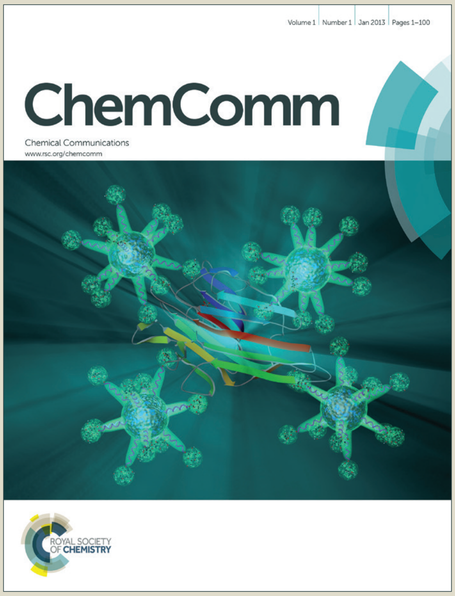

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Silver-Catalyzed Regioselective [3 + 2] Cycloaddition of Arenediazonium Salts with 2,2,2-Trifluorodiazoethane (CF_3CHN_2): A Facile Access to 2-Aryl-5-trifluoromethyltetrazoles

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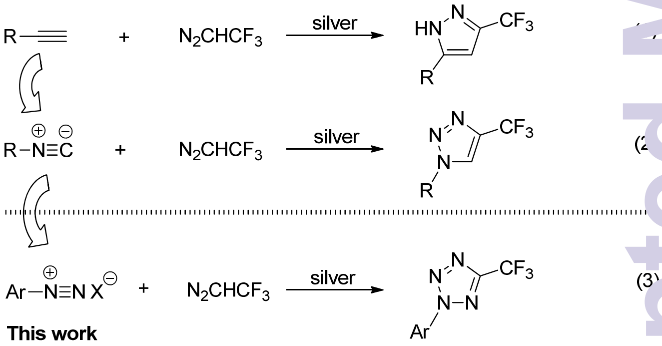
A silver-catalyzed regioselective [3 + 2] cycloaddition reaction of arenediazonium salts with 2,2,2-trifluorodiazoethane (CF_3CHN_2) is reported. Under mild conditions, a series of 2-aryl substituted 5-trifluoromethyltetrazoles were obtained in moderate to excellent yields with wide functional group compatibility. Furthermore, this cycloaddition reaction could be also performed in a one-pot diazotization / cycloaddition sequence from commercially available aniline derivatives.

Tetrazoles are an important class of five-membered heterocycles broadly used in pharmaceuticals, agrochemicals, and material science.[1] Also, this key heterocyclic core has frequently been applied in both organic synthesis and coordination chemistry.[2] The usual methods for the construction of tetrazole structures include base-induced dimerization of α-diazo ketones, direct diazotization of imidohydrazides or amidines with nitrous acid, cycloaddition of azide compounds with organic nitriles or isocyanides, cyclocondensation of acyl hydrazides with arenediazonium salts, as well as substitution-cyclization of amides or imidoyl derivatives with azide compounds.[3, 4] Despite these notable advances, it is still highly desirable to develop new reactions for the construction of diverse tetrazole species.

Recently our group successfully developed silver-triggered [3 + 2] cycloaddition reactions of terminal alkynes or isocyanides with 2,2,2-trifluorodiazoethane (CF_3CHN_2) with excellent regioselectivity for the construction of trifluoromethylated pyrazole and triazole derivatives (eqs 1 and 2 in Scheme 1).[5, 6] Actually, arenediazonium salts (containing a N≡N triple bond) have a certain structural similarity to terminal alkynes (with a C≡C triple bond) and isocyanides (with a N≡C triple bond). We envisioned that silver salts might also be utilized to promote the co-cyclization of arenediazonium with 2,2,2-trifluorodiazoethane (CF_3CHN_2) (eq 3 in Scheme 1). By screening various silver salts, we found that in the presence of silver(I) acetate, this [3 + 2] cycloaddition reaction of arenediazonium salts with CF_3CHN_2 proceeded well under the base conditions with excellent regiocontrol to afford a series of trifluoromethylated tetrazoles. This reaction exhibits remarkable features, such as operational simplicity, mild reaction conditions, easily accessible starting materials, good to high yields, and wide functional group compatibility. Furthermore, this cycloaddition reaction could also be realized in a one-pot diazotization cycloaddition sequence from commercially available anilines. Herein, we report our preliminary results on this subject.



Scheme 1 Silver-triggered cycloaddition reactions for the synthesis of trifluoromethylated pyrazoles, triazoles, and tetrazoles.

We commenced our studies by investigating the reaction of phenyl diazonium tetrafluoroborate **1a** and CF_3CHN_2 under the catalysis of various silver salts in THF at 0 °C with an argon atmosphere (entries 1–7, Table 1). To our delight, AgOAc was found to be optimal, and the cycloaddition reaction proceeded smoothly to furnish the desired cycloadduct **2a** in 84% yield (entry 1). It should be noted that the reaction can be performed under air as well, although the yield fell slightly to

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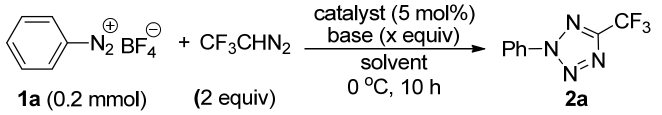
Table 1 Optimization of reaction conditions.[a]



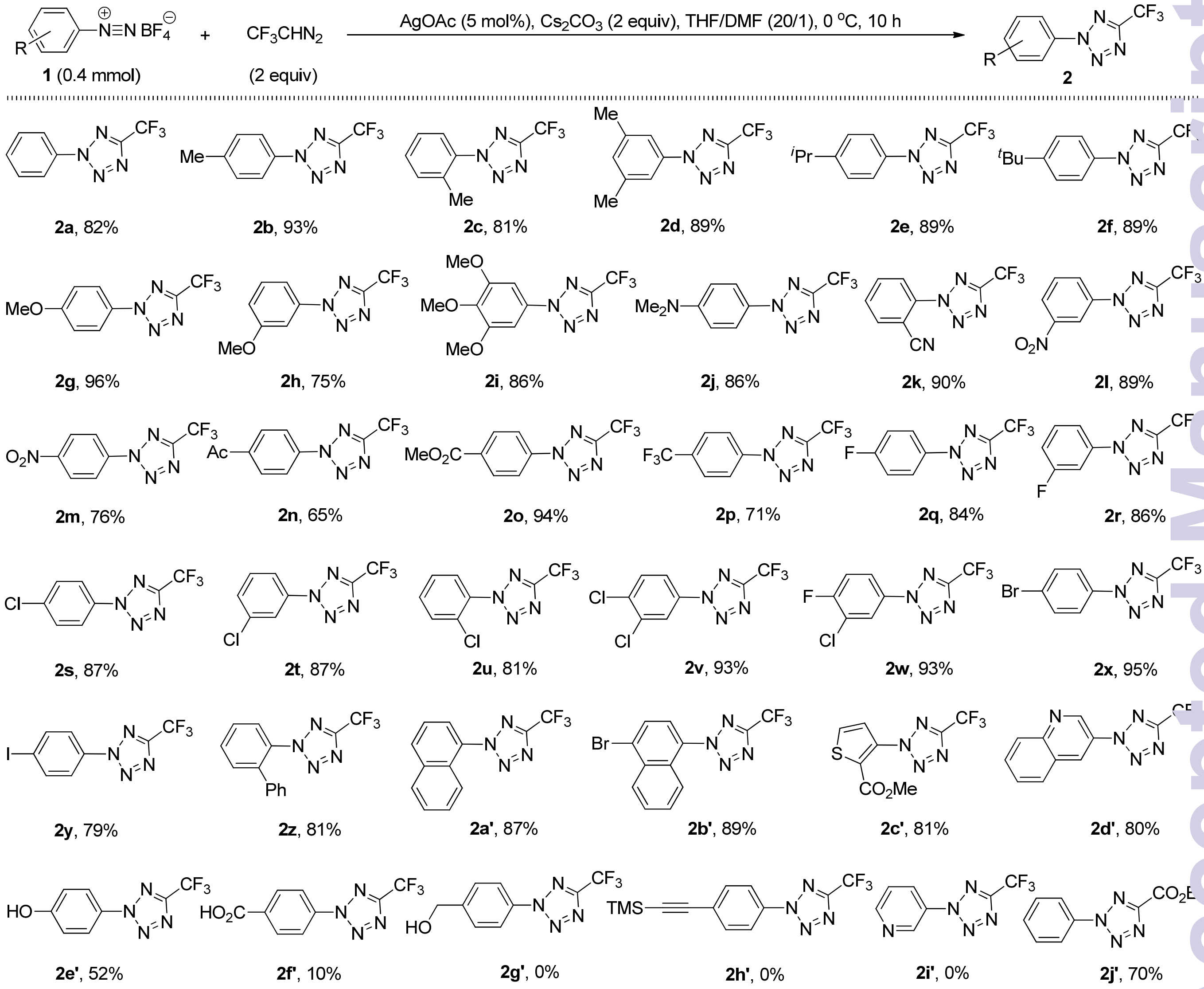
Entry	Catalyst	Base (x)	Solvent	Yield (%)[b]
1	AgOAc	Cs_2CO_3 (2)	THF	84
2	Ag_2CO_3	Cs_2CO_3 (2)	THF	67
3	Ag_2SO_4	Cs_2CO_3 (2)	THF	23
4	$AgNO_3$	Cs_2CO_3 (2)	THF	78
5	AgF	Cs_2CO_3 (2)	THF	77
6	AgOTf	Cs_2CO_3 (2)	THF	73
7	Ag_2O	Cs_2CO_3 (2)	THF	77
8[c]	AgOAc	Cs_2CO_3 (2)	THF	79
9	AgOAc	Na_2CO_3 (2)	THF	78
10	AgOAc	K_2CO_3 (2)	THF	70
11	AgOAc	Et_3N (2)	THF	65
12	AgOAc	DBU (2)	THF	64
13	AgOAc	DABCO (2)	THF	74
14	AgOAc	Cs_2CO_3 (1)	THF	40
15	AgOAc	Cs_2CO_3 (3)	THF	82
16[d]	AgOAc	Cs_2CO_3 (2)	THF	59
17[e]	AgOAc	Cs_2CO_3 (2)	THF	84
18	AgOAc	–	THF	NR
19	–	Cs_2CO_3 (2)	THF	NR
20[f]	AgOAc	Cs_2CO_3 (2)	THF	72
21	AgOAc	Cs_2CO_3 (2)	CH_3CN	53
22	AgOAc	Cs_2CO_3 (2)	Toluene	20
23	AgOAc	Cs_2CO_3 (2)	DCM	28
24	AgOAc	Cs_2CO_3 (2)	DMF	89 (78)
25[g]	AgOAc	Cs_2CO_3 (2)	THF/DMF	(81)
26[h]	AgOAc	Cs_2CO_3 (2)	THF/DMF	(82)
27[i]	AgOAc	Cs_2CO_3 (2)	THF/DMF	(80)

[a] General reaction conditions: **1a** (0.2 mmol), CF_3CHN_2 (0.4 mmol), catalyst (5 mol%), base (x equiv) in 2 mL of solvent under Ar at 0 °C for 10 h. [b] Yields were determined by ^{19}F NMR with trifluorotoluene as an internal standard. The values in parentheses represent the yields of isolated products. [c] Under air. [d] 1 mol% of AgOAc was used. [e] 10 mol% of AgOAc was used. [f] 25 °C for 5 h. [g] THF/DMF = 40/1. [h] THF/DMF = 20/1. [i] THF/DMF = 10/1.

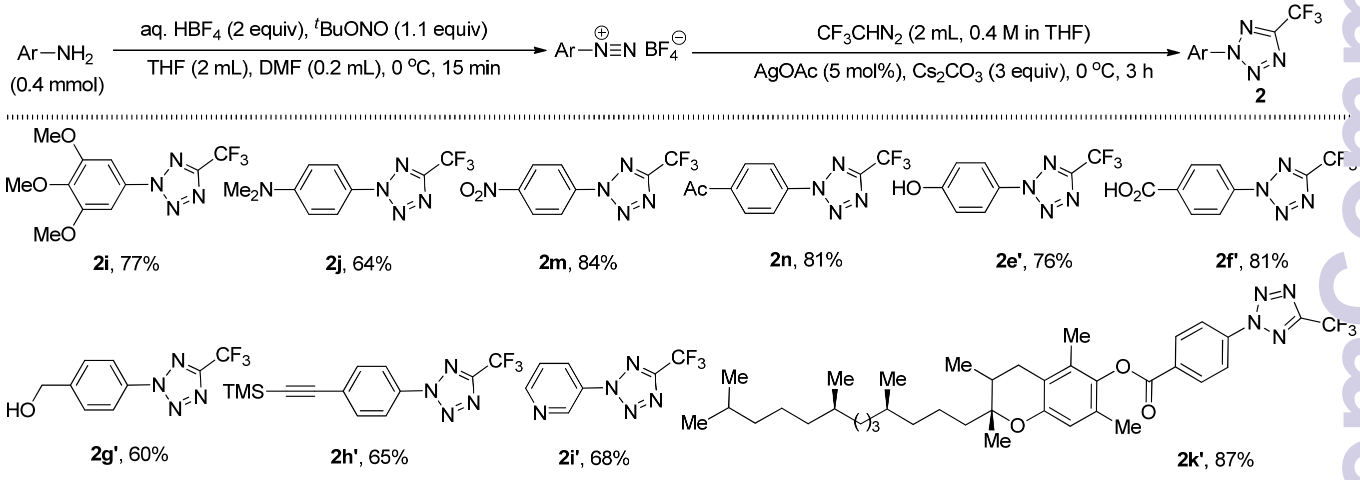
79% (entry 8). Among the bases tested, Cs_2CO_3 was found to be the choice base for this cycloaddition reaction (entries 9–13). A lesser amount of Cs_2CO_3 reduced the reaction yield (entry 14), but 3.0 equivalents of Cs_2CO_3 did not improve the yield when compared to that obtained with 2.0 equivalents of Cs_2CO_3 (entries 15 and 1). A substantial change of the loading of the catalyst (entries 16 and 17) indicated that the good result was attained when 5 mol% of AgOAc were used in this cycloaddition reaction. In sharp contrast, the reaction did not proceed without the silver catalyst or the base (entries 18 and 19). By elevating the temperature to room temperature, the reaction time can be shortened to 5 hours at the expense of yield (entry 20). In addition, the solvent was found to have an important effect on the reactivity (entries 21–27). Among the solvents tested, THF/DMF (20/1) was found to be the co-solvent of choice for this reaction, and the cycloadduct **2a** was obtained in the isolated yield of 82% (entry 26).

With the optimized reaction conditions in hand, we set out to investigate the scope of this Ag-catalyzed [3 + 2] cycloaddition reaction, and the results were summarized in Scheme 2. In the case of phenyl diazonium salts, the cycloaddition reaction tolerates various substitution patterns and a range of different substituents on the phenyl ring. Alkyl-, alkoxy-, amino-, cyano-, nitro-, acetyl-, alkoxycarbonyl-, trifluoromethyl-, and various halo-substituted phenyldiazonium salts all undergo the desired reaction to give the cycloadducts **2a** – **y** in good to high yields. In addition, 1,1'-biphenyl-2-yl-, 1-naphthyl-, 3-thienyl-, and 3-quinolyl diazonium salts were also found to be good subtrates, delivering the desired cycloadducts **2z** – **d'** in 80–89% yields. It is worth noting that the unprotected alcohol group could also tolerate under the standard reaction conditions and give the desired cycloadduct **2e'** in 52% yield. Furthermore, the structures of compounds **2n** and **2e'** were further confirmed to be 2-aryl-substituted 5-trifluoromethyltetrazoles by means of X-ray crystallographic analysis (see the ESI).[7] However, the cycloadduct **2f'** was obtained in poor yield, possibly due to the weak solubility of the starting 4-carboxybenzenediazonium salt in the existing system. Unfortunately, 4-hydroxylmethylphenyl-, 4-((trimethylsilyl)-ethynyl)phenyl-, and 3-pyridyl-substituted tetrazoles **2g'** – **i'** could not be accessed under our current conditions. Notably, the scope of this cycloaddition reaction was not limited to 2,2,2-trifluorodiazoethane, as substitution of CF_3CHN_2 with ethyl diazoacetate proved uneventful, and the desired cycloadduct **2j'** was also obtained in good yield.

As all of arenediazonium salts are not commercially available and are generally synthesized from anilines, we wondered whether a facile one-pot diazotization/cycloaddition sequence might be feasible. Actually, once subjecting a mixture of anilines and HBF_4 in a co-solvent of THF/DMF (10/1) to ^{t}BuONO at 0 °C for 15 minutes, arenediazonium salts could be formed in almost quantitative yields. Next, AgOAc, Cs_2CO_3, and a stock solution of CF_3CHN_2 in THF were added successively, and after 3 hours the desired tetrazole derivatives could be generated in moderate to excellent yields (Scheme 3). In this one-pot sequence protocol, electron-rich anilines delivered the desired tetrazoles **2i** and **2j** in relatively lower yields together with a little amount of uncharacterized by-products, while electron-deficient substrates furnished comparable or even better results (**2m** and **2n**). Substrates with an unprotected hydroxyl or carboxyl group proceeded much more smoothly to give the corresponding cycloadducts **2e'** and **2f'** in the yields of 76% and 81%, respectively. In sharp contrast with the preceding results, 4-hydroxylmethylphenyl-, 4-[(trimethylsilyl)- ethynyl]phenyl-, and 3-pyridyl-substituted tetrazoles **2g'** – **i'** could be obtained in good yields. To use the silver-catalyzed one-pot diazotization / cycloaddition sequence for the modification of biologically interesting compounds, we tested the reaction of tocopherol-derivatized aniline.[8] The reaction sequence proceeded well to afford the cycloadduct **2k'** in 87% yield.

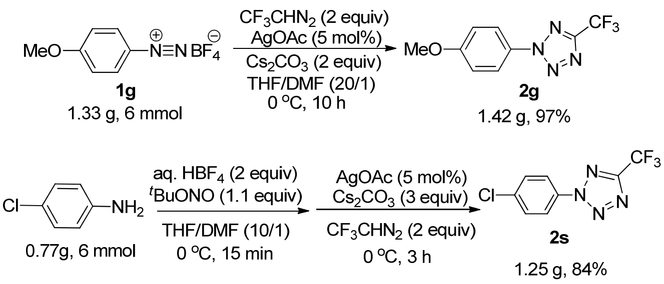


Scheme 2 Substrate scope of cycloaddition reaction of CF_3CHN_2 with aryl diazonium salts **1**.



Scheme 3 One-pot diazotization/cycloaddition sequence reaction of various aniline derivatives.

To further demonstrate the synthetic utility of this protocol, a gram-scale preparation of **2g** and **2s** was carried out. As shown in Scheme 4, when the reaction of **1g** with CF_3CHN_2 was performed on a 6.0 mmol scale, the corresponding trifluoromethylated tetrazole **2g** were produced in the isolated yield of 97%. It should be noted that when 4-chloroaniline was chosen as the starting material, the corresponding trifluoromethylated tetrazole **2s** could also be obtained in 84% yield through the one-pot diazotization / cycloaddition sequence.



Scheme 4 Gram-scale reactions.

In summary, we have successfully disclosed a silver-catalyzed [3 + 2] regioselective cycloaddition reaction of 2,2,2-trifluorodiazoethane with various aryl and heteroaryl diazonium salts. Under mild conditions, a broad range of 2-aryl-5-trifluoromethyltetrazoles were obtained in good to high yields. Furthermore, our methodology can be extended to diazoacetate to demonstrate this reaction scope. The practicality of this methodology was further demonstrated by development of the one-pot diazotization/cycloaddition sequence from commercially available aniline derivatives and its application into late-stage modification of a natural compound. Mechanistic studies and further transformations of the cycloadducts are underway in our laboratory.

Notes and references

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1. (a) R. N. Butler, In *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Katritzky, C. W. Rees, Scriven, E. F. V.), Pergamon: Oxford, 1996, p 621; (b) R. J. Herr, *Bioorg. Med. Chem.*, 2002, **10**, 3379; (c) L. V. Myznikov, A. Hrabalek, G. I. Koldobskii, *Chem. Heterocycl. Compd.*, 2007, **43**, 1.
2. (a) R. N. Bulter, In *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Katritzky, C. W.Rees,), Pergamon: Oxford, 1984; p 791; (b) H. R. Meier, H. Heimgartner, In *Methoden der Organischen Chemie* (Houben-Weyl); (Ed.: E. Schumann), Georg Thieme: Stuttgart, 1994, p 664; (c) P. N. Gaponik, S. V. Voitekhovich, O. A. Ivashkevich, *Russ. Chem. Rev.*, 2006, 507.
3. (a) P. Yates, D. G. Farnum, *Tetrahedron Letters*, 1960, **38**, 2; (b) F. R. Benson, *Chem. Rev.*, 1947, **41**, 1; (c) S. Wittenberger, *Org. Prep. Proced. Int.*, 1994, **26**, 499; (d) Roh, K. Vávrová, A. Hrabálek, *Eur. J. Org. Chem.*, 2012, 6101.
4. For selected leading examples, see: (a) W. Lossen, C. Lossen, *Ann.*, 1891, **263**, 96; (b) A. Pinneb, *Ber.*, 1894, **27**, 990; (c) J. Colman, *Ber.*, 1897, **30**, 2010; (d) G. Schroeter, *Ber.*, 190 **42**, 2336; (e) O. Dimroth, G. De Montmollin, *Ber.*, 1910, **43**, 2907; (f) F. D. Chattaway, G. D. Parkbs, *J. Chem. Soc.*, 1926, 113; (g) J. Von Braun, W. Keller, *Ber. Dtsch. Chem. Ges.*, 1932, **65**, 1677; (h) J. V. Braun, W. Rudolph, *Ber.*, 1941, **74**, 264; (W. G. Finnegan, R. A. Henry, R. Lofquist, *J. Am. Chem. Soc*, 1958, **80**, 3908; (j) S. Ito, Y. Tanaka, A. Kakehi, *Bull. Chem Soc. Jpn.*, 1976, **49**, 762; (k) P. R. Bernstein, E. P. Vace *Synthesis*, 1987, 1133; (l) M. Alterman, A. Hallberg, *J. O Chem.*, 2000, **65**, 7984; (m) Z. P. Demko, K. B. Sharpless, *J. Org. Chem.*, 2001, **66**, 7945; (n) T. Jin, S. Kamijo Yamamoto, *Tetrahedron Lett.*, 2004, **45**, 9435; (o) B. Gutmann, J.-P. Roduit, D. Roberge, C. O. Kappe, *An Chem., Int. Ed.*, 2010, **49**, 7101; (p) Y. Li, L.-X. Gao, F.-S. Ha *Chem. Commun.*, 2012, **48**, 2719; (q) T. Onaka, H. Umemoto Y. Miki, A. Nakamura, T. Maegawa, *J. Org. Chem.*, 2014, 7 6703.
5. (a) F. Li, J. Nie, L. Sun, Y. Zheng, J.-A. Ma, *Angew. Chem., In Ed.*, 2013, **52**, 6255; (b) S. Wang, L.-J. Yang, J.-L. Zeng, Zheng, J.-A. Ma, *Org. Chem. Front.*, 2015, **2**, in press. Othe reactions involving 2,2,2-trifluorodiazoethane in our grou see: (c) C.-B. Liu, W. Meng, F. Li, S. Wang, J. Nie, J.-A. Ma, *Angew. Chem., Int. Ed.*, 2012, **51**, 6227; (d) S. Wang, J. Nie, Zheng, J.-A. Ma, *Org. Lett.*, 2014, **16**, 1606; (e) H.-Y. Xiong, Z. Y. Yang, Z. Chen, J.-L. Zeng, J. Nie, J.-A. Ma, *Chem. Eur.* 2014, **20**, 8325; (f) F.-G. Zhang, Y. Wei, Y.-P. Yi, J. Nie, J. Ma, *Org. Lett.*, 2014, **16**, 3122; (g) L. Sun, J. Nie, Y. Zheng, J.-A Ma, *J. Fluorine Chem.*, 2015, **174**, 88; (h) A.-J. Cai, Y. Zheng, A. Ma, *Chem. Commun.*, 2015, **51**, 8946.
6. For reviews on Ag-catalyzed synthesis of heterocycles, see: (a) M., H. Yamamoto, *Chem. Rev.*, 2008, **108**, 3132; (b) J.- Weibel, A. Blanc, P. Pale, *Chem. Rev.*, 2008, **108**, 3149; (c) Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-Garcí *Chem. Rev.*, 2008, **108**, 3174.
7. The X-ray crystallographic structures for **2n** and **2e'** hav been deposited at the Cambridge Crystallographic Dat Centre (CCDC), under deposition numbers CCDC 141252 and 1412621, repectively. The datas can be obtained free charge from the Cambridge Crystallographic Data Centre *via* http://www.ccdc. cam.ac.uk/data_request/cif.
8. (a) T.-F. Liu, X.-X. Shao, Y.-M. Wu, Q.-L. Shen, *Ange Chem., Int. Ed.*, 2012, **51**, 540; (b) X. Wang, Y. Xu, F.-Y. Me G.-J. Ji, D. Qiu, J.-J. Feng, Y.-X. Ye, S.-N. Zhang, Y. Zhang, B. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 10330.