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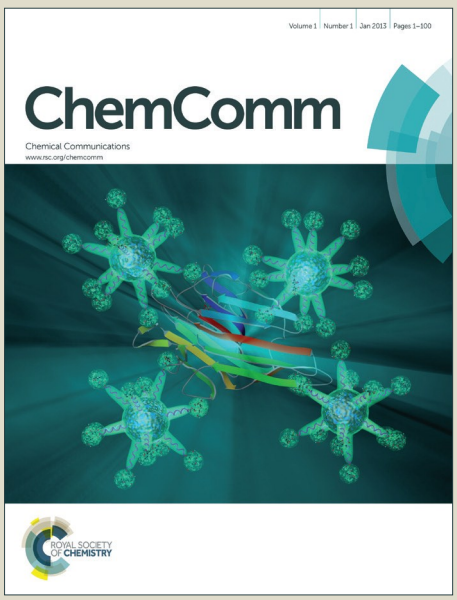





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# Sulfonamides-directed Gold-catalyzed [2+2+2]-Cycloadditions of Nitriles with Two Discrete Ynamides to Construct 2,4-Diamino-pyridine cores

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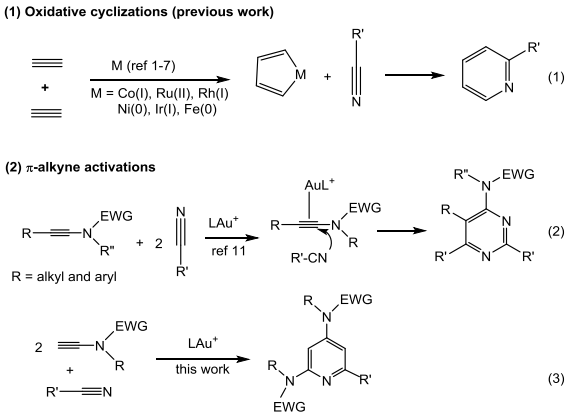
**Gold-catalyzed [2+2+2]-cycloadditions of two discrete ynamides and one nitrile afford 2,4-diaminopyridine derivatives that are not readily prepared from typical low-valent-metal catalysts. Our mechanistic analysis reveal that the reaction chemoselectivity is controlled by the types of sulfonamides of ynamides.**

Pyridine cores are important functionalities in many bioactive molecules; the construction of these moieties rely heavily on metal-catalyzed [2+2+2]-cycloadditions of two alkynes and one nitrile.[1] Such reactions have been extensively studied with various low valent metal catalysts including Co(I),[2] Ru(II),[3] Rh(I),[4] Fe(0),[5] Ni(0)[6] and Ir(1)[7] complexes. The mechanism of these reactions typically involves an initial oxidative cycloaddition of two alkynes with metal to form a metallocyclopentadiene intermediate as the first step (eq 1). These reactions were generally performed in bimolecular processes, including diynes/nitriles or alkynylnitriles/alkynes to attain a high reaction regioselectivity. In the case of terminal alkynes RC≡CH (R = alkyl, aryl and $CO_2R$"), their intermolecular [2+2+2]-cycloadditions with nitriles could be achieved regioselectively with Rh(I) and Fe(0) catalysts of special types; but the examples were very rare.[8]

Au(I)-catalyzed electrophilic activations of alkynes have inspired new cycloadditions of alkynes[9] with weakly nucleophilic alkenes,[10a-c] carbonyl,[10d] imines,[10e] epoxides[10f] and nitriles,[10g-h] providing short synthesis of useful carbo- or hetereocyclic compounds. We recently reported gold-catalyzed syntheses of 4-aminopyrimidine derivatives, as depicted in eq 2, providing the first [2+2+2]-cycloadditions of alkynes with two discrete nitriles.[11a] This cycloaddition was previously reported by Hsung's group using Cu-catalyst, albeit in only one instance with 38% yield.[11b] In this reaction, Au-π-alkynes are presumably attacked by two nitriles sequentially to furnish a 4-aminopyrimidine core; this reaction outcome




reflects the weak nucleophilicity of substituted ynamides relative to nitriles. To alter the reaction chemoselectivity, we tested the cycloadditions of nitriles with unsubstituted ynamides that are better nucleophiles than their substituted analogues. We report herein the catalytic synthesis of 2,4-diaminopyridine derivatives through gold-catalyzed regioselective [2+2+2]-cycloadditions of one nitriles with two discrete unsubstituted ynamides (eq 3). This new method is complementary to low-valent metal catalysts (eq 1) that generally provided 2,4,6-trisubstituted pyridines with low efficiency.[1] The control of this reaction chemoselectivity is

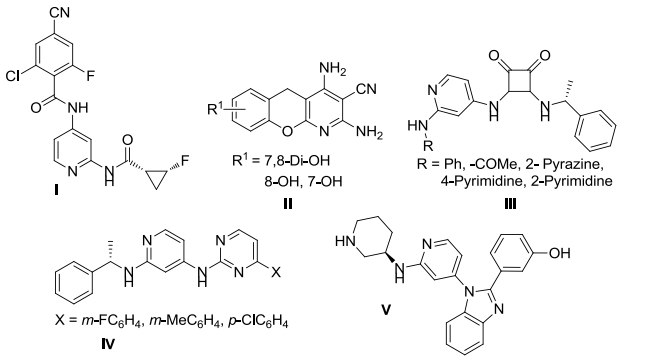



**Figure 1** Representative bioactive molecule

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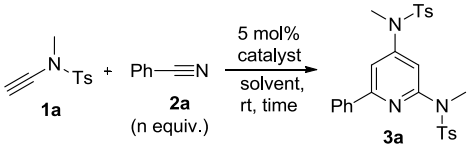
greatly affected by the types of sulfonamides.

2, 4-Diaminopyridine cores are found in many bioactive molecules including compounds **I-V**,[12] as depicted in Figure 1. Molecules **I** and **II-III** are potent inhibitors of TYK2 (non-receptor tyrosine-protein kinase)[12a] and MK-2 (mitogen activated protein kinase-activated protein kinase 2),[12b-c] and species **IV** and **V** are potent CaMKIIδ ($Ca^{+2}$/calmodulin-dependant kinase) and JNK (c-jun N-terminal kinase) inhibitors.[12d-e]

We tested the cycloadditions of ynamide **1a** (1.0 equiv) with benzonitrile **2a** (4 equiv) with commonly used gold catalysts; the yields of cycloadduct **3a** were estimated based on ynamide **1a**. We examined the reactions with $AuCl_3$ (5 mol %) in dichloroethane (DCE, 25 °C, 12 h), leading to a complete consumption of initial **1a**, from which the desired cycloadduct **3a** was obtained in 10% yield. We examined $PPh_3AuCl/AgX$ catalysts (X = $SbF_6$, OTf, $NTf_2$), which to our pleasure, gave desired **3a** in 65-74% yields with $PPh_3AuCl/AgNTf_2$ being the most efficient (entries 2-4). Electron-rich $LAuCl/AgNTf_2$ [L = P(t-Bu)$_2$(o-biphenyl) and 1,3-bis(diisopropyl phenyl)imidazol-2-ylidene (IPr)] became less efficient to afford compound **3a** in 55-61% yields (entries 5-6) whereas $AgNTf_2$ alone was catalytically inactive in DCE (entry 7). The use of $PPh_3AuCl/AgNTf_2$ in dichloromethane (DCM) and chlorobenzene gave pyridine derivative **3a** in 68% and 52% respectively (entries 8-9). We examined the effects of the proportion of benzonitrile **2a** on the reaction efficiency; the yields of compound **3a** were 60% and 65%, respectively, for ratios **1a**/**2a** = 1:1 and 1:6 (entries 10-11); in the latter case, we did not isolate a 4-aminopyrimidine byproduct (eq 3). Benzonitrile in excess proportions (**1a**/**2a** = 1:6) likely

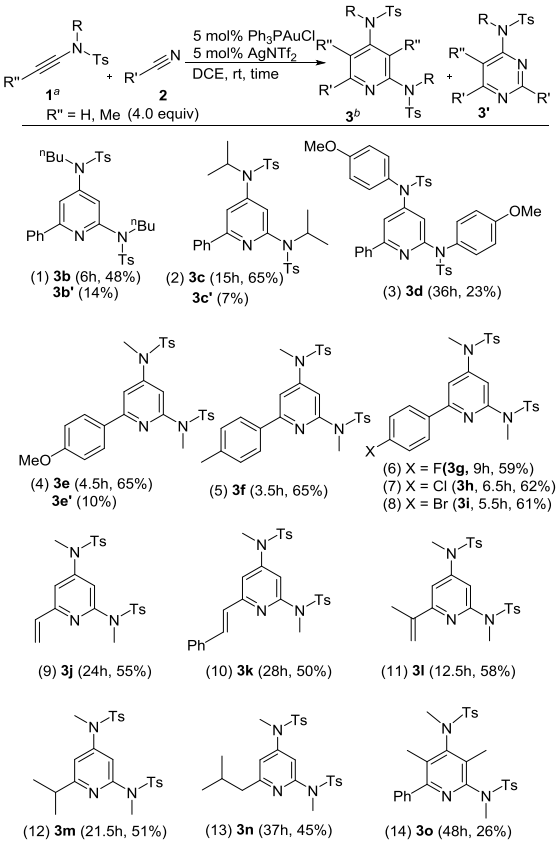
**Table 1**. Cycloadditions on various catalysts




| Entry | Catalyst[a] | n | Solvent[b] | *t* (h) | Yield (%)[c] | |
|---|---|---|---|---|---|---|
| | | | | | **1a** | **3a** |
| 1) | $AuCl_3$ | 4.0 | DCE | 12 | - | 10 |
| 2) | $[Ph_3PAuCl] / AgSbF_6$ | 4.0 | DCE | 7.5 | - | 65 |
| 3) | $[Ph_3PAuCl] / AgOTf$ | 4.0 | DCE | 7 | - | 67 |
| 4) | $[Ph_3PAuCl] / AgNTf_2$ | 4.0 | DCE | 6.5 | - | 74 |
| 5) | [JohnPhosAuCl] / $AgNTf_2$ | 4.0 | DCE | 8 | - | 61 |
| 6) | [IPrAuCl] / $AgNTf_2$ | 4.0 | DCE | 8 | - | 55 |
| 7) | $AgNTf_2$ | 4.0 | DCE | 12 | 45 | - |
| 8) | $[Ph_3PAuCl] / AgNTf_2$ | 4.0 | DCM | 7 | - | 68 |
| 9) | $[Ph_3PAuCl] / AgNTf_2$ | 4.0 | $C_6H_4Cl$ | 24 | 10 | 52 |
| 10) | $[Ph_3PAuCl] / AgNTf_2$ | 1.0 | DCE | 6.5 | - | 60 |
| 11) | $[Ph_3PAuCl] / AgNTf_2$ | 6.0 | DCE | 6.5 | - | 65 |

[a]IPr = 1,3-bis(diisopropyl phenyl)-imidazol-2-ylidene, Tf = tri fluoro methane-sulfonyl, JohnPhos = (2-biphenyl)di-tert-butylphosphine. [b]**[1a]** = 0.20 **M**. [c]Product yields are reported after purification using a silica column.

**Table 2.** [2+2+2]-Cycloadditions with various ynamides and nitriles



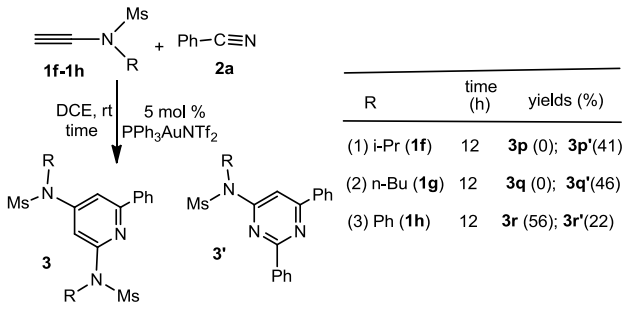

[a]**[1]** = 0.20 **M**, $Ph_3PAuCl/AgNTf_2$ (5 mol%), **[2]** = $2.5x10^{-3}$ **M** [b]Product yields are reported after purification from a silica column.

competed with yanmide **1a** to attack at π-alkynes, thus decreasing the reaction efficiency. Notably, treatment of ynamide **1a** with gold catalyst gave a known product from a tetramerization reaction. The molecular structure of cycloadduct **3a** has been elucidated by x-ray diffraction.[13]

We assess the reactions scope with various unsubstituted sulfonamides and nitriles; a summary of the results appear in Table 2. Besides desired 2, 4-diaminopyridines **3**, we also isolated aminopyrimidine byproducts **3b', 3c'** and **3e'** in small proportions in entries 1, 2 and 4 respectively. Different tosylamides as in ynamides **1b** and **1c** (R = *n*-butyl and isopropyl) still yielded desired cycloadducts **3b** and **3c** in 48% and 65% yields respectively (entries 1-2). The reaction of *N*-aryl tosylamide derived ynamide **1d** gave desired product **3d** in 23% yield, probably due to its decreased nucleophilicity (entry 3). Entries 4-8 show the compatibility of these cycloadditions with both electron-rich and -deficient benzonitriles **2b**-**2f** (R' = 4-$XC_6H_4$, X = OMe, Me, F, Cl and Br), yielding desired products **3e**-**3i** in 59-65% yields. For various alkenylnitriles, their corresponding cycloadditions with ynamide **1a** yielded desired pyridine products **3j**-**3l** in 50-58% yield (entries 9-11). Such cycloadditions were also compatible with common alkylnitriles (R' = *i*-Pr and *i*-Bu, entries 12-13), affording desired products **3m**-**3n** in 51% and 45% respectively. This cycloaddition

reaction was also operable for methyl-substituted alkyne **1e** (R'' = $CH_3$) to give fully substituted pyridine **3o** in 26 % yield (entry 14); its decreased yield is due to its weak nucleophilicity. A large alkyl or aryl-substituted ynamide will give 4-aminopyrimidines (see eq 2).

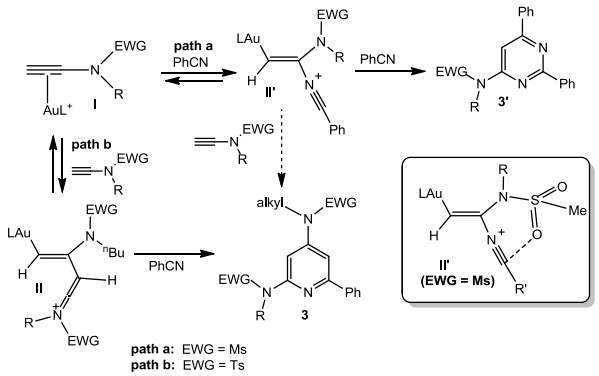
The presence of 4-aminopyrimindine byproducts **3b'** and **3c'** (entries 1-2, Table 2) indicates that electron-rich tosylamides (R = *n*-Bu, isopropyl) tend to form 4-aminopyrimidines **3'**. To confirm this hypothesis, we prepared ynamides **1f**-**1h** bearing a mesylamide (Ms) that is more electron-rich than a tosylamide (Ts); the results are shown in Scheme 1. Of particular interest was a complete alteration of the chemoselectivity when ynamides **1f** and **1g** were tested; only 4-aminopyrimidines **3p'** and **3q**' were produced in 41-46% (entries 1-2). In contrast, their tosyl-derived analogues **1b** and **1c** afforded 2,4-diaminopyridines **3b** and **3c** preferably (entries 1-2, Table 1). If an electron-withdrawing phenyl group replaces alkyl substituents as in species **1h,** 2,4-diaminopyridine **3r** was the major product (56%) again, together with 4-aminopyrimindine **3r'** in a minor proportion (22%). This information confirms that electron-rich sulfonamides NMs(R) (R= alkyl) preferably formed 4-aminopyrimidines **3'** whereas their tosyl-derived amides preferably afforded 2,4-diaminopyridines.




| R | time (h) | yields (%) |
|---|---|---|
| (1) i-Pr (**1f**) | 12 | **3p** (0); **3p'**(41) |
| (2) n-Bu (**1g**) | 12 | **3q** (0); **3q'**(46) |
| (3) Ph (**1h**) | 12 | **3r** (56); **3r'**(22) |

**Scheme 1.** Effects of sulfonamides on reaction Chemoselectivity

Scheme 2 depicts a mechanism to rationalize the sulfonamide-directed chemoselectivity that tosylamides (NTs) favor 2,4-diaminopyridine products **3** and mesylamides




**Scheme 2**. Rationales for the effects of sulfonamides

preferably yield aminopyrimidines **3'**. In our previous work (eq 2), the occurrence of 4-aminopyrimidines was due to the poor nucleophilicity of substituted ynamides (R = alkyl and aryl) so that only nitriles can attack on Au(I)-π-alkynes. Although the formation of 4-aminopyrimidines **3p'**-**3r'** (Scheme 1) indicates a prior nitrile attack (path **a)** for π-ynamides **I**, and this route alone fails to rationalize our observed chemoselectivity. For ynamides **1**, mesylamide derivatives (NMs) is better than their tosylamide analogues (NTs) as nucleophiles, the **II'→3** transformation is expected to be more facile with ynamides **1** bearing NMs whereas **II' →3'** is more favorable with NTs. This predicted trend opposes our observations. Accordingly, we postulate two competitive processes, with path **a** being preferable with ynamides **1** bearing electron-rich mesylamides (NMs) that can stabilize proximate nitrilium intermediates **II'**.[14] If the case of tosylamide-derived ynamides, its nitrilium intermediates **II'** are not stabilized by its sulfonamide group and become unstable relative to 1-azaallenium species **II**,[15] and a subsequent trap of the latter with benzonitrile forms desired 2,4-diaminopyridines **3**.

In summary, we report new gold-catalyzed intermolecular [2+2+2]-cycloadditions of unsubstituted or methyl-substituted ynamides with nitriles to yield 6-substituted 2,4-diaminopyridines; this regioselectivity is not achievable using low-valent metal catalysts. Such pyridine syntheses are applicable to diversified nitriles and tosylamide-derived ynamides; the reaction chemoselectivity can be altered to yield aminopyrimidines when electron-rich mesylamide-derived ynamides are used. We postulate that electron-rich mesylamides can stabilize proximate nitrilium intermediates via electrostatic interaction whereas less basic tosylamides favor 1-azaallenium species because their nitrilium intermediates are less stable. We believe that this new mechanistic insight assists new cycloadditions of ynamides,[16] especially with less reactive nitrile nucleophiles. Examinations of other N-substituted ynes are under current study.[17]

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17 We have tested other *N*-derived ynes **4a**-**4c** with benzonitrile under the standard conditions. In the case of yne-oxazolidinone **4a**, hydrative dimerization product **5a** was obtained in 45% yield. X-ray diffraction of compound **5a** was performed. In the case of yne-amide **4b**, a dimerization reaction occurred to give species **5b** in 34% yield. For yne-carbamate **4c**, an unknown dimerization compound was obtained. For products **5a** and **5b,** their formation seems to be associated with intermediates **II** by hydration or deproprotonation, supporting our reaction mechanism. For examples, in the case of product **5a**, we envisage that cationic charge of their intermediates is not so efficient due to the basicity of its amide, thus difficult to react with nitriles, but feasible with water. Spectra data of these compounds are provided in Supporting Information.