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Synthesis of 2,5-Disubstituted Oxazoles via Cobalt(III)-Catalyzed Cross-Coupling of *N*-Pivaloyloxyamides and Alkynes

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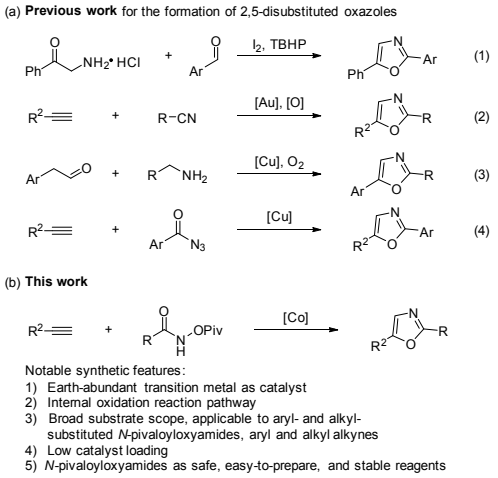
An efficient synthesis of 2,5-disubstituted oxazoles via Co(III) catalysis is described herein. The synthesis is achieved under mild condition through [3+2] cycloaddition of *N*-pivaloyloxylamides and alkynes. The reaction operates through an internal oxidation pathway and features a very broad substrate scope. One-step synthesis of natural products texamine and balsoxin has been demonstrated via this protocol.

The oxazole ring is an important structural motif in compounds with activities relevant to biology and medicinal chemistry.[1] Especially, 2,5-disubstituted oxazoles are prevalent chemical and pharmaceutical synthetic intermediates.[2] Organic chemists have developed many methods to synthesize oxazoles over the past decades.[3] A noteworthy example was the construction of 2,5-diaryl substituted oxazoles via TBHP/I_2-mediated tandem oxidative cyclization (Scheme 1a, eq 1).[4] In 2011, Zhang and coworkers developed a [2+2+1] annulation of a terminal alkyne, a nitrile, and an oxygen atom (from pyridine/quinoline *N*-oxides) through gold catalysis (Scheme 1a, eq 2).[5] In 2012, the Jiao group described a copper-catalyzed oxidative dehydrogenative annulation method starting from aldehydes, amines, and molecular oxygen (Scheme 1a, eq 3).[6] The Pérez group demonstrated another copper-catalyzed synthetic method for oxazoles through the reaction of alkynes and aryl carbonyl azides (Scheme 1a, eq 4).[7] Despite the tremendous progress witnessed in this field, synthetic challenges remain because of the requirement of stoichiometric amount of an external oxidant[3b,c,e,g,h,4-6] or toxic metal salts,[8] limited substrate scope,[4,6,7] and pre-installation of multiple functionalities in a single substrate for intramolecular cyclyzation reactions (potentially generating functionality compatibility issue).[2f,g] In addition, azides and α-functionalized ketones (e.g., α-diazoketones) used for the synthesis are potentially explosive and generally not commercially available.[5,7,9] Therefore, the development of more efficient methods for the synthesis of oxazoles are highly desirable.



Scheme 1. Previous work and this work for the formation of 2,5-disubstituted oxazoles

We have developed several Co(III)-catalyzed C-H activation strategies for the construction of heterocycles in the past years.[10] In an attempt to expand the synthetic scope enabled by this earth-abundant metal, we have uncovered a reactivity pattern not previously identified. Herein, we discolse an efficient [3+2] synthesis of 2,5-disubstituted oxazoles via cobalt(III)-catalyzed cross-coupling of *N*-pivaloyloxyamides and alkynes. Notable features associated with the protocol are three-folds: 1) *N*-Pivaloyloxyamides are safe, easy to prepare, and stable on storage;[11] 2) The reaction proceeds through an internal oxidation pathway; and 3) The substrate scope is broad, applicable to aryl- and alkyl-substituted *N*-pivaloyloxyamides, aryl and alkyl alkynes.

We commenced our studies by investigating the reaction between *N*-(pivaloyloxy)benzamide (**1a**) and ethynylbenzene (**2a**) (Table 1). Preliminary examination (entries 1–4) identified [Cp*Co(MeCN)$_3$(SbF$_6$)$_2$] as the effective catalyst, DCE as the solvent of choice, 80 °C and 20 h as the ideal reaction

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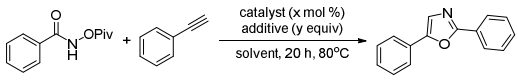
temperature and reaction time, affording target product 2,5-diphenyloxazole (**3a**) in 75% yield with 10 mol % Co(III) catalyst

Table 1. Optimization of reaction conditions[a,b]



1a 2a 3a

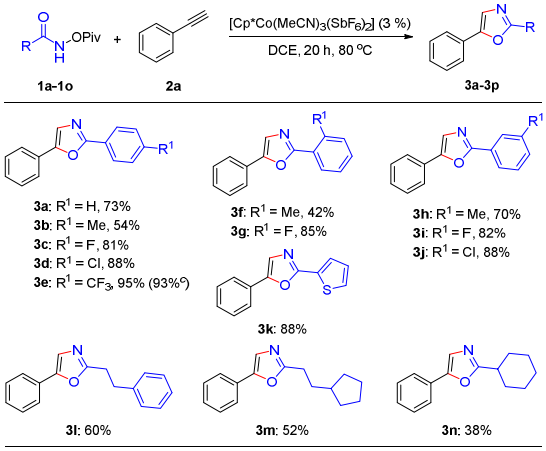
entry	catalyst (x mol %)	additive (y equiv)	solvent	yield (%)
1	$[Cp^*Co(CO)I_2]$ (10)	PivOH (1.0)	DCE	0
2	$Co(acac)_2$ (10)	PivOH (1.0)	DCE	0
3	CuI (10)	PivOH (1.0)	DCE	0
4	$[Cp^*Co(MeCN)_3(SbF_6)_2]$ (10)	PivOH (1.0)	DCE	75
5	$[Cp^*Co(MeCN)_3(SbF_6)_2]$ (10)	KOAc (1.0)	DCE	30
6	$[Cp^*Co(MeCN)_3(SbF_6)_2]$ (10)	-	DCE	77
7	$[Cp^*Co(MeCN)_3(SbF_6)_2]$ (10)	-	DCE	75[c]
8	$[Cp^*Co(MeCN)_3(SbF_6)_2]$ (5)	-	DCE	77
9	$[Cp^*Co(MeCN)_3(SbF_6)_2]$ (3)	-	DCE	75
10	$[Cp^*Co(MeCN)_3(SbF_6)_2]$ (5)	-	MeOH	0
11	$[Cp^*Co(MeCN)_3(SbF_6)_2]$ (5)	-	$CHCl_3$	40
12	$[Cp^*Co(MeCN)_3(SbF_6)_2]$ (5)	-	EtOAc	29
13	$[Cp^*Co(MeCN)_3(SbF_6)_2]$ (5)	-	DCE	63[d]
14	**$[Cp^*Co(MeCN)_3(SbF_6)_2]$ (3)**	-	**DCE**	**73[e]**

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), not excluding air. [b]Isolated yields are shown. [c]N_2. [d]60°C. [e]**2a** (0.3 mmol)

and 2 equiv **2a**. No extra additive proved to be necessary for effecting the transformation (entries 4, 6), and basic condition was detrimental (entry 5). Further optimization indicated that decrease of the amount of Co(III) catalyst to 5 mol % or even 3 mol % and the amount of **2a** to 1.5 equiv did not affect the yield (entries 6, 8, 9, 14). The reaction could proceed efficiently in both air and nitrogen, rendering it unnecessary to exclude air during the reaction (entries 6, 7). The switching of reaction medium from DCE to other solvents (entries 8, 10–12) and decrease of the reaction temperature to 60 °C diminished the yield (entry 13). Taken together, 3 mol % or 5 mol % $[Cp^*Co(MeCN)_3(SbF_6)_2]$, 1.5 equiv alkyne, DCE, 80 °C, and 20 h were selected as the optimized reaction condition.

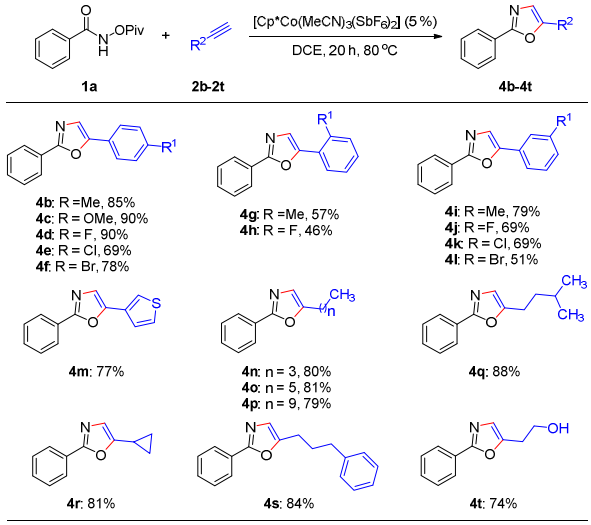
Using the acquired optimized reaction condition and with **2a** as the coupling reagent, the scope of *N*-pivaloyloxyamides was inspected (Scheme 2). Notably, a variety of *N*-pivaloyloxyamides, which bear both electron-donating (**1b**, Me) and electron-withdrawing (**1c**, F; **1d**, Cl; **1e**, CF_3) groups at the *para* position of aryl group, were compatible with the trasformation. The reaction also proceeded effectively for *ortho*- and *meta*-substituted substrates (**1f**, Me; **1g**, F; **1h**, Me; **1i**, F; **1j**, Cl). In addition, *N*-(pivaloyloxy)thiophene-2-carboxamide (**1k**) was a viable substrate. Further exploration suggested the ability to extend substrate scope to alkyl-substituted *N*-pivaloyloxyamides (**1l**-**1n**). *N*-(methoxy)benzamide as a substrate was tested under the optimized reaction condition, and no product was obtained (Only the surplus of the starting material).

The optimized reaction condition was then challenged with a diversity of alkynes to probe its scope, by taking **1a** as the reaction partner (Scheme 3). Satisfactorily, a diverse range of functional groups on ethynylbenzene (**2b**-**2t**), including both electron-donating (**2b**, Me; **2c**, OMe) and electron-withdrawing (**2d**, F; **2e**, Cl; **2f**, Br) groups at the *para* position of aryl group were tolerated. The *ortho*- and *meta*-substituted substrates (**2g**, Me; **2h**, F; **2i**, Me; **2j**, F; **2k**, Cl; **2l**, Br) were also compatible. Alkynes bearing thiophenyl and alkyl groups could also react efficiently to afford the respective target products (**2m**-**2t**). Noteworthy was the ability to incorporate hydroxyl group (**2t**) into the product, providing a potential reaction site for further manipulation. Internal alkynes were tested under the conditions reported herein, and minimal reactivity was observed at the current stage. The reaction conditions for internal alkynes might be different from those for terminal alkynes and need further fine tuning for the best outcome.



[a]Reaction conditions: **1a–o** (0.2 mmol), **2a** (0.3 mmol), not excluding air. [b]Isolated yields are shown. [c]**1e** (1.0 mmol).

Scheme 2. Substrate scope for *N*-pivaloyloxyamides[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2b-t** (0.3 mmol), not excluding air. [b]Isolated yields are shown.

Scheme 3. Substrate scope for alkynes[a,b]

The effectiveness of the reaction and broadness of the substrate scope prompted the investigation of reaction mechanism (Scheme 4). Two different reaction pathways could be envisaged: one proceeds through the formation of a Co(III)–acetylide species; the other proceeds through the formation of a Co(III)-alkyne π-complex. In order to pinpoint the actual pathway, several reactions were performed. A reaction between **1a** and **2c**-*d* (94% D) under optimized reaction

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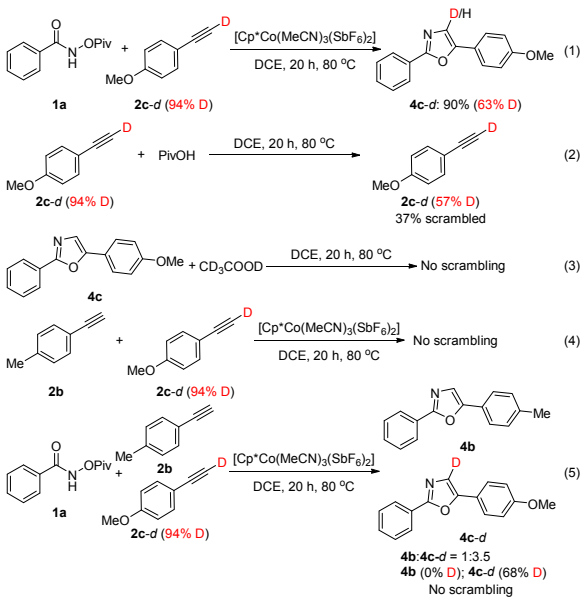
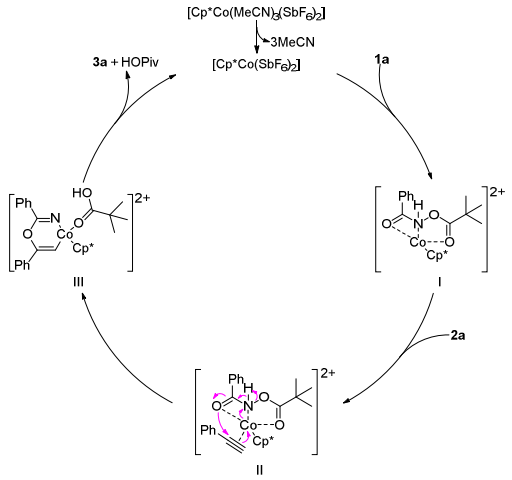
condition generates **4c**-*d* (63% D) (Scheme 4, eq 1). Since the catalysis results in the production of PivOH, the D/H scrambling could come from the exchange between **2c**-*d* and PivOH. This was indeed the case and a reaction between **2c**-*d* and PivOH leads to a decrease of D percentage to 57% (Scheme 4, eq 2). One formed, the product does undergo H/D scrambling reaction (Scheme 4, eq 3). Further, no H/D scrambling occurred between **2b** and **2c**-*d* (Scheme 4, eq 4) under Co(III) catalysis, consistent with the absence of Co(III)–acetylide species. A reaction comprising **1a**, **2b**, and **2c**-*d* under optimized reaction condition afforded strictly non-D-labeled **4b** and D-labeled **4c**-*d* (Scheme 4, eq 5), also supporting the absence of a Co(III)–acetylide species. Taken together, the reaction proceeded through a Co(III)-alkyne π-complex formation pathway.



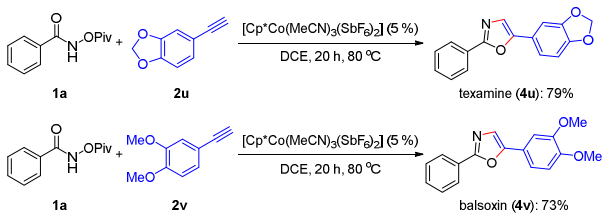
Scheme 4. Mechanistic studies for Co(III)-catalyzed coupling of *N*-pivaloyloxyamides with alkynes



Scheme 5. Proposed catalytic mechanism

With these experiments and literature precedents[7b,10c,12] in hand, a reaction pathway is proposed in Scheme 5. At first, chelation of **1a** with Co(III) catalyst affords complex **I**; and then, **2a** binds to the cobalt center and forms a π-complex **II**; this is followed by a concerted process, featuring cleavage of weak N-O bond and formation of O-C bond, Co(V)-N bond, Co(V)-C bond and yielding complex **III**; Subsequent reductive elimination and C-N bond formation leads to the formation of cyclized product **3a** and regeneration of Co(III) catalyst.

To demonstrate the synthetic utility of the reaction protocol developed herein, direct synthesis of natural products was pursued (Scheme 6). It is noteworthy that natural products texamine (**4u**) [13] and balsoxin (**4v**) [14] could be accessed through a straightforward one-step procedure. In comparison, the synthesis of these natural products typically required either high temperature[15] or stoichiometric metal complexes.[16]



Scheme 6. One-step synthesis of natural products

In summary, an efficient [3+2] synthesis of 2,5-disubstituted oxazoles via cobalt(III)-catalyzed cross-coupling of *N*-pivaloyloxyamides and alkynes has been achieved. The reaction operates through an internal oxidation pathway and as such is compatible with a broad scope of substrates (applicable to aryl- and alkyl-substituted *N*-pivaloyloxyamides, aryl and alkyl alkynes). The synthetic protocol developed herein has demonstrated its synthetic utility in the expedient construction of natural products and is expected to play an crucial role in future synthesis of complex and important oxazole compounds.

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Conflicts of interest

The authors declare no competing financial interest.

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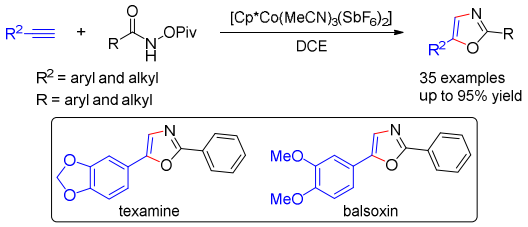

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