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Synthesis of 2,4,5-Trisubstituted Oxazoles via Pd-Catalyzed C−H Addition to Nitriles/Cyclization Sequences

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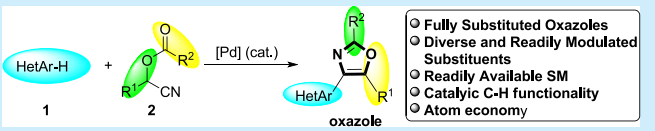
Supporting Information

ABSTRACT: A practical and flexible intermolecular protocol for the diverse synthesis of trisubstituted oxazole derivatives via a Pd-catalyzed direct C−H addition of electronic-rich heteroarenes to *O*-acyl cyanohydrins bearing an α-hydrogen/cyclization sequence is described. A wide range of trisubstituted oxazoles can be prepared from readily available starting materials in good to high yields with high efficiency under redox neutral reaction conditions.



Oxazoles represent one of the most important five-membered nitrogen-/oxygen-containing heterocyclic compounds and were frequently found in biologically active compounds and natural products.[1,2] In particular, 2,4,5-trisubstituted oxazoles have attracted considerable attention because of their various promising biologically activities such as antidiabetic,[3a] antibacterial,[3b] and anti-inflammatory[3c,d] activities (Figure 1). For example, siphonazole is a structurally

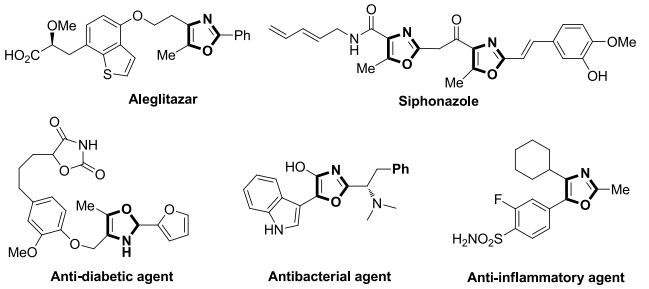


Figure 1. Examples of oxazole containing natural products and biological relevant compounds.

novel natural product isolated from a Gram-negative filamentous gliding bacterium of the Herpetosiphon genus[3e] and aleglitazar is a dual agonist of PPAR-α/PPAR-γ for the treatment of type 2 diabetes.[3f] Moreover, substituted oxazoles can be utilized in fluorescent dyes,[4a] polymers,[4b] and also as ligands for transition-metal catalysis.[4c,d] Consequently, significant effort has been devoted to the development of efficient methodologies for the construction of this privileged heterocyclic motif.

Among them, the intramolecular cyclization of acyclic oxazole precursors such as Robinson−Gabriel synthesis represents an attractive and effective strategy for the preparation of substituted oxazoles, but it is challenging due to the cumbersome preparation of the acyclic precursors.[5] Functionalization of pre-existing oxazole skeletons is another important strategy to access these highly functionalized heterocyclic compounds, but regioselectivity issues and inevitable multistep processes can limit such methods.[6] Moreover, transition-metal-catalyzed transformations[7] and iodine-mediated cyclization reactions[8] have been developed to construct these synthetic scaffolds via the direct cyclization of alkyne, enamide, or other precursors. However, most of them suffer from insufficiency such as utilization of stoichiometric amounts of Lewis acids, additional oxidants, and a limited substrate scope or inaccessible starting materials. Thus, it is still desirable to develop a practical and atom-economic approach to assemble a broad variety of trisubstituted oxazole derivatives, in which the substituents can be readily assembled from available starting materials with high tunability.

Recently, transition-metal-catalyzed C−H bond additions to nitriles have experienced remarkable advances.[9] In most cases, nitriles can serve as C building blocks and provide acyclic aryl ketone products. Very recently, this strategy has been found to be applicable to the assembly of azaheterocyclic skeletons in an atom-economic fashion, in which nitriles serve as C−N building blocks. For example, we have recently developed an intramolecular and intermolecular cyclization approach to prepare indole and thiophene fused polycyclic derivatives via Pd-catalyzed direct C−H bond addition to nitriles.[10] Given the importance of the trisubstituted oxazoles-containing molecules in medicinal chemistry and our ongoing interest in the development of efficient catalytic processes to prepare diverse heterocyclic frameworks, we envision that a practical, modular, and flexible intermolecular method for the efficient assembly of diverse trisubstituted oxazole derivatives would be feasible, in which Pd-catalyzed direct C−H addition of various electronic-rich heteroarenes to the cyano group of *O*-acyl cyanohydrins bearing an α-hydrogen under redox neutral reaction conditions, could lead to ketoimine intermediates, and subsequent cyclization would furnish functionalized targeted products in

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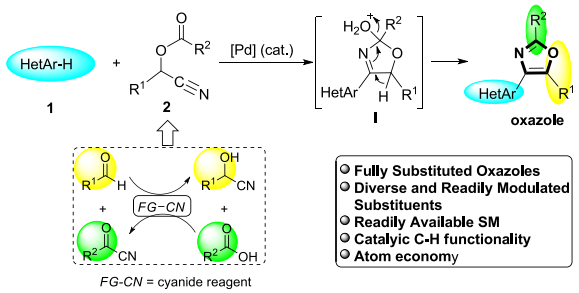
an atom-economic fashion (Scheme 1). Heteroarenes are common feedstock chemicals, while *O*-acyl cyanohydrins

Scheme 1. Working Plan

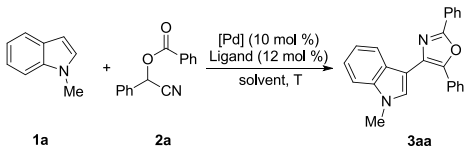


bearing α-hydrogen, which have demonstrated considerable synthetic potential as useful building blocks,[11] are readily prepared from aldehydes and acylcyanides or from cyanohydrins and carboxylic derivatives (Scheme 1). The readily availability and manipulation of reaction partners would enable this transformation to streamline the assembly of diverse trisubstituted oxazoles with high tunability under redox neutral and catalytic reaction conditions. Herein, we report this preliminary work.

We commenced our investigations by studying the reaction of *N*-methyl-indole **1a** with *O*-benzoyl cyanohydrin **2a** as a model reaction. To our delight, the expected C−H addition/cyclization sequence occurred by using $Pd(OAc)_2$ (10 mol %) and 2,2′-bipyridine (bpy) (12 mol %) at 120 °C and NMA/HOAc (3/1) as the mixed solvent, affording the desired 4-(1-methyl-1*H*-indol-3-yl)-2,5-diphenyloxazole **3aa**, but in low yield (Table 1, entry 1). The notably diminished yield was observed when either NMA or HOAc was employed as a sole solvent (Table 1, entries 2−3). Further investigation on solvents revealed that the combination of less polar solvents such as toluene with HOAc provided inferior results to those of polar solvents such as DMA, while NMA was more promising (Table 1, entries 4−5, and Table S1 of the Supporting Information). The influence of the nature and loading of acids on the reaction outcome was subsequently probed. It turned out that the reduced loading of acids such as TFA gave improved yields in the presence of NMA as a solvent, while HOAc gave a deteriorated yield (Table 1, entries 6−8, and Table S1 of the Supporting Information). Notably, the desired C−H addition/cyclization sequence proceeded well with TFA (20 mol %) and gave product **3aa** in 69% yield (Table 1, entry 9; for details, see Table SI-1 of the Supporting Information (SI)). The screening of Pd(II) catalysts and ligands revealed that both catalyst and ligand are essential for this transformation, and either $Pd(TFA)_2$ or cationic Pd(II) intermediate, in situ generated from $PdCl_2$ (10 mol %) and $AgSbF_6$ (20 mol %), afforded a superior result by using 2,2′-bipyridine (bpy) as a ligand (Table 1, entries 10−15). Further survey on other reaction parameters such as the loading of the catalyst, reaction temperature, and ratio of **1a** and **2a** (**1a**/**2a** = 2.5/1) enabled this transformation to provide the product **3aa** in high yield in the presence of $Pd(TFA)_2$ (5 mol %), bpy (6 mol %), and TFA (20 mol %) in NMA at 120 °C (Table 1, entry 16), establishing the optimized reaction conditions (for details see the SI).

With the optimized conditions in hand, we explored the scope of the reaction (Scheme 2). First, versatile synthesis of 4-

Table 1. Selected Optimization of Reaction Conditions[a]



entry	[Pd]	ligand	solvent	*t* (h)	yield (%)[b]
1	$Pd(OAc)_2$	bpy	NMA/HOAc = 3/1	12	50
2	$Pd(OAc)_2$	bpy	NMA	12	8
3	$Pd(OAc)_2$	bpy	HOAc	12	12
4	$Pd(OAc)_2$	bpy	DMA/HOAc = 3/1	12	40
5	$Pd(OAc)_2$	bpy	$PhCH_3$/HOAc = 3/1	12	20
6	$Pd(OAc)_2$	bpy	NMA/TFA = 3/1	9	21
7[c]	$Pd(OAc)_2$	bpy	NMA/TFA	9	68
8[c]	$Pd(OAc)_2$	bpy	NMA/HOAc	12	22
9[d]	$Pd(OAc)_2$	bpy	NMA/TFA	9	69
10[d]	$Pd(TFA)_2$	bpy	NMA/TFA	9	74
11[d,e]	$PdCl_2$	bpy	NMA/TFA	9	74
12[d]	$Pd(TFA)_2$	**L1**	NMA/TFA	9	70
13[d]	$Pd(TFA)_2$	**L2**	NMA/TFA	9	64
14[d]	–	–	NMA/TFA	12	<1
15[d]	$Pd(TFA)_2$	–	NMA/TFA	12	<1
16[d,f,g]	$Pd(TFA)_2$	bpy	NMA/TFA	4	83

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), catalyst (10 mol %), and ligand (12 mol %) in solvent (c = 0.4 M). [b]Isolated yields. [c]Acid (100 mol %). [d]Acid (20 mol %). [e]$AgSbF_6$ (20 mol %) was added. [f]$Pd(TFA)_2$ (5 mol %), ligand (6 mol %). [g]**1a** (0.5 mmol). bpy: 2,2′-bipyridine. **L1**: 1,10-phenanthroline. **L2**: 5,5′-dimethyl-2,2′-bipyridyl. NMA: *N*-methylacetamide. DMA: *N*,*N*-dimethylacetamide.

indolyl-trisubstituted oxazoles from a broad range of substituted indoles and *O*-acyl cyanohydrins **2** was examined. Besides *N*-methyl 3-substituted indole **1a**, both *N*-benzyl substituted indole **1b** and *N*-unsubstituted indole **1c** could also react with **2a** to provide the desired products **3ba** and **3ca** with similar yields to that of substrate **1a**, while the latter can be easily manipulated by introducing different *N*-substituents at the indolyl of trisubstituted oxazole derivatives. Various substituted free (NH) indoles can react with α-cyanobenzyl benzoate **2a** to afford the desired products **3** in high yields, and both the substitution pattern and electronic nature of substitutions at the benzene ring of the indole core were well tolerated (**3ea**−**3ja**). The readily availability and manipulation of *O*-acyl cyanohydrins bearing α-hydrogen **2** also enabled this transformation to streamline the introduction of diverse substituents at the 2- or 5-position of trisubstituted oxazoles under the optimized reaction conditions. For example, electron-rich or -poor aromatic groups, heteroaromatic groups, alkenyl, and alkyl were all well introduced at the 2- (**3fm**−**3fy**) or 5-position (**3fb**−**3fl**) from the readily available starting materials. Notably, a chiral amine unit can be easily incorporated into the oxazole core, which gave (*R*)-1-indolyl-5-phenyloxazol-2-yl)-*N*,*N*,2-trimethylpropan-1-amine **3fz** in 77% yield when 5-chloro-1*H*-indole **1f** and *O*-acyl cyanohydrin prepared from *N*,*N*-dimethyl-D-valine and 2-hydroxy-2-phenylacetonitrile were employed. Biotin, known as vitamin H featured with the fused bicyclic ring system containing ureido and thiophene moieties, is involved in a wide range of metabolic processes, both in humans and in other organisms. By virtue of the facile preparation of biotin-based *O*-acyl cyanohydrin, this key substructure unit can be readily

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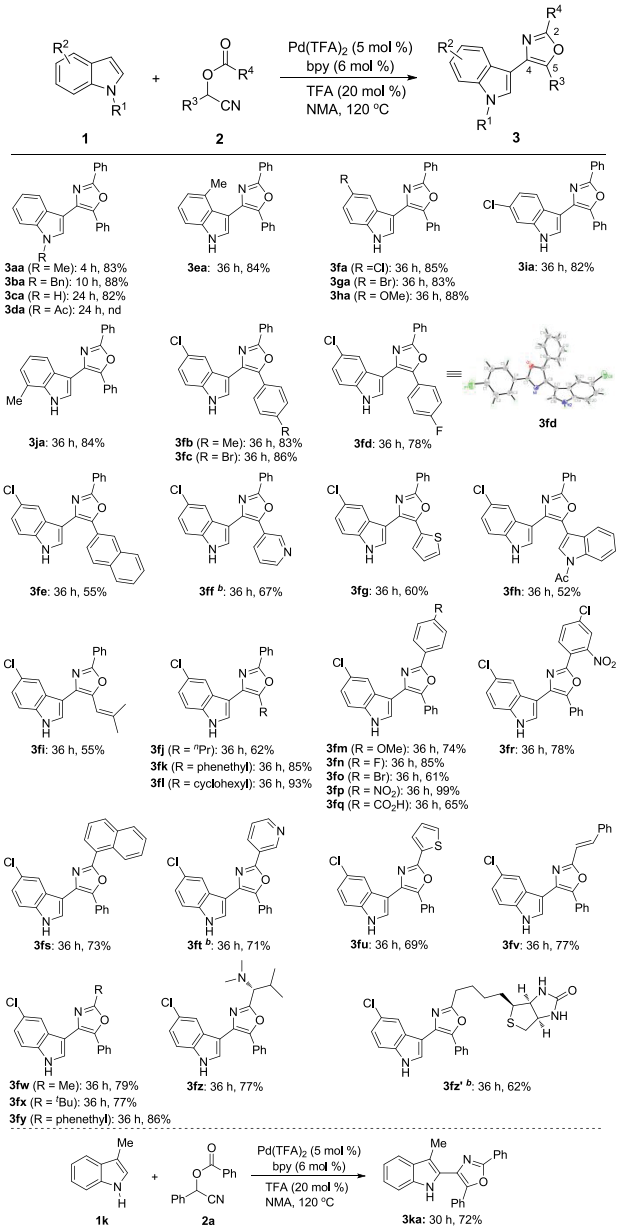
Scheme 2. Substrate Scope with Respect to Indole Derivatives 1 and *O*-Acyl Cyanohydrins 2[a]

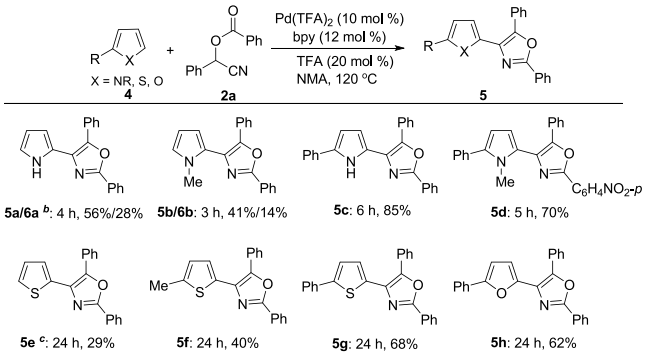


[a]Reaction conditions: **1** (0.5 mmol), **2** (0.2 mmol), $Pd(TFA)_2$ (5 mol %) and bpy (6 mol %) in NMA (c = 0.4 M). Yields shown are of isolated products. [b]$Pd(TFA)_2$ (10 mol %) and bpy (12 mol %).

assembled at the oxazole core with high efficiency (**3fz′**). In addition, 3-substituted indole **3k** was also a suitable substrate which reacted with α-cyanobenzyl benzoate **2a** to provide the desired indol-2-yl oxazole **3ka** in 72% yield. The structures of 4-indolyl-trisubstituted oxazoles were unambiguously confirmed by the exemplification of X-ray crystal structural analysis of product **3fd**. To evaluate the practicality of this catalytic transformation, the reaction of **2a** (1 mmol) with **1a** was carried out, which furnished the desired product **3aa** in 84% yield.

We next explored different heteroarenes (Scheme 3) and were pleased to find that either free (NH) pyrrole or *N*-methylpyrrole can react with α-cyanobenzyl benzoate **2a** to afford the desired product **5a** or **5b** in moderate yield, along

Scheme 3. Substrate Scope with Other Heteroarenes[a]

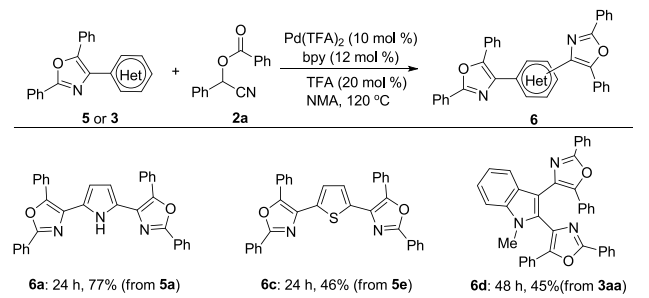


[a]Reaction conditions: **4** (0.5 mmol), **2a** (0.2 mmol), $Pd(TFA)_2$ (10 mol %), and bpy (12 mol %) in NMA (c = 0.4 M). Yields shown are of isolated products. [b]$Pd(TFA)_2$ (5 mol %) and bpy (6 mol %). [c]**4** (1.0 mmol).

with 2,5-bis(2,5-diphenyloxazol-4-yl)-pyrrole **6a** or **6b**. When 2-phenyl (NH) pyrrole and *N*-methyl-2-phenyl pyrrole were employed, the reactions delivered the desired pyrrolyl substituted oxazoles **5c** and **5d** in good yields. The reactivities of thiophene and furan were also investigated, and the reactions of 2-substituted thiophenes and furan with α-cyanobenzyl benzoate **2a** proceeded smoothly and gave the desired products in reasonable yields (**5f**–**5h**), albeit with prolonged reaction times. Unsubmitted thiophene afforded the product **5e** in low yield under the optimized reaction conditions. However, treatment of benzo[*b*]thiophene or benzofuran with **2a** did not give any desired products.

In addition, this approach is also applicable to the introduction of another oxazole unit into heteroarenes via the second C–H addition/cyclization sequence (Scheme 4),

Scheme 4. Substrate Scope[a]



[a]Reaction conditions: $Pd(TFA)_2$ (10 mol %) and bpy (12 mol %) in NMA (c = 0.4 *M*); for substrates **5**: **5a** or **5e** (0.2 mmol), **2a** (0.3 mmol); for substrate **3aa**: **3aa** (0.5 mmol), **2a** (0.2 mmol). Yields shown are of isolated products.

which further extended this method to access multioxazolyl substituted heteroarenes with high efficiency. For example, treatment of mono-oxazolyl substituted pyrrole **5a** with **2a** can furnish 2,5-bis(2,5-diphenyloxazol-4-yl)-1*H*-pyrrole **6a** in 77% yield, while the corresponding thiophene analogue **6c** can be obtained in 46% yield. Interestingly, employing a 3-oxazolyl substituted indole **3aa** as a substrate led to the formation of the 2,3-bis- oxazolyl substituted indole **6d** in 45% yield.

Furthermore, by virtue of the iterative operation of this C–H addition/cyclization sequence, *N*-methyl-2-phenyl pyrrole **4c** can react respectively with 1,4-phenylenebis(cyano-

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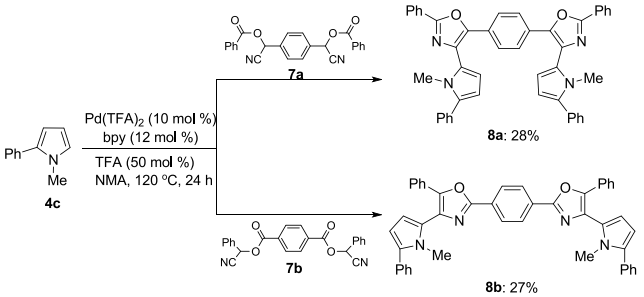
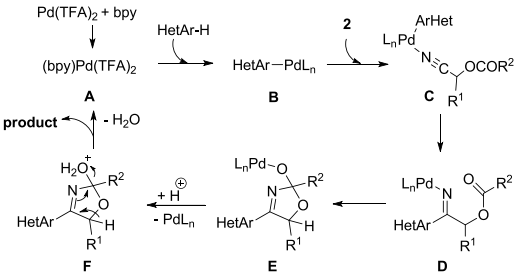
methylene) dibenzoate **7a** and bis(cyano(phenyl)methyl) terephthalate **7b** to give the bis-trisubstituted-oxazole derivatives **8a** and **8b** in reasonable yields (Scheme 5).

Scheme 5. Iterative C−H Addition/Cyclization Sequences



On the basis of our results and the precedent reports,[9d,e,10a] a possible mechanism was proposed (Scheme 6). First, direct

Scheme 6. Proposed Mechanism



palladation at a heteroarene with [(bpy)Pd(TFA)$_2$] **A** would provide a palladium complex **B**. Subsequently, the coordination between the cyano group of *O*-acyl cyanohydrin bearing α-hydrogen **2** and complex **B** provides intermediate **C**, which undergoes an addition of a heteroarene group to a cyano group to generate the ketimine Pd(II) complex **D**. Finally, an intramolecular cyclization of the intermediate **D** would deliver species **E**, which undergoes the protonolysis, elimination, and aromatization to yield the desired product and regenerate the Pd(II) species **A**.

In summary, a practical and flexible intermolecular protocol for the diverse synthesis of trisubstituted oxazole derivatives *via* a Pd-catalyzed direct C−H addition of various electronic-rich heteroarenes to the cyano group of *O*-acyl cyanohydrins bearing α-hydrogen has been developed. Under redox neutral reaction conditions, various trisubstituted oxazoles can be prepared from readily available starting materials in good to high yields with high tunability. Further investigations into the application of this strategy to preparing other azaheterocyclic compounds and biologically relevant compounds are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00700.

Experimental procedures and analytical data for all new compounds (PDF)

^{1}H and ^{13}C NMR spectral copies (PDF)

Accession Codes

CCDC 1898596 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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