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Synthesis of Bicyclic Imidazoles via [2 + 3] Cycloaddition between Nitriles and Regioselectively Generated α-Imino Gold Carbene Intermediates

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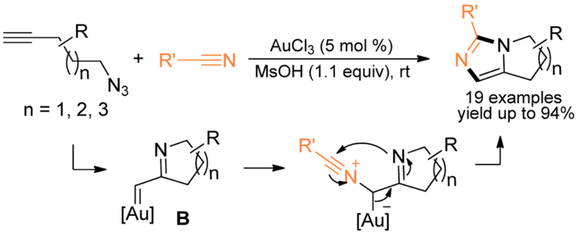
ABSTRACT



The cyclic α-imino gold carbene intermediate B is most likely generated in situ via regioselective nitrene transfer from an azido group to a tethered terminal alkyne in the presence of a gold catalyst and at ambient temperature. This highly electrophilic intermediate can react with a weakly nucleophilic nitrile, which is used as the reaction solvent, to deliver a bicyclic imidazole rapidly in an overall bimolecular [2 + 2 + 1] cycloaddition and in mostly serviceable yield. The competing intramolecular Huisgen reaction, although likely also catalyzed by gold, is minimized by using $AuCl_3$ as the catalyst.

Imidazole is an important *N*-heterocycle that can be found as a critical building block in bioactive molecules[1] and/or natural products.[2] It also serves as a versatile substrate structure for various synthetic transformations,[3] and its derivatives are used as ionic liquids[4] and precursors of *N*-heterocyclic carbenes employed as ligands in various metal complexes.[5] Owing to its importance, novel and efficient methods for constructing this heteroarene ring are still of contemporary importance to the synthetic community and have received continuous attention.[6]

We have recently engaged in extensive studies of the reactivities of α-oxo gold carbenes[7] that are generated as highly reactive intermediates in situ via gold-catalyzed intermolecular oxidation of alkynes.[8] Among the various

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(1) (a) Shalini, K.; Sharma, P. K.; Jumar, N. *Chem. Sin.* **2010**, *1*, 36–47. (b) Baroniya, S.; Anwer, Z.; Sharma, P. K.; Dudhe, R.; Kumar, N. *Pharm. Sin.* **2010**, *1*, 172–182.

(2) (a) Weinreb, S. M. *Nat. Prod. Rep.* **2007**, *24*, 931–48. (b) Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143–1191. (c) De, L. L. *Curr. Med. Chem.* **2006**, *13*, 1–23.

(3) (a) Gupta, R. R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry II: Five-Membered Heterocycles*; Springer: Berlin, 2011. (b) Hofmann, K. *Imidazole and Its Derivatives. Part 1*; Wiley-Interscience: New York, 2007.

(4) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083.

(5) (a) Jacobsen, H.; Correa, A.; Poater, A.; Costabile, C.; Cavallo, L. *Coord. Chem. Rev.* **2009**, *253*, 687–703. (b) Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev.* **2004**, *248*, 2247–2273. (c) Hashmi, A. S. K.; Lothschütz, C.; Böhling, C.; Hengst, T.; Hubbert, C.; Rominger, F. *Adv. Synth. Catal.* **2010**, *352*, 3001–3012.

(6) For selected reviews, see: (a) Kamijo, S.; Yamamoto, Y. *Chem. Asian J.* **2007**, *2*, 568–578. (b) Grimmett, M. R. In *Science of Synthesis*; Georg Thieme Verlag KG: Stuttgart, 2002; Vol. 12, p 325.

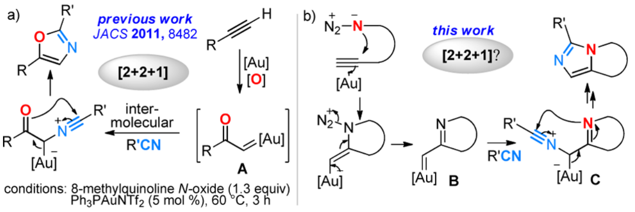
(7) (a) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258–3259. (b) Ye, L.; He, W.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 8550–8551. (c) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, 8482–8485. (d) Ye, L.; He, W.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3236–3239. (e) He, W.; Xie, L.; Xu, Y.; Xiang, J.; Zhang, L. *Org. Biomol. Chem.* **2012**, *10*, 3168–3171. (f) Wang, Y.; Ji, K.; Lan, S.; Zhang, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1915–1918.

(8) For selected works done by other groups, see: (a) Vasu, D.; Hung, H.-H.; Bhunia, S.; Gawade, S. A.; Das, A.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2011**, *50*, 6911–6914. (b) Davies, P. W.; Cremonesi, A.; Martin, N. *Chem. Commun.* **2011**, *47*, 379–381. (c) Mukherjee, A.; Dateer, R. B.; Chaudhuri, R.; Bhunia, S.; Karad, S. N.; Liu, R.-S. *J. Am. Chem. Soc.* **2011**, *133*, 15372–15375. (d) Qian, D.; Zhang, J. *Chem. Commun.* **2011**, *47*, 11152–11154. (e) Liu, R.-S.; Dateer, R. B.; Pati, k. k. *Chem. Commun.* **2012**, *48*, 7200–7202. (f) Bhunia, S.; Ghorpade, S.; Huple, D. B.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2012**, *51*, 2939–2942. (g) Qian, D.; Zhang, J. *Chem. Commun.* **2012**, *48*, 7082–7084.

10.1021/ol302102h

methods developed,[7,8] the rapid assembly of oxazole in a [2 + 2 + 1] cycloaddition is the first example of efficient intermolecular trapping of the highly electrophilic gold carbene moiety (Scheme 1a).[7c] To extend the oxidation strategy, we have developed approaches to the generation of the related α-imino gold carbenes and thereafter new reactions harvesting their reactivities.[9,10] Among the nitrene-transfer reagents employed, the azido group is deemed ideal as an intramolecular variant due to its ease of incorporation and atom economy.[9b,c,10] With respect to the oxazole chemistry,[7c] we reasoned that a similar reaction via the intermediacy of a corresponding α-imino gold carbene would lend a facile access to imidazoles instead of oxazoles. As shown in Scheme 1b, the reaction would commence with a 5-*exo-dig* cyclization of a tethered azido group onto a gold-activated terminal alkyne, followed by the formation of the α-imino gold carbene intermediate **B** upon dinitrogen expulsion; the assumed 5-*exo* selectivity is in line with related precedents in gold catalysis.[11] Notably, in our recent work, an electronic bias of the C−C triple bond was necessary to achieve the same regioselectivity for internal alkynes.[9c] The carbene **B**, likely highly electrophlic, could then be trapped by a nitrile to form a nitrile ylide-type intermediate **C**, which can cyclize to yield a bicyclic imidazole.[12] This imidazole formation[13] can be considered as an overall bimolecular [2 + 2 + 1] cycloaddition and a [3 + 2] cycloaddition between a nitrile and the carbene **B**. Herein, we disclose the successful implementation of this design.

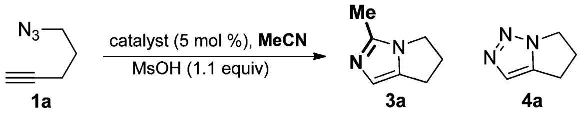
Scheme 1. (a) Published Oxazole Synthesis and (b) Design for a Related Imidazole Synthesis



conditions: 8-methylquinoline *N*-oxide (1.3 equiv) $Ph_3PAuNTf_2$ (5 mol %), 60 °C, 3 h

Our reaction discovery used 5-azidopent-1-yne (i.e., **1a**) as the substrate. It was readily synthesized from commercially available pent-4-yn-1-ol in two steps.[14] In anticipation of the strongly electrophilic nature of **B**, as in the case of the oxazoles synthesis, acetonitrile was used as solvent to achieve efficient trapping of **B**. Table 1 shows the reaction discovery and optimization. When $BrettPhosAuNTf_2$[7d] was used as the gold catalyst, the expected imidazole **3a** was indeed formed, albeit in only 11% yield. The undesired intramolecular Huisgen reaction product,[15] i.e., the triazole **4a** (11%) and the remaining substrate (76%) accounted for the mass balance (entry 1). The slow reaction was expected and consistent with the fact that the basic imidazole and triazole formed can deactivate the gold catalyst via coordination.[16] The addition of MsOH (1.1 equiv) avoided the problem, and the reaction proceeded to completion in 11 h, but the yield remained relatively low, and worse yet the Huisgen reaction was dominant (entry 2). Screening different gold catalysts proved to be fruitful. While $IPrAuNTf_2$ at 60 °C led to improvement on both the chemoselectivity and the reaction yield (entry 3), the more acidic $(C_6F_5)_3PAuNTf_2$ (entry 4) and $(4\text{-}CF_3Ph)_3PAuNTf_2$ (entry 5) allowed the reaction to proceed to completion in a reasonable time frame at ambient temperature. Moreover, the chemoselectivities were further improved. The breakthrough came when Au(III) catalysts (entries 6 and 7) were examined, and the prototypical Au(III) salt, $AuCl_3$ gave an excellent yield of the bicyclic imidazole **3a** while the amount

Table 1. Initial Reaction Discovery and Condition Optimization[a]



entry	catalyst	conditions	3a:4a	yield of 3a[c] (%)
1	$BrettPhosAuNTf_2$	60 °C, 11 h[b]	1:1	11
2	$BrettPhosAuNTf_2$	60 °C, 11 h	1:1.6	38
3	$IPrAuNTf_2$	60 °C, 11 h	2.4:1	68
4	$(C_6F_5)_3PAuNTf_2$	rt, 10 h	4.4:1	48
5	$(4\text{-}CF_3Ph)_3PAuNTf_2$	rt, 10 h	4.6:1	41
6	dichloropicolinatogold(III)	rt, 10 h	6.3:1	88
7	$AuCl_3$	rt, 10 h	25:1	93[d]
8	no catalyst	60 °C, 11 h	–	–

[a] [**1a**] = 0.05 M. [b] No MsOH added. [c] Yields were determined by ^1H NMR spectroscopy using CH_2Br_2 as the internal standard. [d] 89% isolated yield.

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(9) (a) Li, C.; Zhang, L. *Org. Lett.* **2011**, *13*, 1738–1741. (b) Lu, B.; Luo, Y.; Liu, L.; Ye, L.; Wang, Y.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, 8358–8362. (c) Yan, Z.-Y.; Xiao, Y.; Zhang, L. *Angew. Chem., Int. Ed.* **2012**10.1002/anie.201203678.

(10) For work done by other groups, see: (a) Wetzel, A.; Gagosz, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7354–7358. (b) Gorin, D. J.; Davis, N. R.; Toste, F. D. 2005, *127*, 11260-11261; (c) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Ogiwara, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5349–5352.

(11) (a) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391–4394. (b) Harkat, H.; Weibel, J. M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 6273–6276. (c) Hashmi, A. S. K.; Rudolph, M.; Schymura, S.; Visus, J.; Frey, W. *Eur. J. Org. Chem.* **2006**, 4905–4909. (d) Weyrauch, J. P.; Hashmi, A. S. K.; Schuster, A.; Hengst, T.; Schetter, S.; Littmann, A.; Rudolph, M.; Hamzic, M.; Visus, J.; Rominger, F.; Frey, W.; Bats, J. W. *Chem.—Eur. J.* **2010**, *16*, 956–963.

(12) Various gold catalyses have been run in acetonitrile without solvent participation; for an example, see: Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553. For an exception, see: Ibrahim, N.; Hashmi, A. S. K.; Rominger, F. *Adv. Synth. Catal.* **2011**, *353*, 461.

(13) For a recent gold-catalyzed case, see: Li, S.; Li, Z.; Yuan, Y.; Peng, D.; Li, Y.; Zhang, L.; Wu, Y. *Org. Lett.* **2012**, *14*, 1130–1133.

(14) Saito, Y.; Matsumoto, K.; Bag, S. S.; Ogasawara, S.; Fujimoto, K.; Hanawa, K.; Saito, I. *Tetrahedron* **2008**, *64*, 3578–3588.

(15) Huisgen, R. *Proc. Chem. Soc.* **1961**, 357–396.

(16) (a) Wang, D.; Gautam, L. N. S.; Bollinger, C.; Harris, A.; Li, M.; Shi, X. *Org. Lett.* **2011**, *13*, 2618–2621. (b) Wang, D.; Zhang, Y.; Harris, A.; Gautam, L. N. S.; Chen, Y.; Shi, X. *Adv. Synth. Catal.* **2011**, *353*, 2584–2588. (c) Duan, H.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *J. Am. Chem. Soc.* **2009**, *131*, 12100–12102.

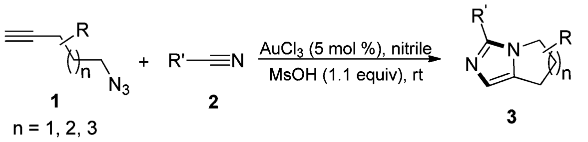
of the triazole **4a** was negligible (entry 7). Notably, without a gold catalyst, neither **3a** nor **4a** was formed at 60 °C even in the presence of MsOH (entry 8), suggesting that the intramolecular Huisgen reaction is also catalyzed by the gold catalyst.[17] While $PtCl_4$, $PtCl_2$, and $AgNTf_2$ were ineffective catalysts, $KAuCl_4$ and $AuBr_3$ were surprisingly inferior to $AuCl_3$ as the reaction proceeded very slowly and with low yields (72 h, < 20% yield).

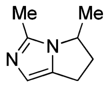
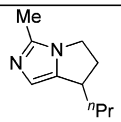
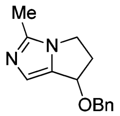
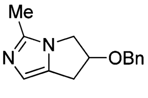
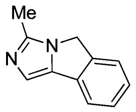
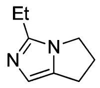
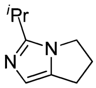
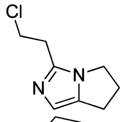
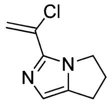
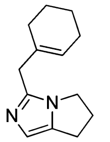
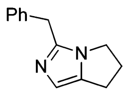
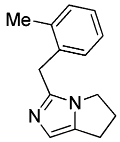
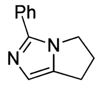
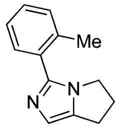
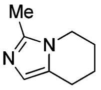
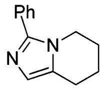
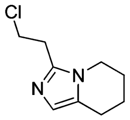
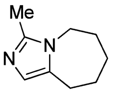
With the optimal reaction conditions (as in Table 1 entry 7) established, the reaction scope was then examined (Table 2). 5-Azidopent-1-ynes with different substituents on the aliphatic linker were first studied in acetonitrile. Substituents such as 5-methyl (entry 1), 3-propyl (entry 2), and a benzyloxy group at either the 3-position (entry 3) or the 4-position (entry 4) all posed no problem, and the bicyclic imidazoles were formed in mostly good yields. The linker could also be fused to a benzene ring. Though the reaction was not complete in 20 h, a serviceable yield was still achieved (entry 5). This reaction also permitted the use of a range of other nitriles as the reaction solvent (entries 6–14). Compared to acetonitrile, propionitrile (entry 6) and isobutyronitrile (entry 7) led to increasingly lower reaction yields. This phenomenon, though explainable by the increasing steric hindrance, might be in part rationalized by the decreasing concentrations of the solvent (CH_3CN, 19.2 M; EtCN, 14.0 M; ^{i}PrCN, 11.2 M), which would be consistent with the likely highly reactive nature of the α-imino gold carbene intermediate **B**. 3-Chloropropionitrile was a suitable substrate, and no HCl elimination from the product **3i** was detected during the reaction, suggesting the mild nature of the reaction conditions (entry 8). However, this elimination did occur to some extent during reaction workup and column chromatography under basic environment. Nitriles containing a conjugated (entry 9) and a skipped (entry 10) C–C double bond were also tolerated; notably, the skipped double bond remained intact in the imidazole **3k**, indicating that the final ring closure was facile. Phenylacetonitrile (entry 11), benzonitrile (entry 13), and the methyl-substituted counterparts (entries 12 and 14) reacted smoothly, affording the corresponding imidazoles in moderate to good yields. The intramolecular Huisgen reaction was the major side reaction in most of the discussed cases, but the corresponding bicyclic triazoles, formed in mostly < 20% yield, are highly polar and were readily removed by column chromatography.

For 6-azidohex-1-yne that possesses a four-carbon linker between the C–C triple bond and the azido group, an excellent yield of the corresponding 6-membered-ring fused imidazole derivative **3p** was achieved in acetonitrile (entry 15). Its reaction in other nitriles also proceeded well (entries 16 and 17). In the case of 7-azidohept-1-yne, the formation of the 7-membered ring-fused imidazole **3s** did occur albeit in a low yield (entry 2), and the major product was the corresponding bicyclic triazole.

Our attempts to limit the amount of the nitrile component to 3 equivalents in either a neat or solvated reaction were unfortunately resulted in the formation of complex mixtures with the desired imidazoles in low yields (typically < 30%). This limitation is attributed to the high reactivities of the in situ generated α-imino gold carbene intermediates.

Table 2. Reaction Scope[a,b]



entry	compound		yield, time	entry	compound		yield, time
1		**3b**	77% (13%), 10 h	2		**3c**	71% (22%), 10 h
3		**3d**	88% (trace), 6 h	4		**3e**	90% (trace), 6 h
5		**3f**	60%[c] (11%), 20 h	6		**3g**	78% (6%), 10 h
7		**3h**	61% (18%), 10 h	8		**3i**	69% (10%), 9 h
9		**3j**	60% (13%), 9 h	10		**3k**	50% (13%), 8 h
11		**3l**	66% (5%), 8 h	12		**3m**	55% (8%), 8 h
13		**3n**	80% (16%), 6 h	14		**3o**	75% (14%), 6 h
15		**3p**	94% (trace), 10 h	16		**3q**	84% (6%), 8 h
17		**3r**	75% (6 %), 8 h	18		**3s**	20% (36%), 10 h

[a] [**1**] = 0.05 M. [b] Isolated yields are given; the yield in parentheses was for the corresponding triazole and estimated by ^{1}H NMR analysis. [c] 14% of the azide substrate recovered.

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(17) For a Huisgen reaction involving stoichiometric gold, see: Partyka, D. V.; Updegraff, J. B.; Zeller, M.; Hunter, A. D.; Gray, T. G. *Organometallics* **2007**, *26*, 183–186.

In summary, we have developed a $AuCl_3$-catalyzed bimolecular [2 + 2 + 1] cycloaddition between a nitrile and an azidoalkyne. The reaction is rationalized by the generation of a highly electrophilic α-imino gold carbene, via a gold-promoted regioselective nitrene transfer from an azido group to the tethered terminal C–C triple bond, followed by its in situ reaction with a weakly nucleophilic nitrile in a [3 + 2] annulation. The nitrile is used as the reaction solvent to achieve good reaction efficiency. The competing intramolecular Huisgen reaction, the main side reaction, is minimized by using $AuCl_3$ as the catalyst.

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Supporting Information Available. Full experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.