Gold(I)/Zn(II) catalyzed tandem hydroamination/annulation reaction of 4-yne-nitriles†

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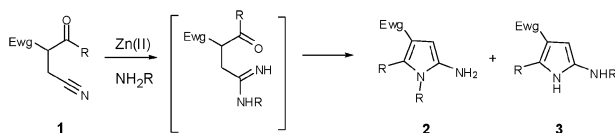**The tandem hydroamination–annulation reaction of 4-pentyne-nitriles in the presence of amine nucleophiles and a cooperatively operating catalyst system, consisting of Ph₃PAuCl and Zn(ClO₄)₂, provides an efficient route to 2-aminopyrroles. Two regioisomeric 2-aminopyrroles were formed in moderate to good yields.**

Over the past six years, gold catalysis has shown to be a powerful tool in organic synthesis. Cationic gold(I) and gold(III) complexes show unique behavior towards unactivated alkenes, alkynes, allenes, 1,3-dienes, and enynes promoting the nucleophilic addition of a variety of functional groups both inter- and intramolecularly.[1] In that respect, a great number of gold catalyzed tandem reactions of various systems with external nucleophiles that enable the formation of cyclic systems are present in the literature.[2] Especially those transformations including the catalytic addition of N–H bonds across C–C multiple bonds (hydroamination) that are catalyzed by both gold(I) and gold(III) complexes have found wide application for the generation of new C–N bonds[3,4] affording nitrogen containing heterocycles, such as pyrroles and pyridines.

Among the various synthetic strategies, catalytic transformations that use transition-metal catalysts are one of the modern approaches for forming pyrroles.[5] Relatively few examples of the gold-catalyzed synthesis of highly substituted pyrroles have been reported, however.[4e,6]

In the course of our research to develop new methodologies for the synthesis of nitrogen containing heterocycles that are promoted by transition metal catalysts, we recently demonstrated Zn(II) salts to be effective catalysts for the activation of the C=O bond and CN triple bond.[7] These principles led us to the discovery of a novel catalytic one-pot synthesis of 2-aminopyrroles starting from α-cyanomethyl-β-ketoesters. Zinc perchlorate smoothly catalyzes the amination of nitriles, and the subsequent cyclocondensation affords five-membered rings (pyrroles) in good yield, as exemplified in the conversion of **1** to **2** and **3** (Scheme 1).[7a]

In light of our previous investigation wherein nitriles could be activated by Zn(II) salts towards nucleophilic attacks, we report herein a conceptually new synthetic approach to substituted pyrroles via a cooperative Au(I)/Zn(II)-catalyzed sequential inter/intramolecular hydroamination reaction of 4-yne-nitriles with various amines.

The most notable aspect of the present reaction is the sequential activation of nitriles as pronucleophiles and alkynes as electrophiles, which enables the rapid assembly of a range of 2-amino substituted pyrroles with high efficiency. 2-Aminopyrroles have been found to show interesting biological properties[8,9] or have been used as precursors[10] for known drugs, in which they have found use as synthetic precursors for the acyclic nucleoside analogs of the pyrrolo[2,3-d]pyrimidine ring system.[11]

In this simple one pot assembly, the α-propargyl methyl nitriles (4-yne-nitriles)[12] **4** and a series of aliphatic and aromatic amines **5**, as nucleophiles, are used as starting materials to produce pyrroles **6** and **7** with high diversity (Scheme 2).

The initial efforts focused on the optimization of an efficient system starting from 4-yne-nitrile **4a** (Ewg = CO₂Et) as a model substrate. In our initial studies, **4a** was treated with aniline (**5a**) under various conditions (Table 1). Firstly, the inclusion of Zn(ClO₄)₂ as a potential catalyst at room temperature only led to the recovery of a starting material, in which only traces of the cyclization products **6aa** and **7aa**
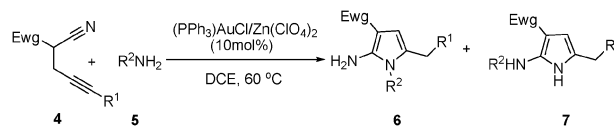
Scheme 2 Au(I)/Zn(II)-catalyzed sequential inter/intramolecular hydroamination reaction of 4-yne-nitriles with amines.

Table 1 Efficiency of the transition-metal catalysts for the transformation of **4a** with aniline **5a** to **6aa**[a] and **7aa**[a]

Entry	Catalyst[a]	Conditions	Yield[c] (%)
1	Zn(ClO₄)₂	80 °C, 12 h	Trace
2	PTSA	80 °C, 12 h	—
3	AgSbF₆	60 °C, 8 h	—
4	AuCl₃	60 °C, 8 h	—
5	(PPh₃)AuCl	60 °C, 8 h	—
6	(PPh₃)AuCl/AgSbF₆	60 °C, 6 h	58
7	AuCl₃/AgSbF₆	60 °C, 8 h	—
8	AuCl₃/Zn(ClO₄)₂	60 °C, 5 h	—
9	(PPh₃)AuCl/Zn(ClO₄)₂	rt, 12 h	40
10	(PPh₃)AuCl/Zn(ClO₄)₂	60 °C, 5 h	65, 70[b]
11	(PPh₃)AuCl/Zn(ClO₄)₂	90 °C, 3 h	68
12	(PPh₃)AuCl/Zn(OTf)₂	60 °C, 5 h	63
13	(PPh₃)AuCl/AgClO₄	80 °C, 8 h	61[d]

[a] 10 mol% of each species in DCE. [b] 15 mol% of each species in DCE. [c] Total yield (%) of **6aa** and **7aa** after column chromatography. [d] A pre-formed cationic gold(I) catalyst is used.

Scheme 1 Zn(II) salt catalyzed formation of pyrroles.

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were observed at higher temperatures (entry 1).[13] To rule out the possible involvement of the conjugate Brønsted acid in alkyne activation, the reaction of **4a** was performed in the presence of a catalytic amount of PTSA, in which no cyclization products were obtained (entry 2). Single metals such as Ag(I), Au(I), and Au(III) did not work as well (entries 3–5). As was planned beforehand, a combination of Zn(II) and Au(I) or Au(III) was feasible to catalyze this conversion. Unfortunately, Au(III) together with Zn(II) or Ag(I) did not induce the reaction sought (entries 7 and 8). However, the presence of Au(I), instead of Au(III), together with Zn(II), showed the formation of two products (**6aa**, **7aa**) (40%) at room temperature (entry 9). An increase in the reaction temperature was necessary to improve the conversion of the starting material (5 hours, 60 °C, 65%) (entry 10). At higher temperatures, however, other unidentified side products were observed.

The outcome of this experiment unambiguously demonstrated that the gold-based catalysis was uniquely responsible for the alkyne activation. Control reactions clearly indicate that the cationic Au(I) species is required for the reaction to proceed. In the absence of either Zn(II) or Au(I), no cyclization products were obtained at all. By far the best catalyst system was a combination of Ph_3PAuCl (10 mol%) and Zn(II) (10 mol%) carried out in DCE (1,2-dichloroethane) at 60 °C in order to efficiently afford the pyrroles **6** and **7**. The reaction can be carried out in various solvents, such as DCM, DCE, toluene, acetonitrile, and ethanol, which gave similar results. Practical reasons made DCE the solvent of choice. Zinc perchlorate and zinc triflate salts were used as the Zn(II) source, which showed similar effects on the reaction yields and reaction time (entries 10 and 12).

The product distribution was carefully investigated (Table 2). The reaction of 4-yne-nitrile (**4**) with various amines ended up being regioselective, in turn giving pyrrole **6** as the major and pyrrole **7** as the minor product. The ratio of pyrrole **6** to **7** increases when carried out with the more nucleophilic in character aliphatic amines (benzylamine) (entry 7), which runs up (6/1), whereas the ratio decreases when carried out with comparably less nucleophilic aromatic amines (aniline, 3/2) (entries 1 and 13).

Except for the products carried out with 1-phenylethyl amine (entries 8 and 18), we were pleased that all of the regioisomeric pyrroles could be separated by column chromatography. The value of the product ratio was determined according to the isolated product yields. However, for inseparable isomers, this ratio was determined by ^{1}H-NMR.

With optimized reaction conditions in hand, two possible 2-aminopyrroles (**6** and **7**) were formed. This reaction works for a range of different amines. A variety of amines, such as aliphatic or aromatic amines, except for electron poor anilines (entries 4 and 16), reacted smoothly to afford the desired products. Starting yne-nitriles, possessing both internal and terminal alkynes, were employed for this cyclization (entries 10–12). For terminal alkynes, the reaction proceeded through an *exo*-dig cyclization in order to afford the corresponding five membered rings (pyrrole). For the methyl substituted internal alkyne (**4d**), however, the cyclization gave a six membered ring (compound **8**) through a possible *endo*-dig cyclization (entry 11). Despite our great effort, the cyclization did not tolerate the internal alkynes substituted with both aryl and TMS groups (entries 10 and 12). In the case of TMS

Table 2 Scope of the reaction

Entry	Ewg-**4**	R²-(**5**)	Ratio **6/7**[a]	Time/h	Yield[b] (%)
1		Ph-**5a**	**6aa/7aa** 3/2	5	65
2	EtO_2C CN (4a–d structure)	3,4-Dimethyl-Ph-**5b**	**6ab/7ab** 2/1	5	62
3		*p*-MeO-Ph-**5c**	**6ac/7ac** 3/1	4	74
4	**4a** (R¹ = H)	*p*-NO₂-Ph-**5d**	**6ad/7ad** 1/0	7	13
5		*p*-Cl-Ph-**5e**	**6ae/7ae** 3/2	5	65
6		*m*-Cl-Ph-**5f**	**6af/7af** 3/1	5	60
7		Benzyl-**5g**	**6ag/7ag** 6/1	3	81
8		1-Phenylethyl-**5h**	**6ah/7ah** 3/1	3	75
9		Ethyl-**5i**	**6ai/7ai** 2/1	4	56
10	**4c** (R¹ = TMS)	*p*-MeO-Ph-**5c**	**6ac**	8	<5[c]
11	**4d** (R¹ = CH₃)	*p*-MeO-Ph-**5c**	**8**	9	61[c,d]
12	**4e** (R¹ = Ph)	Benzyl-**5g**	—	9	nr[c]
13		Ph-**5a**	**6ba/7ba** 3/2	5	67
14	NC CN (4b structure)	3,4-Dimethyl-Ph-**5b**	**6bb/6bb** 1/0	4	65
15		MeO-Ph-**5c**	**6bc/6bc** 4/1	4	72
16	**4b** (R¹ = H)	NO₂-Ph-**5d**	**6bd/6bd** 1/0	7	16
17		Benzyl-**5g**	**6bg/7bg** 1/0	3	73
18		1-Phenylethyl-**5h**	**6bh/7bh** 3/1	3	70

[a] Average ratio of at least two experiments. [b] Total yield of compounds **6** and **7**. [c] Reaction carried out at 90 °C. [d] Yield of compound **8**.

substitution, the only product that was isolated was a trace amount of pyrrole **6ac** after *in situ* desilylation (entry 10).

The loading of both catalysts from 10 to 15 mol% slightly (5%) increased the reaction yield. However, higher amounts had no dramatic effect on the reaction yields. The Ph_3PAuCl/Ag(I) catalyst system was also proven to catalyze this reaction (entry 6). In this system, Ag(I) may act in the same way as Zn(II). However, this combination was less effective than the Ph_3PAuCl/Zn(II) catalyst system. The additional parallel experiments were carried out with $AgSbF_6$ and $Zn(ClO_4)_2$ under the standard conditions described above, in which the yields with $Zn(ClO_4)_2$ were in all cases higher (56–81%) than with $AgSbF_6$ (41–58%) (Table S3, see ESI†).

A plausible mechanism for the Au(I)/Zn(II)-catalyzed cyclization is shown in Scheme 3. First, Zn(II) enhances the electrophilicity of the nitrile, which allows the attack of the amine (**5**) at the nitrile to give the intermediate **I**. It seems to be that Zn(II) has a dual effect of nitrile activation and chloride ligand abstraction
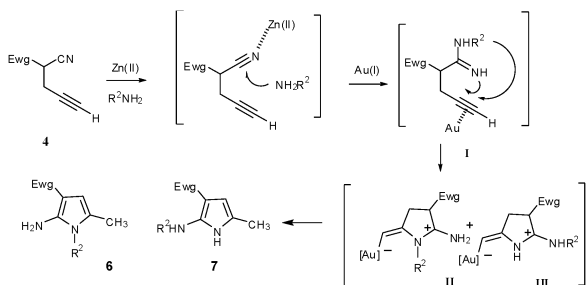
Scheme 3 Plausible mechanism for pyrrole formation.

from Ph$_3$PAuCl. This is also supported by the parallel experiments carried out with AgSbF$_6$ and Zn(ClO$_4$)$_2$, in which the yields with Zn(ClO$_4$)$_2$ were in all cases higher than with AgSbF$_6$, and where the attack of both nitrogen pronucleophiles of intermediate **I** at the Au(I) activated alkyne would allow for the intermediates **II** and **III**. Further arrangement leads to the formation of 2-aminopyrroles **6** and **7** (Scheme 3).

We succeeded in developing an Au(I)/Zn(II) catalyzed tandem cyclization of 4-pentyne-nitriles with various amines that provided an efficient and general route to pyrroles with a wide range of substituents. To our knowledge, this is the only report in which the cationic Au(I) species has been combined with Zn(II) salts, which cooperatively catalyze the hydroamination/annulation reaction of 4-yne-nitriles. Further studies on the mechanism, elucidating the product distribution of this reaction, and extending the scope of synthetic utility are currently in progress in our laboratory.

Notes and references

1 For recent reviews on gold catalyzed reactions, see: (a) Y. Yamamoto, I. D. Gridnev, N. T. Patil and T. Jin, *Chem. Commun.*, 2009, 5075–5087; (b) R. Skouta and C.-J. Li, *Tetrahedron*, 2008, **64**, 4917–4938; (c) Z. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, **108**, 3239–3265; (d) A. Arcadi, *Chem. Rev.*, 2008, **108**, 3266–3325; (e) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326–3350; (f) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351–3378; (g) N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395–3442; (h) H. C. Shen, *Tetrahedron*, 2008, **64**, 3885–3903; (i) N. Krause, V. Belting, C. Deutsch, J. Erdsack, H. T. Fan, B. Gockel, A. Hoffmann-Roder, N. Morita and F. Volz, *Pure Appl. Chem.*, 2008, **80**, 1063–1069; (j) A. Fürstner and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 3410–3449; (k) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180–3211; (l) D. J. Gorin and F. D. Toste, *Nature*, 2007, **446**, 395–403; (m) N. Marion and S. P. Nolan, *Chem. Soc. Rev.*, 2008, **37**, 1776–1782; (n) A. S. K. Hashmi, *Angew. Chem.*, 2005, **117**, 7150–7154 (*Angew. Chem., Int. Ed.*, 2005, **44**, 6990); (o) A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem.*, 2006, **118**, 8064–8105 (*Angew. Chem., Int. Ed.*, 2006, **45**, 7896); (p) A. Hoffmann-Röder and N. Krause, *Org. Biomol. Chem.*, 2005, **3**, 387–391; (q) A. S. K. Hashmi, *Gold Bull.*, 2004, **37**, 51–65; (r) A. S. K. Hashmi, *Gold Bull.*, 2003, **36**, 3–9.
2 For selected gold-catalyzed tandem reactions with external nucleophiles, see: (a) J. Meng, Y.-L. Zhao, C.-Q. Ren, Y. Li, Z. Li and Q. Liu, *Chem.–Eur. J.*, 2009, **15**, 1830–1834; (b) V. Belting and N. Krause, *Org. Biomol. Chem.*, 2009, **7**, 1221–1225; (c) L. Leseurre, P. Y. Toullec, J.-P. Genet and V. Michelet, *Org. Lett.*, 2007, **9**, 4049–4052; (d) A. K. Buzas, F. M. Istrate and F. Gagosz, *Angew. Chem., Int. Ed.*, 2007, **46**, 1141–1144; (e) T. Yang, L. Campbell and D. J. Dixon, *J. Am. Chem. Soc.*,

2007, **129**, 12070–12071; (f) A. K. Buzas, F. M. Istrate and F. Gagosz, *Angew. Chem., Int. Ed.*, 2007, **46**, 1141; (g) C. H. M. Amijs, C. Ferrer and A. M. Echavarren, *Chem. Commun.*, 2007, 698–700; (h) L.-Z. Dai, M.-J. Qi, Y.-L. Shi, X.-G. Liu and M. Shi, *Org. Lett.*, 2007, **9**, 3191–3194; (i) J. Zhang and H.-G. Schmalz, *Angew. Chem., Int. Ed.*, 2006, **45**, 6704–6707; (j) A. S. K. Hashmi, M. Rudolph, S. Schymura, J. Visus and W. Frey, *Eur. J. Org. Chem.*, 2006, 4905–4909; (k) V. Belting and N. Krause, *Org. Lett.*, 2006, **8**, 4489–4492; (l) Y. Horino, M. R. Luzung and F. D. Toste, *J. Am. Chem. Soc.*, 2006, **128**, 11364–11365; (m) S. Park and D. Lee, *J. Am. Chem. Soc.*, 2006, **128**, 10664–10665.
3 For a microreview on hydroamination of multiple systems, see: A. Ross, R. A. Widenhoefer and X. Han, *Eur. J. Org. Chem.*, 2006, 4555–4563.
4 For selected gold-catalyzed hydroamination reactions, see: (a) A. S. K. Hashmi, M. Buhrle, M. Wolfle, M. Rudolph, M. Wieteck, F. Rominger and W. Frey, *Chem.–Eur. J.*, 2010, **16**, 9846–9854; (b) Y. Zhang, J. P. Donahue and C.-J. Li, *Org. Lett.*, 2007, **9**, 627–630; (c) J.-E. Kang, H.-B. Kim, J.-W. Lee and S. Shin, *Org. Lett.*, 2006, **8**, 3537–3540; (d) I. Nakamura, Y. Yamagishi, D. Song, S. Konta and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2007, **46**, 2284–2287; (e) I. V. Seregin, A. W. Schammel and V. Gevorgyan, *Org. Lett.*, 2007, **9**, 3433–3436; (f) D. J. Gorin, N. R. Davis and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 11260–11261; (g) N. Morita and N. Krause, *Org. Lett.*, 2004, **6**, 4121–4123; (h) Z. Zhang, C. F. Bender and R. A. Widenhoefer, *Org. Lett.*, 2007, **9**, 2887–2889; (i) P. H. Lee, H. Kim, K. Lee, M. Kim, K. Noh, H. Kim and D. Seomoon, *Angew. Chem., Int. Ed.*, 2005, **44**, 1840–1843; (j) R. L. LaLonde, B. D. Sherry, E. J. Kang and F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 2452–2453; (k) C. F. Bender and R. A. Widenhoefer, *Org. Lett.*, 2006, **8**, 5303–5308; (l) C. F. Bender and R. A. Widenhoefer, *Chem. Commun.*, 2006, 4143–4144; (m) X.-Y. Liu, C.-H. Li and C.-M. Che, *Org. Lett.*, 2006, **8**, 2707–2710; (n) C.-Y. Zhou and C.-M. Che, *J. Am. Chem. Soc.*, 2007, **129**, 5828–5829; (o) T. Enomoto, A.-L. Girard, Y. Yasui and Y. Takemoto, *J. Org. Chem.*, 2009, **74**, 9158; (p) X.-Y. Liu, P. Ding, J.-S. Huang and C.-M. Che, *Org. Lett.*, 2007, **9**, 2645–2648.
5 For transition metal catalyzed pyrrole synthesis, see: (a) S. Kamijo, C. Kanazawa and Y. Yamamoto, *J. Am. Chem. Soc.*, 2005, **127**, 9260–9266; (b) A. I. Siriwardana, K. K. A. D. S. Kathriarachchi, I. Nakamura, I. D. Gridnev and Y. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 13898–13899; (c) X. Yuan, X. Xu, X. Zhou, J. Yuan, L. Mai and Y. Li, *J. Org. Chem.*, 2007, **72**, 1510–1513; (d) B. Gabriele, G. Salerno and A. Fazio, *J. Org. Chem.*, 2003, **68**, 7853–7861; (e) D. U. Braun, K. Zietler and T. J. J. Müller, *Org. Lett.*, 2001, **3**, 3297–3300; (f) H. Shiraishi, T. Nishitani, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 1998, **63**, 6234–6238.
6 For gold-catalyzed pyrrole synthesis, see: (a) Y. Lu, X. Fu, H. Chen, X. Du, X. Ji and Y. Liu, *Adv. Synth. Catal.*, 2009, **351**, 129–134; (b) X. Shu, X. Liu, H. Xiao, K. Ji, L. Guo and Y. Liang, *Adv. Synth. Catal.*, 2008, **350**, 243; (c) N. Martin and P. W. Davies, *Org. Lett.*, 2009, **11**, 2293–2296; (d) J. T. Binder and S. T. Kirsch, *Org. Lett.*, 2006, **8**, 2151–2153; (e) C. A. Witham, P. Mauleon, N. D. Shapiro, B. D. Sherry and F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 5838–5839.
7 (a) A. S. Demir, M. Emrullahoğlu and G. Ardahan, *Tetrahedron*, 2007, **63**, 461–468; (b) A. S. Demir and M. Emrullahoğlu, *Tetrahedron*, 2006, **62**, 1452–1458; (c) A. S. Demir and M. Emrullahoğlu, *Tetrahedron*, 2005, **61**, 10482–10489.
8 (a) A. Trani and E. Bellasio, *Farmaco, Ed. Sci.*, 1983, **38**, 940–949; (b) C. Yaroslavsky, P. Bracha and R. Glaser, *J. Heterocycl. Chem.*, 1989, **26**, 1649–1654.
9 (a) M. T. Cocco, C. Congiu, A. Maccioni, M. L. Schivo, A. De Logu and G. Palmieri, *Farmaco, Ed. Sci.*, 1988, **43**, 951–960; (b) O. M. Z. Howard, J. J. Oppenheim, M. G. Melinda, J. M. Covey and J. Bigelow, *J. Med. Chem.*, 1998, **41**, 2184–2193.
10 S. H. Krawezyk, M. R. Nassiri, L. S. Kucera, E. R. Kern and R. G. Ptak, *J. Med. Chem.*, 1995, **38**, 4106–4114.
11 S. M. Bennett, N. Ba Nghe and K. K. Ogilvie, *J. Med. Chem.*, 1990, **33**, 2162–2173.
12 D. P. Curran and C. M. Seong, *Tetrahedron*, 1992, **48**, 2175–2190; A. Goeta, M. M. Salter and H. Shah, *Tetrahedron*, 2006, **62**, 3582–3599.
13 K. Okuma, J. Seto, K. Sakaguchi, S. Ozaki, N. Nagahora and K. Shioji, *Tetrahedron Lett.*, 2009, **50**, 2943–2945.