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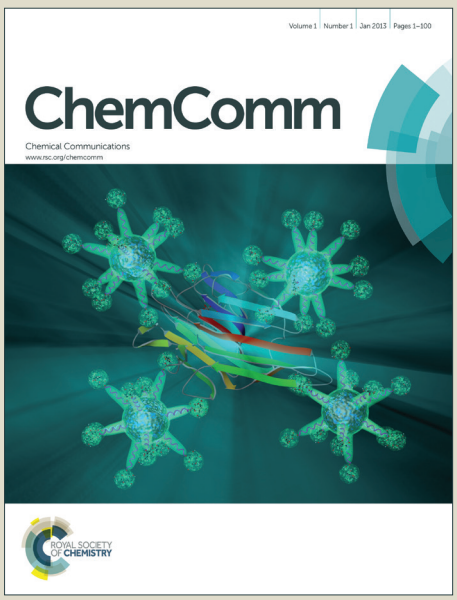

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Iron-Catalyzed Direct α-Arylation of Ethers with Azoles

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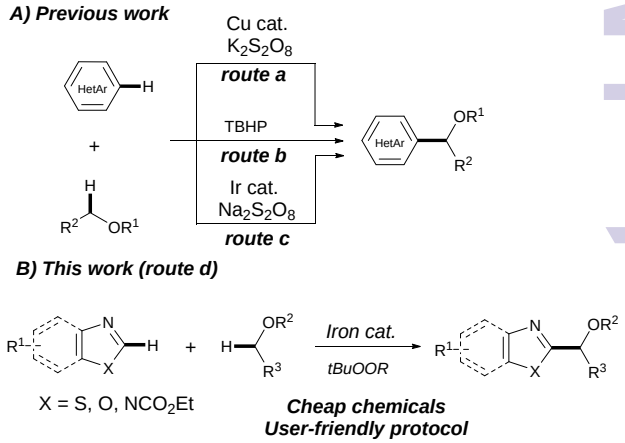
The direct α-arylation of cyclic and acyclic ethers with azoles has been achieved featuring a novel iron-catalyzed cross-dehydrogenative coupling (CDC) process. This practical oxidative method allowed the efficient C2-alkylation of a variety of (benzo)azoles constituting a straightforward access to heterocycles of utmost medicinal significance and highlighting the convenient use of feedstock substrates and iron catalysis. Preliminary mechanism supported by DFT calculations is discussed as well.

Since the end of the last century sustainable development constitutes a matter of genuine concern for our society and scientific community. As a result, "Green Chemistry" represents one of the key factors for scientists when designing new chemical processes.[1] In this respect, the use of ethers such as tetrahydrofuran (THF) and related derivatives as important raw chemicals for the construction of more complex molecules of pharmaceutical interest has recently received a great deal of attention.[2] Indeed, direct functionalization of molecules containing C(sp^3)–H bonds stands out today as one of the most challenging and relevant areas in modern organic chemistry offering numerous attractive advantages such as reducing the reliance on existing functional groups while improving atom economy and energy efficiency.[3] The last years have witnessed a blooming of the Cross-Dehydrogenative Couplings (CDCs) involving the use of catalytic amounts of first-row transition metals.[4] Based on their low-price, readily availability, and environmentally friendly character iron salts[5] constitute potentially ideal catalysts which offer attractive advantages in this particular area of expertise. Despite the impressive achievements, the assembly of new C–C linkages based upon iron-catalyzed C(sp^3)–H functionalization events are still rare in the literature.[6]

Azoles are prevalent key motifs in a myriad of biologically active compounds, agrochemicals and organic functional materials such as liquid crystals and fluorescent dyes.[7] Accordingly, C–H functionalization of azoles is an active area of research which provides simple and rapid access to a plethora of valuable functionalized heterocyclic cores. Whereas arylation, alkenylation, alkynylation and amination processes of azole derivatives have been widely explored,[8] the direct alkylation stills represents a challenge.[9] *N*-Tosylhydrazones[10] and carboxylic acids[11] are among the most common coupling partners to perform C2-alkylation reactions of azoles. Nevertheless, the most straightforward and convenient approach involves the use of non-functionalized ethers via the addition of *in situ* generated α-oxyalkyl radical species to heteroarenes generally referred as the Minisci reaction.[12] Such processes are of prime importance within medicinal chemistry and have been accomplished with both copper[13a] and photoredox iridium catalyst[13b] and even under metal-free conditions.[13c] While efficient and elegant procedures, they still suffer from certain limitations such as the restricted use of (benzo)thiazoles (*route a*), isoquinolines and pyridines (*route c*) or harsh reaction conditions like using 4.0 equiv. of oxidant at high temperatures (*route b*). In this context, we envisioned whether the use of iron salts would facilitate the development of a complementary and advantageous strategy for the C2-alkylation of azoles with a relatively broader scope and operational simplicity. In fact, iron complexes are known to react with alkyl peroxides to generate organic radical species



Scheme 1 Direct α-arylation of cyclic and acyclic ethers with azoles.

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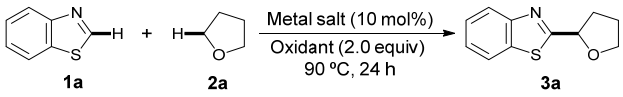
Table 1 Optimization of reaction conditions for the iron-catalyzed CDC of **1a** with THF.[a,b]



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

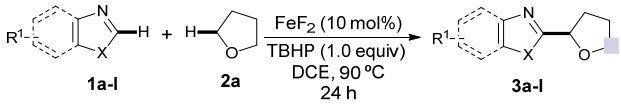
Entry	Metal salt	Oxidant	**3a** (%)[b]
1	FeF_2	$K_2S_2O_8$	0
2	FeF_2	DDQ	0
3	FeF_2	cumene hydroperoxide	0
4	FeF_2	dicumyl peroxide	0
5	FeF_2	*t*BuOO*t*Bu	traces
6	FeF_2	*t*BuOOBz	51
7	FeF_2	TBHP	62
8	FeF_2	TBHP aq	41
9	$FeCl_2$	TBHP	traces
10	$Fe(OAc)_2$	TBHP	43
11	$Fe(acac)_3$	TBHP	38
12	FeF_3	TBHP	61
13	CoF_2	TBHP	47
14	CuF_2	TBHP	29
15	none	TBHP	9
16	FeF_2	none	0
17	***FeF_2***	***TBHP***	***80[c] (62)[c,d]***
18	FeF_2	TBHP	60[c,e]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mL), metal salt (10 mol%), oxidant (2.0 equiv) at 90 ºC for 24 h under argon. [b] Yield of isolated product after column chromatography. [c] TBHP (1.0 equiv) using **2a** (0.5 mL) in 1,2-dichloroethane (0.5 mL). [d] under air. [e] 80 ºC. TBHP = *tert*-butyl hydroperoxide (5.0-6.0 M in decane); TBHP aq = 70 wt% *t*BuOOH in H_2O.

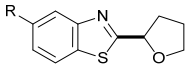
which can further act as powerful oxidizing agents.[14] Herein we describe a novel CDC of (benzo)azoles and ethers featuring the efficient use of a combination of FeF_2 and organic peroxides as oxidant.

We initially selected the direct coupling of benzothiazole (**1a**) and tetrahydrofuran (THF, **2a**) as the model system to evaluate the feasibility of our approach. We anticipated that the nature of the metal source and oxidant would have a profound impact on reactivity and accordingly the effect of such variables was systematically examined.[15] To our delight, the target CDC event took place in a remarkable 51% yield when utilizing a combination of FeF_2 and *tert*-butyl peroxybenzoate at 90 ºC (Table 1, entry 6). Further screening of the oxidants clearly revealed that TBHP was the best choice while other common oxidants were much less effective (Table 1, entries 1-8). It is worth noting that the process was found compatible with the use of an aqueous solution of TBHP, albeit the product was obtained in comparatively lower yield (entry 8). Importantly, the catalytic activity was highly dependent of the counteranion and the use of other fluoride salts seemed to have a crucial effect on the reaction outcome. FeF_3 was found as efficient as FeF_2 (entry 12), but other iron sources (entries 9-11) as well as other fluoride metal salts (entries 13-14) provided lower yields.[15] Remarkably, the yield was dramatically improved when reducing the amount of THF and adding 1,2-dichloroethane as co-solvent. Under those conditions the amount of oxidant could be importantly reduced to 1.0 equivalent and **3a** was obtained in 80 % yield (entry 17). The performance of the process under air atmosphere was detrimental for the reaction, although **3a** was obtained in 62% yield. The addition of other additives or variation of the temperature was found ineffective to improve the catalyst performance.[15-16] Additionally, several control experiments

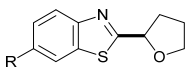
Table 2 Iron-catalyzed CDC of azoles **1a-l** with THF.[a,b]



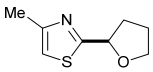
1a-l **2a** **3a-l**



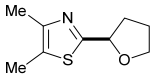
80% (R = H, **3a**)
54% (R = Br, **3b**)



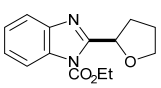
63%[c] (R = CO_2*t*Bu, **3c**)
78%[c] (R = NHBz, **3d**)
51%[c] (R = F, **3e**)
65%[c] (R = OMe, **3f**)



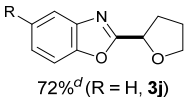
53%[c] (**3g**)



55% (**3h**)



51% (**3i**)



72%[d] (R = H, **3j**)
65%[d] (R = Me, **3k**)
60%[d] (R = Cl, **3l**)

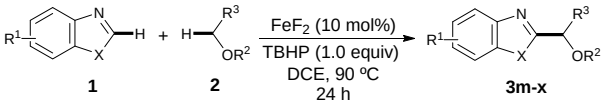
[a] Reaction conditions: **1** (0.5 mmol), FeF_2 (10 mol%), TBHP (1.0 equiv, 5.0-6.0 M in decane) in a mixture **2a**:DCE (1:1, 1.0 mL) at 90 ºC for 24 h under argon. [b] Yield of isolated product after column chromatography, average of at least two independent runs. [c] TBHP (2.0 equiv) using **2a** (1.0 mL). [d] *t*BuOOBz (2.0 equiv) using **2a** (1.0 mL).

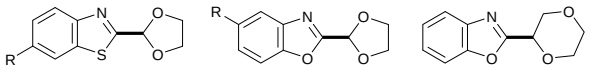
evidenced that both iron catalyst and peroxide were critical for success (Table 1, entries 15-16).

Having identified the optimal reaction conditions, we next focused on examining the preparative scope and generality of our iron catalyzed direct arylation event. As shown for **3a-f**, moderate to good yields were obtained when differently substituted benzothiazoles were utilized. Noteworthy, electron-deficient derivatives provided lower yields since full conversion was not achieved. Importantly, several functional groups were accommodated such as ester (**3c**), amide (**3d**), halides (**3b**, **3e**), and ethers (**3f**). Strikingly, strongly coordinating nitrogen motif in **3d** did not interfere in the coupling, which reveals a low Lewis acidity, if any, of our catalyst system. Of particular importance is the compatibility with the presence of halides which provides additional functionalization opportunities via cross-coupling techniques. Notably, the method was found applicable to the use of non-benzofused thiazoles (**3g-h**) and benzimidazoles (**3i**), albeit the products were obtained in moderate yields. When benzoxazole derivatives were submitted to the optimized conditions, the desired products were not detected. Gratifyingly, minor modifications of the reaction conditions such as replacing the use of TBHP by *tert*-butyl peroxybenzoate allowed for the efficient coupling of several benzoxazoles (**3j-l**).[17] In these cases, less basic benzoate species are generated by homolytic cleavage of the oxidant and hence the corresponding coupling product can be satisfactorily obtained,[18] a significant improvement comparing to the parent Cu-catalyzed process.[13a]

Aside from THF, other related cyclic and acyclic ethers are commonly used as solvents in chemical processes as well as prevalent key structures in a wide range of valuable compounds. Of particular interest is 1,3-dioxolane given that its coupling would provide a masked formyl derivative through a practical and aldehyde-free synthetic protocol. Accordingly, we next explored the scope of our iron-catalyzed heteroarylation process regarding the ether coupling partner. As shown in Table 3, a wide variety

Table 3 Iron-catalyzed CDC of azoles with other ethers.[a,b]

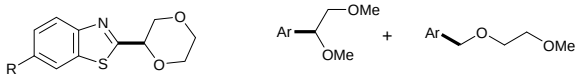




82% (9:1)[c] (R = H, **3m**)
72% (R = NHBz, **3n**)
64% (R = CO_2*t*Bu **3o**)
76% (9:1)[c,d] (R = F, **3p**)

72% (85:15)[c,e] (R = H, **3q**)
63% (85:15)[c,e] (R = Me, **3r**)
62% (6:4)[c,e] (R = Cl, **3s**)

77%[e] (**3t**)

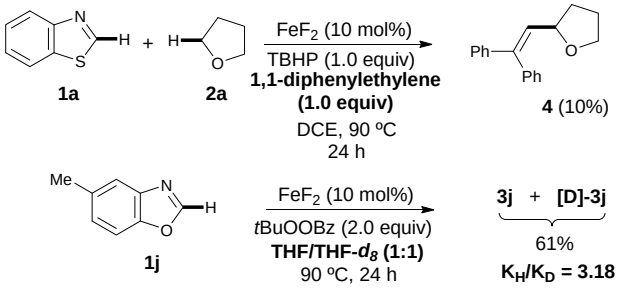


59%[d] (R = H, **3u**)
51%[d] (R = OMe, **3v**)

74% (7:3)[e] (Ar = benzothiazole, **3w:3w'**)
63% (8:2)[e] (Ar = 6-fluorobenzothiazole, **3x:3x'**)

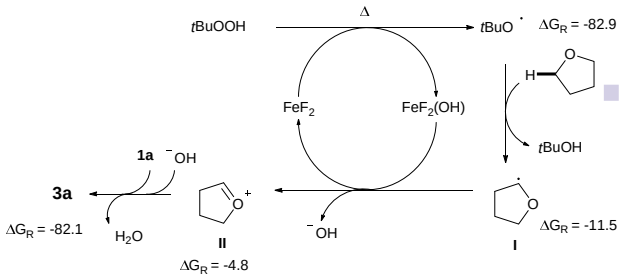
[a] Reaction conditions: **1** (0.5 mmol), FeF_2 (10 mol%), TBHP (1.0 equiv, 5.0-6.0 M in decane) in a mixture **2a**:DCE (1:1,1.0 mL) at 90 ºC for 24 h under argon. [b] Yield of isolated product after column chromatography, average of at least two independent runs. [c] Ratio of C2 *vs* C4 isomer. [d] TBHP (2.0 equiv) using **2** (1.0 mL). [e] *t*BuOOBz (2.0 equiv) using **2** (1.0 mL).

differently substituted benzothiazoles and benzoxazoles smoothly underwent the coupling with 1,3-dioxolane to afford the corresponding acetal derivatives in good yields (**3m-s**). Remarkably, 1,3-dioxolane reacted selectively at C2 position versus the less reactive C4 atom providing **3n** and **3o** as a single isomer. However, in most cases both isomers were detected with high regioselectivity (up to 9:1); whereas the products **3m** and **3p** bearing benzothiazole core were easily separated by column chromatography, benzoxazole derivatives **3q-3s** were isolated as inseparable mixtures of both isomers (regioselectivity up to 85:15 determined by ^{1}H NMR spectroscopy). Interestingly, 1,4-dioxane could also be utilized to furnish the corresponding coupling products in moderate to good yields (**3t-v**). Noteworthy, the acyclic ether 1,2-dimethoxyethane also underwent the target reaction at both the methylene and methyl sites with good combined yields and high regioselectivities (up to 8:2; **3w:3w'** and **3x:3x'**). Unfortunately, other coupling partners such as dibutyl ether and ethanol or less acidic heterocycles such as 1,2,3-triazoles and indole were found unreactive under our optimized conditions.



Scheme 2 Control experiments.

Although a detailed mechanistic picture clearly requires further studies, several control experiments as well as DFT studies[15,19] were performed to gain some insights into the reaction mechanism. The CDC event was entirely suppressed upon addition of radical scavengers such as BHT and 1,1-diphenylethylene; interestingly, in the latter case the coupling product **4** was isolated instead in 10% yield.[20] Besides, the addition of TEMPO results in very low



Scheme 3 Proposed mechanism

conversion of the azole and just traces of the product were detected. These experimental evidences tentatively support a radical pathway. Notably, subsequent competition experiments with benzoxazole **1j** utilizing an equimolecular mixture of THF/THF-d_8 showed a significant kinetic isotopic effect (k_H/k_D = 3.18) thus suggesting that the C(sp^3)–H bond cleavage with concomitant formation of an α-oxyalkyl radical is likely the rate-determining step. In order to clarify the role of the iron catalyst, Sc(OTf)$_3$, Bi(OTf)$_3$ and $AlCl_3$ were used instead and the coupling product **3a** was obtained in much lower yields; hence FeF_2 is unlikely acting as a simple Lewis acid.[15,21] Based on the above results, a plausible mechanism supported by DFT studies is outlined in scheme 3. Initially, FeF_2 facilitates the homolytic cleavage of the starting oxidant to form the hydroxyde and *tert*-butoxy radical species under heating conditions.[6b,22] Computational data confirm that the homolytic cleavage of *t*BuOOH is a highly endergonic process, with an uphill Gibbs Free energy of 5.1 kcal/mol and Fe catalyst helps stabilizing the arising radical species by formation of a very stable Fe(III) complex, which lies ca. 80 kcal/mol lower in energy than the starting reactants. Next, the C(sp^3)–H adjacent to the oxygen atom of THF can be abstracted by *tert*-butoxy radical species to furnish **I** with an activation energy of only 12.5 kcal/mol,[23] and further oxidized through a SET event to the corresponding oxonium cation **II** by FeF_2(OH), lying ca. 5 kcal/mol lower in energy than the sum of the starting Fe(III) complex and radical species.[24] Finally, the hydroxyde anion is basic enough to easily deprotonate the azole **1a** with a low activation energy of only 2.6 kcal/mol, which eventually reacts with oxonium ion **II** through an extremely favorable process (ΔG_R = -82.1 Kcal/mol).[25] On balance then, we assume that FeF_2 plays a key redox role to assist both the heterolytic cleavage of the oxidant and the oxidation of the carbon radical **I** to oxonium ion **II**.

In summary, we have developed a novel catalytic approach to the direct α-heteroarylation of cyclic and acyclic ethers with azoles. This practical and environmentally friendly protocol highlights the advantageous use of iron salts and cheap feedstock substrates while featuring a dual C–H bond oxidative cross-coupling. Furthermore, the method was found applicable to the assembly of a wide variety of functionalized heterocycles of paramount medicinal importance and represents an attractive, yet complementary, strategy for the C–H alkylation of azoles. We anticipate that our experimental and computational studies could lead to new knowledge in catalyst design, thus opening up new vistas in iron-catalyzed C–H functionalization events.

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15 For more details see the supporting information.

16 All attempts to use iodide sources such as tetrabutylammonium iodide, sodium iodide or potassium iodide were unsuccessful. Besides, the addition of supporting ligands such as DMEDA, TMEDA or phen was detrimental for the catalyst performance.

17 This distinct reactivity profile of benzothiazole *vs* benzoxazole could be attributed to the higher acidity of the latter and its tendency to open up under basic conditions.

18 When using *t*BuOOBz as oxidant, benzoic acid was observed as side-product, which was easily eliminated upon basic workup of the reaction crude prior to chromatographic purification.

19 DFT studies were carried out using the M06 functional as implemented in Gaussian 09 and the 6-311++G** basis set (SDD for Fe).

20 Compound **4** has been previously isolated in other processes involving the formation of radical species, see: (*a*) R. [illegible] Pandit and Y. R. Lee, *Adv. Synth. Catal.*, 2014, **356**, 3171; (*b*) Ref. 2c. For selected CDC events between olefins and C(sp^3)–H bonds, see: (*c*) K. Cheng, L. Huang and Y. Zhang, *Org. Lett.*, 2009, **11**, 2908; (*d*) G. Majji, S. Guin, S. K. Rout, A. Behera and B. K. Patel, *Chem. Commun.*, 2014, **50**, 12193; (*e*) D. Liu, C. Liu, H. Li and A. Lei, *Chem. Commun.*, 2014, **50**, 3623; (*f*) Y. Zhu and Y. Wei, *Chem. Sci.*, 2014, **5**, 2379.

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23 Radical **I** will be probably involved in an equilibrium between its free form and a Fe(III)-O*t*Bu complex by combination with the Fe(II) catalyst, thus compromising the availability of the free radical. See Ref. 15.

24 Computational data confirm the experimentally observed distinct reactivity profile of $FeCl_2$ and FeF_2. Whereas FeCl$_2$ could also facilitate the homolytic cleavage of *t*BuOOH through a favourable process (ΔG_R = -111.1 Kcal/mol), the subsequent oxidation of intermediate **I** to oxonium ion **II** remains a rather unfavourable pathway when using $FeCl_2$ (ΔG_R = 47.0 Kcal/mol).

25 At this stage the intermediacy of a radical into the azole derivative and subsequent C–C bond formation through termination of such species and intermediate **I** cannot be entirely ruled out. However, it remains unlikely given the fact that bisheteroaryl compound resulting from the corresponding homocoupling was never detected.