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Silver-Catalysed Tandem Hydroamination and Cyclization of 2-Trifluoromethyl-1,3-Enynes with Primary Amines: A Modular Entry to 4-Trifluoromethyl-3-Pyrrolines †

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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A highly efficient tandem hydroamination and cyclization reaction of 2-trifluoromethyl-1,3-enynes with primary amine leading to 4-trifluoromethyl-3-pyrrolines was developed by using $AgNO_3$ as a catalyst under mild reaction conditions. This new method is compatible with alkyl, aryl, and allyl primary amines, representing an atom-economic protocol for the construction of 4-trifluoromethyl-3-pyrrolines for the first time.

3-Pyrrolines, also called 2,5-dihydropyrroles, present an important class of five-membered nitrogen-containing heterocycles due to their presence in natural and synthetic biologically active compounds. [1] 3-Pyrrolines are also widely used as important versatile precursors for the synthesis of pyrrolidines, pyrroles and pyrrolidinones, common structural scaffolds in natural products,[2] bioactive molecules,[3] and useful building blocks.[4] Consistent with their biological and synthetic importance, various methods for the synthesis of 3-pyrrolines via transition-metal or organo-catalysis have been developed.[5] Meanwhile, fluorine-containing organic molecules often possess elevated reactivity, lipophilicity, and bioactivity compared to their nonfluorinated counterparts.[6] For example, the inclusion of the electron-withdrawing CF_3 group in drug candidates has appeared as a general strategy to increase robustness against metabolic oxidation in the "hit to lead" approach.[7] In this context, the development of efficient methods for fluorinated 3-pyrrolines synthesis has continuously attracted the attention of many chemists.[8] With regard

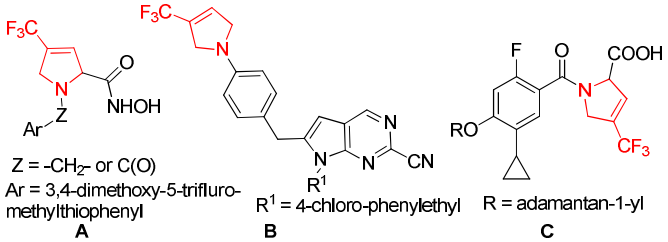
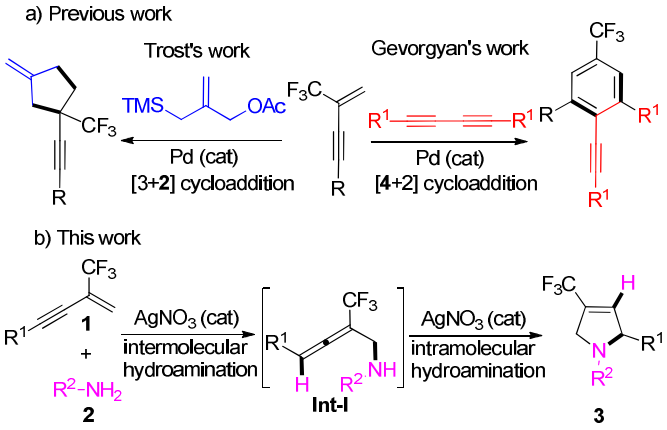


Figure 1. Bioactive molecules featuring with trifluoromethyl-3-pyrroline.



Scheme 1. The transition metal-catalysed transformations of 2-trifluoromethyl-1,3-enynes.

to their significance in organic synthesis and interest in bioactive molecules (Figure 1),[9] the development of novel, general and efficient methods for synthesis of 4-trifuoromethyl-3-pyrrolines from readily available starting materials, especially in an atom-economic manner, is still highly desirable.

2-Trifluoromethyl-1,3-enynes are easily prepared from commercially available terminal alkynes with 2-bromo-3,3,3-trifluoroprop-1-ene in large scale via the Sonagashira cross-coupling reaction. Gevorgyan and Trost have reported palladium catalyzed intermolecular formal [4+2] or [3+2] cycloaddition reactions with diynes[10] or trimethylene-methane (TMM),[11] leading to trifluoromethyl benzenes or exomethylene cyclopentanes derivatives, in which the 2-trifluoromethyl-1, 3-enynes act as four- or two-carbon component, respectively (Scheme 1a). As part of our ongoing program on the synthesis of fluorine-containing heterocycles,[12] and continuous interest in the chemistry of 2-trifluoromethyl-1,3-enynes with bisnucleo-philes,[13] we became interested in whether simple primary amine could be employed in

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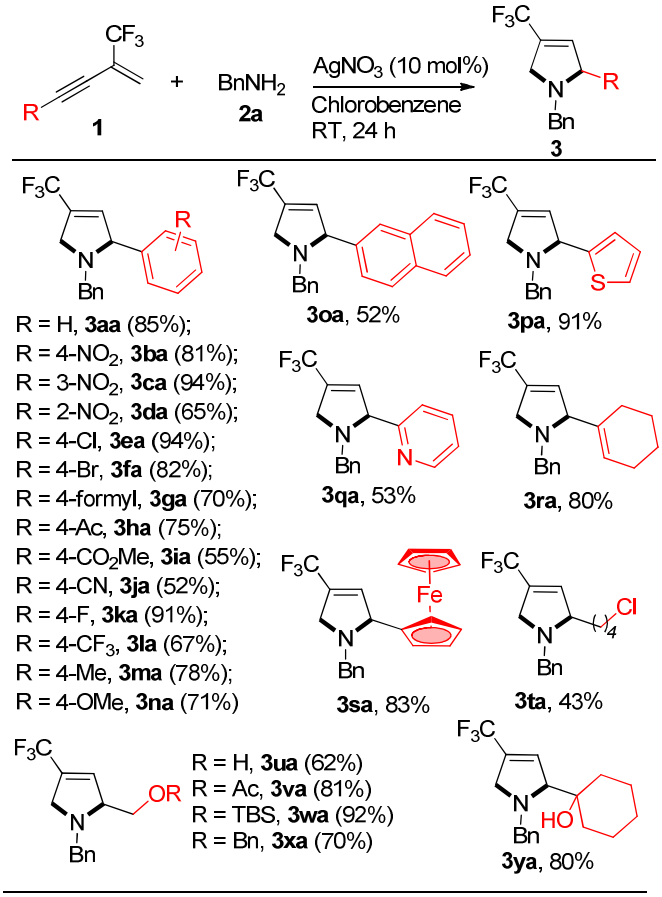
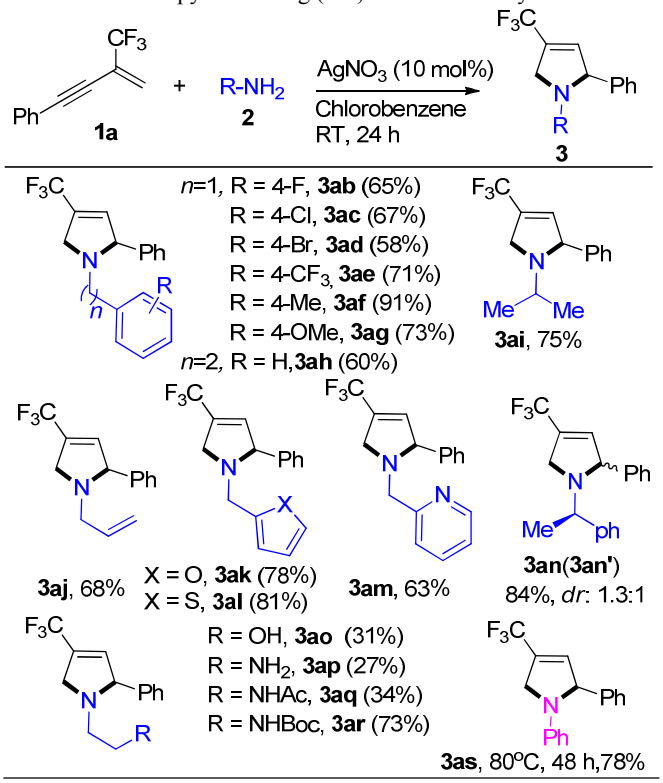
transition-metal catalysed tandem hydroamination and cyclization (double hydroaminations) reaction with 2-trifluoromethyl-1,3-enynes to construct 4-trifluoromethyl-3-pyrroline through allenyl amine intermediate **Int-I** (Scheme 1b). If this approach is successful, it will provide an atom-economic protocol access to valuable 4-trifluoromethyl-3-pyrroline framework. Herein, we wish to report a silver-catalysed tandem hydroamination[14] and cyclization reaction of 2-trifluoromethyl-1,3-enynes with primary amines furnishing valuable 4-trifluoromethyl-3-pyrrolines through allenyl amine intermediate [8d,15] We found that silver catalyst enhances the electrophilicity of the enynes towards primary amines and accelerate the allene intermediate formation.



Scheme 2. Scope of 2-trifluoromethyl-1,3-enyne.

After many attempts, we are pleased to find that 10 mol % of $AgNO_3$ could catalyse the tandem reaction well in chlorobenzene at room temperature, leading to 85% yield of **3aa** (see *ESI*).[16] The enyne substrate scope was then examined and demonstrated with twenty four examples shown in Scheme 2. In general, this new method is broad in scope, and diverse 4-trifluoromethyl-3-pyrrolines could be obtained in moderate to excellent yields. Enynes possessing different aryl groups on the alkyne moiety are suitable, delivering the corresponding products **3ba-3oa** in 52%-94% isolated yield. Meanwhile the reactions also tolerate various substitution patterns (*o*-, *m*-, and *p*-) on the phenyl ring (**3ba**, **3ca** and **3da**). Furthermore, enynes bearing heteroaryls such as 2-thiophenyl and 2-pyridyl and alkenyl such as 1-cyclohexenyl on the alkyne moiety also exhibited acceptable or good reactivity, and the reaction yields were moderate to excellent (**3pa-3ra**). Notably, ferrocene framework could be well introduced onto 3-pyrroline ring (**3sa**). It is noteworthy that



Scheme 3. Scope of primary amine.

differently substituted alkyl possessing valuable functionalities, such as free primary hydroxyl (**3ua**), free tertiary hydroxyl (**3ya**), ester group (**3va**), silyloxy (**3wa**), benzyl ether (**3xa**), were well tolerated.

Next, the scope of primary amine toward this tandem reaction was investigated (Scheme 3). Several points are noteworthy: (1) The substituted benzylamines bearing electron-withdrawing or electron-donating groups on phenyl ring were all tolerant, affording the corresponding products **3ab-3ag** in moderate to excellent yields; (2) This reaction also permitted the use of a range of other aliphatic amines such as 2-phenylethanamine, isopropylamine, allylamine, as well as aliphatic primary amines containing heteroaryl moieties such as furan-2-ylmethanamine, thiophen-2-ylmethanamine and pyridine-2-ylmethanamine, furnishing the corresponding 3-pyrrolines **3ah-3am** in 63% to 81% yields; (3) The reaction of enyne **1a** with chiral 1-phenylethan-1-amine (*R*)-**2n** afforded a mixture of diastereoisomers (**3an/3an'**) in 84% combined yield in a ratio of 1.3 : 1; (4) Aliphatic amine possessing another functional group such as free hydroxyl or amine gave relative lower yields (**3ao**, 31% and **3ap,** 27%, respectively), due to the further cyclization between the functional group with the alkene moiety in the product. This issue could be well addressed by introduction of a bulky protecting group (**3ar**, 73%); (5) The reaction also works well for aniline, furnishing 78% yield of 3-pyrroline **3as** albeit requiring higher temperature.

To gain insight into this tandem reaction and the role of silver catalyst, some control experiments were then carried out. Treatment of enyne **1a** with benzylamine **2a** in chlorobenzene at room temperature in the absence of $AgNO_3$ catalyst for 45 h, both allenyl amine **4** and homopropargylic amine **5** were obtained in 41% and 26% isolated yield, respectively, along with 28% enyne **1a** substrate

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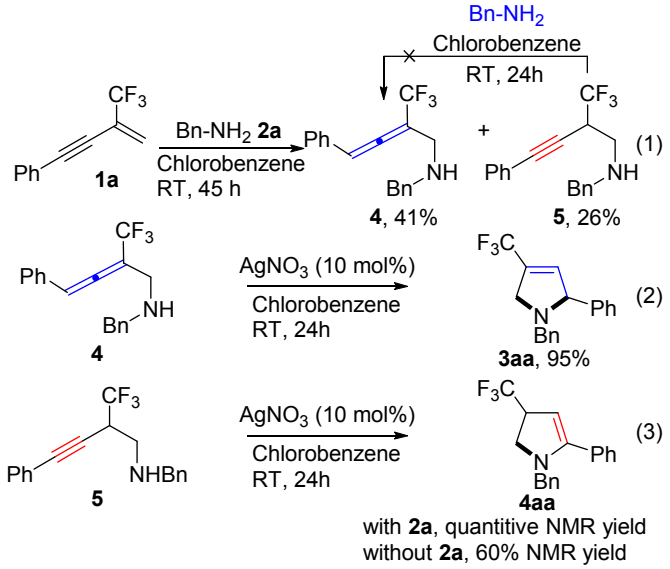
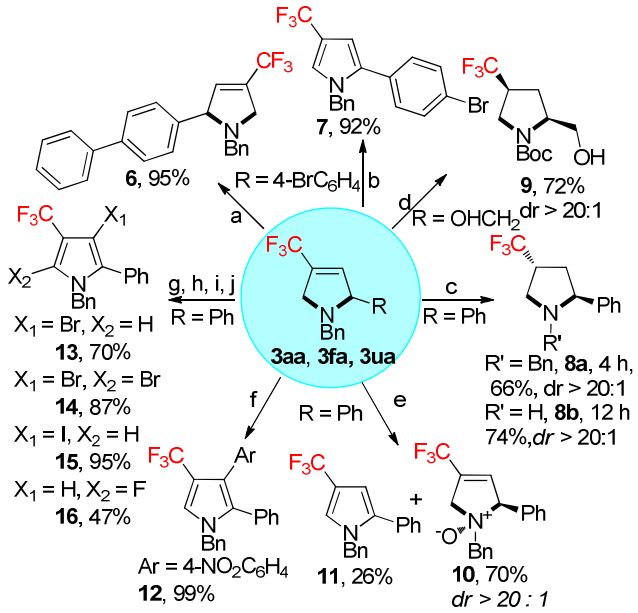
recovered [eqn (1)]. It is noteworthy that the homopropargylic amine **5** could not undergo isomerization to allenyl amine **4** under basic conditions.[17] Allenyl amine **4** could afford 95% isolated yield of **3aa** in the presence of $AgNO_3$ catalyst [eqn (2)], which was consistent with our original hypothesis. With or without benzylamine **2a**, homopropargylic amine **5** could undergo smoothly the 5-*endo*-*dig* cyclization to afford the acid and air-sensitive 2-pyrroline **4aa**[18] [eqn (3)], which easily decomposed during the purification process via silica-gel chromatography. These results indicated that the coordination of the triple bond of 2-trifluoromethyl-1,3-enyne **1** to the silver catalyst enhances the electrophilicity of the enynes towards primary amines,[19] thus accelerates the allene intermediate formation and then catalyses the subsequent cyclization.



To highlight the synthetic utilities of this transformation, diverse transformations of the representative products **3aa**, **3fa** and **3ua** are showcased in Scheme 4. The results showed that 4-trifluoromethyl-3-pyrrolines are versatile organic building blocks in organic synthesis. For example, palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of **3fa** with organoboronic acid could produce **6** in excellent yield. Oxidative aromatization of **3fa** was easily realized by DDQ and 4-trifluoromethyl pyrrole **7** was obtained in 95% isolated yield. Hydrogenations of **3aa** under the catalysis of Pd/C in ethanol at room temperature could deliver *N*-benzyl-pyrrolidine **8a** in 66% yield and further debenzylation pyrrolidine **8b** in 74% yield, respectively, with high diastereoselectivity (*d.r.*> 20:1). The *trans*-configuration of **8a** and **8b** were further confirmed by HSQC and NOESY spectra analysis (see *ESI*). Similarly, *N*-Boc-*cis*-4-trifluoromethyl-prolinol **9** with high diastereoselectivity (*d.r.* > 20: 1) could be efficiently prepared from pyrroline **3ua** in two steps. According to the procedure of literature,[20] an alternative synthetic route to racemic-*cis*-4-trifluoromethyl-proline, the significant subunit in bioactive molecules, was then well established. When pyrroline **3aa** was treated with 1.2 equivalent of *m*-CPBA in DCM, pyrroline *N*-oxide **10** other than epoxypyrrolidine was obtained in 70% isolated yield as a single diastereoisomer, along with minor pyrrole **11** (26%).[5c] Moreover, pyrroline **3aa** easily undergoes Heck-Matsuda arylation[21] with the aryldiazonium tetrafluoroborate salts followed by dehydro-aromatization to afford diaryl-substituted pyrrole **12** in quantitative yield. It is also important to highlight that pyrroline **3aa** exhibits diverse chemical reaction properties towards different electrophilic halogenating agents such as bromine, *N*-halosuccinimides (NXS), N-fluorobenzenesulfonimide (NFSI) affording diverse halogenated products and halogen atoms could be selectively introduced to 3- and (or) 5-positons of pyrroline ring. For example, treatment of **3aa** with two equivalents of bromine in DCM at 0 °C, after a warming period at room temperature, the resulting solution was treated with excess of Et_3N only affording 3-bromo-pyrrole **13** in 70% isolated yield. Interestingly, synthetically valuable 2,4-dibromo-pyrrole **14** could be delivered in 87% isolated yield upon treatment of **3aa** with three equivalents of *N*-bromosuccinimide (NBS) in acetonitrile. However, the replacement of *N*-bromosuccinimide (NBS) with *N*-iodosuccinimide (NIS) led to the corresponding 3-iodo-pyrrole **15**[16] under identical reaction conditions. By employing *N*-fluorobenzenesulfonimide (NFSI) as the fluorinating reagent under same reaction conditions, unexpectedly 2-fluoro-pyrrole **16** along with pyrrole **11** was delivered.



Conditions: a) $Pd(PPh)_3Cl_2$, K_2CO_3, THF/H_2O, 95 °C, 13 h; b) DDQ,DCE, RT; c) 1. Pd/C, H_2, EtOH, aq HBr, RT; 2. 1N NaOH; d) 1. Pd/C, H_2, EtOH, aq HBr, RT; 2. $(Boc)_2O$, DCM/Et_3N, RT; e) *m*-CPBA, DCM, 0 °C~rt; f) $Pd_2(dba)_3$.dba (5 mol%), 4-$NO_2C_6H_4N_2BF_4$(3.0 equiv), NaOAc (3.0 equiv), MeCN, RT; g) 1. Br_2, DCM, 0 °C~RT; 2. Et_3N; h) NBS, MeCN, RT; i) NIS, MeCN, RT; j) NFSI, MeCN, RT.

Scheme 4. Diverse transformations of representative products.

In summary, we developed the first example of tandem intermolecular hydroamination and cyclization reaction of 2-trifluoromethyl-1,3-enynes with primary amines by the employing a cheap silver catalyst under mild reaction conditions. This method provides a reliable strategy for efficient construction of 4-trifluoromethyl-3-pyrrolines from readily available starting materials in an atom-economical manner. The salient features of this tandem include high efficiency, general substrate scope, an inexpensive silver catalyst, mild reaction conditions, outstanding functional-group tolerance and diverse transformations. Financial supports by National Natural Science Foundation of China (21372084,

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DOI: 10.1039/C6CC09590

21425205), MOE (PCSIRT) and the 973 Programs (2015CB-856600), are greatly appreciated.

Notes and references

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† Electronic Supplementary Information (ESI) available: Complete experimental procedures and characterization data for all new compounds. For ESI and crystallographic data in CIF or other electronic format See DOI: 10.1039/c000000x/

1 (*a*) T. Sano, Y. Tsuda in *The Alkaloids*, *Vol. 48* (Ed.: G. A. Cordell), Academic Press, New York, 1996, pp. 249 –337; (*b*)W.-S. Yap, C.-Y. Gan, Y.-Y. Low, Y.-M. Choo, T. Etoh, M. Hayashi, K. Komiyama, T.-S. Kam, *J. Nat. Prod*. 2011, **74**, 1309; (*c*) Z. Wang, S. Castellano, S. S. Kinderman, C. E. Argueta, A. B. Beshir, G. Fenteany, O. Kwon, *Chem. Eur. J*. 2011, **17**, 649.

2 For reviews, please see: (*a*) A. B. Mauger, *J. Nat. Prod*. 1996, **59**, 1205; (*b*) D. O'Hagan, *Nat. Prod. Rep*. 2000, **17**, 435; (*c*) F.-X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* 2003, 3693; (*d*) C. T. Walsh, S. Garneau-Tsodikova, A. R. Howard-Jones, *Nat. Prod. Rep*. 2006, **23**, 517; (*e*) H. Fan, J. Peng, M. T. Hamann, J.-F. Hu, *Chem. Rev.* 2008, **108**, 264.

3 (*a*) J. W. Huffman, *Curr. Med. Chem*. 1999, **6**, 705; *(b*) S. Youssef, O. Stüve, J. C. Patarroyo, P. J. Ruiz, J. L. Radosevich, E. M. Hur, M. Bravo, D. J. Mitchell, R. A. Sobel, L. Steinman, S. S. Zamvil, *Nature*, 2002, **420**, 78; (*c*) A. Fürstner, *Angew. Chem., Int. Ed.* 2003, **42**, 3582.

4 (*a*) P. Novák, K. Müller, K. S. V. Santhanam, O. Haas, *Chem. Rev.* 1997, **97**, 207; (*b*) J. L. Sessler, S. Camiolo, P. A. Gale, *Coord. Chem. Rev*. 2003, **240**, 17; (*c*) P. A. Gale, *Acc. Chem. Res*. 2006, **39**, 465.

5 Selected very recent examples for 3-pyrrolines synthesis via transition-meta- or organo-catalysis, please see: (*a*) M. Sampath, P.-Y. B. Lee, T.-P. Loh, *Chem. Sci.,* 2011, **2**, 1988; (*b*) I. P. Andrews, B. R. Blank, O. Kwon, *Chem. Commun.,* 2012, **48**, 5373; (*c*) A. Desmarchelier, V. Coeffard, X. Moreau, C. Greck, *Chem. Eur. J.* 2012, **18**, 13222; (*d*) X. Han, F. Zhong, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* 2012, **51**, 767; (*e*) J. Brioche, C. Meyer, J. Cossy, *Org. Lett.* 2013, **15**, 1626; (*f*) C. E. Henry, Q. Xu, Y. C. Fan, T. J. Martin, L. Belding, T. Dudding, O. Kwon, *J. Am. Chem. Soc.* 2014, **136**, 11890; (*g*) I. Chogii, J. T. Njardarson, *Angew. Chem. Int. Ed.* 2015, **54**, 13706.

6 (*a*) J.-P. Bégué and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley-VCH, Weinheim, 2008; (*b*) A. Tressaud and G. Haufe, *Fluorine and Health: Molecular Imaging, Biomedical Materials and Pharmaceuticals*, Elsevier, Oxford, 2008; (*c*) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, 2006.

7 (*a*) R. Filler, Y. Kobayashi, L. M. Yagupolskii, *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Elsevier: Amsterdam, 1993; (*b*) W. K. Hagmann, *J. Med. Chem*. 2008, **51**, 4359; (*c*) D. Barnes-Seeman, M. Jain, L. Bell, S. Ferreira, S. Cohen, X.-H. Chen, J. Amin, B. Snodgrass, P. Hatsis, *ACS Med. Chem. Lett.* 2013, **4**, 514.

8 (*a*)T. Tajima, H. Ishii, T. Fuchigami, *Tetrahedron Lett.,* 2001, **42**, 4857; (*b*) T. Tajima, A. Nakajima, T. Fuchigami, *J. Org. Chem*, 2006, **71**, 1436; (*c*) G. Tran, R. Meier, L. Harris, D. L. Browne, S. V. Ley, *J. Org. Chem*, 2012, **77,** 11071; (*d*) T. Xu, X. Mu, H. Peng, G. Liu, *Angew. Chem. Int. Ed.* 2011, **50**, 8176.

9 (*a*) B. G. Raju, H. Odowd, H. Gao, D. V. Patel, J. Trias, WO 2004007444, 2004; (*b*) F. P. Buxton, T. Ehara, P. Ganju, A. Hallett, O. Irie, A. Iwasaki, T. Kanazawa, K. Masuya, K. Nonomura, J. Sakaki, C. R. Snell, C. Song, K. Tanabe, N. Teno, I. Umemura, F. Yokokawa, WO 2004069256, 2004; (*c*) J.-C. Andrez, P. Bergeron, P. R. Bichler, S. Chowdhury, C. M. Dehnhardt, T. Focken, W. Gong, M. E. Grimwood, A. Hasan, I. W. Hemeon, Q. Jia, B. Safina, S. Sun, M. S. Wilson, A. Y. Zenova, WO 2016007534, 2016.

10 O. V. Zatolochnaya, V. Gevorgyan, *Org. Lett.,* 2013, **15**, 2562.

11 B. M. Trost, L. Debien, *J. Am. Chem. Soc.* 2015, **137**, 11606.

12 (*a*) J. Yang, A. Mao, Z. Yue, W. Zhu, X. Luo, C. Zhu, Y. Xiao and J. Zhang, *Chem. Commun.*, 2015, **51**, 8326; (*b*) J. Yang, X. Zhou, Y. Zeng, C. Huang, Y. Xiao, J. Zhang, *Chem. Commun*., 2016, **52,** 4922.

13 (*a*) Q. Zeng, L. Zhang, J. Yang, B. Xu, Y. Xiao, J. Zhang, *Chem. Commun.*, 2014, **50**, 4203; (*b*) L. Zhang, Q. Zeng, A. Mao, Z. Wu, T. Luo, Y. Xiao, J. Zhang, *Org. Biomol. Chem*., 2014, **12**, 8942.

14 For a recent review, please see: L. Huang, M. Arndt, K. Gooßen, H. Heydt, L. J. Gooßen, *Chem. Rev.* 2015, **115**, 2596. For recent examples involving hydroamination with primary amines, please see: (*a*) S. Cacchi, G. Fabrizi, A. Goggiamani, A. Iazzetti, *Org. Lett.* 2016, **18**, 3511; (*b*) B. R. Reiner, M. W. Bezpalko, B. M. Foxman, C. R. Wade, *Organometallics*, 2016, **35**, 2830.

15 For selected silver catalysed intramolecular hydroamination of *α*-amino allenes, please see: (*a*) R. K. Dieter, N. Chen, H. Y. Yu, L. E. Nice, V. K. Gore, *J. Org. Chem*. 2005, **70**, 2109; (*b*) R. K. Dieter, N. Chen, V. K. Gore, *J. Org. Chem*. 2006, **71**, 8755; (*c*) M. Sai, S. Matsubara, *Org. Lett*. 2011, **13**, 4676.

16 CCDC 1486638 (**3aa**), 1498966 (**15**), please see ESI.†

17 H. Qian, X. Yu, J. Zhang, J. Sun, *J. Am. Chem. Soc*. 2013, **135**, 18020.

18 J. Cheng, X. Jiang, C. Zhu, S. Ma, *Adv. Synth. Catal*. 2011, **353**, 1676.

19 For nice reviews on silver-catalyzed reactions, see: (*a*) G. Fang, X. Bi, *Chem. Soc. Rev.* 2015, **44**, 8124; (*b*) M. Naodovic, H. Yamamoto, *Chem. Rev*. 2008, **108**, 3132; (*c*) J.-M. Weibel, A. Blanc, P. Pale, *Chem. Rev.* 2008, **108**, 3149; (*d*) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev.* 2008, **108**, 3174; (*e*) *Silver in Organic Chemistry* (Ed.: M. Harmata), Wiley, Hoboken, 2010; for selected recent leading examples of Ag-catalyzed reactions, see: (*f*) G. C. Geary, E. G. Hope, A. M. Stuart, *Angew. Chem.* 2015, **127**, 15124; (*g*) S. Lv, J. Wang, C. Zhang, S. Xu, M. Shi, J. Zhang, *Angew. Chem. Int. Ed*. 2015, **54**, 14941; (*h*) M. Gao, C. He, H. Chen, R. Bai, B. Cheng, A. Lei, *Angew. Chem. Int. Ed*. 2013, **52**, 6958; (*i*) J. Liu, Z. Fang, Q. Zhang, Q. Liu, X. Bi, *Angew. Chem. Int. Ed*. 2013, **52**, 6953; (*j*) Y. Li, M. Sun, H. Wang, Q. Tian, S.-D. Yang, *Angew. Chem. Int. Ed*. 2013, **52**, 3972; (*k*) M. Zhou, R. Song, C. Wang, J.-H. Li, *Angew. Chem. Int. Ed*. 2013, **52**, 10805.

20 (*a*) J. R. Del Valle, M. Goodman, *Angew. Chem. Int. Ed*. 2002, **41**, 1600; (*b*) X.-L. Qiu , F.-L. Qing, *J. Chem. Soc*., *Perkin Trans*. **1**, 2002, 2052.

21 (*a*) A. L. L. Garcia, M. J. S. Carpes, A. C. B. M. de Oca, M. A. G. dos Santos, C. C. Santana, C. R. D. Correia, *J. Org. Chem*. 2005, **70**,

Journal Name View Article Online DOI: 10.1039/C6CC09559B COMMUNICATION

1050; (*b*) K. P. da Silva, M. N. Godoi, C. R. D. Correia, *Org. Lett.* 2007, **9**, 2815.

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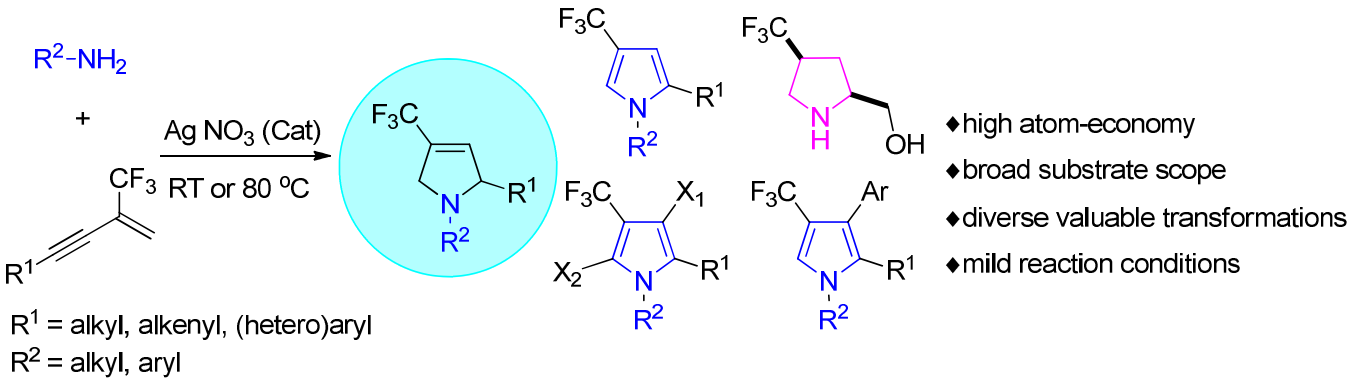

A highly efficient $AgNO_3$-catalyzed tandem intermolecular hydroamination and cyclization reaction of 2-trifluoromethyl-1,3-enynes with primary amines, leading to 4-trifluoromethyl-3-pyrrolines under mild conditions was developed. Diverse valuable transformations of the products were demonstrated.