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Metal-Free [2 + 2 + 2] Cycloaddition of Ynamides with Nitriles to Construct 2,4-Diaminopyridines

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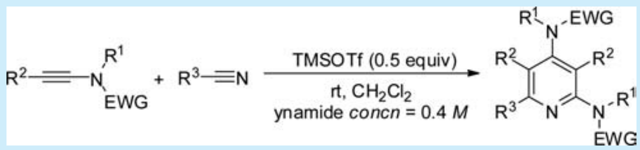
Supporting Information

ABSTRACT: We present a metal-free [2 + 2 + 2] cycloaddition of ynamides with nitriles that enables highly efficient access to 2,4-diaminopyridines. This catalytic protocol is more environmentally friendly and allows for a concomitant construction of C−C and C−N bonds between ynamides and nitriles, exhibiting excellent chemoselectivity, regioselectivity, and wide functional groups tolerance.



The pyridine nucleus belongs to the privileged structural motifs in the field of natural products as well as in the area of pharmaceutically active compounds.[1] Many natural product, such as vitamin B, nicotinamide, and nicotinic acid, which play important roles in metabolism and possess a wide spectrum of biological activities, contain a pyridine ring.[2] As important pyridine derivatives, 2,4-diaminopyridines are of particular utility. For examples (Figure 1), 2,4-diaminopyridines **I** and **II** can be used as sterilants allowing for their obverse inhibition effect on *Rhizoctonia solani*, *Cladosporium cucumerinum*, pepper phytophora blight, *Fusarium oxysporum*, wheat leaf blight, etc., and can be also used as virtual components in Echinochloa crusgalli herbicide owing to their obverse inhibition effect on *Echinochloa crusgalli*;[3] compounds **III** and **IV** are strong adenosine A_3 receptor ligands preferably antagonists.[4] Though metal-catalyzed [2 + 2 + 2] cycloadditions of alkynes and nitriles have been extensively studied for the construction of pyridine cores,[5,6] the examples about achieving high regioselectivity were rare.[6o,7] Furthermore, preparation of 2,4-diaminopyridines in a one-pot manner is also rarely reported,[8] and most of them suffer from low yields with narrow substrate scopes.

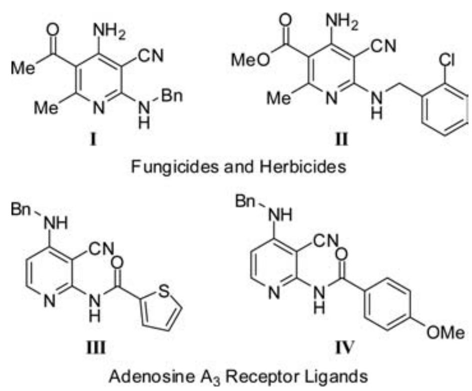
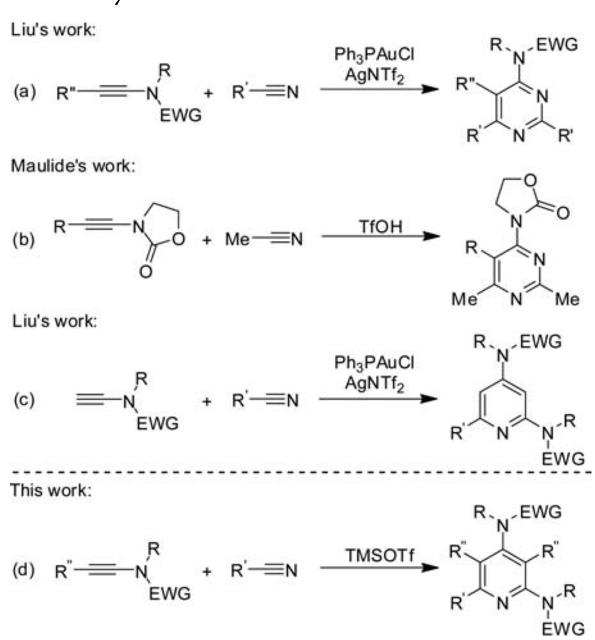


Figure 1. Selected biologically active 2,4-diaminopyridines.

As a subgroup of heteroatom-substituted alkynes, ynamides are special because nitrogen is one of the most privileged elements in nature. Consequently, many transformations involving ynamides offer a diverse array of novel structural entities that are not only powerful platforms for further transformations but also prevalent among important pharmacophores.[9,10] Ynamides have recently shown to be suitable candidates for regioselective cycloaddition with nitriles to construct 4-aminopyrimidines, in the present of gold catalyst and TfOH, respectively (Scheme 1a,b[11,12]). Later, Liu used the

Scheme 1. Cycloaddition of Ynamides with Nitriles



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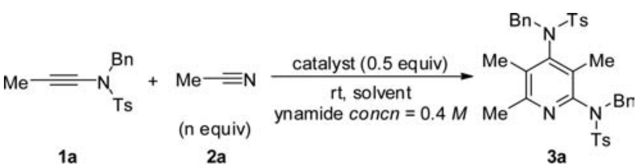
same gold catalyst to catalyze the cycloaddition reaction of terminally unsubstituted ynamides with nitriles, leading to 2,4-diaminopyridine cores with low to moderate yields (Scheme 1c).[8g] Although at the same time, we have discovered TMSOTf could efficiently catalyze the cycloaddition of ynamides with nitriles and were assessing the scope of this new reaction; to the best of our knowledge, that is the first example being reported to construct 2,4-diaminopyridines via the reactions of ynamides.[13] We describe here a novel and highly efficient metal-free strategy to construct 2,4-diaminopyridines via the TMSOTf-catalyzed regioselective [2 + 2 + 2] cycloadditions of various ynamides with nitriles (Scheme 1d). This outcome is surprising as it is in direct contrast to previous studies of the related terminally substituted ynamides (Scheme 1a,b), which showed no evidence for the 2,4-diaminopyridines formation.

The feasibility of this cycloaddition was first tested using ynamide **1a** with acetonitrile **2a** (Table 1). To our surprise, 2,4-diaminopyridine **3a** was isolated in 47% yield under the catalyst $BF_3 \cdot Et_2O$ in toluene (entry 1), which could not be observed from the reported reactions of terminally substituted ynamides with nitriles (Scheme 1a,b). Considering the long reaction time (26.0 h), we tried other solvents such as ether, DCE, and CH_2Cl_2 (entries 2−4), solvent screening revealed that no improvement was made in ether, but fortunately DCE or CH_2Cl_2 led to cycloadduct **3a** in high yield within short reaction time. Further investigation showed that there appears to be a noticeable stoichiometry effect: when the proportion of acetonitrile **2a** was reduced from 2.4 equiv to 1.2 or 0.6 equiv, the yield improved significantly (entries 4−6). We then tried other Lewis acids. Compared with $BF_3 \cdot Et_2O$, monodentate Lewis acids $AlCl_3$, $FeCl_3$, AgOTf, and bidentate Lewis acids $Zn(OTf)_2$, $ZnCl_2$, $SnCl_4$ were poor promoters overall (entries 7−12), with $SnCl_4$ appearing to impede the reaction (entry 12), but excitingly, nonmetallic MeOTf and TMSOTf could also catalyze the reaction affording product **3a**, with TMSOTf resulting in a quantitative yield (entries 13 and 14).[14] Further lowering the catalyst loading (0.25 equiv) led the yield suffer (entry 15).

The scope and generality of this cycloaddition are accentuated in Scheme 2. Initially, we examined several nitriles **2a−2f** under the optimized conditions. For various alkyl nitriles, their corresponding cycloadditions with ynamide **1a** gave the desired 2,4-diaminopyridines **3a−3e** with high to excellent yields. Remarkably, alkyl nitriles bearing functional groups such as aryl rings (**2c** and **2d**) or a halide atom (**2e**) were compatible with the reaction conditions. We were also pleased to find that this

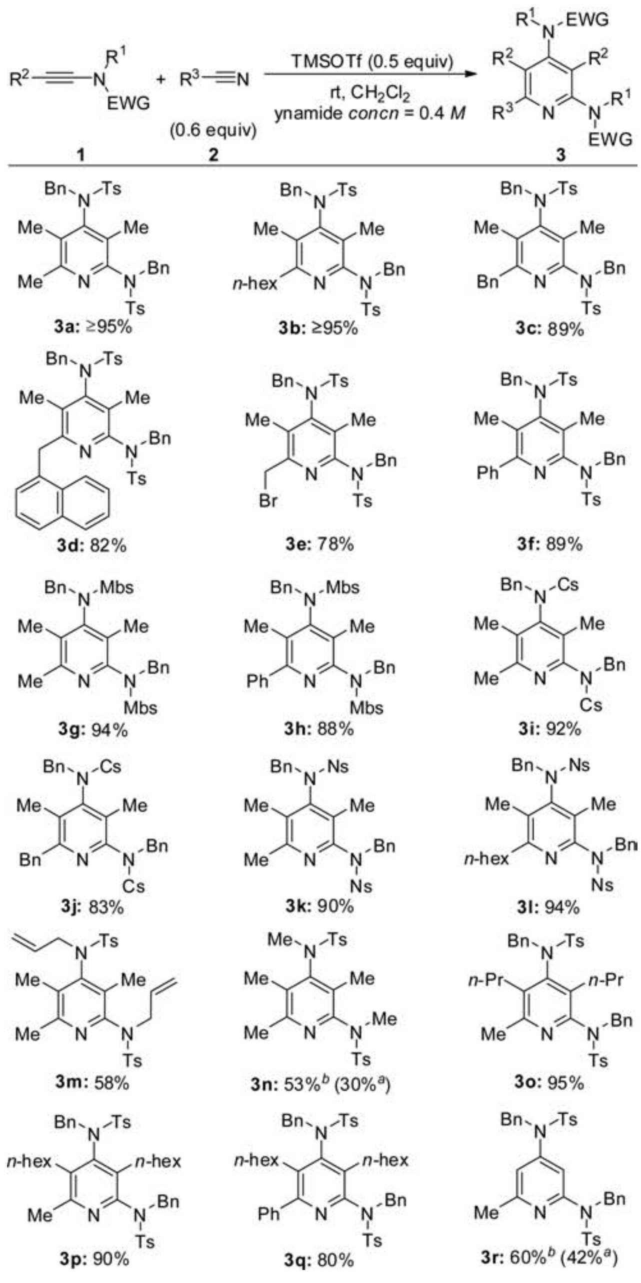
Table 1. Condition Optimization of the Cycloaddition



entry[a]	catalyst	n (equiv of MeCN)	solvent	time (h)	yield (%)[b]
1	$BF_3 \cdot Et_2O$	2.4	toluene	26.0	47
2	$BF_3 \cdot Et_2O$	2.4	Et_2O	62.0	18
3	$BF_3 \cdot Et_2O$	2.4	DCE	4.3	75
4	$BF_3 \cdot Et_2O$	2.4	CH_2Cl_2	5.0	78
5	$BF_3 \cdot Et_2O$	1.2	CH_2Cl_2	4.0	86
6	$BF_3 \cdot Et_2O$	0.6	CH_2Cl_2	7.0	87
7	$AlCl_3$	0.6	CH_2Cl_2	0.5	34
8	$FeCl_3$	0.6	CH_2Cl_2	18	20
9	AgOTf	0.6	CH_2Cl_2	25	27
10	$Zn(OTf)_2$	0.6	CH_2Cl_2	23	8
11	$ZnCl_2$	0.6	CH_2Cl_2	22	59
12	$SnCl_4$	0.6	CH_2Cl_2	22	trace
13	MeOTf	0.6	CH_2Cl_2	41	30
14	TMSOTf	0.6	CH_2Cl_2	3.0	≥95
15[c]	TMSOTf	0.6	CH_2Cl_2	4.5	85

[a]Unless otherwise noted, reactions were carried out using **1a** (0.20 mmol) and **2a** (0.12 mmol) with catalyst (0.10 mmol) in solvent (0.5 mL) under N_2. [b]Isolated yields. [c]0.25 equiv of catalyst was used.

Scheme 2. Synthesis of 2,4-Diaminopyridines[a]



[a]Unless otherwise specified, reactions were carried out using **1** (0.20 mmol) and **2** (0.12 mmol) with TMSOTf (0.10 mmol) in CH_2Cl_2 (0.5 mL) under N_2. [b]0.5 equiv of $BF_3 \cdot Et_2O$ was used. Mbs = *para*-methoxy-benzene-sulfonyl; Ns = *para*-nitro-benzene-sulfonyl; Cs = *para*-chloro-benzene-sulfonyl.

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cycloaddition was amenable to the synthesis of product **3f** with high yield using the bulkier aryl nitrile **2f**. Subsequently, a broad range of ynamides were submitted to this protocol. Ynamides with electron-donating and electron-withdrawing sulfonyl systems were tested first, the cycloaddition proceeded smoothly to furnish the desired 2,4-diaminopyridines **3g**−**3l** with high to excellent yields, even for the low reactive *N*-Ns substituted ynamide **1d**, which worked not well in our previous reported annulation reactions.[15] Other *N*-alkenyl- and alkyl-substituted ynamides were also tolerated giving cycloadducts **3m** and **3n** with moderate and low yields, respectively. This loss of yield is likely due to the allyl and methyl substituents increasing the nucleophilicity of ynamide, thereby inducing side reactions such as hydrolytic reaction, etc. We also found an interesting effect on the yield. Most notably, the *N*-methyl-substituted ynamide **1f** eroded the yield under the catalyst TMSOTf compared with $BF_3 \cdot Et_2O$ (see **3n**). A similar phenomenon also occurred for the formation of **3r**. Other alkyl-terminated ynamides (R^2 = *n*-Pr and *n*-hex) also afford the desired 2,4-diaminopyridines **3o**−**3q** with high to excellent yields. We were also pleased to find that this cycloaddition was amenable to the synthesis of **3r** using terminally unsubstituted ynamide **1i** with acetonitrile **2a**. Moreover, 4-aminopyrimidines, which were isolated as by-products under Liu's reaction condition (Scheme 1c),[8f] could not be observed from this TMSOTf-catalyzed cycloaddition. The relative stereochemistry was assigned using the single-crystal X-ray structure of **3f** (Figure 2).

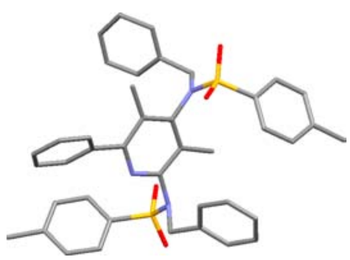
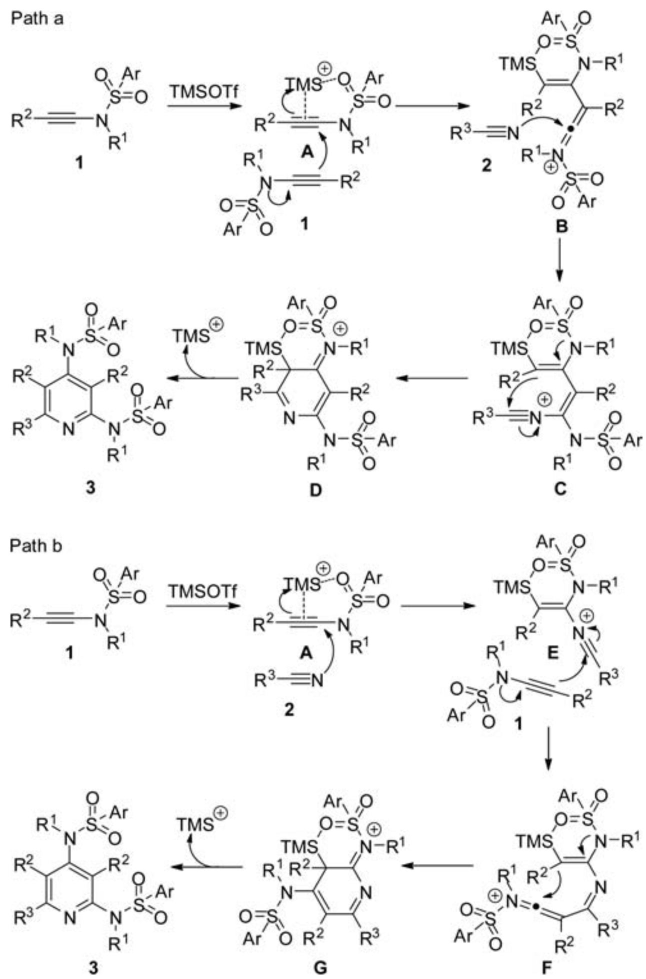


Figure 2. X-ray structure of **3f**.

Two postulated mechanisms leading to the formation of 2,4-diaminopyridine **3** are proposed as shown in Scheme 3. The reaction would be initiated by the formation of silicon π-alkyne species **A** via the coordination to ynamide **1** by TMSOTf. The following nucleophilic attack of intermediate **A** has two possible pathways: addition of the species **A** with another ynamide **1** gives the keteniminium ion **B** (Path a), which undergoes a subsequent attack by nitrile **2** to form the nitrilium species **C**. A subsequent intramolecular cyclization of **C** via the intermediate **D** furnishes the final product **3**; the other optional path for the intermediate **A**, subsequent nucleophilic addition by nitrile **2** occurs to afford nitrilium species **E** (Path b), which is highly electrophilic and induces a second attack by ynamide **1** to form the keteniminium ion **F**. Then intermediate **F** undergoes an intramolecular cyclization via the intermediate **G** to achieve the desired product.

We have documented here a novel and highly efficient TMSOTf-catalyzed [2 + 2 + 2] cycloaddition of ynamides with nitriles. The strategy provides a general and straightforward way to construct 2,4-diaminopyridines with excellent selectivities and tolerates a wide range of functional groups. Such pyridine syntheses are applicable to diversified alkyl or aryl nitriles and sulfonamide-derived ynamides. More importantly, this method enables the preparation of 2,4-diaminopyridines from terminally substituted or unsubstituted ynamides, which is in direct contrast to previous studies[11,12] of the related terminally substituted ynamides. Plausible mechanisms of the reaction have been proposed. Further studies on the construction of other nitrogen heterocycles via the reactions of ynamides are under current study and will be reported in due course.

Scheme 3. Proposed Mechanisms for the Cycloaddition



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01546.

Detailed experimental procedures (PDF)
Characterization data for the new compounds (PDF)
Crystallographic data for **3f** (CIF)

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Notes

The authors declare no competing financial interest.

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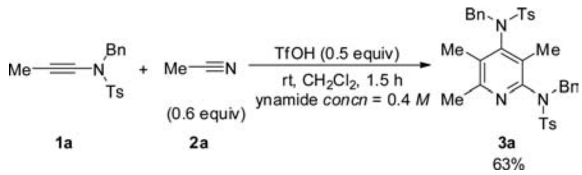

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