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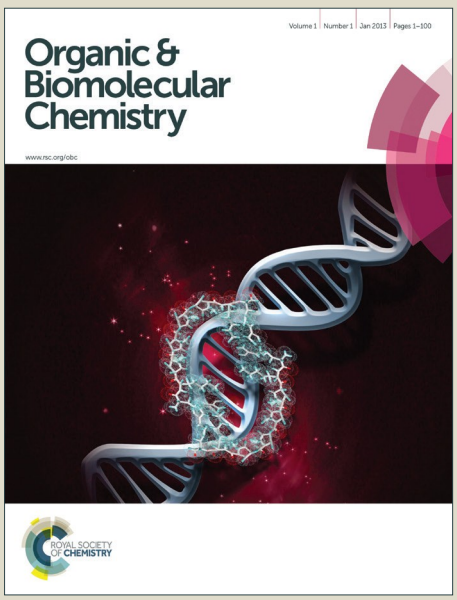

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ARTICLE TYPE

Zn/Sc bimetallic relay catalysis: one pot cycloisomerization/carbonyl–ene reaction toward oxazole derivatives

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A novel Zn(II)-catalyzed cycloisomerization and Sc(III)-catalyzed carbonyl–ene reaction combined tandem metal relay catalytic system has been successfully developed. By using this unprecedented Zn/Sc bimetallic relay catalysis, a variety of oxazole derivatives were obtained from easily available N-(propargyl)arylamides and aldehydes under mild conditions.

Oxazole nucleus have attracted intense attentions due to their promising biological activities widely spread in the natural compounds and pharmaceuticals (Figure 1).[1] For example, Dolastain I, which is a cyclic hexapeptide containing an oxazole and oxazoline moiety, displays cytotoxicity against HeLa S_3 cells.[2] The Bistratamide family also exhibit cytotoxic and antineoplastic activities as well as the possibility of acting as metal ion chelating metabolites, such as Bistratamide D, which has been proved to induce sedation in mice when administered by intracerebral injection.[3] Bengazole A, as another example, stands out as particular bisoxazoles motif containing a carbohydrate-like polyol side chain, which shows antihelminthic activity and also could be potent antifungal agent.[4] Hennoxazole A is active against herpes simplex type I and presents peripheral analgesic activity comparable with that of indomethacin.[5] Oxazoles are also important intermediates in organic synthesis and as ligands for catalysis.[6] Therefore, the development of an efficient and practical approach for the synthesis of oxazole derivatives is highly desirable.

Recently, transition-metal-catalyzed cyclization of propargylic amides to prepare oxazole framework has gained considerable attentions and significant progress has been achieved in this area.[7] For instance, Broggini and co-workers reported an elegant Pd-catalyzed 5-*exo-dig* oxidative cyclization into 5-oxazolecarbaldehydes in 2008.[8] Later in 2012, Hashmi and co-workers developed a gold(I)-catalyzed protocol to transform

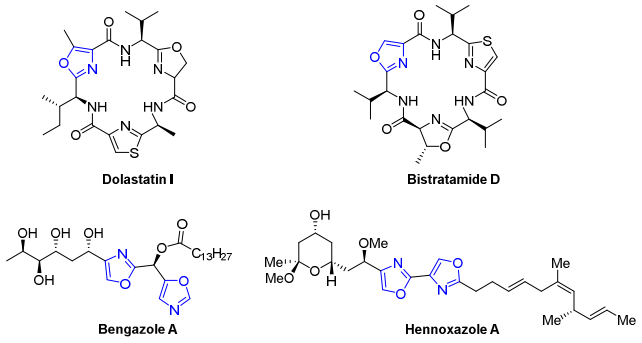
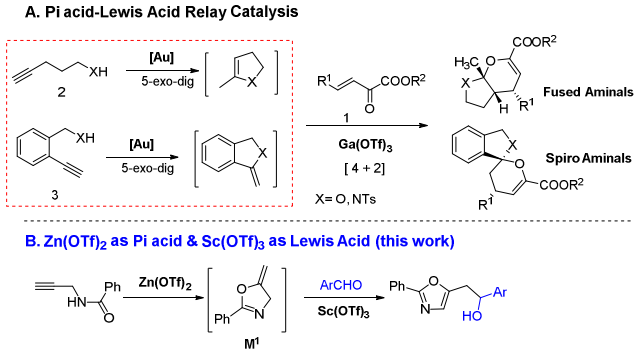


Figure 1. Natural products and pharmaceuticals containing oxazole unit.



Scheme 1. Zn/Sc bimetallic relay catalysis strategy to construct oxazole.

the propargylic amides to homologous alkylideneoxazolines. [9] In 2014, Wan and coworkers reported a novel approach toward functionalized oxazoles by a silver(I)-catalyzed [3,3]-rearrangement/sulfonyl migration tandem reaction of N-sulfonyl propargylamides.[10] In this communication, we report here a Zn(II)/Sc(III) bimetallic catalysis approach to construct functionalized oxazole derivatives from easily available propargylic amides and aldehydes.

Previously we combined Au as the π acid and another early transition metal as the σ acid together and developed a series of bimetallic relay catalysis. By using this relay catalysis, various biologically important fused or spiroaminals could be efficiently synthesized in one step (Scheme 1A).[11] These reactions went through a gold(I)-catalyzed cyclization[12] forming an electron-rich enamide intermediate and subsequent Lewis acid-catalyzed inverse-electron-demand hetero-Diels-Alder reactions. We

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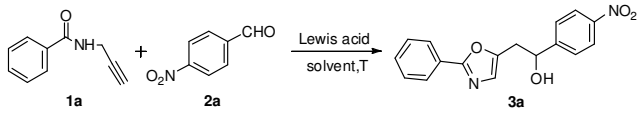
reasoned that the cyclization of propargylic amide furnished a similar nucleophilic exocyclic double bond. This cyclization could be catalysed by Au(I) or Zn(II) catalyst.[8] Then another Lewis acid catalyzed carbonyl-ene type reaction[13] with an aldehyde would furnish oxazole derivatives (Scheme 1 B). This carbonyl–ene reaction is a versatile and useful method to construct carbon–carbon bond formation owing to its high atom-economy.

Table 1. Optimization of Reaction Conditions[a]

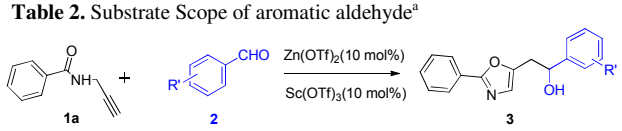


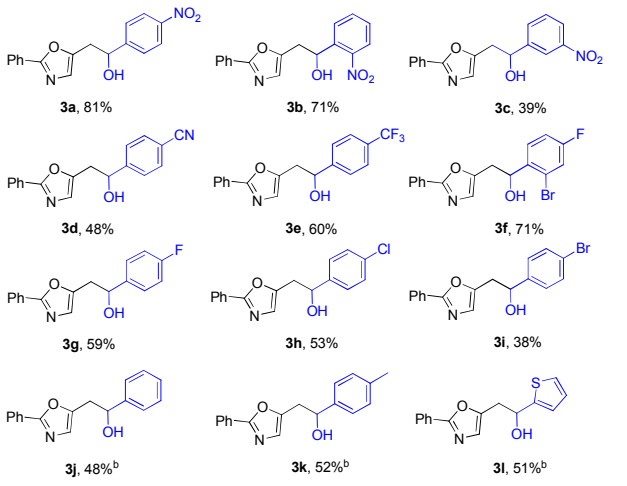
Entry	Catalyst **A**	Catalyst **B**	Solvent	T/°C	Yield(%)[b]
1	$Zn(OTf)_2$	$In(OTf)_3$	DCM	45	35
2	$Zn(OTf)_2$	$Ga(OTf)_3$	DCM	45	38
3	$Zn(OTf)_2$	$La(OTf)_3$	DCM	45	66
4	**$Zn(OTf)_2$**	**$Sc(OTf)_3$**	**DCM**	**45**	**81**
5	$Zn(OTf)_2$	$Y(OTf)_3$	DCM	45	50
6	$Zn(OTf)_2$	$Bi(OTf)_3$	DCM	45	73
7	$In(OTf)_3$	$Sc(OTf)_3$	DCM	45	45
8	$Ga(OTf)_3$	$Sc(OTf)_3$	DCM	45	16
9	AgOTf	$Sc(OTf)_3$	DCM	45	30
10	$Cu(OTf)_2$	$Sc(OTf)_3$	DCM	45	11
11[c]	$Ph_3PAuNTf_2$	$Sc(OTf)_3$	DCM	45	76
12[d]	$Zn(OTf)_2$	-	DCM	45	16
13	-	$Sc(OTf)_3$	DCM	45	trace
14	$Zn(OTf)_2$	$Sc(OTf)_3$	DCM	55	78
15	$Zn(OTf)_2$	$Sc(OTf)_3$	DCE	60	36
16	$Zn(OTf)_2$	$Sc(OTf)_3$	DCE	70	60

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol),Catalyst **A** (10 mol%), Catalyst **B** (10 mol%), solvent (2 mL), overnight; [b]isolated yield; [c]5 mol% of PPh_3AuCl catalyst, 10 mol% of $Ag(NTf)_2$ catalyst.[d]oxazoline intermediate M[1] was isolated in 41% yield.

At the outset, we initiated our study with N-(prop-2-yn-1-yl)benzamide **1a** and *p*-nitrobenzaldehyde **2a** in the presence of $Zn(OTf)_2$ as π acid[14] and other Lewis acid catalysts. Fortunately, all the tested Lewis acids such as $Sc(OTf)_3$, $Ga(OTf)_3$, $La(OTf)_3$, $In(OTf)_3$, $Y(OTf)_3$, and $Bi(OTf)_3$ could produce the target oxazole products **3a**. In particular, $Sc(OTf)_3$ gave the best yield (entries 1-6). Then various π acid catalysts were screened together with $Sc(OTf)_3$. It turned out that other π acid catalysts such as Ag(I) and Au(I) produced much lower yields(entries 7-11). Control experiments confirmed that both the $Zn(OTf)_2$ and $Sc(OTf)_3$ catalyst are necessary in this process (entries 12-13). The reaction with only $Zn(OTf)_2$ catalyst gave product **3a** in 16% yield, together with oxazoline intermediate M[1] in 41% yield. Merely a trace amount of product **3a** could be detected TLC with only $Sc(OTf)_3$ catalyst. Further optimization of solvents and reaction temperatures showed that the reaction with Zn(II) and Sc(III) as catalysts at 45 °C is the best condition (entry 4).

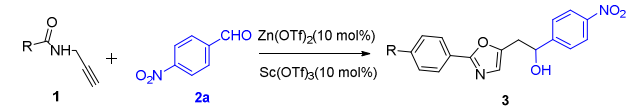
Table 2. Substrate Scope of aromatic aldehyde[a]

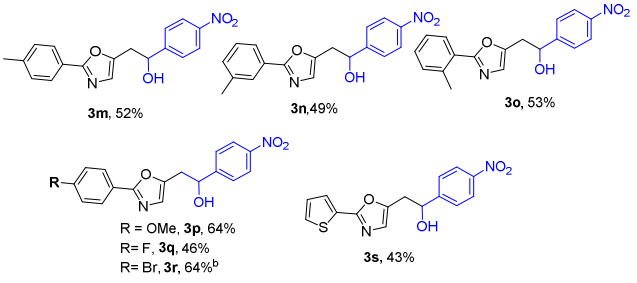




[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), $Zn(OTf)_2$ (10 mol%), $Sc(OTf)_3$ (10 mol%), DCM (2 mL), 45°C, overnight, isolated yield. [b]at 55 °C.

Table 3. Substrate Scope of propargylic amides[a]





[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), $Zn(OTf)_2$ (10 mol%), $Sc(OTf)_3$ (10 mol%), DCM (2 mL), 45°C, overnight, isolated yield. [b]at 55 °C.

With the optimized reaction condition established, the scope of various aromatic aldehyde were tested (Table 2). Different substituents at different positions (*p*-, *o*-, *m*-) on the phenyl ring didn't affect this reaction and afford the corresponding product in moderate yields (**3a-c**). Various halogens were all tolerated in this reaction giving acceptable yields (**3f-i**), thus allowing further functionalization by cross coupling reaction. Electron-withdrawing groups such as CF_3, CN (**3d, 3e**) could give the corresponding products in very good yields. Electron rich aldehydes were less reactive, however, reasonable yields could be obtained by raising temperature to 55 °C (**3k**, **3l**). The structure of

3b was unambiguously characterized by single X-ray crystallography (Figure 2).

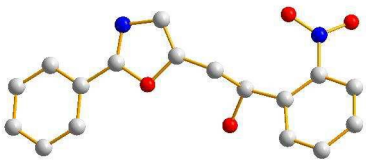
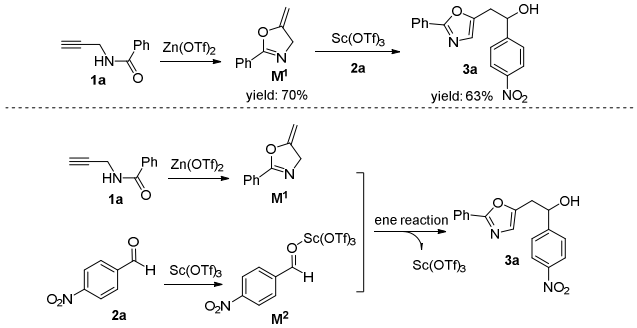


Figure 2.The crystal structure of **3b**.



Scheme 3. Proposed reaction mechanism.

We then investigated the scope of the reaction with respect to N-(propargyl)arylamides and the results are shown in Table 3. The methyl group at different position of the phenyl ring had no obvious influence on the reaction (**3m-o**). Moreover, irrespective of halogen (**3q, 3r**) or electron-donating (**3p**) substituents on the phenyl ring could get the desired product in tolerable yield. Heteroaromatic propargylic amide was also suitable substrate in the reaction (**3s**).

Control experiments were conducted to understand the mechanism. The reaction of **1a** in the presence of $Zn(OTf)_2$ could form oxazoline M^1 in 70% yield. This intermediate could react with aldehyde **2a** in the presence of $Sc(OTf)_3$, giving the product **3a** in 63% yield (Scheme 3). Based on aforementioned results, a conceivable mechanism-Zn/Sc bimetallic sequential catalyzed cascade reaction was proposed. Firstly, $Zn(OTf)_2$ acted as π acid to activate the triple bond of **1a** and subsequent intramolecular 5-*exo-dig* cyclization forming the oxazoline intermediate $\mathbf{M^1}$. On the other side, $Sc(OTf)_3$ coordinated with the carbonyl group of the aldehyde to form an electrophilic intermediate M^2. The carbonyl–ene reaction between M^1 and M^2 would produce the target oxazole product and regenerate $Sc(OTf)_3$ catalyst.

In conclusion, we have demonstrated an atom-economic intermolecular cycloisomerization/carbonyl–ene cascade reaction to construct oxazole derivatives. Such a facile construction of aromatic heterocycles from two easily available acyclic substrates will find more applications in organic synthesis and also medicinal chemistry. In this bimetallic relay catalytic process, the $Zn(OTf)_2$ catalyst acted as π acid and the $Sc(OTf)_3$ catalyst played a role of σ acid. Application of such bimetallic strategy in other reactions is underway in our laboratory.

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