-withdrawing halogens, such as fluoro (**4i**, **4k**) and chloro (**4j**, **4l**) groups, were also well-tolerated, while the substrate bearing a strongly electron-donating group NO_2 afforded a decreased yield of 42% (**4m**). The naphthyl-substituted substrate gave **4n** in 73% yield. Notably, 4-phenyl-3-(thiophene-3-carbonyl)-1*H*-isochromen-1-one (**4o**) was obtained in 50% yield.

Table 5. Scope of cyanomethyl 2-benzoylbenzoates.[a]



[a] Conditions: **1** (0.3 mmol), **2** (0.6 mmol), $Pd(TFA)_2$ (5 mol%), **L1** (10 mol%), TFA (2 equiv.), dioxane (2 mL), 95 °C, 24 h, N_2, isolated yield.

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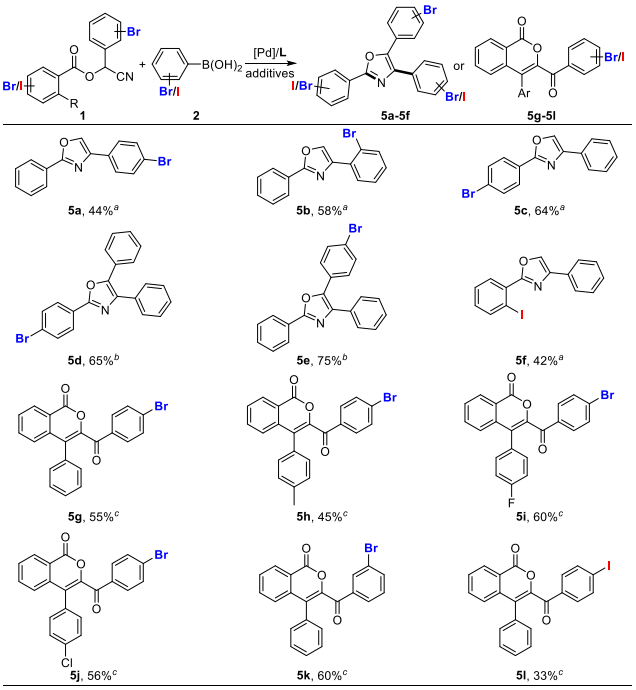
As shown in Table 5, both electron-rich substituents, such as methyl (**4p**–**4s**) and methoxy (**4t**–**4v**), and electron-deficient substituents, such as fluoro (**4w**–**4z**) and chloro (**4za**–**4zd**), at the *para*-position of the phenyl ring (Ar^1) were tolerated, affording the desired products in moderate yields.

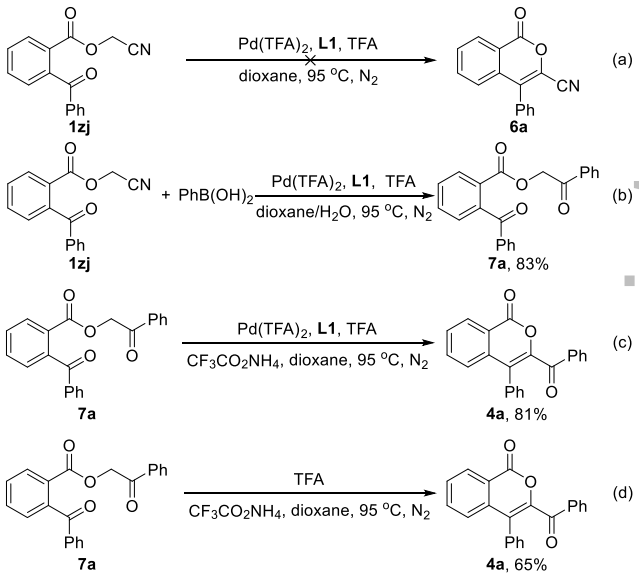
Table 6. Synthesis of bromo- and iodo-substituted oxazoles and isocoumarins.[a]



[a] Conditions: **1** (0.3 mmol), **2** (0.45 mmol), $Pd(acac)_2$ (5 mol%), **L4** (10 mol%), TfOH (2 equiv.), THF (2 mL), 95 °C, 24 h, air, isolated yield.
[b] $Pd(TFA)_2$ (5 mol%), **L4** (10 mol%), TFA (2 equiv.), THF (2 mL), 95 °C, 12 h, air, isolated yield.
[c] **1** (0.3 mmol), **2** (0.6 mmol), $Pd(TFA)_2$ (5 mol%), **L1** (10 mol%), TFA (2 equiv.), dioxane (2 mL), 95 °C, 24 h, N_2, isolated yield.

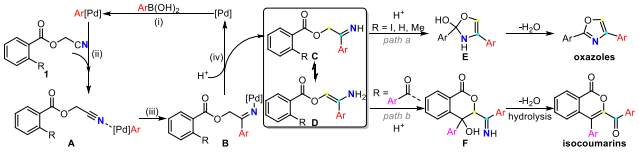
To obtain halogen-substituted products for further synthetic transformations, we examined the scope of bromo- and iodo-substituted substrates (Table 6). Several representative bromo-substituted substrates were amenable to the reaction conditions, affording the corresponding bromo-substituted oxazoles (**5a**–**5e**) in 44–75% yields. A representative iodo-substituted oxazole (**5f**) was obtained in 42% yield. Furthermore, bromo- and iodo-substituted substrates for the synthesis of isocoumarins (**5g**–**5l**) showed good compatibility with this reaction.

Several control experiments were performed under the optimized conditions. The attempted reaction in the absence of phenyboronic acid failed to afford **6a** (Scheme 3a). This result indicated that the tandem transformation was initiated by carbopalladation of the nitrile. 2-Oxo-2-phenylethyl 2-benzoylbenzoate (**7a**) was obtained in 83% yield from hydrolysis of the ketimine intermediate in the presence of H_2O (Scheme 3b). We found that desired product **4a** was obtained in 81% yield when **7a** was used as substrate in the presence of ammonium trifluoroacetate (Scheme 3c). Of note, this reaction did not work in the absence of Pd catalyst (Table S3 in SI, entry 24). However, the cyclization of **7a** gave the desired **4a** in a relatively low yield (65%) without a Pd catalyst and ligand (Scheme 3d), indicating that the Pd catalyst is essential for the formation of intermediate **7a** but not crucial for further cyclization.



Scheme 3. Control experiments.

A possible pathway for the formation of oxazoles and isocoumarins was proposed (Scheme 4). This reaction involves the following key steps: (i) Transmetalation between the Pd catalyst and arylboronic acid to form a Pd–aryl species; (ii) coordination of the nitrile to Pd to form intermediate **A**; (iii) carbopalladation of the nitrile to give imine-Pd complex **B**; (iv) protonation of intermediate **B** in the presence of acid to generate imine intermediate **C** (or tautomerization of the imine to enamine intermediate **D**) and regenerate the Pd catalyst. Substitution at the 2-position of cyanomethyl benzoates was found to be crucial for the selective synthesis of oxazoles and isocoumarins. The cyanomethyl benzoates afforded 2,4-diaryloxazoles as the sole products via intermediate **E** (path a), while 2-benzoyl-substituted cyanomethyl benzoates delivered a new class of 3-benzoyl-4-aryl-isocoumarins selectively via intermediate **F** (path b). We assumed that carbonyl activation in the presence of acid would accelerate the intramolecular cyclization of intermediate **C** or **D**.



Scheme 4. Proposed reaction pathway.

Conclusion

In summary, we have demonstrated a palladium-catalyzed tandem reaction of readily available cyanomethyl benzoates with arylboronic acids. This methodology allows the efficient and selective synthesis of oxazoles and isocoumarins with good functional group tolerance under mild reaction conditions.

Experimental Section

General Information. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured on a 400 MHz or 500 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given n δ relative to TMS, and the coupling constants *J* are given in hertz. High-resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometer. Cyanomethyl benzoates[14] was synthesized according to the method described in the literature. Column chromatography was performed using EM silica gel 60 (300−400 mesh). X-ray crystallographic analysis was performed at the X-ray crystallography facility, Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (CAS).

General Experimental Procedure for the Synthesis of 2,4-Diaryl Oxazoles

Cyanomethyl benzoates **1** (0.3 mmol), arylphenylboronic acid **2** (0.45 mmol), Pd $(acac)_2$ (5 mol%), **L4** (10 mol%), TfOH (0.6 mmol) and THF (2.0 mL) were successively added into a Schlenk reaction tube under an air atmosphere. The reaction mixture was stirred vigorously at 95 °C in an oil bath for 24 h. After the reaction equilibrium, the mixture was poured into ethyl acetate, which was washed with saturated $NaHCO_3$ (2 × 10 mL) and then brine (10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under a vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (16:1) to afford the desired products **3a-3s**, **5a-5c**, **5f**.

General Experimental Procedure for the Synthesis of 2,4,5-Triaryl Oxazoles

Cyanomethyl benzoates **1** (0.3 mmol), phenylboronic acid (0.45 mmol), Pd $(TFA)_2$ (0.015 mmol, 5 mol%) and **L4** (0.03 mmol, 10 mol%), TFA (0.6 mmol) and THF (2.0 mL) were successively added into a Schlenk reaction tube under an air atmosphere. The reaction mixture was stirred vigorously at 95 °C in an oil bath for 12 h. After the reaction equilibrium, the mixture was poured into ethyl acetate, which was washed with saturated $NaHCO_3$ (2 × 10 mL) and then brine (10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under a vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (16:1) to afford the desired products **3t-3zn**, **5d-5e**.

General Experimental Procedure for the Synthesis of Isocoumarins

Cyanomethyl benzoates **1** (0.3 mmol), arylboronic acid **2** (0.6 mmol), Pd $(TFA)_2$ (5 mol%), **L1** (10 mol%), TFA (0.6 mmol) and dioxane (2.0 mL) were successively added into a Schlenk reaction tube under a nitrogen atmosphere. The reaction mixture was stirred vigorously at 95 °C in an oil bath for 24 h. After the reaction equilibrium, the mixture was poured into ethyl acetate, which was washed with saturated $NaHCO_3$ (2 × 10 mL) and then brine (10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under a vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (8:1) to afford the desired products **4a-4zd**, **5g-5l**.

Acknowledgements

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