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Silver(I)-Catalyzed Addition-Cyclization of Alkyne-Functionalized Azomethines

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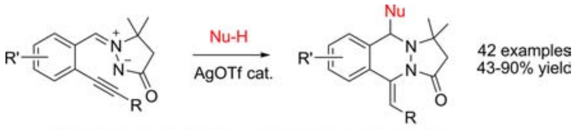
ABSTRACT



NuH = ketone, nitroalkane, water, and terminal alkyne

AgOTf can catalyze an addition-cyclization tandem between alkyne-azomethine and a nucleophile such as ketone, nitroalkane, water, and terminal alkyne to give a polycyclic amide via *six-exo-trig* selectivity.

Alkynes are widely used in synthetic chemistry and it has been well documented that, upon coordination to metals such as Au(I), Au(III), Pt(II), Pd(II), Ag(I) and I(I), alkynes are susceptible to nucleophilic attack, leading to cyclization reactions.[1] Such a metal-induced process has played an important role in the synthesis of complex synthetic targets. Compared to the vast majority of gold-catalyzed heterocyclization of alkynes, related Ag(I)-catalyzed reactions are less common, although silver catalysts are generally more cost-effective and can offer complementary reactivity and higher functional group compatibility.[1i,j,2] When an *ortho* alkyne-functionalized aldehyde was applied as a substrate in the presence of an external nucleophile (NuH) such as an alcohol, nucleophilic addition of the aldehyde to alkyne can trigger a further addition of the NuH to the carbonyl group, giving rise to cyclization with additional functionalization.[2f,3] Despite the success, this type of reactivity has been mostly observed for alkyne-tethered carbonyl compounds and in most cases *endo* cyclization selectivity was followed.[2k] Thus alkyne-functionalizaed imines have been less explored.[4] In order to further explore and expand the utility of Ag(I) catalysis in cyclization reactions for molecular diversity and complexity, it is necessary to broaden the scope of both the alkyne-imine and the external nucleophile substrates.

We recently reported rhodium-catalyzed C–H activation of azomethine imines derived from arylaldehydes,[5]

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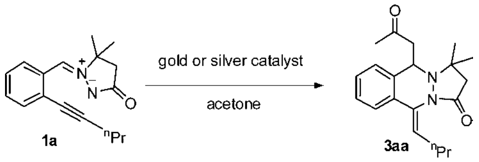
where the anionic nitrogen acts as an efficient directing group. We now report Ag(I)-catalyzed nucleophilic addition-cyclization between azomethine-alkynes and different nucleophiles. A series of heterocycles bearing an exocyclized C=C bond have been constructed via a selective *6-exo-dig* cyclization pathway.

The N−O bond in nitros, nitrones, and amine *N*-oxides are known to undergo gold-catalyzed inter- and intramolecular oxygen transfer to alkynes, leading to α-oxo carbenoid intermediates.[6,7] Given the structural similarity between N−O and N−N bonds, we think that the internal nitrogen transfer[8] of azomethine-alkyne such as **1a** can be possible. However, no analogous nitrogen transfer occurred for **1a** after extensive screenings, likely due to the tethering effect.

Table 1. Optimization Studies[a]



entry	catalyst (mol %)	additive (mol %)	temp (°C)	time (h)	yield[b] (%)
1	Au(PPh$_3$)Cl (5)	AgSbF$_6$ (6)	130	24	35
2	Au(IPr)Cl (5)	AgSbF$_6$ (6)	130	24	30
3	AgSbF$_6$ (10)		110	18	46
4	AgOTf (10)		110	18	78
5	AgPF$_6$ (10)		110	18	52
6	AgNTf$_2$ (10)		110	18	35
7	AgOTf (20)		80	24	83
8	AgOTf (20)	L-proline (20)	25	12	90

[a] Conditions: Azomethine **1a** (0.3 mmol), metal catalyst (5−20 mol %), acetone (3 mL), reaction time and temperature indicated in the table. [b] Isolated yield after column chromatography.

When we switched the solvent to acetone using a Au(PPh$_3$)Cl/AgSbF$_6$ (5 mol %/6 mol %) catalyst, product **3aa** was isolated (35%) as a polycyclic amide bearing an exocyclic C=C bond (Table 1, entry 1). This product was generated as a result of a tandem of *6-exo-dig* cyclization and the addition of acetone. Both the connectivity and the (*Z*)-configuration of the olefin were secured by X-ray crystallography. Further screening using another Au(I)/Ag(I) catalyst failed to improve the efficiency (entry 2). Importantly, gold catalysis proved not necessary and a slightly higher yield was obtained when AgSbF$_6$ (10 mol %) alone was used as a catalyst (entry 3). Screening of different silver salts gave AgOTf as the best catalyst (entries 3−6) and an isolated yield of 83% was reached when the catalyst loading was increased to 20% (entry 7). Addition of L-proline (20 mol %) significantly increased the efficiency, and the reaction proceeded smoothly even at room temperature in 90% yield (entry 8). This nucleophilic activation of acetone by proline has been previously reported.[4a,9] Nucleophilic addition of methyl ketones to an iminium is a well-known strategy for C−C bond formation as in the Mannich reaction, and there has been increasing interest in the addition of carbon nucleophiles to iminiums generated from the single-electron oxidation of tertiary amines.[10] In our system, acetone is added to a unique iminium, and this process is in tandem with nucleophilic cyclization of an alkyne.

With the optimized conditions in hand, we next explored the generality of this reaction. A broad scope of alkynes can be applied (Scheme 1). Thus both terminal (**3da**) and internal alkynes with different alkyl, benzyl, aryl (**3ga**−**3ja**), and heteroaryl (**3ka**) groups reacted efficiently to afford the acetone adduct in 62−90% yield (**3aa**−**3ka**). For aryl-substituted alkynes, *ortho*, *meta*, and *para* substituents in the phenyl ring are well tolerated. In contrast, a SiMe$_3$-substituted alkyne underwent clean but desilylated cyclization to give **3da** in a yield (84%) higher than that obtained using the terminal alkyne counterpart. Electron-donating (**3la**, **3na**) and -withdrawing (**3ma**) substituents in the phenylene linker between the azomethine and the alkyne can be accommodated without much variation of the isolated yield. When an azomethine bearing a mono methyl-substituted pyrazolidinone was subjected to the same conditions, good yield but poor diastereoselectivity (1.1:1) was achieved (**3oa**). We next explored the scope of the ketone in the reaction with **1a**. Other methyl ketones and methylene ketones are viable substrates, although the isolated yield is generally lower. In some cases a higher reaction temperature (80 °C) is necessary (**3ab**, **3ac**, **3ae**). When 1,1,1-trifluoroacetone was applied, **3af** was isolated together with its hydrate **3ag** as a mixture in 67% combined yield. In contrast, no desired ketone adduct was observed when 3,3-dimethyl-2-butanone was allowed to react with **1a** even at 80 °C, whereas only hydration-cyclization product **4a** was isolated (62% yield) and was characterized by X-ray crystallography. With decreased nucleophilicity of this ketone, the adventitious water reacts preferentially. In fact, product **4a** was consistently isolated in variable yields when **1a** was allowed to react in other (wet) solvents such as methanol, acetonitrile, and acetic acid at 70 °C (eq 1). These results suggest a competitive

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(5) Zhen, W.; Wang, F.; Du, Z.; Li, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 11819.

(6) For a recent review, see: Xiao, J.; Li, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 7226.

(7) For recent reports, see: (a) Luo, Y.; Ji, K.; Li, Y.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 17412. (b) Noey, E. L.; Luo, Y.; Zhang, L.; Houk, K. N. *J. Am. Chem. Soc.* **2012**, *134*, 1078. (c) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482. (d) Wang, Y.; Ji, K.; Lan, S.; Zhang, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1915. (e) Mukherjee, A.; Dateer, R. B.; Chaudhuri, R.; Bhunia, S.; Karad, S. N.; Liu, R.-S. *J. Am. Chem. Soc.* **2011**, *133*, 15372.

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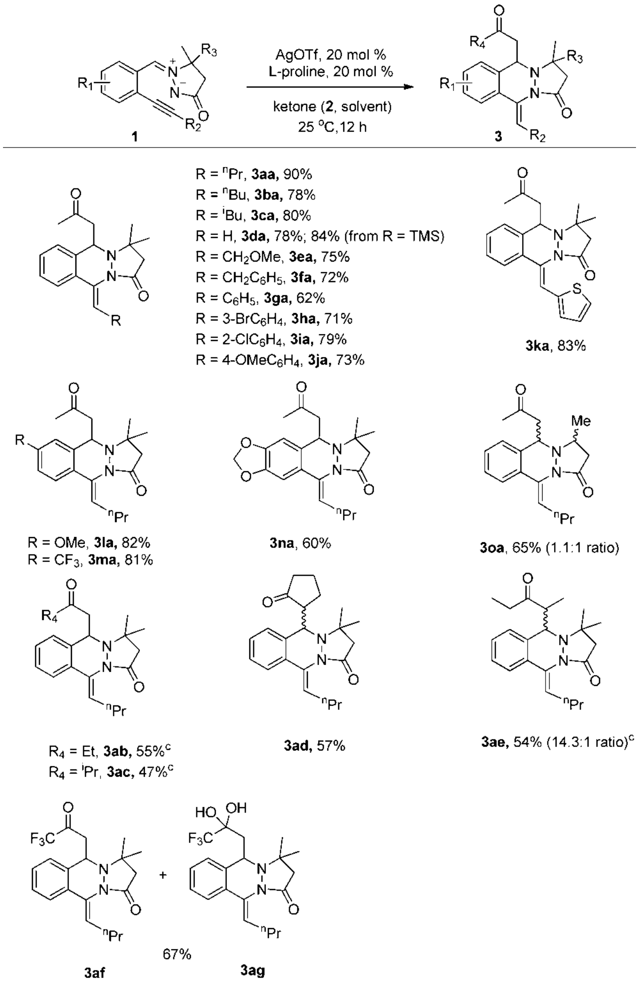
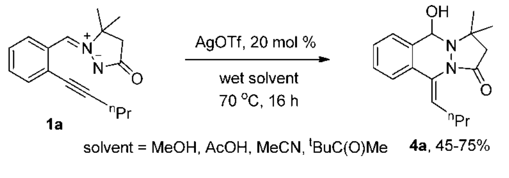
Scheme 1. Addition-Cyclization with Ketones[a]

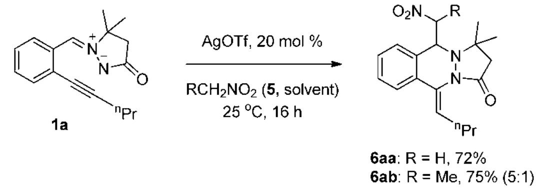


[a] Conditions: azomethine-alkyne (0.3 mmol), L-proline (0.06 mmol), AgOTf (0.06 mmol), ketone (3 mL), 25 °C, 12 h. [b] Isolated yield after column chromatography. [c] Reaction was conducted at 80 °C.

reaction between ketones and water, but soft nucleophiles tend to give higher reactivity. Despite the possiblility of competitive hydration-cyclization, essentially no (< 5%) **4a** was isolated in the synthesis of **3ab**–**3ae**. In contrast to these nucleophiles, activated methylenes such as dimethyl melonate and ethyl acetylacetate failed to give any clean reaction.



(1)



(2)

The nucleophile is not limited to a ketone. Nitromethane can also be applied as a solvent nucleophile,[11] and the addition-cyclization reaction between nitromethane and **1a** also proceeded smoothly at room temperature to give **6aa** in 72% isolated yield. Furthermore, good yield but moderate diastereoselectivity (5:1) was achieved for nitroethane (**6ab**, eq 2).

We reasoned that terminal alkynes and acetone are of comparable reactivity and may undergo the same type of reaction.[12] Indeed, a clean reaction between PhC≡CH and **1a** was achieved at 60 °C in MeCN, from which adduct **8aa** was isolated in 89% yield and no simple direct 1,2-addition was observed.[13] Here the adventitious water competes unfavorably with the alkyne substrate. The scope of this reaction is given in Scheme 2. The efficiency and the scope of this reaction parallel those of the methyl ketones. Thus the internal alkyne in the azomethine-alkyne substrate can bear an alkyl, benzyl, aryl, or heteroaryl group, and the coupled product was isolated in moderate to high yield (43–89%). A low yield (45%) was obtained for the coupling of azomethine-terminal alkyne with PhC≡CH, likely due to complications of both homo- and cross-couplings between these two terminal alkynes. In line with the addition of acetone, $SiMe_3$-substituted alkyne-azomethine reacted with PhC≡CH to furnish the desilylated product in 84% yield, which provides a more efficient alternative. Variation of substituents in the phenylene linker is also allowed (**8ma**, **8na**, **8oa**). In addition, the terminal alkyne substrate is not limited to PhC≡CH;[14] different aryl- and alkyl-substituted terminal alkynes reacted with comparable efficiency (**8ab**–**8ae**).

Several experiments have been performed to probe the reaction mechanism. We attempted but failed to add these nucleophiles to a simple azomethine bearing no ortho alkynyl group even at a higher temperature, indicating that this direct 1,2-addition is thermodynamically and/or kinetically unfavorable without the cyclization process. In a labeling experiment using acetone-d_6 as a solvent, ^{1}H NMR analysis of the isolated product indicated that H/D exchange occurred at the olefinic and the methine positions (eq 3). The fact that the olefinic position is mostly protio-substituted suggests that adventitious water participates readily in protonolysis of the Ag–C bond.

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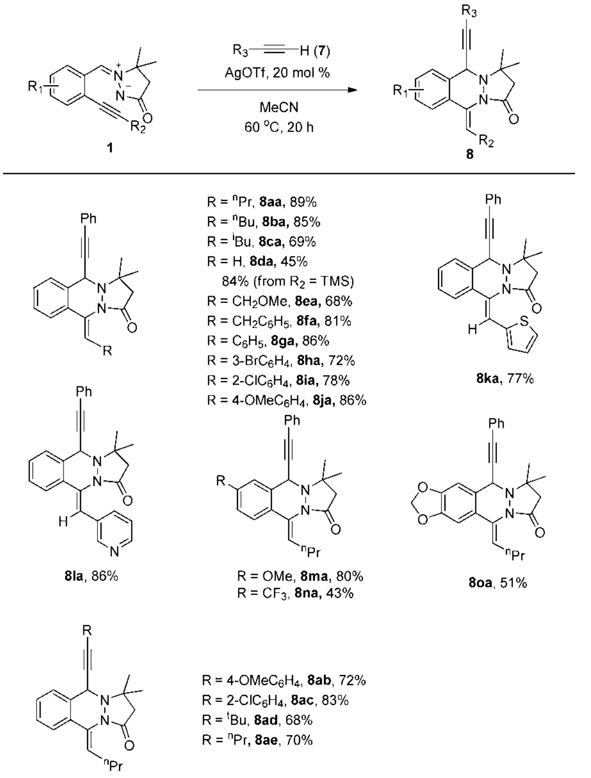
(11) For selected reports on addition of nitroalkane to iminiums via oxidation, see: (a) Zhang, B.; Cui, Y.; Jiao, N. *Chem. Commun.* **2012**, *48*, 4498. (b) Xie, J.; Li, H.; Zhou, J.; Cheng, Y.; Zhu, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 1252. (c) Meng, Q.-Y.; Liu, Q.; Zhong, J.-J.; Zhang, H.-H.; Li, Z.-J.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *Org. Lett.* **2012**, *14*, 5992. (d) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672.

(12) For a recent review, see: (a) Li, C. J. *Acc. Chem. Res.* **2010**, *43*, 581. Addition of terminal alkynes to imines: (b) Zeng, T.; Yang, L.; Hudson, R.; Song, G.; Moores, A. R.; Li, C.-J. *Org. Lett.* **2011**, *13*, 442. Addition of terminal alkynes to other in situ generated electrophiles: (c) He, C.; Guo, S.; Ke, J.; Hao, J.; Xu, H.; Chen, H.; Lei, A. *J. Am. Chem. Soc.* **2012**, *134*, 5766. (d) Li, Z.; Li, C. J. *Org. Lett.* **2004**, *6*, 4997.

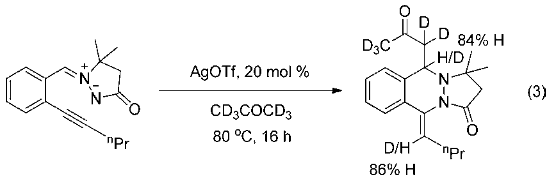
(13) For a recent report on alkyne addition to the imine group of an azomethine, see: Imaizumi, T.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 20049.

(14) Gold-catalyzed addition-cyclization of terminal alkynes to ortho-alkynylaryl aldehydes has been achieved, but the terminal alkyne seems limited to aryl or alkenyl substitution because poor yield was obtained for aliphatic alkynes. See: Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 1953.

Scheme 2. Addition-Cyclization with Terminal Alkyne[a]



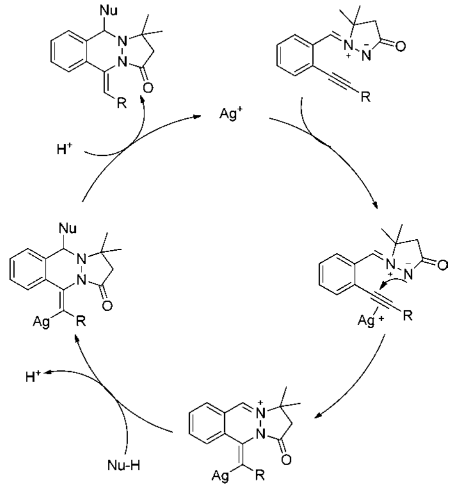
[a] Conditions: azomethine-alkyne (0.4 mmol), 1-alkyne (3 equiv), AgOTf (0.2 equiv), MeCN (3 mL), 60 °C, 20 h. [b] Isolated yield after column chromatography.



(3)

A general mechanism has been proposed for the formation of these adducts. Ag(I) coordination to the alkyne activates it toward the *6-exo-dig* attack of the amide nitrogen to give a silver(I) alkenyl intermediate. This cyclization process also renders the iminium more electrophilic, which can be attacked by a ketone, nitroalkane, and terminal alkyne. Protonolysis of the Ag–C bond completes the catalytic cycle with the regeneration of the Ag(I) catalyst (Scheme 3).

Scheme 3. Proposed Catalytic Cycle



In summary, we have achieved a silver-catalyzed nucleophilic addition-cyclization tandem between alkyne-functionalized azomethines and soft nucleophiles, leading to the synthesis of tricyclic products. A broad scope of substrates has been established using AgOTf as a catalyst. The reaction proceeded with high chemoselectivity but, if relevant, moderate to low diastereoselectivity. Given the broad scope and operational simplicity, this method may find applications in the synthesis of related structures. Future work will be conducted on the enantioselective synthesis of these products using chiral ancillary groups.

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Supporting Information Available. Experimental procedures and spectroscopic, analytical, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.