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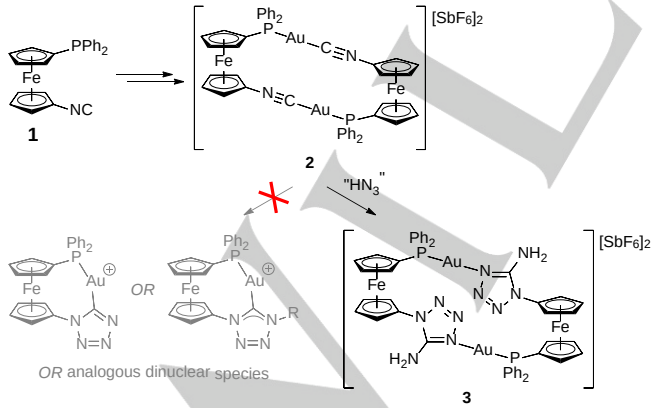
Selective gold-catalysed synthesis of cyanamides and 1-substituted 1*H*-tetrazol-5-amines from isocyanides

Karel Škoch,[a] Ivana Císařová,[a] and Petr Štěpnička*[a]

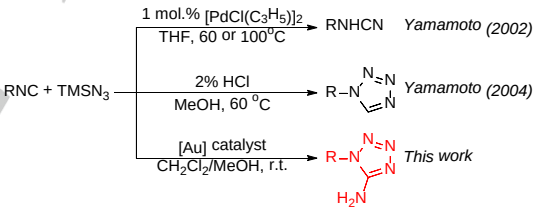
Abstract: The newly discovered gold-catalysed reaction of isocyanides with hydrazoic acid generated *in situ* from trimethylsilyl azide and methanol (or, alternatively, from NaN_3/AcOH) produces either cyanamides or 1-substituted 1*H*-tetrazol-5-amines, depending on the amount of available HN_3. The reaction proceeds selectively and in generally high yields of either product, thus providing a particularly convenient access to a wide range of substituted 1*H*-tetrazol-5-amines that are rather difficult to access otherwise.

Tetrazoles, nitrogen-rich heterocycles, which are not found in the structures of natural products, have recently generated considerable research interest for their prospective applications as energetic materials,[1] pharmaceuticals,[2] and constituents of metal-organic frameworks.[1c, 3] As a part our recent studies focused on the reactivity of 1'-(diphenylphosphino)-1-isocyanoferrocene (**1**),[4] we have also examined the interactions of its dimeric Au(I) complex **2** with azides (Scheme 1). Considering the established reactions of transition metal azides with isocyanides that produce tetrazole and tetrazolate complexes,[5] we hypothesized that compound **2** could behave similarly, thereby yielding a structurally interesting chelate or bridged phosphine-tetrazole(ate) complex (Scheme 1). Surprisingly, complex **2** reacted with trimethylsilyl azide ($TMSN_3$) through a different mechanism, producing dimeric complex **3**, which contains ferrocene-bound 5-amino-1*H*-tetrazol-1-yl moieties that coordinated *via* their N4 atoms (Scheme 1). We assumed that hydrazoic acid was the key reagent in this transformation, resulting from $TMSN_3$ decomposition.[6]



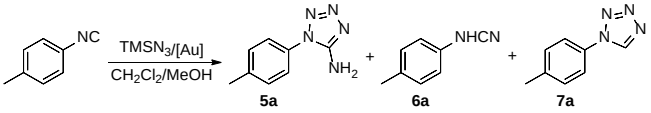
Scheme 1. Formation of complex **3** by addition of *in situ* formed HN_3 across the C≡N groups in dimer **2** (R = H or $SiMe_3$). For preparative details and the crystal structure of **3**, see the Supporting Information.

Although Echavarren *et al*.[7] and Shi, Jiao and *et al*.[8] have recently reported formally related Au-catalysed $TMSN_3$ additions across alkynes that produce tetrazoles, analogous reactions with *isocyanide* substrates have been mostly overlooked.[9] To the best of our knowledge, only Yamamoto *et al*. have previously reported that $TMSN_3$ addition to isocyanides gives rise to either cyanamides[10] or 1-substituted 1*H*-tetrazoles,[11] depending on the catalyst used and on the reaction conditions (Scheme 2). Thus, based on our serendipitous discovery that a 1*H*-tetrazol-5-amine (or 5-aminotetrazole) can be easily formed from an isocyanide, we subsequently assessed whether other isocyanides would react similarly to coordinated **1** and whether these transformations could be performed catalytically.[12,13]



Scheme 2. Catalysed reactions of isocyanides with $TMSN_3$.

As a model reaction for further studies, we used the reaction of 4-tolyl isocyanide (**4a**) with an excess of $TMSN_3$ (5 equiv.) in the presence of $[Au(MeCN)(PPh_3)][SbF_6]$ (**8**) catalyst and methanol as a proton source (Scheme 3).



Scheme 3. Gold-catalysed cyclization reaction of 4-tolyl isocyanide (**4a**) with $TMSN_3$/MeOH as a HN_3 surrogate.

Gratifyingly, $TMSN_3$ addition to a mixture of **4a** and catalyst **8** (5 mol.%) in dichloromethane and methanol resulted in vigorous effervescence (N_2 evolution) and, ultimately, produced 1-(4-tolyl)-1*H*-tetrazol-5-amine (**5a**) in a virtually quantitative yield after a simple chromatographic work-up. While optimising the reaction conditions (Table 1), we found that as little as 0.1

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mol.% catalyst **8** suffices to achieve complete conversion of **4a** into **5a** within 1 h when 5 equiv. of $TMSN_3$ are used. The only by-product detected was cyanamide **6a**, which became the sole (and isolable) product when lowering the quantity of $TMSN_3$ to 1 equiv. (entry 5). $TMSN_3$ itself also reacted with **4a**, but the HN_3 resulting from its decomposition reacted much faster (entry 6); HN_3 neutralisation with an amine basically stopped the reaction (entry 7).

A catalyst amount lower than 0.1 mol.% resulted in selectivity loss and in the preferential formation of cyanamide **6a**. When further decreasing the loading of the Au(I) catalyst, or in its absence, the reaction produced only tetrazole **7a** because the rather slow, known non-catalysed addition of HN_3 across **4a** that leads to this product became the main reaction pathway (entries 8-13).

Rather unexpectedly, Au(I) complexes with phosphite and N-heterocyclic carbene ligands, which have been advantageously used in gold catalysis,[14] led to disappointing results. They not only afforded slower reacting catalysts but typically promoted the formation of **6a** (note: this applies even to the azide complex $[AuN_3(PPh_3)]$). Cationic Au(I) complex featuring the bulky JohnPhos ligand also produced a mixture of **5a** and **6a**, whereas its PMe_3 analogue $[Au(MeCN)(PMe_3)][SbF_6]$ was as efficient as the initially chosen catalyst **8**. Lastly, [AuCl(tht)] and $AuCl_3$ yielded mixtures of **5a** and **6a**, although **6a** was the major product. Other Lewis and Brønsted acids were either inactive or generated only minor amounts of **6a** (entries 25-33). In line with the previous report,[10] cyanamide **6a** was also obtained when using $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ as the catalyst.

Table 1. Summary of the Screening Experiments.[a]

Entry	Catalyst [amount (mol.%)]	Yield (%)		
		5a	**6a**	**7a**
1	$[Au(MeCN)(PPh_3)][SbF_6]$ (**8**) [5]	99	0	0
2	**8** [1]	99	0	0
3	**8** [0.1]	**99(93)**	0	0
4[b]	**8** [0.1]	58	42	0
5[c]	**8** [0.1]	0	**98(96)**	2
6[d]	**8** [0.1]	0	48	0
7[e]	**8** [0.1]	7	5	6
8	**8** [0.05]	38	62	0
9	**8** [0.01]	0	94	6
10[c]	**8** [0.01]	0	68	12
11[c]	**8** [0.005]	0	11	2
12	none	0	0	10
13[f]	none	0	0	**88(85)**
14	$[AuCl(PPh_3)]$ [0.1]	44	56	0
15	$[AuCl\{P(OPh)_3\}]$ [0.1]	44	56	0
16[g]	[AuCl(L)] [0.1]	0	80	6
17[g]	$[Au(MeCN)(L)][SbF_6]$ [0.1]	0	96	4
18[h]	[AuCl(IPr)] [0.1]	5	89	7
19[h]	$[Au(MeCN)(IPr)][BF_4]$ [0.1]	0	80	6
20[i]	$[Au(MeCN)(JP)][SbF_6]$ [0.1]	42	58	0
21	$[Au(MeCN)(PMe_3)][SbF_6]$ [0.1]	94	0	6
22	$[AuN_3(PPh_3)]$ [0.1]	85	13	2
23[j]	[AuCl(tht)] [0.1]	22	78	0
24	$AuCl_3$ [0.1]	32	68	0
25	$ZnCl_2$ [1]	0	0	13
26	$Yb(OTf)_3$ [1]	0	5	8
27	$Sc(OTf)_3$ [1]	0	6	10
28	$[Cu(MeCN)_4][BF_4]$ [1]	0	0	8
29	$Ag[SbF_6]$ [1]	0	0	8
30	$[PdCl(C_3H_5)]_2$ [0.5][k]	0	77	5
31	$B(C_6F_5)_3$ [1]	0	5	10
32	CF_3CO_2H [1]	0	4	9
33	CSA[l] [1]	0	24	7

[a] Conditions: $TMSN_3$ (5 mmol if not stated otherwise) was added to a solution of **4a** (1.0 mmol) and catalyst in dichloromethane-methanol (3 mL + 1 mL). The mixture was stirred at room temperature for 1 h, before a small aliquot was collected, evaporated and analysed by ^{1}H NMR spectroscopy. Isolated yields are given in parentheses. [b] Reaction with 2.5 equiv. of $TMSN_3$. [c] Reaction with 1 equiv. of $TMSN_3$. [d] Reaction in pure dichloromethane. [e] Reaction with added *i*-Pr_2NEt (5 equiv.). [f] Reaction time: 22 h. [g] L = $P(OC_6H_3t\text{-}Bu_2\text{-}2,4)_3$. [h] IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [i] JP = 2-(di-*tert*-butylphosphino)biphenyl (JonhPhos). [j] tht = tetrahydrothiophene. [k] 1 mol.% Pd. [l] CSA = (1*S*)-(+)-camphorsulfonic acid.

In addition, the screening experiments revelaed that the course of the reaction can be efficiently controlled by changing the quantity of $TMSN_3$ added, thereby allowing for selective synthesis of aminotetrazoles **5** *or* cyanamides **6** (compare entries 3 and 5 in Table 1). This was indeed confirmed by the subsequent reaction scope experiments (Table 2), which further demonstrated that the substituents virtually have no effect on the reactions producing cyanamides. Conversely, reactions leading to aryl-substituted aminotetrazoles proceeded more easily with substrates bearing electron-donating substituents.[15] Aliphatic substrates with primary and secondary alkyl substituents ($PhCH_2$ and Cy) also reacted well, whereas the conversion of 1-adamantyl isocyanide (**4t**) into **5t** proved rather difficult. Thus, our combined results (Tables 1 and 2) show that a wide range of substituted isocyanides (including functionalised ones) can be efficiently and selectively transformed into the corresponding

1*H*-tetrazol-5-amines and cyanamides through gold-catalysed reactions with *in situ*-formed hydrazoic acid.

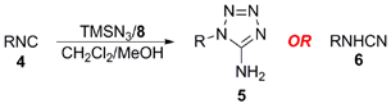


Table 2. Summary of the Reaction Scope Experiments.[a]

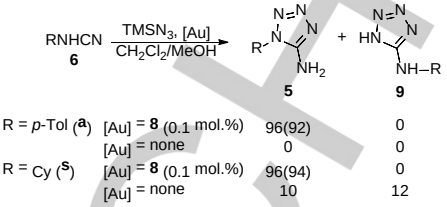
R	Yield (%)[b]		R	Yield (%)[b]	
	5	**6**		**5**	**6**
4-MeC_6H_4 (**a**)	93	96	4-NCC_6H_4 (**k**)	97[c]	90
Ph (**b**)	95[c]	90	4-$EtO_2CC_6H_4$ (**l**)	96[c]	92
2-MeC_6H_4 (**c**)	96[d]	90[c]	4-$MeOC_6H_4$ (**m**)	97	85
2,6-$Me_2C_6H_3$ (**d**)	93[e]	92[d]	4-$MeSC_6H_4$ (**n**)	94	90
1-naphthyl (**e**)	92[c]	88	4-$Me_2NC_6H_4$ (**o**)	97	90
1,1'-biphenyl-2-yl (**f**)	95[e]	90[c]	2-pyridyl (**p**)	75[e,f]	95
4-$Me_3SiC{\equiv}CC_6H_4$ (**g**)	95[c]	92	ferrocenyl (**q**)	92[c]	–[g]
4-BrC_6H_4 (**h**)	96[c]	95	$PhCH_2$ (**r**)	92	93[g,h]
4-IC_6H_4 (**i**)	94[c]	94	Cy (**s**)	96[c]	95
4-$O_2NC_6H_4$ (**j**)	95[c]	86	1-adamantyl (**t**)	41[i,j]	85[i]

[a] Conditions: Isocyanide 4 (1 mmol) was dissolved in dichloromethane (3 mL). Catalyst **8** (0.1 mol.%), $TMSN_3$ (**5 mmol for 5; 1 mmol for 6**) and methanol (1 mL) were added successively, and the mixture was stirred for 1 h (unless specified otherwise). The products were isolated by column chromatography following evaporation of the solvents. [b] Isolated yields, unless stated otherwise. [c] After 3 h. [d] After 8 h. [e] After 24 h. [f] 20% cyanamide **6p** was also isolated. [g] Not isolated; compound unstable. [h] NMR yield: 93%. [i] 1 mol.% catalyst **8** was used. [j] The reaction was performed for 5 h with 1 mmol $TMSN_3$ added every 1 h. When $TMSN_3$ was added in one portion, the yield of **6t** decreased to 41%, whereas **7t** was isolated in a 50% yield.

Subsequently, we tried to develop a more practical variant of aminotetrazole synthesis by using NaN_3 as a source of HN_3 (for details, see the Supporting Information). The testing reaction (Scheme 3) did not proceed without an acid additive (*i.e.*, with NaN_3 alone) or when using methanolic HCl, whereas adding various ammonium salts (NH_4Cl, $(Et_3NH)Cl$, and $(PhCH_2NH_3)Cl$) resulted in the preferential formation of cyanamide **6a**, albeit in rather low conversions (<50%). However, when using equimolar quantities of NaN_3 and acetic acid (both 5 equiv.), the cyclisation reaction proceeded efficiently, providing **5a** in a 96% NMR yield (with 0.1 mol.% of catalyst **8**). The practical applicability of this approach exploiting an inexpensive and safe HN_3 source was further demonstrated by synthesizing **5a** from **4a** in a 92% isolated yield at a 20-mmol scale.

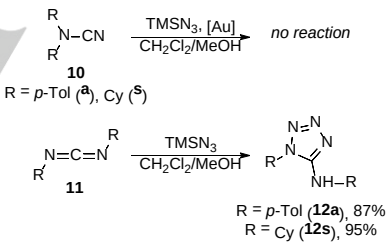
In following experiments aimed at understanding the reaction course, we confirmed that cyanamides **6** are the key reaction intermediates. For instance, the model compounds **6a** and **6s** were smoothly converted to the respective aminotetrazoles when adding $TMSN_3$ and catalyst **8** (Scheme 4).

No reaction with **6a** was observed in the absence of the catalyst, whilst **6s** was partly transformed to **5s** and to the isomeric *N*-cyclohexyl-1*H*-tetrazol-5-amine (**9s**).[13a,b]



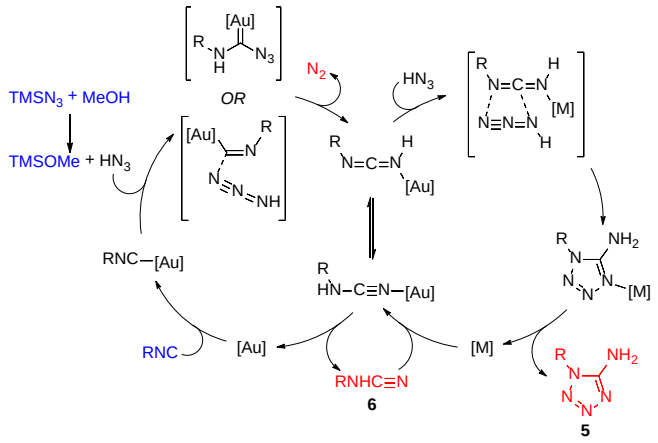
Scheme 4. Reactions of cyanamides **6** with $TMSN_3$/MeOH (the reaction times were 1 h for **5a** and 2 h for **5s**; isolated yields are given in parentheses).

Cyanamides obtained from secondary amines (**10**) did not react under similar conditions, even when increasing the amount of catalyst to 0.5 mol.% and extending the reaction time (Scheme 5, top). By contrast, their isomeric 1,3-carbodiimides **11** were easily converted into 1,*N*-disubstituted 1*H*-tetrazol-5-amines **12** (Scheme 5), even without the gold catalyst.[16] Lastly, no reaction was observed when treating isocyanide **4a** with HN_3-free organic azides ($PhCH_2N_3$ and 4-$MeC_4H_6N_3$) in the presence of 1 mol.% **8** in CH_2Cl_2/MeOH.



Scheme 5. Reactions of carbodiimides **11** with $TMSN_3$/MeOH (isolated yields are given).

The aforementioned results suggest that aminotetrazoles **5** are formed in two steps. In the first step, the *in situ*-generated hydrazoic acid adds to isocyanide, thus producing cyanamide **6**, which then undergoes a [3+2] cycloaddition with another molecule of HN_3, ultimately producing aminotetrazole **5**, as tentatively formulated in Scheme 6. The gold catalyst certainly plays a key role in the first reaction step because, in its absence, the system only yields tetrazole **7** by HN_3 addition to the starting isocyanide and by subsequent cyclisation. However, the gold catalyst may even facilitate the equilibrium between cyanamide and carbodiimide, which actually provides access to tetrazole **5** *via* spontaneous or Au-catalysed [3+2] cycloaddition between the carbodiimide and HN_3 (if the latter is available!). The role of carbodiimides is also crucial because cyanamides **10**, which cannot isomerise by H-shift,[17] do not react under similar conditions.



Scheme 6. Plausible reaction mechanism showing the two interconnected processes. Note: [M] = [Au] for Au-mediated transformation or void for a possible spontaneous process suggested by other reactivity studies.

In conclusion, we describe the highly efficient (only 0.1 mol.% Au catalyst is required) and selective catalytic conversion of isocyanides into cyanamides[18] or 1-substituted 1*H*-tetrazol-5-amines, which is easily and reliably controlled by changing the amount of the HN_3 source. Furthermore, the reactions are widely applicable and functional group-tolerant, thereby providing safe[19] and nearly unlimited access to 1-substituted 1*H*-tetrazol-5-amines, which are rapidly emerging as promising compounds in several fields.[20]

Acknowledgements

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Conflict of interests

The authors declare no conflict of interest.

Keywords: gold • cycloaddition • homogeneous catalysis • isocyanides • tetrazoles

[1] a) T. M. Klapötke, Chemistry of High-Energy Materials, 3rd ed., Walter de Gruyter, Berlin, **2015**; b) H. Gao, J. M. Shreeve, *Chem. Rev.* **2011**, *111*, 7377; c) S. Zhang, Q. Yang, X. Liu, X. Qu, Q. Wei, G. Xie, S. Chen, S. Gao, *Coord. Chem. Rev.* **2016**, *307*, 292; d) P. Yin, J. M. Shreeve, *Adv. Heterocycl. Chem*. **2017**, *121*, 89.

[2] R. J. Herr, *Bioorg. Med. Chem.* **2002**, *10*, 3379; b) L. V. Myznikov, A. Hrabalek, G. I. Koldobskii, *Chem. Heterocycl. Compd.* **2007**, *43*, 1; c) V. A. Ostrovskii, R. E. Trifonov, E. A. Popova, *Russ. Chem. Bull.* **2012**, *61*, 768.

[3] J.-P. Zhang, Y.-B. Zhang, J.-B. Lin, X.-M. Chen, *Chem. Rev.* **2012**, *112*, 1001.

[4] K. Škoch, I. Císařová, J. Schulz, U. Siemeling, P. Štěpnička, *Dalton Trans*. **2017**, *46*, 10339.

[5] a) W. Beck, W. P. Fehlhammer, *Angew. Chem.* **1967**, *79*, 146; *Angew. Chem. Int. Ed.* **1967**, *6*, 169; b) W. Beck, K. Burger, W. P. Fehlhammer, *Chem. Ber.* **1971**, *104*, 1816; c) W. P. Fehlhammer, L. F. Dahl, *J. Am. Chem. Soc.* **1972**, *94*, 3370; d) M. Wehlan, R. Thiel, J. Fuchs, W. Beck, W. P. Fehlhammer, *J. Organomet. Chem.* **2000**, *613*, 159; e) Y.-J. Kim, Y.-S. Kwak, Y.-S. Joo, S. W. Lee, *J. Chem. Soc., Dalton Trans.* **2002**, 144; f) W. F. Gabrielli, S. D. Nogai, J. M. McKenzie, S. Cronje, H. G. Raubenheimer, *New J. Chem.* **2009**, *33*, 2208; g) M. A. Kinzhalov, A. S. Novikov, K. V. Luzyanin, M. Haukka, A. J. L. Pombeiro, V. Y. Kukushkin, *New J. Chem.* **2016**, *40*, 521; h) M. A. Kinzhalov, A S. Legkodukh, T. B. Anisimova, A. S. Novikov, V. V. Suslonov, K. V. Luzyanin, V. Y. Kukushkin, *Organometallics* **2017**, *36*, 3974.

[6] M. Jafarzadeh, *Synlett* **2007**, 2144.

[7] M. Gaydou, A. M. Echavarren, *Angew. Chem.* **2013**, *125,* 13710; *Angew. Chem. Int. Ed.* **2013**, *52*, 13468.

[8] C. Qin, Y. Su, T. Shen, X. Shi, N. Jiao, *Angew. Chem.* **2016**, *128*, 358; *Angew. Chem. Int. Ed.* **2016**, *55*, 350.

[9] For a recent review on the metal-catalysed reactions of isocyanides, see: V. P. Boyarskiy, N. A. Bokach, K. V. Luzyanin, V. Y. Kukushkin, *Chem. Rev.* **2015**, *115*, 2698.

[10] S. Kamijo, T. Jin, Y. Yamamoto, *Angew. Chem.* **2002**, *114*, 1858; *Angew. Chem. Int. Ed.* **2002**, *41*, 1780.

[11] T. Jin, S. Kamijo, Y. Yamamoto, *Tetrahedron Lett.* **2004**, *45*, 9435.

[12] A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.* **2013**, *113*, 3084.

[13] Although the latter transformation corresponds to an established route to 1*H*-tetrazol-5-amines, the currently reported Au-catalysed reaction proceeds much more selectively and under mild conditions: a) R. von Stollé, F. Henke-Stark, *J. Prakt. Chem.* **1930**, *124*, 261; b) W. L. Garbrecht, R. M. Herbst, *J. Org. Chem.* **1953**, *18*, 1014; c) D. Habibi, M. Nasrollahzadeh, A. R. Faraji, Y. Bayat, *Tetrahedron* **2010**, *66*, 3866; c) D. Habibi, M. Nasrollahzadeh, H. Sahebekhtiari, S. M. Sajadi, *Synlett* **2012**, *23*, 2795; d) D. Habibi, A. R. Faraji, D. Sheikh, M. Sheikhi, S. Abedi, *RSC Adv.* **2014**, *4*, 47625; e) S. N. M. Boddapati, A. E. Kola, S. B. Kesana, H. B. Bollikolla, *J. Organomet. Chem.* **2018**, *866*, 177.

[14] a) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351; b) B. Ranieri, I. Escofet, A. M. Echavarren, *Org. Biomol. Chem.* **2015**, *13*, 7103; c) A. H. Christian, Z. L. Niemeyer, M. S. Sigman, F. D. Toste, *ACS Catal* **2017**, *7*, 3973.

[15] Some cyanamides could not be isolated due to their low stability.

[16] O. Tsuge, S. Urano, K. Oe, *J. Org. Chem.* **1980**, *45*, 5130.

[17] F. Tordini, A. Bencini, M. Bruschi, L. De Gioia, G. Zampella, P. Fantucci, *J. Phys. Chem. A* **2003**, *107*, 1188.

[18] For an overview of the chemistry of cyanamides, see: a) M.-H. Larraufie, G. Maestri, M. Malacria, C. Ollivier, L. Fensterbank, E. Lacôte, *Synthesis* **1992**, 1279; b) N. A. Bokach, V. Y. Kukushkin, *Coord. Chem. Rev.* **2013**, *257*, 2293.

[19] For an alternative synthesis of 1*H*-tetrazol-5-amines from primary amines and dangerous cyanogen azide, see: Y.-H. Joo, J. M. Shreeve, *Org. Lett.* **2008**, *10*, 4665.

[20] For representative applications of 1-substituted 1*H*-tetrazol-5-amines, see: a) D. J. Häbich, *Synthesis* **1992**, 358; b) Y. Nakamura, K. Ohno, K. Fushikida, T. Ueki, K. Nakamoto, S. Komori, Y. Kumakura, H. Tanaka, K. Izakura (Ishihara Sangyo Kaisha), WO 2014126070, **2014**; c) C. Banglin**,** T.-L. Hu (University of Texas), WO2016154300, **2016.**

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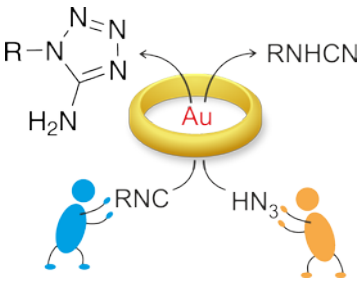
Depending on the amount of the available HN_3 source, reactions of organic isocyanides with trimethylsilyl azide/MeOH catalysed by as little as 0.1 mol.% of $[Au(MeCN)(PPh_3)][SbF_6]$ selectively produce either cyanamides or 1-substituted 1*H*-tetrazol-5-amines in high yields.



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