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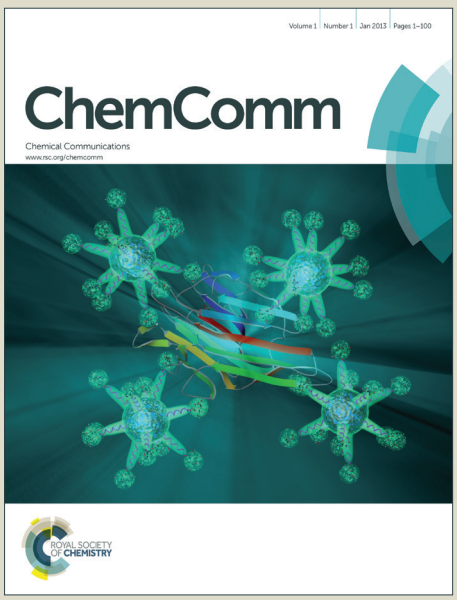

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Communication

Pyrroles *versus* Cyclic Nitrones: Catalyst-Controlled Divergent Cyclization of *N*-(2-perfluoroalkyl-3-alkynyl) hydroxylamines

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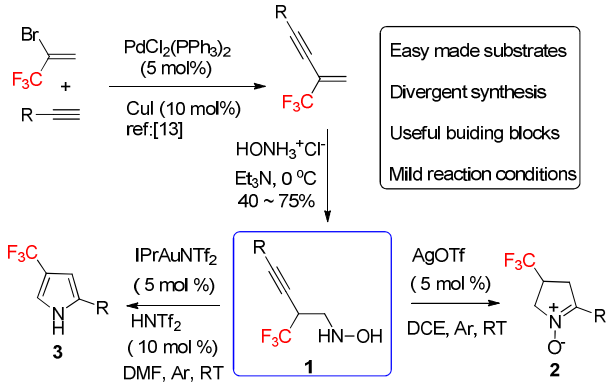
The IPrAuNTf$_2$ / HNTf$_2$ co-catalyzed cyclization of *N*-(2-perfluoroalkyl-3-alkynyl) hydroxylamines produces pyrroles in moderate to excellent yield, whereas the AgOTf-catalyzed reaction affords cyclic nitrones in high yields.

Pyrroles and cyclic nitrones are two types of important nitrogen containing heterocycles. Pyrrole is a privileged structural motif frequently found in a number of natural products,[1] pharmaceutical compounds,[2] and functional materials.[3] Cyclic nitrones are widely used as building blocks in the synthesis of various natural and biologically active compounds,[4] as precursors in the synthesis of a variety of heterocycles,[5] as spintrapping reagents in the identification of transient radicals[6] and as therapeutic agents.[7] In particular, trifluoromethyl substituted pyrroles and other five-membered heterocycles have drawn considerable attention,[8] owing to the the CF_3 group on the enhancement and modification of their original biological activities.[9] The search for a simple and efficient access to such compounds with a CF_3 group at a specific position from readily available starting materials still remains an active area of research.

Intramolecular cyclization of propargyl hydroxylamine, allenic hydroxylamine and *N*-sulfonyl hydroxylamine have been extensively studied, which provide rapid accesses to diverse heterocycles such as 2,3-dihydroisoazoles, 2,5-dihydroisoazoles, *N*-hydroxypyrrolines, dihydroisoxazoles, isoxazolidines, dihydro-1,2-oxazines, tetrahydrooxazines, and 3-pyrrolidinones. Groups of Carreira, Shin, Bates, Krause, and Toste have made significant contribution to this field.[10] Recently, L. Zhang has demonstrated an elegant synthesis of indoles from *N*-arylhydroxylamines and alkynes via gold and zinc cooperative catalysis.[11]

Divergent synthesis of a set of structure distinct valuable compounds from the same starting material is highly attractive, but highly challenging.[12] As a continuation of our interest in divergent synthesis,[12a-12e] we become interested in the divergent



Scheme1. Divergent access to pyrroles and cyclic nitrones.

cyclizations of *N*-(2-(perfluoroalkyl)-3-alkynyl)hydroxylamines **1** (Scheme 1), which are easily prepared from the corresponding commercial available terminal alkyne, 2-bromo-2-perfluoroalkyl-1-ene and hydroxylamine hydrochloride via a simple two-steps procedure.[13] Herein, we wish to report the divergent synthesis of 4-perfluoroalkyl substituted cyclic nitrones **2** and 4-perfluoroalkyl substituted pyrroles **3** from the same starting material **1** under the catalysis of silver and gold (I)[14] with brønsted acid as co-catalyst, respectively.

We chose the *N*-(4-phenyl-2-(trifluoromethyl)but-3-yn-1-yl) hydroxylamine **1a** as the model substrate (Table 1). Initially, the reaction was carried out under the catalysis of gold(I) chloride[10d] in 1,2-dichloroethane (DCE) at ambient temperature. Surprisingly, the reaction proceeds very slowly and afford only 14% yield of 2-phenyl-4-(trifluoromethyl)-1H-pyrrole **3a** through the unexpected dehydrative cyclization process together with some unidentified products, in which 60% of starting material **1a** was recovered (Table 1, entry 1). This result indicated that gold(I) chloride is much less efficient in this reaction than in the previously reported cycloisomerization of allenic hydroxylamines.[10d] To speed up the reaction, we then tested a range of other gold and silver catalysts (Table 1, entries 2-8). The phosphine derived gold(I) chloride Ph_3PAuCl showed no catalytic activity(Table 1, entry 2). However, the cationic gold complex in-situ generated from 1:1 mole ratio of Ph_3PAuCl and AgOTf produce an alternative cyclic nitrone **2a** in 65% yield together with 13% yield of pyrrole **3a** (Table 1, entry 3). Gratifyingly, the use of AgOTf alone led to a

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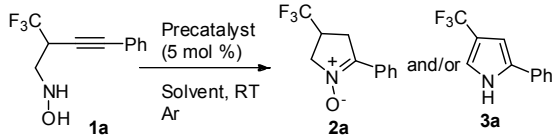
†Electronic Supplementary Information (ESI) available: Complete experimental procedures and characterization data for all new compounds. See DOI: 10.1039/b000000x/

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

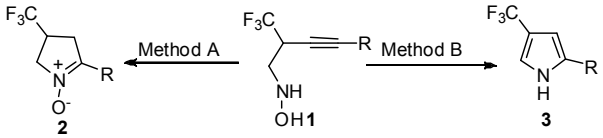


Entry	Precatalyst	Solvent	T [h]	**2a** [%][b]	**3a** [%][b]
1[c]	AuCl	DCE	20	--	14
2[d]	$AuCl(PPh_3)$	DCE	20	--	--
3	$[AuCl(PPh_3)]$ /AgOTf	DCE	7	65	13
4	**AgOTf**	**DCE**	**5**	**95**[e]	**--**
5	$AuCl_3$	DCE	5	8	27
6[f]	$AuCl_3$	DCE	10	5	13
7[g]	Gold (III) A	DCE	6	13	30
8	$IPrAuNTf_2$	DCE	7	34	44
9	$IPrAuNTf_2$	CH_3CN	8	57	17
10	$IPrAuNTf_2$	THF	7	60	29
11	$IPrAuNTf_2$	Toluene	9	16	38
12	$IPrAuNTf_2$	DMSO	10	--	61
13	$IPrAuNTf_2$	DMAC	11	10	75
14	$IPrAuNTf_2$	DMF	10	8	76
15[h]	$IPrAuNTf_2$	DMF	10	30	25
16[i]	**$IPrAuNTf_2$**	**DMF**	**10**	**--**	**87**[e]
17[j]	$IPrAuNTf_2$	DMF	10	--	84
18[j]	$HNTf_2$	DMF	12	--	--

[a][**1a**] = 0.1M. [b] NMR yields using CH_2Br_2 as the internal reference. [c]60% of starting material was recovered. [d] 100% of starting material was recovered. [e]Isolated yield. [f] The reaction was performed at 0℃. [g] Gold(III) A is dichloropicolinatogold(III). [h] 50 mg of 4ÅMS was added. [i] 10 mol% of $HNTf_2$ was added. [j] 20 mol% of $HNTf_2$ was added.

complete formation of cyclic nitrone **2a** in 95% isolated yield (Table 1, entry 4), which is assigned as the optimal conditions for synthesis of the cyclic nitrone (Mehod **A**). The use of gold(III) catalysts, such as dichloropicolinato gold(III) and $AuCl_3$, gave inferior results in terms of the selectivity(Table 1, entries 5-7). Both catalyst and solvent had dramatic effect on the product selectivity (Table 1, entries 8-14), in which the $IPrAuNTf_2$ was found to be the most promising catalyst and polar, coordinating solvent *N*, *N*-dimethylformamide (DMF) is the best solvent for the synthesis of pyrrole **3a** (Table 1, entry 14). In order to facilitate dehydration process to further improve the yield of pyrrole **3a**, 4Å molecule sieves was added to the reaction, however, to our surprise, the reaction became sluggish and in turn, the cyclic nitrone **2a** became the major product (Table 1, entry 15). Gratifyingly, addition of $HNTf_2$ (10 mol%) to the reaction system could substantially improve the isolated yield of **2a** to 87% (Table 1, entry 16). The higher loading of $HNTf_2$ (20 mol %) did not give better result (Table 1, entry 17). Notably, without the gold catalyst, no reaction occurred at all (Table 1, entry 18), indicating that the $HNTf_2$ may facilitate the dehydration step rather than the cyclization step. Therefore, the combination of using $IPrAuNTf_2$ and $HNTf_2$ as co-catalyst and DMF as solvent was found to be the optimal reaction conditions for synthesis of pyrrole (Method **B**). The structure of product **2a**, **3a** and its *N*-tosylated derivate **4** were further confirmed by means of X-ray crystallographic analysis. (See supporting information).[15]

Table 2. Substrate scope of divergent cyclization of **1**[a]



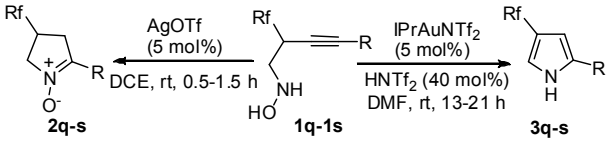
Entry	Substrate **1** R	Method A **2** (time, yield %)[b]	Method B **3** (time, yield %)[b]
1	4-MeC_6H_4 (**1b**)	**2b**(84)	**3b**(86)
2	4-$MeOC_6H_4$ (**1c**)	**2c** (97)	**3c** (86)
3	4-ClC_6H_4 (**1d**)	**2d** (82)	**3d** (90)
4	4-BrC_6H_4 (**1e**)	**2e** (87)	**3e** (90)
5	4-$CF_3C_6H_4$ (**1f**)	**2f** (82)	**3f** (84)
6	4-$NO_2C_6H_4$ (**1g**)	**2g** (98)	**3g** (86)
7	3-$NO_2C_6H_4$ (**1h**)	**2h** (85)	**3h** (89)
8	2-$NO_2C_6H_4$ (**1i**)	**2i** (90)	**3i** (94)
9	4-CNC_6H_4 (**1j**)	**2j** (96)	**3j** (91)
10	4-$CHNOHC_6H_4$ (**1k**)	**2k** (77)[c]	**3k** (68)
11	4-$CO_2MeC_6H_4$ (**1l**)	**2l** (96)	**3l** (90)
12	1-Naphthyl (**1m**)	**2m** (92)	**3m** (90)
13	2-Thiophenyl (**1n**)	**2n**(95)	**3n** (90)
14	2-Pyridinyl (**1o**)	**2o** (94)	**3o** (70)
15	1-Cyclohexenyl (**1p**)	**2p** (92)	**3p** (70)

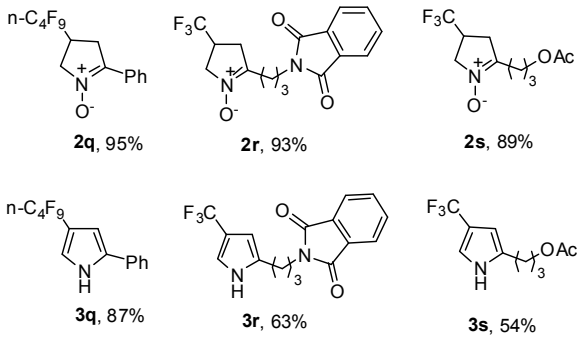
[a] Unless otherwise specified, Method **A** : AgOTf (5 mol%) in 2 mL of 1,2-dichloroethane at rt for 0.5-4 h. Method **B** : **1**(0.2 mmol), $IprAuNTf_2$ (5 mol%) and $HNTf_2$(10 mol%) in 2 mL of DMF at rt for 10-20 h [b] Isolated yield of the isolated product. [c] Acetonitrile was used as solvent.

With the optimal reaction conditions in hand, we turn on our attention on the investigation of the substrate scope of this divergent synthesis. It is noteworthy that the reaction scope of silver catalyzed transformation is quite general, and diverse 4-trifluoromethyl-2,4-disubstituted cyclic nitrones could be obtained in good to excellent yields (Table 2, entries 1-15, Method **A**). The reaction under the silver catalysis displays toleration of various substituted aryl groups bearing electron-donating and electron-withdrawing substituents, heteroaryl such as 2-thiophenyl and 2-pyridyl, and alkenyl group (R).

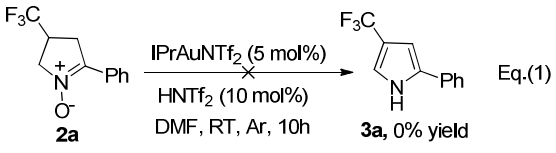
We next turned to examine the scope and limitation of $IPrAuNTf_2$-catalyzed cyclization, leading to 4-CF_3-pyrrole **3** under optimal reaction conditions and the results are outlined in Table 2 (Method **B**). The results indicated that the substrate scope of this reaction is also quite general, leading to the desired pyrroles in 70-94% isolated yields. In those cases of substrates bearing substituted phenyl ring (R) on the alkyne moiety, the reactions also tolerate various substitution patterns (*o*-, *m*-, *p*-) and all types of substituents on the phenyl ring (Table 2, entries 1-11, Method **B**). Furthermore, the reactions of substrates bearing 1-naphthyl, 2-thiophenyl and alkenyl on the alkyne moiety also worked well to afford the corresponding pyrrole derivatives (Table 2, entries 12-15, Method **B**).

Other perfluoroalkyl group such as n-C_4F_9 could be well introduced and the divergent reactions proceeded smoothly, affording the corresponding 4-perfluorobutyl nitrone **2q** and pyrrole **3q** in 95% and 87% yields, respectively (Scheme 2). The R substituent could also be switched to alkyl groups containing ester and amido functional groups. The desired nitrones **2r** and **2s** could be produced in excellent yields under the catalysis of silver, satisfactory yields of pyrroles **3r** and **3s** coule be achieved under the catalysis of gold, albeit 40 mol % of $HNTf_2$ was required otherwise, a significant amount of cyclic nitrone would be detected.



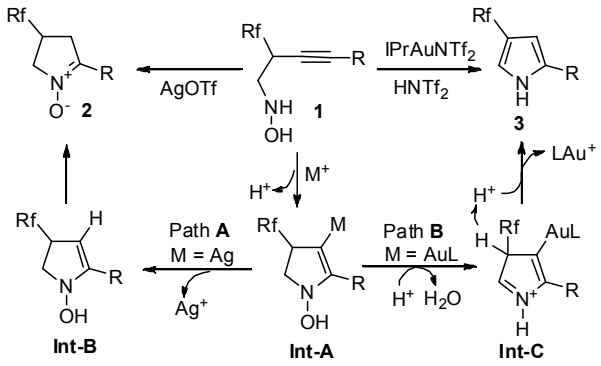


Scheme 2. Divergent synthesis of **1q-s**.

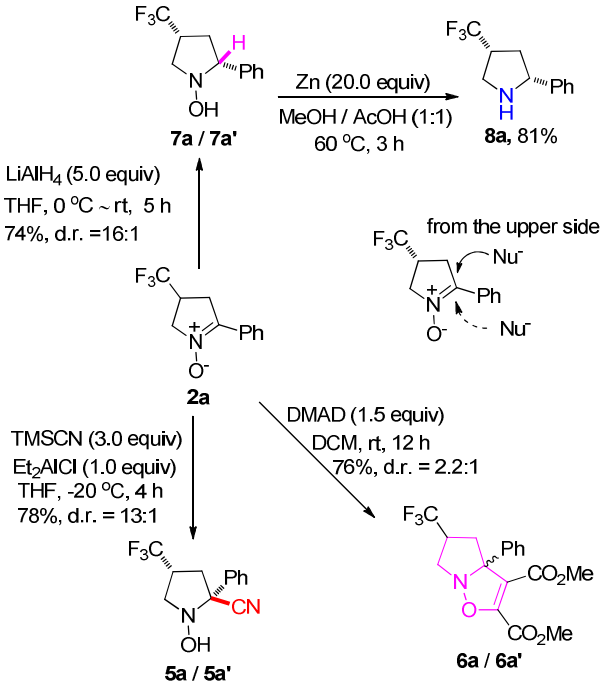


To gain insight into the reaction mechanism, we conducted the following control experiment. When cyclic nitrone **2a** was subjected to the standard reaction conditions for the pyrrole formation, no any pyrrole **3a** was detected and 100% of **2a** was recovered [Eq.(1)]. This result indicated that cyclic nitrone and pyrrole formation proceeded via two independent reaction pathways.

Based on the above experimental results, we proposed a plausible reaction mechanism for these catalyst-controlled divergent cyclizations, which is outlined in Scheme 3. Initially, the coordination of the triple bond of **1** to metal catalyst enhances the electrophilicity of the alkyne, and subsequent 5-*endo*-dig ring closure occurs primarily from nitrogen atom rather than the oxygen atom to afford an intermediate **Int-A**.[10f] Under the catalysis of AgOTf (Path **A**), the intermediate **Int-A would** undergo protodemetalation to give *N*-hydroxyl enamine intermediate **Int-B**, followed by isomerization to the more stable cyclic nitrone **2**. In the case of using $IPrAuNTf_2$ as catalyst and $HNTf_2$ as the co-catalyst (Path **B**), with the help of $HNTf_2$, the dehydration of intermediate **Int-A** generates the iminium species Int-C. Subsequent deprotonation and protodeauration deliver pyrrole product 3 and regenerate gold catalyst.



Scheme 3. Proposed mechanism for divergent synthesis.



Scheme 4. Synthetic transformations of cyclic nitrone **2a**.

Synthetic applications of trifluoromethylated cyclic nitrones have been showcased by the selective transformations of the representative 4-trifluoromethylated cyclic nitrone **2a** (Scheme 4). Using nitrone **2a** as electrophiles, the addition of Me_3SiCN to nitrone **2a** proceeded smoothly in the presence of a Lewis acid catalyst, affording the expected adduct **5a**/**5a'** in 78% isolated yield with 93:7 diastereoselectivity, which can be considered as the precursors of amino methyl pyrrolidines.[16] Direct treatment of **2a** with $LiAlH_4$ would deliver the reductive product **7a**/**7a'** in 74% isolated yield with high diastereoselectivity. Compound **7a** then underwent further reduction upon treatment with zinc in methanol and acetic reduction, yielding the corresponding pyrrolidine **8a** in 81% isolated yield.[17] Using nitrone **2a** as 1, 3-dipole, the dipolar cycloaddition reaction of nitrone **2a** with dimethylacetylenedicarboxylate (DMAD) in dichloromethane at

room temperature afforded the cycloadduct **6a**/**6a'** in 76% isolated yield with moderate diastereoselectivity.[18]

In summary, we have developed novel divergent cyclizations of *N*-(2-(perfluoroalkyl)-3-alkynyl)hydroxylamines by subtle choice of the catalyst system, leading to two important fluorinated nitrogen containing heterocycles such as 4-perfluoroalkyl cyclic nitrone and pyrrole. The notable features of the method are its easily accessible starting materials, mild reaction conditions and divergent synthesis. Additional investigation on the application of the developed methods and detailed mechanistic studies are currently underway in our laboratory. We thank National Natural Science Foundation of China (21372084), Changjiang Scholars and Innovative Research Team in University (PCSIRT) and Shanghai Natural Science Foundation (13ZR1412900) for kind financial support.

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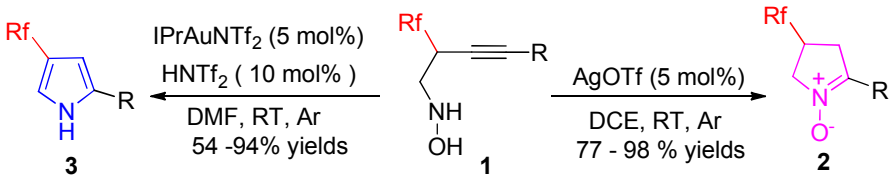
Communication

Table of graphic abstract



Divergent cyclizations of *N*-(2–(perfluoroalkyl)-3-alkynyl)hydroxylamines **1** have been realized by subtle choice of the catalyst under mild conditions, leading to two distinct types of synthetic valuable compounds, cyclic nitrones **2** or pyrroles **3**, in moderate to excellent yields.