Synthetic Methods

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Regiocontrolled Gold-Catalyzed [2+2+2] Cycloadditions of Ynamides with Two Discrete Nitriles to Construct 4-Aminopyrimidine Cores**

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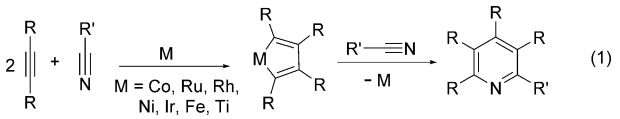
Abstract: *Reported herein is the novel gold-catalyzed intermolecular [2+2+2] cycloaddition of ynamides with two discrete nitriles to form monomeric 4-aminopyrimidines, which are pharmaceutically important structural motifs. The utility of this new cycloaddition is demonstrated by the excellent regioselectivity obtained using a variety of ynamides and nitriles.*

Metal-catalyzed [2+2+2] cycloadditions are powerful tools for constructing six-membered carbo- or heterocyclic frameworks with atom economy.[1] Alkynes and nitriles are two common triple-bond motifs, and catalytic [2+2+2] cycloadditions between alkynes and nitriles have been extensively studied with many catalysts, including Co,[2] Ru,[3] Rh,[4] Fe,[5] Ni,[6] Ir,[7] and Ti.[8] Such reactions were reported to afford pyridines nearly exclusively, thus involving two discrete alkynes and one nitrile as a result of the initial formation of metallocyclopentadienes [Eq. (1)]. In contrast, the construction of a monomeric pyrimidine core from one alkyne and two discrete nitriles still remains unprecedented even though such an azacycle is a pharmaceutically important structural motif.[9]

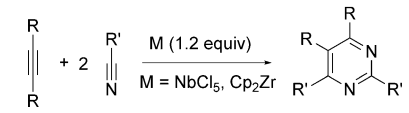


(1)

Obora et al.[10a] and Liu et al.[10b] reported the synthesis of pyrimidines from alkynes and arylnitriles, but $NbCl_5$ (1.2 equiv) or [Cp_2Zr] (1.3 equiv) were used in large proportions to attain satisfactory yields [Eq. (2); Cp = cyclopentadiene]. Although Louie et al.[10c] reported the synthesis of pyrimidines using FeI_2/Zn catalysts, the applicable substrates were limited to 5-cyano-1-ynes and cyanamides in a bimolecular process, and the reactions suffered from low product yields (< 50%) in most instances [Eq. (3)].

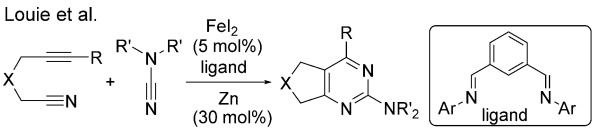
This work reports the catalytic synthesis of monomeric 4-aminopyrimidines through gold-catalyzed regioselective [2+2+2] cycloadditions between various ynamides and nitriles [Eq. (4); EWG = electron-withdrawing group]. Ynamides are substrates widely used in numerous organic reactions because of their versatile reactivity.[11] Such alkynes are potent nucleophiles but become reactive electrophiles upon coordination with gold catalysts.[12] We searched for gold catalysts to implement a nucleophilic attack of nitriles onto gold π-alkyne species to initiate the reaction. Monomeric 4-aminopyrimidine cores are commonly found in many bioactive molecules including minoxidil (**I**),[13a] thiamine (**II**),[13b] pyrimethamine (**III**),[13c] epiroprim (**IV**),[13d] bacimethrin (**V**),[13e] and sulfamethomidine (**VI**)[13f] as depicted in Figure 1.

Obora et al. and Liu et al.



(2)

Louie et al.



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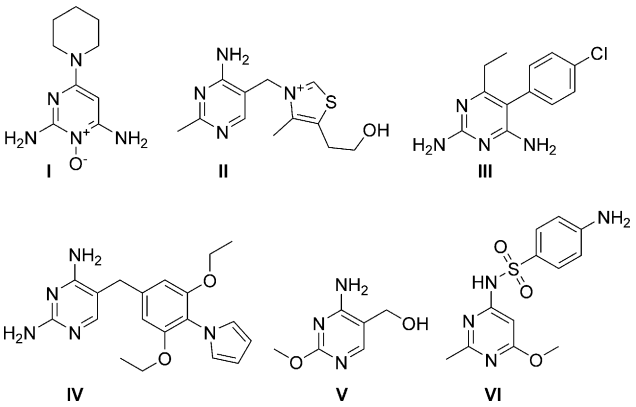

Figure 1. Representative bioactive molecules.

This work

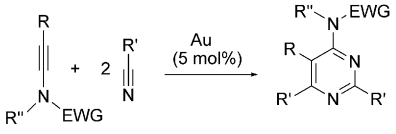

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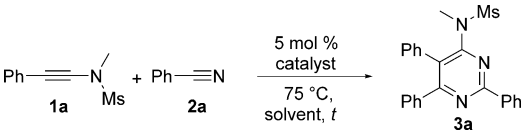
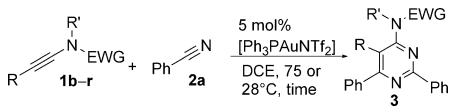
Table 1: Catalytic reactions over gold catalysts.

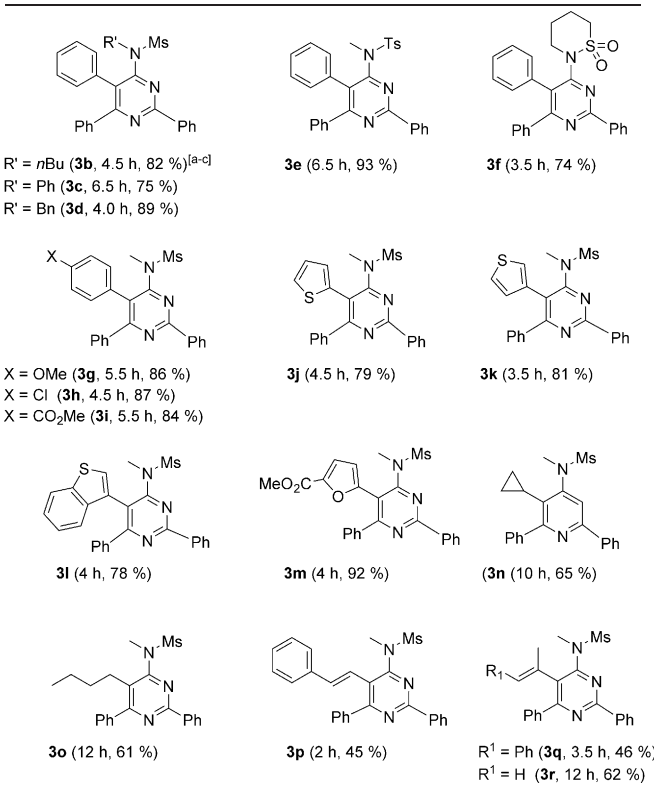


Entry	Catalyst[a]	Solvent[b]	t [h]	Yields [%][c]	
				1a	**3a**
1	$AuCl_3$	DCE	12	65	20
2	[LAuCl]/$AgNTf_2$	DCE	9	–	75
3	[IPrAuCl/$AgNTf_2$	DCE	10.5	–	73
4	[Ph_3PAuCl]/$AgNTf_2$	DCE	4	–	95
5	[Ph_3PAuCl]/$AgSbF_6$	DCE	4	–	89
6	[Ph_3PAuCl]/AgOTf	DCE	3.5	–	93
7	$AgNTf_2$	DCE	12	75	–
8	[Ph_3PAuCl]/$AgNTf_2$	toluene	7.5	–	84
9	[Ph_3PAuCl]/$AgNTf_2$	C_6H_5Cl	2.5	–	86
10	[Ph_3PAuCl]/$AgNTf_2$	1,4-dioxane	9	–	65

[a] **2a** (4 equiv). [b] [**1a**] = 0.20 M. [c] Product yields are reported after purification using a silica column. IPr = 1,3-bis(diisopropyl phenyl)-imidazol-2-ylidene, L = P(tBu)$_2$(o-biphenyl), Ms = methanesulfonyl, Tf = trifluoromethansesulfonyl.

Table 2: Catalytic cycloadditions with various ynamides.





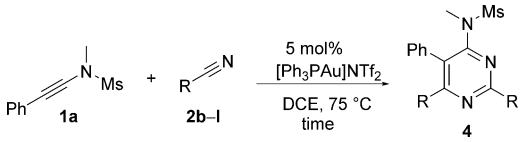
[a] [**1**] = 0.20 M, [Ph_3PAuCl]/$AgNTf_2$ (5 mol%), benzonitrile (4.0 equiv). [b] Product yields are reported after purification on a silica column. [c] Reactions were carried out at 75 °C for **1b–m** and at 28 °C for **1n–r**.

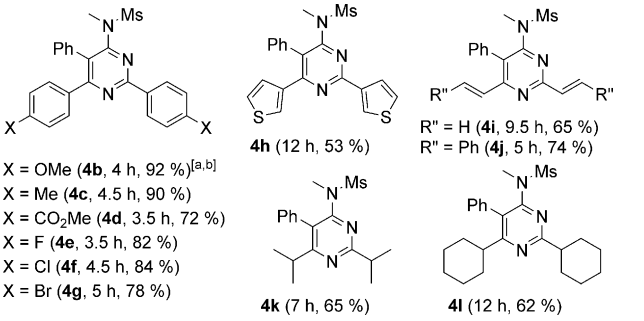
Table 1 shows the realization of a catalytic synthesis of the pyrimidine species **3a** using the ynamide **1a** and benzonitrile (**2a**; 4 equiv). We first tested the reaction with $AuCl_3$ (5 mol%) in hot 1,2-dichloroethane (DCE, 75 °C, 12 h), from which **3a** and unreacted **1a** were obtained in 20 and 65%, respectively (entry 1). The cationic gold catalysts [P(tBu)$_2$(o- biphenyl)AuCl]/$AgNTf_2$ and [IPrAuCl]/$AgNTf_2$ enabled complete consumption of **1a** in hot DCE (75 °C, 9–10.5 h) to afford **3a** in 75 and 73% yield, respectively (entries 2 and 3). The yield of **3a** was greatly improved to 95% with [PPh_3AuCl]/$AgNTf_2$ within a brief period (4 h, entry 4). Other anions in [PPh_3AuCl]/AgX (X = SbF_6 and OTf) maintained high yields (89–93%) of **3a** (entries 5 and 6). $AgNTf_2$ alone was found to be inactive in hot DCE (75 °C) for a prolonged period (entry 7). With [PPh_3AuCl]/$AgNTf_2$ in other solvents, the yields of **3a** were 84%, 86%, and 65%, respectively, in toluene, chlorobenzene, and 1,4-dioxane (entries 8–10). The molecular structure of **3a** was confirmed with X-ray diffraction.[14]

We prepared additional ynamides (**1b–r**) to assess the substrate scope (Table 2). Most reactions were performed with [PPh_3AuNTf_2] (5 mol%), ynamides, and benzonitrile (4 equiv) in hot DCE (75 °C; **1b–m**) whereas in the cases of **1n–r** the reactions were run at 28 °C. For the ynamides **1b–d**, bearing various sulfonamide substituents (R′ = n-butyl, phenyl, and benzyl), the corresponding pyrimidine products **3b–d** were obtained in 75–89% yields. The cycloadditions were applicable also to the ynamides **1e** and **1f** comprising tosyl-substituted and cyclic sulfonamides, thus giving the desired **3e** (93%) and **3f** (74%), respectively. We tested the reactions on the ynamides **1g–i** in which the phenyl group bears different substituents (X = OMe, Cl and CO_2Me), thus yielding the desired **3g–i** in satisfactory yields. The reactions were compatible with 2- and 3-thienyl-substituted ynamides (**1j** and **1k**), thus yielding the corresponding pyrimidine derivatives **3j** (79%) and **3k** (81%), respectively. For other heteroaryl-substituted ynamides, **1l** and **1m**, the corresponding cycloadducts **3l** and **3m** were produced efficiently. The alkyl-substituted ynamides **1n** and **1o** (R = cyclopropyl and n-butyl) were also amenable to this reaction at 28 °C, thus yielding pyrimidines **3n** and **3o** in 65 and 61% yield, respectively. Such cycloadditions were extended to the alkenyl-substituted ynamides **1p–r**, thus giving compounds **3p–r** in reasonable yields.

Table 3 depicts the nitriles **2b–l** which are compatible with our catalytic cycloadditions. For the 4-substituted benzonitriles **2b**,**c**, bearing electron-donating groups (X = OMe and Me), the gold-catalyzed cycloadditions proceeded smoothly to yield the pyrimidine products **4b**,**c** in excellent yields. This synthetic method was also feasible for the electron-deficient benzonitriles **2d–g** (X = CO_2Me, F, Cl and Br), thus providing the desired **4d–g** in 72–84% yields. For 3-thienylnitrile, the resulting product **4h** was obtained in 53% yield. We also examined the reactions on two alkenylniriles, **2i** and **2j** (R″ = H and Ph), thus yielding the desired **4i** and **4j** in 65 and 74% yield, respectively. To our delight, this method was also compatible with the aliphatic nitriles **2k** and **2l**, thus yielding the desired pyrimidine species **4k** and **4l**, respectively in 62–

Table 3: Gold-catalyzed cycloadditions with various nitriles.

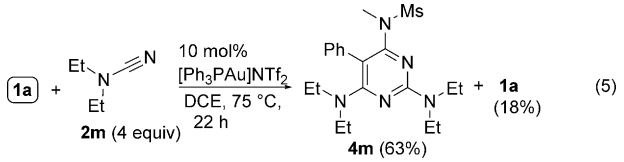




[a] [**1a**] = 0.20 M, [Ph_3PAuCl]/$AgNTf_2$ (5 mol%), nitrile (4.0 equiv).
[b] Product yields are reported after purification on a silica column.

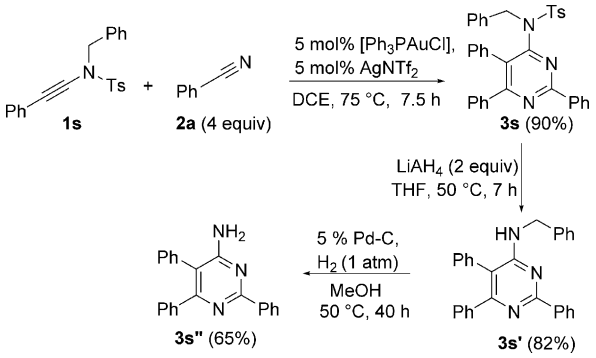
65% yields. The molecular structure of the cycloadduct **4i** was determined by X-ray diffraction.[14]

Inspired by the presence of triamino substituents as in minoxidil (see structure in Scheme 1), we undertook a gold-catalyzed cycloaddition between the ynamide **1a** and diethylaminonitrile (**2m**; 4 equiv) in hot DCE [75 °C, 22 h, Eq. (5)], thus providing the triamino-containing pyrimidine **4m** in 63% yield, together with unreacted **1a** in 18% yield. Such a highly electron-rich pyrimidine core did not inhibit the catalytic reaction, and further highlights the utility of this synthetic method.

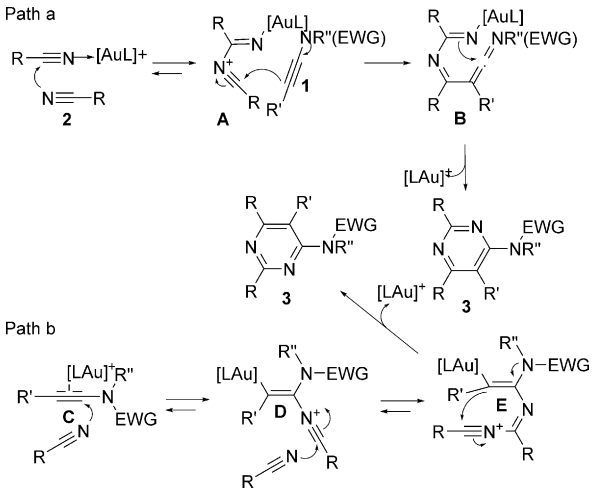


The sulfonamide group of the resulting pyrimidines can be transformed into an amine (NH_2) which is present in most bioactive molecules (Figure 1). Treatment of the ynamide **1s** with benzonitrile and [PPh_3AuNTf_2] (5 mol%) in hot DCE (75 °C, 7.5 h) gave the 4-aminopyrimidine **3s** in 90% yield (Scheme 1). Subsequent reduction[15] of **3s** with $LiAlH_4$ led to the removal of tosyl to yield the species **3s′** in 82% yield. A subsequent reductive degradation of this 4-benzylaminopyrimidine with Pd/C and H_2 in MeOH afforded the amine-containing compound **3s″** in 65% yield.

Shown in Scheme 2 are two postulated mechanisms to rationalize the formation of the 4-aminopyrimidines **3**. We envisage that a gold catalyst might catalyze dimerization of the nitrile **2** to form the intermediate **A**, which is subsequently attacked by **1** to yield the ketenimine species **B** (path a). A ring closure of **B** is expected to give the desired product **3**, a pathway postulated by Obora co-workers.[10a] Alternatively, the nitrile might attack the gold π-alkyne species **C** to form



Scheme 1. Transformation of a sulfonamide into an amine. Ts = 4-toluenesulfonyl.



Scheme 2. Mechanisms for the synthesis of 4-aminopyrimidines.

the nitrilium species **D** which is highly electrophilic and induces a second attack by a nitrile to form another nitrilium species, **E**. A subsequent intramolecular cyclization of **E** forms the same product **3** (path b).

We envisage that path a will give stable trimers of nitriles if only the gold catalyst is present. Our control experiments revealed that [PPh_3AuNTf_2] failed to catalyze the trimerization of **2a** in hot DCE (75 °C) after 12 hours and the starting **2a** was recovered in 87%.[16] According to literature reports, the trimerizations of nitriles are facilitated only with alkaline metals in PhM (M = Na, Li), or Mg^0, Fe^0, and Ni^0 salts. Their dimers were postulated as intermediates.[17] Although we were unable to obtain supportive data for path a involving initial dimerization of nitriles, this mechanism cannot be excluded completely. In contrast, path b indicates the feasibility of a gold π-alkyne inducing a dimerization of nitriles in a reversible process before it is trapped by a tethered nucleophile.

Before this work, metal-catalyzed intermolecular [2+2+2] cycloaddition reactions of alkynes with nitriles were mainly limited to the production of pyridines rather than pyrimidines. We herein report new gold-catalyzed [2+2+2] cycloadditions between ynamides and nitriles to afford monomeric 4-aminopyrimidines, which are commonly

found in many bioactive molecules. The practicability of such intermolecular cycloadditions[18–20] is demonstrated by the wide scope with respect to both the ynamides and nitriles. We postulate that the reaction mechanism involves initial attack of a π-alkyne on two nitriles followed by a ring closure. Extension of this method to construct complicated pyrimidine frameworks is under current investigation.

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