

Synthetic Methods

Iron-Catalyzed Trifluoromethylation of Enamide

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Abstract: Herein the first example of the iron(II)-catalyzed trifluoromethylation of enamide using mild and simple reaction conditions is reported. The method is cost-effective and uses the easy-to-handle Togni's reagent as the electrophilic CF_3 source. This transformation is totally regioselective at the C3 position of enamides and exhibits broad substrate scope, good functional group tolerance and thus demonstrates its useful application in a late-stage fluorination strategy.

Among molecular substituents containing fluorinated moieties, the trifluoromethyl group has unique physical, chemical and biological properties with many applications in the pharmaceutical and agrochemical industries.^[1] Consequently, the development of a new method to form C(sp₃)-CF₃ bonds has recently attracted great attention. Transition-metal-catalyzed trifluoromethylation reactions of alkenes using electrophilic fluoroalkylating reagents have been extensively explored due to the versatility and large scope of this method.^[2,3] The development of a reaction for direct trifluoromethylation in late-stage of synthetic routes is still a great challenge, however. As part of our ongoing research towards developing a new methodology to functionalize C-H bonds of non-aromatic enamide,[4] we focused on iron-catalyzed trifluoromethylation reactions (Figure 1). Iron-catalyzed reactions have recently emerged as a greener alternative to traditional cross-coupling reactions and have been intensively studied due to the high abundance, low cost and low toxicity of iron.^[5] While iron salts have already been identified to perform the trifluoromethylation of alkene,^[6] to our knowledge, the Fe-catalyzed olefinic trifluoromethylation of non-aromatic enamide remains undeveloped^[7] and would constitute a powerful, selective and atom-economic strategy to reach fluorinated aromatic or non-aromatic azaheterocycles, which are still highly required.

At the outset of our study, it was unclear which catalyst or reagent would enable the desired sequence of bond-forming processes. The reaction condition was optimized using six-

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Figure 1. Metal-catalyzed fluorofunctionalization of enamide.

membered cyclic enamide **1a** as a model substrate. Standard screening of solvents, catalysts, temperature, and ratio of reagents established that the optimized conditions were FeCl₂ (10 mol%) as a catalyst in the presence of Togni's reagent **2** (1.2 equiv) in CH₂Cl₂ at only 35 °C (Table 1). Accordingly, we were pleased to isolate enamide **3a** in 84% yield along with a complete β -regioselectivity (entry 1). β -Trifluoromethylated enamides are polyvalent building blocks for bioactive compounds bearing a trifluoromethyl moiety.

Table 1. Optimization of the iron-catalyzed trifluoromethylation of 1 a.						
	$O = \bigvee_{i=1}^{i} \underbrace{Catalyst (10 mol%)}_{CF_3 \text{ source } (1.2 \text{ equiv})} O = \bigvee_{i=1}^{i} \underbrace{CF_3}_{Solvent, 35 °C, 6h} O = \bigvee_{i=1}^{i} \underbrace{CF_3}_{i=1} O = \bigcup_{i=1}^{i} O = $					
Entry	Catalyst	CF ₃ source	Solvent	Yield [%] ^[a]		
1	FeCl ₂	2	DCM	84		
2	FeCl ₂	2	ACN	81		
3	FeCl ₂	2	PEG-200	0		
4 ^[b]	FeCl ₂	2	TPGS-750	11		
5	FeCl ₂	2	glycerol	21		
6	FeCl ₂	2	[BMIM][PF ₆]	43		
7	FeCl ₂	2	NMP	29		
8	none	2	DCM	0		
9 ^[c]	FeCl ₂	2	DCM	77		
10 ^[d]	FeCl ₂	2	DCM	58		
11 ^[e]	FeCl ₂	2	DCM	77		
12	FeCl₂	CF ₃ SO ₂ CI	DCM	59		
13	FeCl ₂	CF ₃ SO ₂ Na	DCM	0		
14	FeCl ₃	2	DCM	39		
15	ferrocene	2	DCM	55		
16	Cu(OAc) ₂	2	DCM	58		
17	Cu₂O	2	DCM	0		
18	CuCl	2	DCM	32		
19	AICI₃	2	DCM	38		
20	Sc(OTf)₃	2	DCM	0		
21	SnCl ₂	2	DCM	65		
22 ^[f]	FeCl ₂	2	DCM	54		
[a] Isolated vield after purification by flash chromatography: [b] 2 wt% of						

[a] Isolated yield after purification by flash chromatography; [b] 2 wt% of TPGS-750M was used; [c] ultrapure FeCl₂ (99.998% based on trace metals, Sigma–Aldrich) was used; [d] 0.9 equiv of Togni's reagent **2** was used; [e] reaction conducted at RT; [f] 2 equiv of K₂CO₃ was used.

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Recently, efforts have been made to perform reactions in greener or more environmentally acceptable media.^[8] Due to their low toxicity and recyclability, polyethylene glycols (PEGs)^[9] or glycerol^[10] have been used as green media for various transformations including homogenous catalysis. Since 2008, Lipshutz et al. have also demonstrated the viability of surfactants to promote transition-metal-catalyzed chemistry in water.^[11] They have shown that polyoxyethanyl- α -tocopheryl succinate (TPGS-750M), a non-ionic amphiphile, allows crosscoupling reactions to be carried out in water by forming nanomicellar reactors. Unfortunately, in our case, the process was ineffective in PEG-200 (entry 3) and led to lower conversion in TPGS-750M (entry 4). Interestingly, [BMIM][PF₆]^[9] was shown to be fully suitable for C-H bond functionalization of enamide using iron catalysis (entry 6). Glycerol (entry 5) and NMP (entry 7), which are both polar protic solvents, were less effective. In addition, no detectable amounts of β -trifluoromethylated product 3a was observed in the absence of metal catalyst (entry 8). The use of ultrapure FeCl₂ resulted in an equally efficient trifluoromethylation of 1, thus suggesting that the catalyst system is iron based (entry 9). Moreover, yield decreased by using a lower amount of the CF₃ electrophilic source (entry 10), by performing the reaction at room temperature (entry 11) or by using CISO₂CF₃ or NaSO₂CF₃ as economic and stable CF₃ sources (entries 12 and 13). Modifying the nature of the iron source was also unsatisfactory (entries 14 and 15). In contrast to Loh's work,^[6] copper salts worked as catalyst but with low to moderate yields (entries 16-18). Considering the Lewis acid character of FeCl₂, we investigated whether product formation may be achieved by using Lewis acid catalysis through the direct formation of a cationic intermediate (Scheme 2, **B**). To validate this hypothesis, $AICI_3$ and $Sc(OTf)_3$ were thus tested without any satisfactory yields (entries 19 and 20). However, an interesting result was obtained by using a catalytic amount of SnCl₂. It is worth noting that to the best of our knowledge, this is the first example of tin(II)-catalyzed trifluoromethylation reaction onto C(sp₂).^[12] As an elimination step may be involved for the formation of enamide 3 a, the addition of an inorganic base (K₂CO₃) was studied, however it did not lead to a significantly improved yield (entry 22). It is noteworthy that in addition to the benefits of cost and the possible use of green solvent, the ortho-iodobenzoic acid residue released during the reaction was easily recycled in a one-pot procedure for preparing again Togni's reagent.^[13]

The scope of the reaction was then extended to a range of enamides which serve as suitable reaction partners, furnishing the desired trifluoromethylated compound in moderate to good yield with a complete β -regioselectivity (Scheme 1). In view of the better results obtained with dichloromethane as solvent it was used here, but with the promising results obtained in our preliminary studies (Table 1), different green solvents could also have been employed. The nature of the electron-withdrawing group onto the nitrogen atom was first investigated leading to the desired trifluoromethylated enamides **3a-f** with high yields. The oxotrifluoromethylated derivative **4a** was isolated in 55% yield as a mixture of diastereoisomers (*cis/trans* 45:55), when the reaction was conducted for only

2 h. This product results from the nucleophilic addition of the released $ArCO_2^-$ (Scheme 2).

A lower yield was observed starting with the seven-membered ring enamides 3g,h. Moreover, the reaction turned out to be compatible with other functional groups which are amenable to further transformation (enaminone 3i). The vinylogous pyridinone compound 3j was isolated albeit in moderate yield. Racemic acetate 3k and chiral diethylester 3l also proved to be applicable in this reaction. In the case of acyclic enamides 3m-p a clean regio- and diastereoselectivity was observed. Their E configuration was confirmed by NOE experiments. Meanwhile, it was found that in the ysatine series, the oxotrifluoromethylated adduct 4q was isolated. In this case, we assume that no elimination step occurred as the electrondonor property of the nitrogen atom lowers the acidity of 4q. A similar result was obtained in the benzoxazine series, leading to the oxotrifluoromethylated adduct 4r isolated as a 3:7 ratio (cis/trans). As expected, when benzopyridoxazine derivative was used as a substrate, no coupling product was obtained (4s), demonstrating the probable complexation of iron with the pyridyl nitrogen atom. The reaction was also performed with NH-indole leading to a mixture of CF₃-indole derivatives 3t at the C2, C3 or C7 positions. No reaction occurred with the deactivated N-SO₂Ph indole, and unfortunately no chemoselectivity was observed for compound 3v. It is worth noting that the nature of the solvent can be advantageously modified by using methanol, as reported in Scheme 1. Compound 5a, isolated with 59% yield as a cis/trans isomer mixture, demonstrates the ability of a potential iminium ion intermediate to react with different nucleophiles. No elimination step was observed. Mixed acetals represent an important class of intermediate that can be further functionalized and give access to diversity.

While the mechanistic details of this iron-catalyzed trifluoromethylation of enamide remains still unclear, we propose that FeCl₂ acts first as a single-electron oxidant, triggering this transformation via a CF₃-alkyl radical (A, Scheme 2) and releasing ortho-iodobenzoate.^[14] To probe this hypothesis, we initiated an investigation in the presence of a catalytic amount (20 mol%) of radical inhibitors or scavengers: TEMPO, benzoquinone or TBHT. In all cases, inhibition of the coupling reaction was observed. A complete inhibition occurred in the presence of TEMPO, and the corresponding TEMPO adduct derived from CF₃ or the proposed CF₃ alkyl radical A was observed which is suggestive of an atom transfer-type radical addition pathway.^[15] Then the iron assists single-electron oxidation of intermediate A leading to the corresponding cation B and its resonance cation C. This process allows the regeneration of the catalyst as initiator. Finally, the nucleophilic attack of the ortho-iodobenzoate anion proceeds with cation C to generate the intermediate 4 as a mixture of cis and trans isomers.

The structure of **4a**-*trans* was unambiguously determined by X-ray analysis (Figure 2).^[16] This hypothesis was confirmed by HRMS analysis and ¹⁹F NMR spectroscopy studies which confirm the formation of the disubstituted compound **4** first, prior to the enamide formation.^[15] We assume that the oxotrifluoromethylated product **4** is then deprotonated by *ortho*-io-

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Scheme 1. Scope of the Fe-catalyzed trifluoromethylation of enamides 1. [a] Oxotrifluoromethylated compound 4 was not isolated unless otherwise specified. [b] Reaction con ducted for 2 h only. [c] Reaction conducted in the presence of methanol as solvent.



Scheme 2. Proposed reaction mechanism

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dobenzoate (ArCO₂⁻) to afford the desired β -CF₃-enamide 3. It is likely that FeCl₂ occurs for the second time in the reaction as a Lewis acid to promote the elimination step. In order to gain insight into energetic and structural properties, ab initio calculations were performed on compound 4a. The optimization at the DFT level of theory^[17] of the four isomer geometries of 4a (mol1 R/R, mol2 S/S, mol3 S/R and mol4 or 4a-trans R/S) provides some information on the relative energies compared to the 4a-trans crystal structure (Figure 2). All four isomers have lower total energy relative to crystal structure, and as attempted, the 4a-cis isomer, formed from cationic intermediate (B or C) via a favored chair transition state, has the lowest energy conformation. Interestingly, during geometry optimization the 4a-cis molecule adopts a conformational change from an initial axial and equatorial position to an equatorial and axial for CF₃ and ArCO₂ substituents, respectively. Importantly, the 4a-cis (mol1) and 4a-trans (mol4) isomers have the lowest total energy compared to other corresponding isomers such as mol2 (S/S cis) and mol3 (S/R trans) respectively. This result suggests a more stable conformation of the 4a-cis (R/R) and 4a-trans (R/S) isomers, which corroborates the proposed reaction mechanism.

For acyclic enamide, the stereochemical outcome of this reaction may be explained by the steric interaction between CF₃ and the amido group, thereby giving the more stable E compound.

In summary, this method is the first example of iron(II)-catalyzed trifluoromethylation of enamide using mild and simple reaction conditions. The method is cost-effective and uses the easy to handle Togni's reagent as the electrophilic CF₃ source. Of importance, greener reaction conditions can also be used to achieve this process. This methodology allows rapid access to a variety of β -trifluoromethylated useful nitrogen-containing building blocks. We are



Figure 2. X-ray structure of 4a-trans.

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continuing work to gain insight into the reaction mechanism and expand the scope of this efficient iron-catalyzed enamide functionalization strategy.

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- [17] See the Supporting Information for computational details.

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The iron age: The first example of the Fe^{II}-catalyzed trifluoromethylation of enamide using mild and simple reaction conditions is reported (see scheme). The

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