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COMMUNICATION

Copper-Triggered Three-Component Reaction of CF_3CHN_2 , Nitriles, and Aldehydes: Highly Diastereoselective Synthesis of CF_3 -Substituted Oxazolines and Vicinal Amino Alcohols

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A novel, three-component C–C, C–N and C–O bonds forming reaction is described. In the presence of 20 mol% CuO, this condensation reaction of CF_3CHN_2 , nitriles, and aldehydes proceeds to afford CF_3 -substituted oxazolines in moderate to high yields with excellent diastereoselectivities. Subsequent ring-opening of oxazolines gives rise to the corresponding vicinal amino alcohols.

The development of highly efficient synthetic methods for rapid construction of complex molecular architectures continues to be a challenge in modern organic chemistry.¹ Multicomponent reactions (MCRs) have emerged as an important area in the disciplines of organic synthesis, medicinal chemistry, and chemical biology.² Compared to traditional divergent reaction strategies, MCRs provide a highly efficient approach for the preparation of polyfunctional molecules from simple starting materials in an operationally simple and atom-economical manner, such as lowing costs, saving time and energy, simplicity and flexibility, as well as environmentally friendly aspects.³

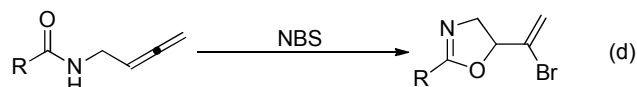
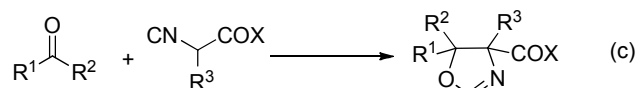
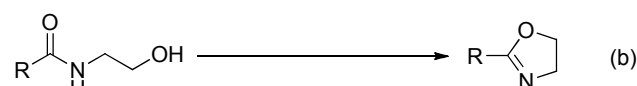
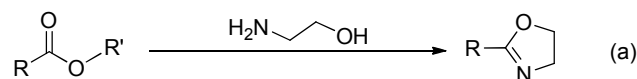
Oxazolines are frequently encountered structural motifs in numerous natural products and biologically active molecules.⁴ They are also versatile intermediates in polymer chemistry and organic synthesis.⁵ In addition, these moieties play an important role in asymmetric synthesis, extensively serving as ligands and auxiliaries.⁶ Generally, there are four methods for the synthesis of oxazolines, including the reaction of carboxylic acids and its esters with β -amino alcohols (Scheme 1a),⁷ the cyclodehydration of β -hydroxy amides (Scheme 1b),⁸ the condensation of isocyanoacetic acid derivatives with carbonyl compounds (Scheme 1c),⁹ and the cyclization of *N*-(buta-2,3-dienyl)amides with *N*-bromosuccinimide (Scheme 1d).¹⁰ Despite these notable progresses, the development of new methods for the facile construction of oxazolines is still highly desirable.

Fluorinated units modify the physicochemical and biological properties of an organic compound profoundly. Especially,

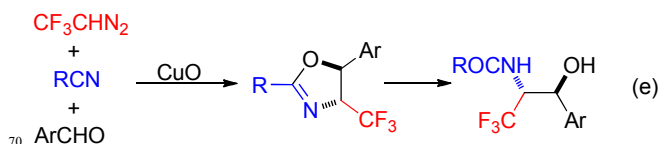
trifluoromethyl-substituted heterocycles have been found with widespread applications in pharmaceutical and agrochemical sciences because the fluorinated groups can alter the steric, lipophilic, electronic, and metabolic characteristics of the active pharmaceutical ingredients.¹¹ As a reactive intermediate, 2,2,2-trifluorodiazoethane (CF_3CHN_2) is an attractive C2 synthon for the construction of trifluoromethyl-containing building blocks.¹² Recently, Cahard and co-workers successfully developed an organocatalyzed asymmetric three-component reaction of CF_3CHN_2 with aryl glyoxal monohydrates and amines for the enantioselective synthesis of chiral CF_3 -substituted aziridines,^{13a} whereas Molander's group nicely introduced an interesting three-component reaction of CF_3CHN_2 with nitrosoarenes and alkenes to access trifluoroethyl-substituted isoxazolidines.^{13b} Inspired by these reports, in combination with our continuing interest in this area,¹⁴ we have discovered a novel copper-triggered three-component reaction of CF_3CHN_2 with nitriles and aldehydes,

Scheme 1 Procedures for the synthesis of oxazolines.

Previous work



This work



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delivering trifluoromethylated oxazolines under mild conditions in moderate to high yields with excellent diastereoselectivities. Furthermore, the corresponding oxazolines could be readily converted into CF₃-substituted vicinal amino alcohols in excellent yields and diastereoselectivities. Herein, we report our preliminary results on this subject.

We began our investigations by exploring the reaction of *p*-nitrobenzaldehyde with CF₃CHN₂ in acetonitrile in the presence of CuCl₂ (20 mol%) at room temperature. To our delight, the desired CF₃-substituted oxazoline **2a** was obtained in 55% yield with excellent diastereoselectivity (dr > 99:1), and no additional bases or ligands were needed (Table 1, entry 1). The structure of **2a** was further confirmed by means of X-ray crystallographic analysis.¹⁵ This result encouraged us to further optimize the reaction conditions. A series of copper salts [CuCl, Cu(OTf)₂, Cu(NO₃)₂, CuBr, CuI, Cu₂O, Cu(OAc)₂, Cu(acac)₂, CuOTf, CuSO₄, and CuO] were screened (Table 1, entries 2–12). It was found that CuO was the promising catalyst for the texted reaction and the product **2a** was obtained in 80% yield with > 99:1 dr (Table 1, entry 12). Then the catalyst amount and temperature were further optimized. Lowering the amount of CuO to 10 mol% resulted in lower yield (Table 1, entry 13). The change of

temperature did not have a significant effect on the reaction activity (Table 1, entry 14). The control experiment indicated the necessity of the copper salt (Table 1, entry 15). Based on the above experiments, the employment of CuO (20 mol%) at room temperature was determined to be the best reaction conditions for this three-component reaction.

With the optimized reaction conditions in hand, the scope of the substrates for this copper-promoted three-component reaction of 2,2,2-trifluorodiazooethane with nitriles and aldehydes was

Scheme 2 The scope of three-component reaction.^a

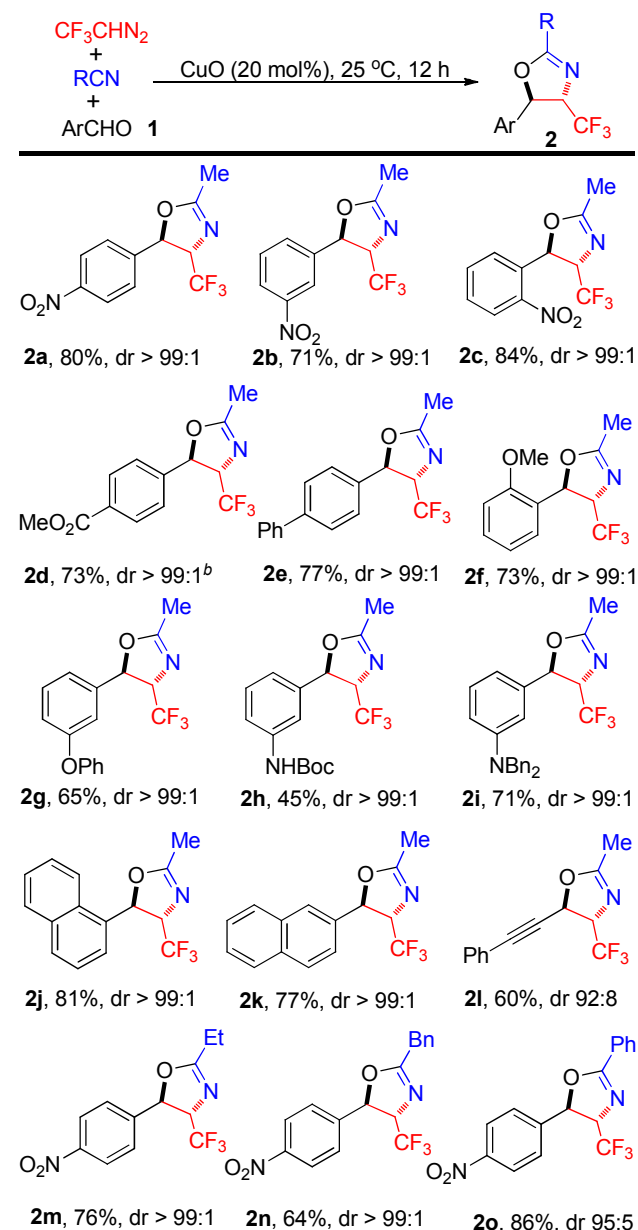
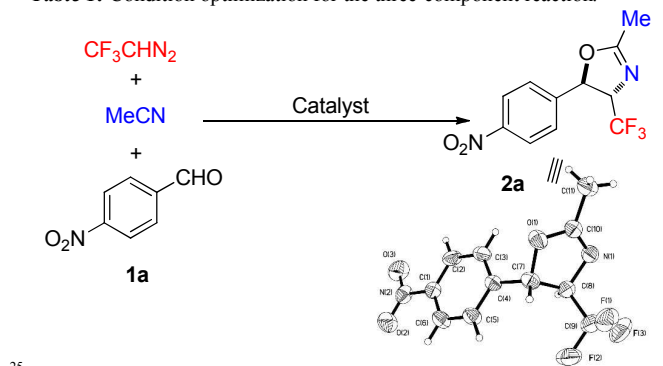


Table 1: Condition optimization for the three-component reaction.^a



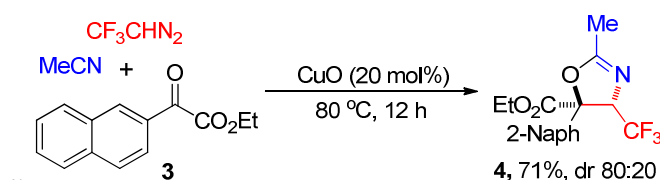
Entry	Copper salt (mol %)	T (°C)	Yield (%) ^b	D.r. ^c
1	CuCl ₂ (20)	25	55	> 99 : 1
2	CuCl (20)	25	51	> 99 : 1
3	Cu(OTf) ₂ (20)	25	47	> 99 : 1
4	Cu(NO ₃) ₂ (20)	25	46	> 99 : 1
5	CuBr (20)	25	34	> 99 : 1
6	CuI (20)	25	22	> 99 : 1
7	Cu(OTf) (20)	25	65	> 99 : 1
8	Cu(OAc) ₂ (20)	25	trace	–
9	Cu(acac) ₂ (20)	25	29	> 99 : 1
10	Cu ₂ O (20)	25	67	> 99 : 1
11	CuSO ₄ (20)	25	75	> 99 : 1
12	CuO (20)	25	80	> 99 : 1
13	CuO (10)	25	69	> 99 : 1
14	CuO (20)	40	73	> 99 : 1
15	–	25	0	–

^a Unless otherwise noted, all reactions were carried out with **1a** (0.2 mmol), CF₃CHN₂ (0.4 mmol) and CH₃CN (2 mL). ^b Isolated yield was obtained from an average of two runs. ^c The diastereomeric ratio (dr) was detected by ¹⁹F NMR analysis of crude reaction mixture.

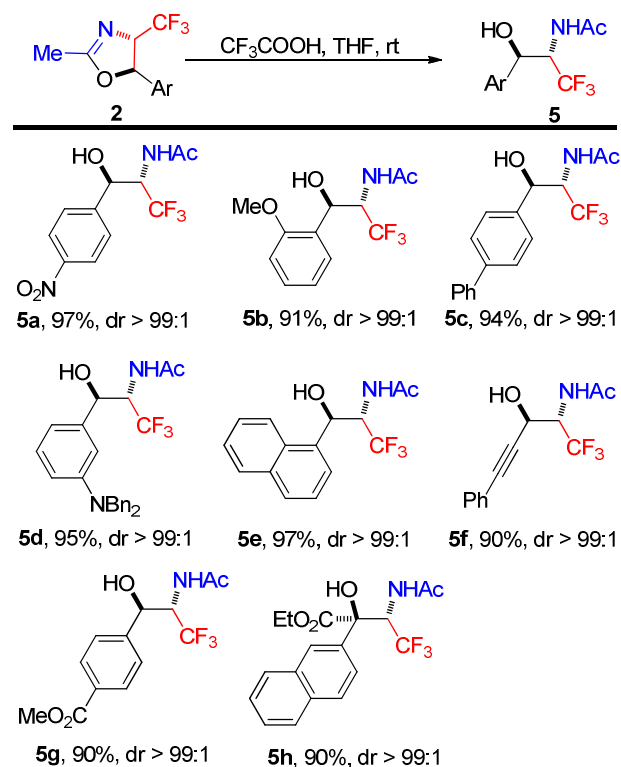
^a Unless otherwise noted, the reactions were carried out with aldehyde **1** (0.2 mmol), CF₃CHN₂ (0.4 mmol) and nitrile (2.0 mL) in the presence of CuO (20 mol%) at room temperature for 12 h; Isolated yield was obtained from an average of two runs; The diastereomeric ratio was detected by ¹⁹F NMR analysis of crude reaction mixture. ^b The reactions were carried out at 80 °C for 12 h.

investigated and the results were summarized in Scheme 2. A series of aryl aldehydes have been successfully employed in this reaction, and the corresponding CF₃-substituted oxazolines **2a-i** were obtained in 45–84% yields with high diastereoselectivities. The reaction tolerated different substitution patterns and a range of substituents on the aryl ring. Many synthetically important functional groups, including nitro, alkoxy, phenyl, alkoxy, phenoxy, and *N*-protecting amino groups, are well-tolerated in this three-component reaction. 1- and 2-Naphthaldehydes as well as 3-phenylpropionaldehyde were also found to be good substrates, delivering the products **2j-l** in good yields with excellent diastereoselectivities. However, the use of benzaldehyde, 4-methylbenzaldehyde, and 3-chlorobenzaldehyde did not give the expected oxazolines.^{15, 16} In addition, aliphatic aldehydes cannot be converted using the present protocol, even when the reaction conditions were further optimized including the

Scheme 3 The reaction of α -keto ester with CF₃CHN₂ and CH₃CN.



Scheme 4 Synthesis of the CF₃-substituted vicinal amino alcohols **5**.^a



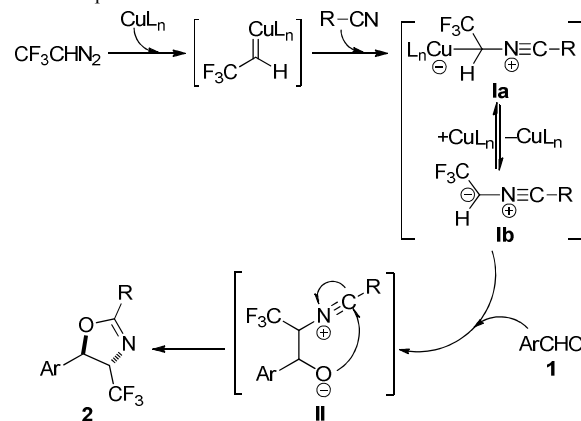
^a Unless otherwise noted, the reactions were carried out with **2** (0.4 mmol), CF₃COOH (4.0 equivalent) and THF (2 mL) at room temperature for 36 h; Isolated yield; The diastereomeric ratio was detected by ¹⁹F NMR analysis of crude reaction mixture.

change of the temperature and/or the use of other copper salts. Subsequently, the use of other nitriles was investigated, and the desired products **2m-o** were obtained in good to high yields. We also investigated the reaction of α -keto ester **3** with CF₃CHN₂ and acetonitrile. This less reactive substrate was found to be also suitable for this three-component reaction, and the desired product **4** was obtained in 71% yield with 80:20 dr (Scheme 3).

Trifluoroethylated oxazolines are also versatile synthetic intermediates and can be readily transformed into highly functionalized organofluorine compounds that are otherwise difficult to access (Scheme 4). For example, treatment of **2** with CF₃CO₂H in THF at room temperature led to the formation of CF₃-substituted vicinal amino alcohols **5a-h** in excellent yields (90–97%) and diastereoselectivities (dr > 99:1).

To obtain more information about our reaction, we conducted the CuO-promoted three-component reaction of deuterium-labelled CF₃CH(D)N₂ with *p*-nitrobenzaldehyde and acetonitrile under the standard reaction conditions. It was found that the ratio of deuterium to hydrogen at 4-position of the oxazoline ring is similar to that in the substrate (see ESI). Therefore, the intermolecular exchange and the intramolecular proton shift in this three-component reaction are impossible. On the basis of this observation and previous studies,^{17, 18} the proposed reaction mechanism is shown in Scheme 5. Initially, in the presence of copper salts, the copper carbenoid is formed from 2,2,2-trifluorodiazooethane. Then, the reaction of this carbenoid with nitrile undergoes to afford the ammonium ylide intermediates **Ia** or **Ib**, which trapped by aldehyde **1** to furnish the intermediate **II**. The subsequent step is the intramolecular cyclization of the intermediate **II**, thus giving rise to trifluoromethylated oxazolines.

Scheme 5 Proposed reaction mechanism for the formation of **2**.

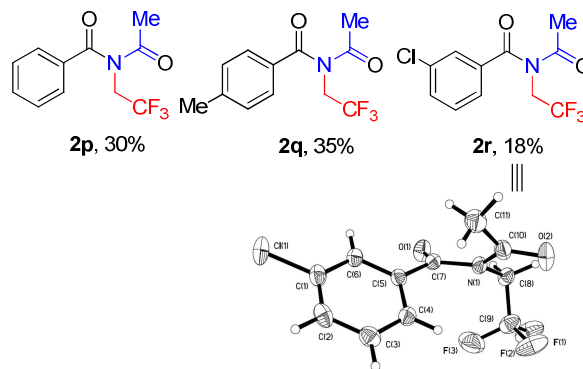


In summary, a novel copper(II)-catalyzed three-component reaction of CF₃CHN₂ with aldehydes and nitriles has been developed. The present protocol provides a mild and rapid way for the synthesis of trifluoromethylated oxazolines in good yields with high diastereoselectivities. The products can be readily converted into CF₃-substituted vicinal amino alcohols. Further application of this three-component reaction and detailed mechanistic studies are ongoing in our laboratories.

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