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ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Stereoselective Synthesis of Trifluoromethyl-substituted 2*H*-Furan-Amines from Enaminones†

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A straightforward strategy to synthesis of highly functionalized trifluoromethyl 2*H*-furans is described. The copper catalyzed method relies on a cascade cyclic reaction between enaminones and *N*-tosylhydrazones. The method allows the synthesis of 2-amino-3-trifluoromethyl-substituted 2*H*-furan derivatives carrying a quaternary stereogenic center as single diastereomers. The proposed reaction mechanism involves an amino-cyclopropane intermediate formed in the cyclopropanation of enaminone. The developed method tolerates a broad spectrum of functionalities, and the obtained 2*H*-furan derivatives are useful synthetic intermediates for preparing other trifluoromethyl-substituted compounds.

2*H*-Furans, especially 2,3-dihydrofurans, are an important class of five-membered heterocycles widely present in many natural products and pharmaceuticals.[1] 2*H*-Furans are also useful building blocks as they can easily be further functionalized.[2] Thus, 2*H*-furan derivatives have gained significant attention both in biological and organic chemistry communities, promoting synthetic chemists to explore various strategies for their construction.[3] Representative strategies include [4+1] cycloadditions,[4] [3+2] cycloadditions,[5] cyclopropane ring expansions[6] and others.[7] These methods allow efficient routes to poly-substituted 2,3-dihydrofurans. In many cases, though, the methods still have several limitations, such as the use of stoichiometric quantities of transition metals, harsh reaction conditions and limited functional group tolerance.

Trifluoromethylated heterocycles have found wide uses in the agrochemical and pharmaceutical industries as well as for material science.[8] Recent years have witnessed remarkable advances in synthetic methods allowing the introduce of CF_3 groups into reserved cycles.[9] However, the unique property of fluorine chemistry normally makes one-pot trifluoromethylation/cyclization reactions especially hard to control. Preparing high functionalized trifluoromethylated 2*H*-furans are still limited to a few of methods (**Figure 1**).[10] For example, directly trifluoromethylation of furan rings by employing Togni's reagent-II and Umenoto's reagent can construct trifluoromethylated 2,5-2*H*-furans.[11] Zhang group reported an one-pot trifluoromethylation/cyclization reaction of conjugated enyne aldehydes and ketones, which provides modular access to highly substituted trifluoromethylated 2,3-dihydrofurans.[12] It should be noted that there is only one example to introduce CF_3 into 3-position of 2*H*-furans from *β*-(trifluoromethyl)vinyl sulfonium salts.[13] In spite of these developments, it is still highly desirable to design more general and straightforward methods to construct highly functionalized trifluoromethylated 2*H*-furans with diverse substituents.

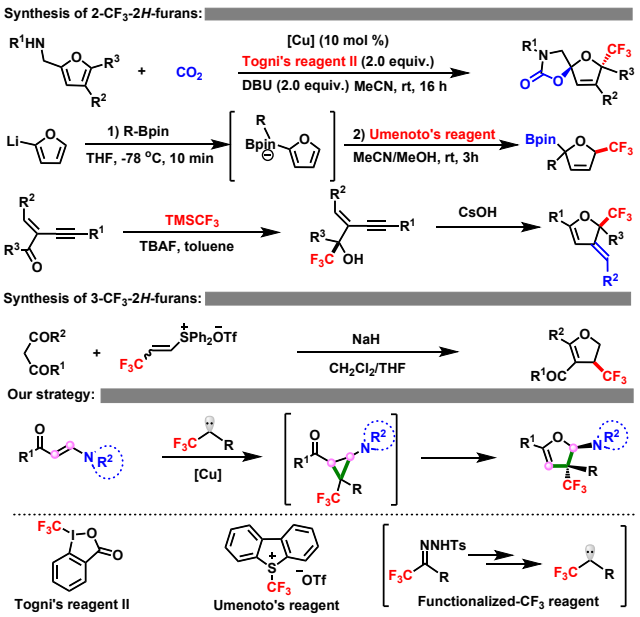

Figure 1. Representative methods to prepare CF_3-2*H*-furans.

Enaminones as known bench-stable synthetic units have attracted widely attention in recently years.[14] *N*-Tosylhydrazones are known carbene precursors, however using trifluoromethyl *N*-tosylhydrazones[15] as functionalized-CF_3 reagent to prepare heterocycles are rare reported. In our continuing research in this area,[16] we envisioned the use of easily available trifluoromethyl *N*-tosylhydrazones as functionalized-CF_3 carbene precursors in a reaction with enaminones to generate CF_3-substituted amino-cyclopropane intermediates (**Figure 2**). Rearrangement of the obtained amino-cyclopropane intermediate would result in trifluoromethylated 2*H*-furans. Herein, we demonstrate a straightforward method to synthesize 2-amino functionalized 2,3-2*H*-furans with complete diastereoselectivity on the CF_3-bearing

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures analytical data, See DOI: 10.1039/b000000x/

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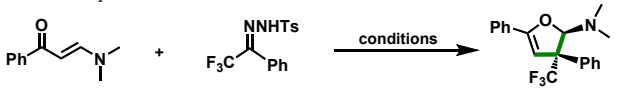
DOI: 10.1039/C9CC08582C

quaternary all-carbon stereogenic center through carbon-carbon double bond cleavage of stable enaminones.

We began our investigations by giving priority to several potential metal catalysts such as $Rh(OAc)_2$, $FeCl_2$ and CuCl. In the initial screen, CuCl outperformed other catalysts, giving the desired trifluoromethyl-substituted 2*H*-furan **3aa** in 65% yield (**Table 1,** entries 1-3). The structure of **3aa** was determined by NMR spectroscopy. The geometry of **3da** was further analyzed by a single crystal X-ray data (CCDC: 1572376) (**Table 2** and see **SI**). Further screening of different copper salts showed bivalent copper catalysts to be more efficient compared to monovalent coppers (**Table 1,** entries 4-7). Then various bases were examined to improve the reaction efficiency. The initially used KO^{t}Bu was the best base (72% yield), with K_2CO_3 performing almost equally well (71% yield), while organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and triethylamine (TEA) gave no desired product (**Table 1,** entries 7-11). Exploration of various solvent conditions revealed that CH_2Cl_2 was the optimal reaction medium and provided **3aa** with up to 81% yield (**Table 1,** entries 12-14). Furthermore, the reaction efficiency was not affected significantly by decreasing the catalyst loading to 5 mol % (**Table 1,** entry 15). When the reaction was finally carried out in 5 mol % $CuCl_2$ and 2.6 equivalent KO^{t}Bu in CH_2Cl_2 at 80 °C under argon atmosphere, 2*H*-furan **3aa** could be observed in the highest isolated yield (87%) (**Table 1,** entry 16). Needing more amount of base (2.6 equiv.) compared to **2a** (2.5 equiv.) may be due to having to keep the mixture basic enough to generate the carbene completely from trifluoromethyl *N*-tosylhydrazones.

Table 1. Optimization of reaction conditions.[a]



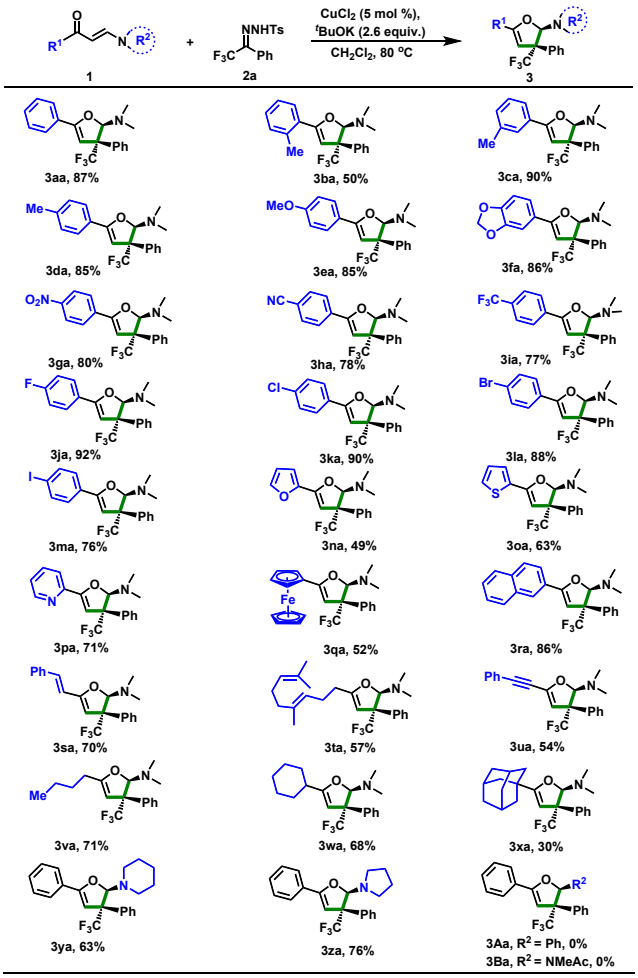
1a 2a 3aa

Entry	Metal	Base	Solvent	Conv.(%)[b]
1	$Rh_2(OAc)_4$	KO^{t}Bu	toluene	5
2	$FeCl_2$	KO^{t}Bu	toluene	2
3	CuCl	KO^{t}Bu	toluene	65
4	CuBr	KO^{t}Bu	toluene	62
5	CuI	KO^{t}Bu	toluene	48
6	$Cu(OAc)_2$	KO^{t}Bu	toluene	71
7	$CuCl_2$	KO^{t}Bu	toluene	72
8	$CuCl_2$	K_3PO_4	toluene	61
9	$CuCl_2$	K_2CO_3	toluene	71
10	$CuCl_2$	DBU	toluene	-
11	$CuCl_2$	Et_3N	toluene	-
12	$CuCl_2$	KO^{t}Bu	CH_2Cl_2	81
13	$CuCl_2$	KO^{t}Bu	DCE	33
14	$CuCl_2$	KO^{t}Bu	PhCl	66
15	$CuCl_2$[c]	KO^{t}Bu	CH_2Cl_2	82
16	$CuCl_2$[c]	KO^{t}Bu	CH_2Cl_2	86[d]/87[e]

[a]Experiments were performed with **1a** (0.10 mmol, 1.0 equiv.), **2a** (0.20 mmol, 2.0 equiv.), catalyst (20 mol %) and base (0.21 mmol, 2.1 equiv.) in solvent (4 mL) with stirring at 80 °C under Ar atmosphere until **1a** was completely consumed. [b]Yields were determined by ^{1}H NMR with tetrachloroethane as an internal standard. [c]5 mol % catalyst loading. [d]**2a** (0.25 mmol, 2.5 equiv.), base (0.26 mmol, 2.6 equiv.). [e]Isolated yields. DCE = dichloroethane.

With the optimized reaction conditions in hand, we began investigating the substrate scope of enaminones **1 (Table 2)**. The reaction worked efficiently for various functionalized enaminones to afford the corresponding trifluoromethyl-substituted 2*H*-furans in moderate to excellent yields with complete stereoselectivity. Enaminones with aryl groups bearing methyl groups either at *meta* or *para*-position reacted efficiently and gave 90% and 85% yields, respectively (**3ca** and **3da**), while the *ortho*-methyl substitution resulted in decreased yield (**3ba**, 50%). Both electron-rich (**3ea** and **3fa**) and electron-deficient (**3ga-3ia**) substituents on the phenyl group are well tolerated without obvious electronic influence. Enaminones with aryl halides (F, Cl, Br and I) also generated the corresponding 2*H*-furans in good yields (**3ja-3ma**). Notably, the halide products can easily be further functionalized by cross-coupling reactions (Suzuki, Heck, *etc.*),[17] and this offers the possible transformations to prepare other useful heterocycles containing a CF_3 group. The method was also compatible with heterocyclic enaminones including furan, thiophene and pyridine albeit in decreased yields (**3na-3pa**). Remarkably, ferrocene-substituted enaminones also led to the formation of the corresponding dihydrofuran in 52% yield (**3qa**). Naphthalenyl-substituted substrates could also provide the corresponding product as single regioisomer in 86% yield (**3ra**). When polyene enaminones were used, high degrees of regioselectivity was observed with only the enamine C-C double bond reacting over conjugated (**3sa**) and unconjugated double bonds (**3ta**). An alkynyl functional group also remained intact under the reaction conditions in promising yield (**3ua**). The react-

Table 2. Substrate scope of enaminones.[a,b]



[a]Unless otherwise noted, reactions were carried out using **1** (0.20 mmol), **2a** (2.5 equiv.), $CuCl_2$ (5 mol %) and KO^{t}Bu (2.6 equiv.) in CH_2Cl_2 (0.05 M, 4 mL) at 80 °C under argon atmosphere, and the products are obtained as single diastereomer. [b]Isolated yield.

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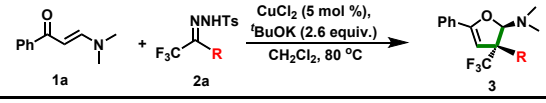
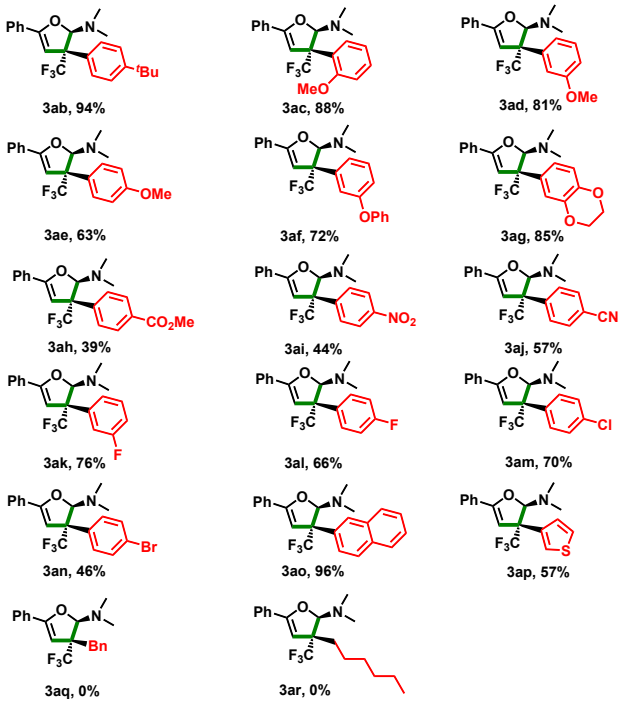
-ion scope could be further extended as it tolerated not only aromatic but also aliphatic enaminones (**3va-3xa**). Changing *N*-substituents to saturated cyclic groups, the corresponding 2*H*-furan products were observed in promising yields (**3ya** and **3za**). However, the reaction failed to react without amino group (**3Aa**).

Then, the substrate scope of trifluoromethyl *N*-tosylhydrazones were examined under the same reaction conditions (**Table 3**). The reaction tolerates a broad number of aromatic substituents (halogen, nitrile, ester, nitro and *etc.*). An electronic effect was observed as the electron-donating substitutions (**3ab-3ag**) gave slightly higher yields compared to electron-withdrawing groups (**3ag-3aj**). Aryl halides including F, Cl and Br gave desired five member rings in moderate to good yields (**3ak-3an**). Notably, the naphthalenyl tosylhydrazone gave the corresponding 2*H*-furan as single diastereoisomer in quantitative yield (**3ao**). Finally, heterocyclic tosylhydrazone was also tolerated and gave promising yield (**3ap**). Unfortunately, no desired 2*H*-furan was isolated when aliphatic *N*-tosylhydrazones were employed as carbene precursors (**3aq-3ar**).

Table 3. Substrate scope of trifluoromethyl *N*-tosylhydrazones.[a,b]

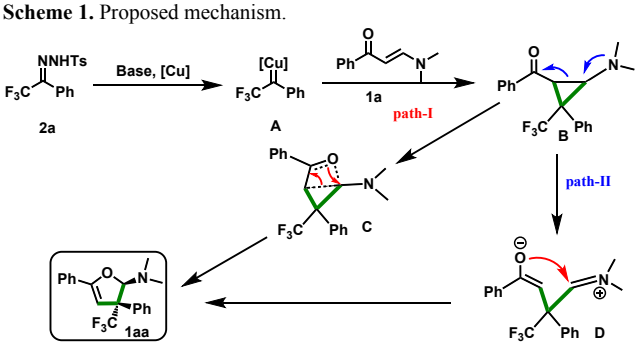




[a]Unless otherwise noted, reactions were carried out using **1a** (0.20 mmol), **2** (2.5 equiv.), $CuCl_2$ (5 mol %) and KO^{t}Bu (2.6 equiv.) in CH_2Cl_2 (0.05 M, 4 mL) at 80 °C under argon atmosphere, and the products are obtained as single diastereomer. [b]Isolated yield.

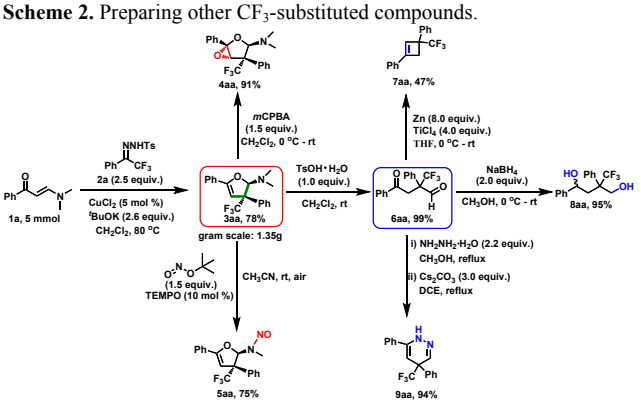
A plausible mechanism is proposed based on obtained results (**Scheme 1**). Initially, a diazo compound is generated *in situ* from the trifluoromethyl tosylhydrazone in the presence of base. The diazo compound then coordinates with the copper catalyst to give the carbenoid-**A**.[18] The resulting intermediate **A** cyclopropanates enaminone **1a** to produce the amino cyclopropane intermediate **B**.[19] It's failed to isolate the intermediate **B** may due to its high reactivity. However, it might be a diastereomeric mixture of compounds according to our previous study, in which we characterized a similar amino cyclopropane intermediate as a mixture of isomers.[16d] After then, two possible pathways from amino cyclopropane intermediate-**B** to the 2*H*-furan product are proposed. For path-I, the oxygen attacking and cleavage of the C-C bond occurs at the same time. The oxygen attacking may take place either on the same side of the phenyl group or trifluoromethyl group. In this case, the oxygen only attacks on the same side of trifluoromethyl group and gives the final obtained *cis*-2*H*-furan product **1aa**. On the other hand, it's also possible to proceed stepwise through ring-opening followed by ring-closure involving an iminium ion intermediate-**D**, which would be favored by the donor-acceptor nature of the cyclopropane intermediate-**B**. Considering the high possibility of formation of diastereomeric mixtures of intermediates-**B**, the high diastereoselectivity of this reaction can be highly according to the thermodynamic formation of the most stable anomer at the cyclic hemiaminal ether through stepwise pathway (path-II).

Scheme 1. Proposed mechanism.



To demonstrate the utility of the reaction, a gram scale experiment was performed to give **3aa** in 78% yield (1.35 g). The product **3aa** was then further functionalized (**Scheme 2**). An epoxidation of the 2*H*-furan ring of **3aa** proceed smoothly to afford the epoxide **4aa** in 91% yield.[20] The *N*,*N*-dimethyl amino group could be oxidized to give **5aa** in 75% yield.[21] Hydrolysis of the 2*H*-furan **3aa** yielded the trifluoromethylated 1,4-ketoaldehyde **6aa** bearing a quaternary all-carbon stereogenic in the almost quantitative yield (99%).[22] 1,4-Ketoaldehydes are useful synthetic intermediates, and the obtained **6aa** was further transformed into useful compounds bearing CF_3 group. For instance, an intramolecular McMurry coupling reaction gave unsaturated four-member ring **7aa** in 47% yield in the presence of Ti/Zn catalytic system.[23] Carbonyl reduction of **6aa** allowed the synthesis of 1,4-diol **8aa** in 95% yield with a mixture of diastereomers. Finally, the ketoaldehyde also cyclized with hydrazine hydrate to afford 4,6-diphenyl-4-(trifluoromethyl)-1,4-

Scheme 2. Preparing other CF_3-substituted compounds.



dihydropyridazine **9aa**.[24] The method thus represents an easy

DOI: 10.1039/C9CC08582C

access to a variety of compounds housing an all-carbon stereogenic center with a CF_3 group.

In summary, we have demonstrated an efficient and practical approach to prepare highly functionalized 2-amino-3-trifluoromethyl-substituted 2*H*-furan derivatives with a quaternary all-carbon stereogenic center as single diastereomers. The reaction proceeds *via* a cascade cyclization between enaminones and *N*-tosylhydrazones and employs a cheap copper catalyst under basic conditions. We believe the reaction involves an initial formation of an amino-cyclopropane intermediate, which undergoes selective C-C bond cleavage. The method tolerates a broad spectrum of functionalities, and the obtained 2*H*-furan derivatives can be further applied to prepare unique trifluoromethyl-substituted compounds.

Acknowledgement

The authors gratefully acknowledge funding from the National Natural Science Foundation of China (21971112), Jiangsu Province Funds Surface Project (BK 20161541) and the Starting Funding of Research (39837107) from Nanjing Tech University. Dr. Li Yongxing (NTU) is thanked for single crystal X-ray diffraction analysis. Dr. Juha Siitonen and Mr. Stephen Chamness (Rice University) are thanked for proofreading the manuscript.

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