Iron-catalyzed benzylic addition of 2-methyl azaarenes to substituted trifluoromethyl ketones

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Abstract: This paper demonstrated a new and economical methodology using $Fe(ClO_4)_2 \cdot H_2O$ as a catalyst for the direct C(sp^3)-H functionalization of 2-methyl azaaarenes via addition to trifluoromethyl ketones. The use of Fe salts as a Lewis acid catalyst has shown great potential as an accessible, affordable and effective catalyst for the reaction. Under mild, optimized conditions, an extensive range of 2-alkenylated azaarenes were produced with yields of up to 95%.

Keywords: C-H functionalization; trifluoromethyl ketones**;** iron-catalyzed, quinalidine, benzylic addition

INTRODUCTION

Over the years, C-H functionalization has remained an area of great interest among the synthetic community as it opens up a multitude of ground-breaking possibilities in expediting organic synthesis routes. In isolation, the ubiquitous C-H bond is apolar and inert[1] but initial developments in C-H functionalization strategies found organometallic routes to be effective in activating C-H bonds[2].Current research continues to be focused on overcoming two of the main challenges of C-H functionalization – controlling site selectivity and enhancing catalytic efficiency[3]. It has been found that directing groups not only trigger the cleavage of the C-H bond but the nature and steric effect of the directing group also plays a key role in determining the regioselectivity of the product[3]. The appeal of directed C-H functionalization lies in its potential to refine traditional synthesis routes and serve as a more efficient and green alternative to cross-coupling reactions[4], which often involve multiple pre-preparation steps and require boron or halide containing compounds. C-H functionalization also presents new schemes of logic for the retrosynthesis of complex molecules[5]. Through these simplified transformation routes, a new class of precursors can be employed for synthesis[6].

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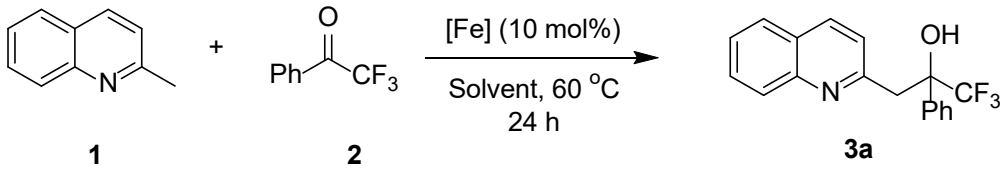
Particularly, the direct C(sp^3)-H functionalization[7] of azaarenes is of great interest due to the prevalence of the moiety in various natural products and pharmaceuticals, such as the drug Montelukast, alkaloid natural products[8] (-)-Angustrureine and (-)-Galipeine as well as the fluorescent probe Quinaldine Red[9]. Through strategies such as late-stage functionalization[10], there is great potential to speed up synthesis processes of such medicinal products as well as discover new effective drugs. The C(sp^3)-H bond in the methyl group of methyl azaarenes has been successfully functionalized via addition to a variety of carbonyl compounds, such as the aldehydes[11], isatins[12] and α-oxoesters[13].

Ketones generally have lower reactivity than aldehydes because they have an additional electron donating group, which not only reduces their partial positive charge on the carbonyl carbon but also contributes to steric hindrance. These factors make it challenging for ketones to undergo nucleophilic addition compared to aldehydes. As a strategy to overcome this problem, Shaikh[14] reported that an electron withdrawing CF_3 moiety adjacent to the reactive carbonyl carbon site was effective in activating the ketonic carbon, allowing for direct benzylic addition. The reaction was conducted in the presence of excess methylazaarenes at a temperature of up to 110 °C using the lanthanide salt $Yb(OTf)_3$ as a catalyst for the addition reaction. However, the drawbacks of the reaction were the use of expensive rare metal catalysts and the rather high temperature requirement. In this context, we have reported a practical and convenient strategy for the benzylic addition of azaarenes to trifluoromethyl ketone using $InCl_3$ under mild condition[15]. Based on this precedent, we observed that the reaction can also be catalyzed by 10 mol% $FeCl_3$ catalyst in THF at 60 °C (Table 1, entry 1). Iron salts are inexpensive, relatively less toxic and, in consequence more environmentally benign in comparison to other transition metals. $Fe(OAc)_2$ has previously been used as a Lewis acid catalyst in several C(sp^3)-H functionalization reactions, including the addition of methyl azaarenes to α-oxoesters[13] and to aldimines[16]. Moreover, the application of Fe salts as Lewis acid for C-H functionalization[17] still remains limited. Encouraged with this initial result, we decided to venture into broadening the scope for the benzylic addition of azaarenes to trifluoromethyl ketone using Fe salts as catalysts which has yet to be reported.

RESULTS AND DISCUSSION

In our initial study, quinalidine **1** and 2,2,2-trifluoroacetophenone **2** were used as model substrates for the C-H functionalization reaction. The reaction was carried out using 2,2,2-trifluoroacetophenone (1 equiv), Quinaldine (2.5 equiv), Fe salt (10 mol%) in 0.5 mL THF at 60 °C for 24 hours. The results are shown in Table 1.

Table 1. Optimization studies of Fe-catalyzed C-H functionalization of Quinaldine and 2,2,2-Trifluoroacetophenone[a]



1 **2** **3a**

Entry	[Fe] source	Solvent	Yield[b] (%)
1	$FeCl_3$	THF	90[14]
2	$FeBr_3$	THF	86
3	$Fe(acac)_3$	THF	Trace
4	$Fe_2(C_2O_4)_3 \cdot 6H_2O$	THF	57
5	Fe_2O_3	THF	Trace
6	$Fe(acac)_2$	THF	62
7	$Fe(OAc)_2$	THF	87
8	$Fe(ClO_4)_2 \cdot H_2O$	THF	93
9	$Fe(ClO_4)_2 \cdot H_2O$	Dioxane	89
10	$Fe(ClO_4)_2 \cdot H_2O$	t-BuOH	91
11	$Fe(ClO_4)_2 \cdot H_2O$	DCE	72
12	$Fe(ClO_4)_2 \cdot H_2O$	DCM	70
13	$Fe(ClO_4)_2 \cdot H_2O$	DMSO	97
14	$Fe(ClO_4)_2 \cdot H_2O$	DMF	95
15	$Fe(ClO_4)_2 \cdot H_2O$	Toluene	60
16	$Fe(ClO_4)_2 \cdot H_2O$	Water	89
17	$Fe(ClO_4)_2 \cdot H_2O$	DMSO	95[c]
18	$Fe(ClO_4)_2 \cdot H_2O$	DMSO	87[d]
19	$Fe(ClO_4)_2 \cdot H_2O$	DMSO	28[e]
20	$Fe(ClO_4)_2 \cdot H_2O$	DMSO	93[f]

[a] General reaction conditions: Quinaldine (2.5 equiv.), 2,2,2-trifluoroacetophenone (0.5 mmol), [Fe salt] (10 mol%), solvent (0.5 mL), 60°C, 24 h.
[b] Isolated yield after column chromatography
[c] $Fe(ClO_4)_2 \cdot H_2O$ (5.0 mol %).
[d] $Fe(ClO_4)_2 \cdot H_2O$ (5 mol %), 40°C.
[e] $Fe(ClO_4)_2 \cdot H_2O$ (5 mol %), R.T.
[f] $Fe(ClO_4)_2 \cdot H_2O$ (5 mol %) with Quinaldine (1.5 equiv.).

In the first stage, the catalytic efficiency of eight iron salts were tested and compared. $Fe(ClO_4)_2 \cdot H_2O$ was found to be the most effective catalyst, giving the alkenylated product in the highest yield of 93% (Table 1, entry 8). $FeCl_3$, $FeBr_3$, $Fe(OAc)_2$ also gave the alkenylated product in good yield, ranging from 84% to 90% (entries 1, 2 and 7). The remaining Fe salts were not effective, giving moderate to poor yields of the product (entries 3 to 6).

Proceeding to the second stage with $Fe(ClO_4)_2 \cdot H_2O$ as the chosen catalyst, a variety of solvents were screened. Polar aprotic solvent DMSO afforded the alkenylated product in the highest yield of 97% (entry 13). Similarly, other polar aprotic solvents such as DMF, THF, Dioxane, DCE and DCM worked well with good yields ranging from 70% to 95% (entries 8, 9, 11, 12 and 14). A representative polar protic solvent, t-BuOH, was also explored which gave an excellent yield of 91% yield (entry 10). It is remarkable to highlight that the reaction can also proceed well using water as the sole solvent which afforded the product with an excellent yield of 89% (entry 16). The only solvent that performed relatively poorly was toluene, a non-polar solvent, which afforded a yield of only 60%, perhaps suggesting the importance of a polar medium for the reagents to dissolve and the reaction to proceed.

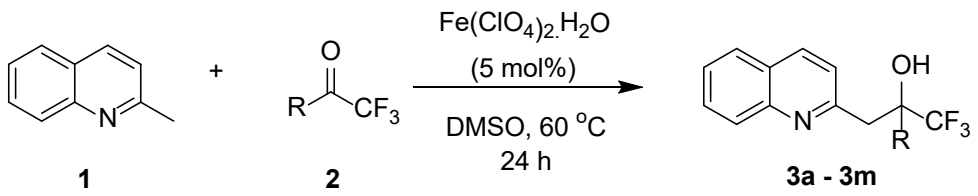
The next stage involved the reduction of $Fe(ClO_4)_2 \cdot H_2O$ catalyst loading from 10 mol% to 5 mol%, an important step in ensuring maximum cost effectiveness. It was noted that even at 5 mol% $Fe(ClO_4)_2 \cdot H_2O$ catalyst loading, the yield was still excellent at 95% (entry 17).

Finally, it was found that lowering the reaction temperature from 60°C to 40°C and ambient room temperature caused the yield to be significantly compromised, with it decreasing from 95% to 87% and 28%, respectively (entries 17 to 19). On the other hand, scaling down the amount of quinaldine substrate used in excess from 2.5 equivalents to 1.5 equivalents did not drastically affect the yield, with 93% yield still being afforded at the end of the reaction (entry 20).

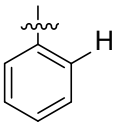
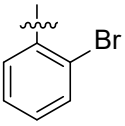
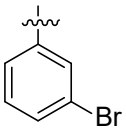
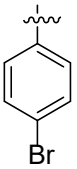
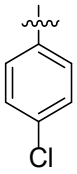
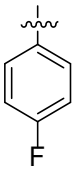
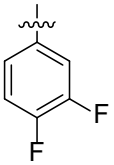
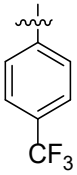
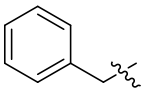
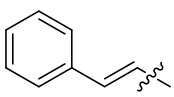
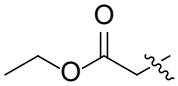
Therefore, the overall optimised conditions for the C-H functionalization reaction between Quinaldine and 2,2,2-Trifluoroacetophenone were decided to be $Fe(ClO_4)_2 \cdot H_2O$ (5 mol%) in DMSO at 60°C, with 1.5 equivalents of Quinaldine in excess. These conditions afforded an excellent yield of 93% (entry 20).

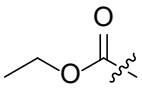
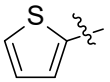
With the above optimized conditions at hand, a range of trifluoromethyl ketones were then reacted with quinaldine to test the generality of the system. The results are reported in Table 2.

Table 2. C-H functionalization of quinaldine with a range of trifluoromethyl ketones catalyzed by $Fe(ClO4)_2 \cdot H_2O$ in DMSO[a]



1 **2** **3a - 3m**

Entry	R	Product	Yield[b] (%)
1		**3a**	93
2		**3b**	73
3		**3c**	87
4		**3d**	95
5		**3e**	91
6		**3f**	74
7		**3g**	85
8		**3h**	92
9		**3i**	63
10		**3j**	68
11		**3k**	50

12		**3l**	60
13		**3m**	94

[a] General reaction conditions: Quinalidine (1.5 equiv), trifluromethyl ketone (0.5 mmol), $Fe(ClO_4)_2 \cdot H_2O$ (5 mol%), DMSO (0.5 mL), 60 °C, 24 h.

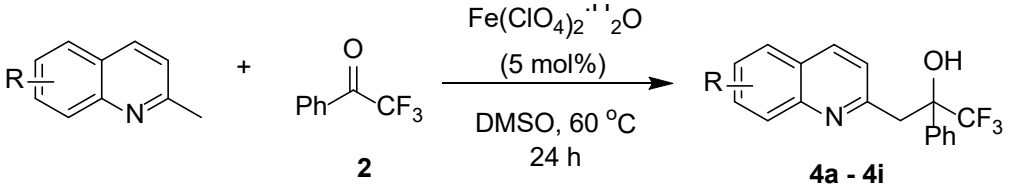
[b] Isolated yield after column chromatography.

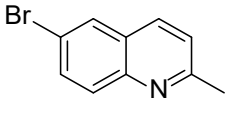
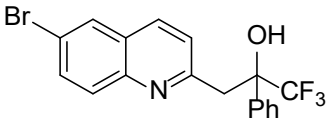
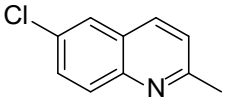
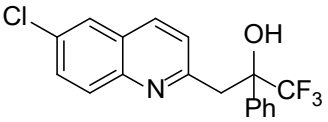
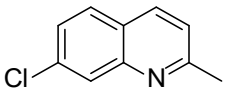
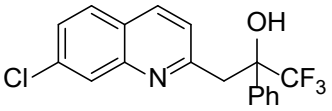
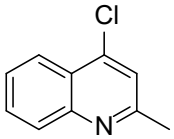
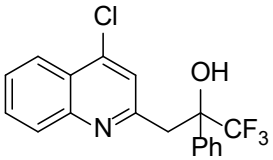
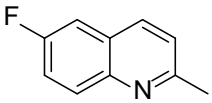
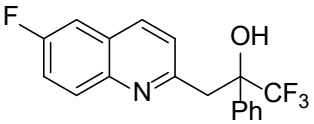
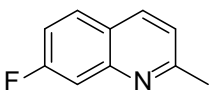
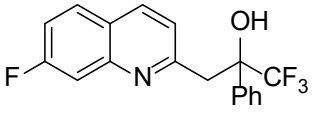
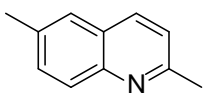
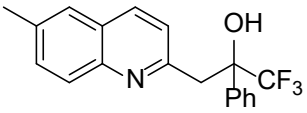
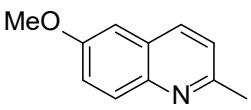
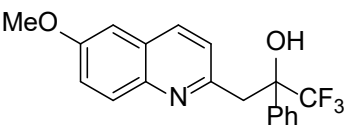
In this study, a series of Br-, Cl- and F-substituted trifluroacetophenones were reacted with quinalidine under the optimized conditions to broaden the reaction scope. Although all the reactions afforded reasonably good yields from 73% to 95% (Table 2, entries 1 to 5), there appeared to be a corresponding trend between the position of the electron-withdrawing halogen substituent on the aromatic ring and the resultant yield. Specifically, the para position was most favourable – moving the Br substituent from ortho to meta to para position on the aromatic ring resulted in the yield increasing from 73% to 87% to 95%, respectively (Table 2, entries 1 to 3). Similarly, the Cl substituent in the para position of the aromatic ring gave an excellent yield of 91% (Table 2, entry 4). Only the F substituent in the para position did not have the same effect on the reaction, with a comparably lower yield of 74% (Table 2, entry 5). The favourability of the para position may suggest that steric hindrance near the reactive carbonyl carbon may impede the reaction. Having two F substituents at the meta and para positions of the aromatic ring of trifluroacetophenone did however raise the yield to 85% (Table 2, entry 6), which may indicate that the presence of an additional electronegative F atom was able to further activate the carbonyl carbon towards nucleophilic attack. This effect is further corroborated by the reaction using the next substrate, trifluroacetophenone with an electron-withdrawing CF_3 substituent at the para position of the aromatic ring, which gave an excellent yield of 92% (Table 2, entry 7).

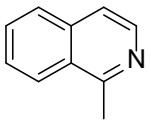
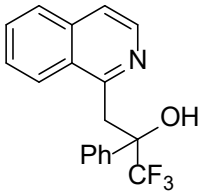
The scope of substrates was expanded to trifluoromethyl ketones with substituents of different electronic properties (Table 2, entries 8 to 12). The electron-donating 3-phenyl substituent (Table 2, entry 8) appeared to stabilize instead of activate the carbonyl carbon and thus the yield was significantly lower than before at 63%. The yield was slightly raised to 68% (Table 2, entry 9) with a conjugated phenyl substituent (Table 2, entry 9), whereby the compound was pre-synthesised[14] and then further reacted with quinaldine. Comparing the reactions using ethyl 4,4,4-trifluoroacetoacetate (Table 2, entry 10) and ethyl 3,3,3-trifluoropyruvate (Table 2, entry 11), the electron withdrawing effect of the C=O bond of the ester group was stronger in the latter due to its proximity to the reactive carbonyl carbon, thus activating the carbonyl carbon to a greater extent. Thus, the latter had a higher yield of 60% (Table 2, entry 11) compared to the former with a yield of 50% (Table 2, entry 10). It is also interesting to note that the substrate with an electrophilic thiophene substituent directly bonded to the reactive carbonyl carbon produced an excellent yield of 94% (Table 2, entry 12).

Under the same optimized conditions, a range of 2-methyl azaarenes were then reacted with 2,2,2-trifluoroacetophenone to further broaden the substrate scope of the catalytic system. The resulting experimental yields are reported in Table 3.

Table 3. C-H functionalization of a range of 2-methyl azaarenes with 2,2,2-trifluoroacetophenone catalyzed by $Fe(ClO_4)_2 \cdot H_2O$ in DMSO[a]



Entry	Amine	Product		Yield[b] (%)
1			**4a**	41
2			**4b**	50
3			**4c**	30
4			**4d**	71
5			**4e**	44
6			**4F**	42
7			**4g**	82
8			**4h**	38

9			**4i**	95

[a] General reaction conditions: 2-Methylazaarene (1.5 equiv), 2,2,2-trifluoroacetophenone (0.5 mmol), $Fe(ClO_4)_2 \cdot H_2O$ (5 mol%), DMSO (0.5 mL), 60 ºC, 24 h..

[b] Isolated yield after column chromatography.

In this section, several Br-, Cl- and F-substituted quinalidines (Table 3, entries 1 to 6). were reacted with 2,2,2-trifluoroacetophenone, with the halogen atom bonded to different positions on the aromatic ring. Across the board, the C6 and C7 positions were found to be less favourable than the C4 position, resulting in low yields ranging from 30% to 50% (Table 3, entries 1, 2, 3, 5 and 6). Only the Cl atom in the C4 position gave a good yield of 71% (Table 3, entry 4). Between the C6 and C7 position, both the Cl- and F-substituted quinaldines afforded better yields at the C6 position. The effect of electron donating substituent on the quinoline was also investigated. Interestingly, at the same C6 position, a weakly donating methyl substituent gave a much higher yield of 82% (Table 3, entry 7) compared to 38% when a strongly donating OMe substituent was used (Table 3, entry 8). In addition, 1-methyl isoquinoline, an isomer of 2-methylquinoline (Quinaldine), was just as effective as its counterpart, bringing in an excellent yield of 95% (Table 3, entry 9), suggesting feasibility of reaction using other substituted 1-methyl isoquinolines. Other monocyclic azaarenes, such as 2-methylpyridine and 2,6 lutidine, provided negligible returns in yield. Similarly, quinolines with substituents at the C8 position and 2-methylquinoxaline produced trace amounts of the product.

EXPERIMENTAL

General Procedure

0.75 mmol of quinalidine (1.5 equiv), 0.5 mmol 2,2,2-trifluroacetophenone (1.0 equiv), 0.025 mmol of $Fe(ClO_4)_2 \cdot H_2O$ (5 mol%) and 0.5 mL of DMSO were added to an 8-mL reaction vial containing a magnetic stir bar and a screw cap was fitted to it. The reaction vial was immersed in a preheated 60˚C oil bath and the mixture was stirred in a closed system for 24 hours. After 24 hours, the heterogeneous mixture was cooled to room temperature and dichloromethane was added into the vial to dilute the mixture. Using vacuum filtration, the mixture was then filtered through a pad of Celite. The vial was washed with 5 x 8mL of dichloromethane and the washings from each time were filtered through the Celite as well. Anhydrous Na_2SO_4 was added to the collected filtrate to remove any water from the organic extracts and the solvent was then removed by rotary evaporation under reduced pressure. Thereafter, the crude product was purified by silica-gel flash column chromatography (hexane:ethyl acetate) to afford the intended addition product. The identity and purity of the product were confirmed by ^1H NMR, ^{13}C spectroscopic analysis and elemental analysis.

1,1,1-trifluoro-2-phenyl-3-(quinolin-2-yl)propan-2-ol (3a)

White solid (93 %, 148.9 mg); m.p.104.2 – 104.6 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (d, *J* = 14.8 Hz, 1H), 3.79 (d, *J* = 14.8 Hz, 1H), 7.22 – 7.31 (m, 4H), 7.49 – 7.53 (m, 1H), 7.68 – 7.76 (m, 4H), 7.97 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.48 (bs, 1H)

^{13}C NMR (100MHz, CD_3OD): δ 42.3, 78.7 (q, *J* = 30.0 Hz), 122.8 (overlapping q signal), 124.2, 125.6 (overlapping q signal), 127.8, 128.2, 128.4, 129.0, 129.1, 129.2, 129.4, 131.2, 138.3, 139.2, 147.8, 159.1

Analytical Calculated for $C_{18}H_{14}F_3NO$: C, 68.13; H, 4.45; N, 4.41. Found: C, 68.28; H, 4.51; N, 4.49.

All spectral data correspond to those given in the literature.[14, 15]

CONCLUSION

In summary, a new Fe catalytic system has been successfully developed for the C-H functionalization of 2-methylazaarenes via addition to trifluoromethyl ketones. The yields obtained for the benzylic addition of quinaldine to substituted trifluoromethyl ketones were comparable to those obtained using the indium catalytic system. The affordability and sustainability of Fe salts as catalysts poses a great advantage and the exploration of trifluoromethyl ketones is a significant step towards widening the scope of substrates to be used for future research.

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Supporting Information: Full experimental detail, ^{1}H and ^{13}C NMR spectra and elemental analysis. This material can be found via the "Supplementary Content" section of this article's webpage.'

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