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Radical C−H Arylation of Oxazoles with Aryl Iodides: dppf as an Electron-Transfer Mediator for Cs_2CO_3

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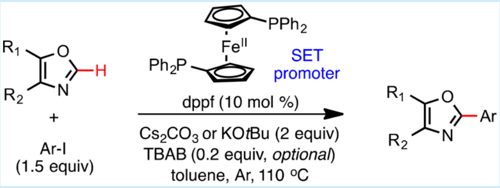
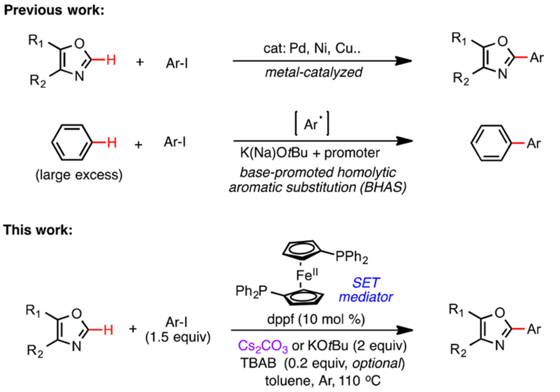
Supporting Information

ABSTRACT: A radical C−H arylation reaction of oxazoles with (hetero)aryl iodides using Cs_2CO_3 as base/electron donor and 1,1′-bis(diphenylphosphino) ferrocene (dppf) as a catalytic SET mediator is reported. The overall reaction likely follows the general base-promoted homolytic aromatic substitution mechanism through a radical-chain pathway. DFT calculations suggest that dppf forms a complex with $CsCO_3^-$, enhancing its SET reducing ability to generate an aryl radical from ArI.



Aryl- and heteroaryl-substituted oxazole motifs are widely found in natural products and drugs.[1] Over the past decade, significant progress has been made toward developing transition-metal-catalyzed C−H arylation reactions of simple oxazoles.[2−4] More recently, radical-mediated C−H arylation reactions that do not require transition metals have emerged to offer new syntheses of various biaryl motifs.[5−10] Notably, Itami,[8a] Shi,[8b] Hayashi,[8c] and Lei[8d] and others have shown that arenes and heteroarenes, typically used in excess, undergo arylation with aryl halides in the presence of sodium or potassium *tert*-butoxide, which serve as both base and electron donor, and promoters, such as phenanthroline and diamines.[8] The mechanism of base-promoted homolytic aromatic substitution (BHAS), coined by Studer and Curran, has been widely invoked for these reactions, implicating aryl radical intermediates.[7] More efficient methods for generating aryl radicals and improved mechanistic understanding will further advance this class of arylation chemistry.[8,9] Herein, we report a radical-mediated C−H arylation reaction of oxazoles with (hetero)aryl iodides using an unique combination of Cs_2CO_3 as base/electron donor and 1,1′-bis(diphenylphosphino) ferrocene (dppf) as an electron-transfer mediator (Scheme 1).

Scheme 1. C−H Arylation of (Hetero)arenes with Aryl Iodides



We began our development with the C−H arylation of 4-(ethoxycarbonyl)oxazole **1** with 4-(trifluoromethyl)phenyl iodide **2**. A previous study by Greaney[3b] showed that such a reaction can proceed under the catalysis of palladium complexes (e.g., $PdCl_2(dppf)_2$) and phosphine ligands (e.g., PPh_3) (entry 1).[3] Interestingly, we found that the application of a variety of other metal complexes, such as $Cu(OAc)_2$, $Ni(OAc)_2$, and $Fe(OAc)_2$ in the presence of dppf ligand and Cs_2CO_3 base in toluene at 110 °C, gave **3** in moderate to good yield (entries 2−6). Furthermore, the use of Cs_2CO_3 (2 equiv) in the absence of any metal catalysts also gave **3** in excellent yield (entry 7). Modification of the dppf ligand revealed that both diphenylphosphine and ferrocene motifs are critical.[11] Ferrocene derivatives such as unsubstituted (**P1**) and 1,1′-bis(acetyl)- or (dialkylphosphino)ferrocenes (**P2−P4**) gave trace amounts of **3**. Other mono- or diphosphine ligands such as PPh_3, SEGPHOS (**P9**), DIOP (**P10**), and Xantphos (**P12**) showed little or very weak promoting effects. Moreover, the addition of 0.2 equiv of tetrabutylammonium bromide (TBAB) or iodide (TBAI) further accelerated the reaction, giving **3** in 90% yield in a shorter reaction time (12 h, entries 18 and 19).[12] Reaction at a gram scale gave **3** in 88% yield under the same conditions. Regarding the optimization of this C−H arylation reaction, we note the following: (1) use of Cs_2CO_3 base is critical, as other alkaline carbonate bases gave little **3** (entries 7 vs 12);[13] (2) use of NaO*t*Bu and KO*t*Bu caused the decomposition of **1** (entries 13 and 14);[14] (3) the reaction yield dropped dramatically under air or O_2 atmosphere (entry 16); (4) use of high-purity Cs_2CO_3 (>99.99%) and dppf (99.9%) reagents gave similar results (entry 15);[15] (5) addition of 0.5 equiv of TEMPO shut down the reaction (entry 20); (6) the corresponding aryl bromide and chloride gave no product; (7) the monophosphine oxide of dppf

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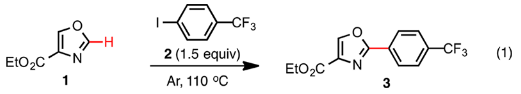
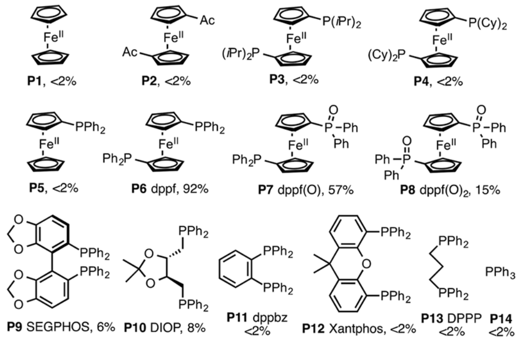
(**P7**, dppf(O)) exhibited decreased activity (57%), and diphosphine oxide of dppf (**P8**, dppf$(O)_2$) was much less effective (15%);[16] and (8) diphenylphosphinoferrocene (**P5**) is inactive.

Table 1. C2 C−H Arylation of 1 with Aryl Iodide 2



entry	reagents (equiv)	3[a]
1	$PdCl_2$(dppf) (0.05), PPh_3 (0.1), Ag_2CO_3 (2), H_2O, 60 °C, 24 h	60
2	$Pd(OAc)_2$ (0.05), dppf (0.1), Cs_2CO_3 (2), toluene, 110 °C, 24 h	55
3	$Cu(OAc)_2$ (0.05), dppf (0.1), Cs_2CO_3 (2), toluene, 110 °C, 24 h	72
4	$Ni(OAc)_2$ (0.05), dppf (0.1), Cs_2CO_3 (2), toluene, 110 °C, 24 h	75
5	$Fe(OAc)_2$ (0.05), dppf (0.1), Cs_2CO_3 (2), toluene, 110 °C, 24 h	85
6	$FeCl_2$ (0.05), dppf (0.1), Cs_2CO_3 (2), toluene, 110 °C, 24 h	90
7	dppf (0.1), Cs_2CO_3 (2), toluene, 110 °C, 24 h	95 (92[b])
8	dppf (0.05), Cs_2CO_3 (2), toluene, 110 °C, 24 h	85
9	Cs_2CO_3 (2), toluene, 110 °C, 24 h	<2
10	dppf (0.1), Cs_2CO_3 (2), C_6H_5Cl, 110 °C, 24 h	80
11	dppf (0.1), Cs_2CO_3 (2), dixoane, 110 °C, 24 h	<5
12	dppf (0.1), K_2CO_3 (2), toluene, 110 °C, 24 h	6
13	dppf (0.1), KO*t*Bu (2), toluene, 110 °C, 24 h	<2
14	dppf (0.1), NaO*t*Bu (2), toluene, 110 °C, 24 h	<2
15[c]	dppf (0.1), Cs_2CO_3 (2), toluene, 110 °C, 24 h	92
16	dppf (0.1), Cs_2CO_3 (2), toluene, 110 °C, 24 h, air	<2
17	dppf (0.1), Cs_2CO_3 (2), toluene, 110 °C, 12 h	45
18	dppf (0.1), Cs_2CO_3 (2), TBAI (0.2 equiv), toluene, 110 °C, 12 h	90 (85[b])
19	dppf (0.1), Cs_2CO_3 (2), TBAB (0.2 equiv), toluene, 110 °C, 12 h	92
20	dppf (0.1), Cs_2CO_3 (2), TEMPO (0.5), toluene, 110 °C, 24 h	<2

Performance of selected promoters under conditions in entry 7:



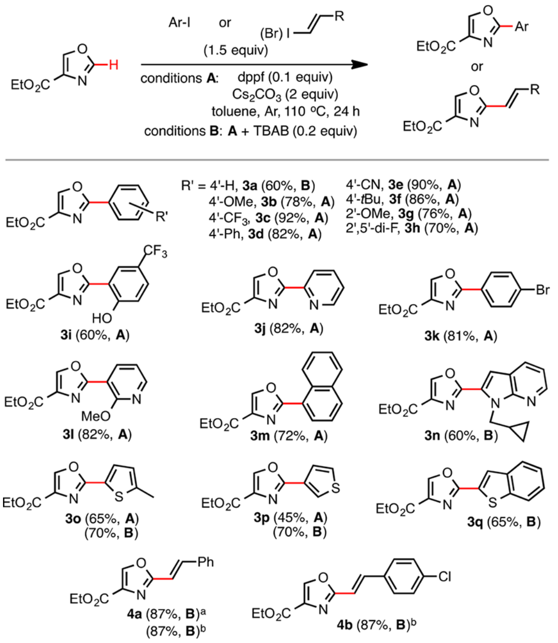
[a] ^{1}H NMR yield on a 0.2 mmol scale, *c* ~0.1 M, anhydrous solvent was used. [b] Isolated yield. [c] dppf (99.9%) and Cs_2CO_3 (99.99%) were used.

The scope of aryl halides was next examined using the arylation of **1** under the optimized conditions (Scheme 2). Conditions B (with TBAB) are typically more effective than A, especially for challenging coupling partners (see **3p**). As shown in **3a−h**, aryl iodides bearing either electron-withdrawing or -donating groups gave good yields of product. Coupling of a variety of heterocycles, such as pyridine (**3j**, **3l**), azaindole (**3n**), an thiophene (**3o−q**) worked well. Functional groups, such as phenol OH (**3i**) and cyclopropyl groups (**3n**), were tolerated. Sterically more hindered *ortho*-substituted aryl iodides (**3g**, **3h**, **3l**) also worked well. C−H alkenylation reactions with alkenyl bromides or iodides also proceed in good yield and excellent selectivity under conditions B (**4a**,**b**).[17]

The scope of oxazoles is examined in Scheme 3. Similar to the reactivity trends observed in Minisci-type reactions,[6] electron-deficient oxazoles exhibit higher reactivity. Reaction of 4-(ethoxycarbonyl)-5-aryloxazoles with various aryl and heteroaryl iodides proceeded in good yield under conditions B (**5a**,**b**, **6a**,**b**). Reactions of 4- or 5-aryloxazoles also worked well. For example, natural product taxamine **10** was generated in good yield. C−H arylation of benzoxazoles (**11a**,**b**) gave moderate yield under conditions B. Interestingly, the reactions of benzoxazoles were improved under conditions C, in which Cs_2CO_3 was replaced by KO*t*Bu (see entry 13 in Table 1). In contrast, use of NaO*t*Bu base gave little product. As seen with conditions A and B, dppf is critical to the success of conditions C with KO*t*Bu base (see conditions D for **11a**).

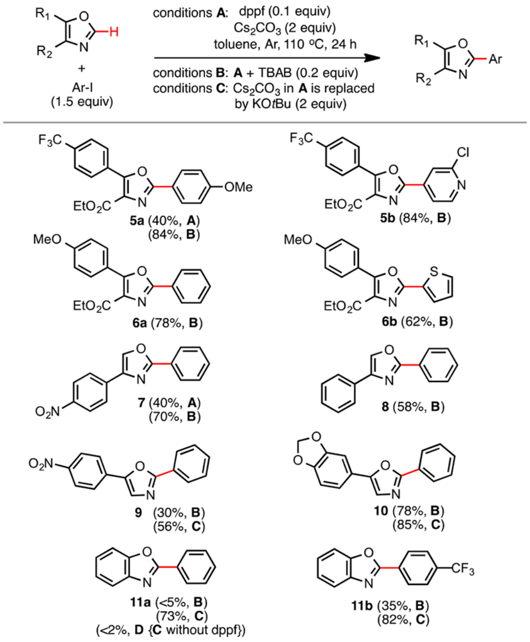
Some experiments and density functional theory (DFT) calculations have been performed to understand the functional roles of dppf and base in this C−H arylation reaction.[18] Residual metals in our reagents are unlikely to be responsible for promoting this reaction.[15] The quenching effect observed with

Scheme 2. Substrate Scope of Aryl and Vinyl Halides*



*Isolated yield on 0.2 mmol scale under the standard conditions A or B. [a] With vinyl iodide. [b] With vinyl bromide.

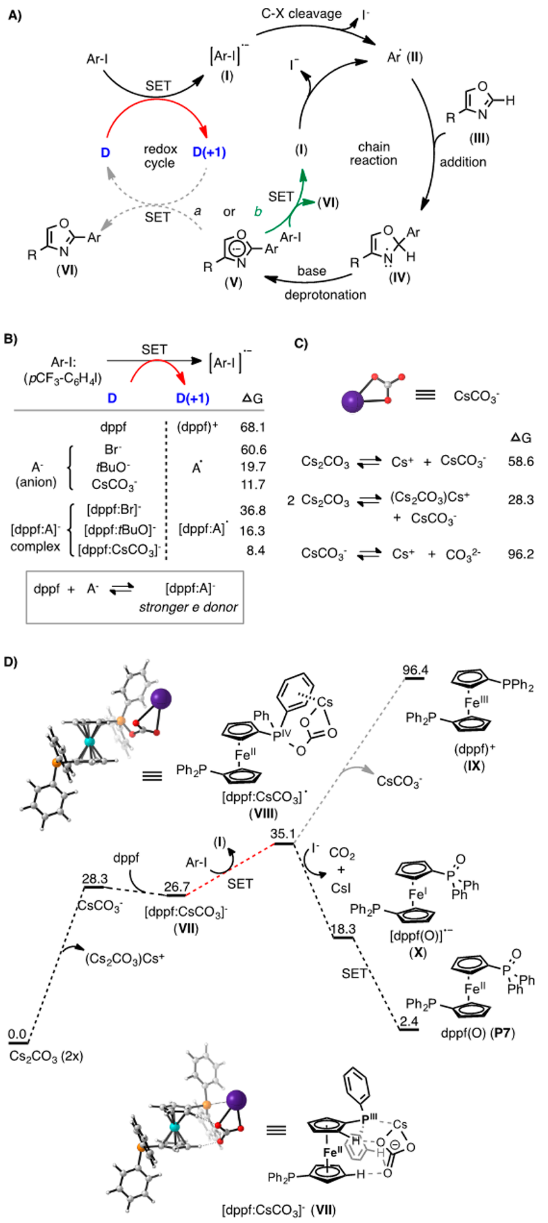
Scheme 3. Substrate Scope of Oxazoles[a]



[a] Isolated yield on 0.2 mmol scale.

TEMPO additive suggests a radical pathway. As outlined in Scheme 4A, the overall reaction likely follows the general BHAS mechanism featuring addition of nucleophilic aryl radical **II** to C2 of electrophilic oxazoles **III**.[7] The reaction is presumably initiated by single electron transfer (SET) reduction of aryl iodide by an electron donor **D** to form radical anion intermediate **I**, which then undergoes C−I bond cleavage to generate **II**. Addition of **II** to **III** gives **IV**, and subsequent deprotonation gives radical anion **V**. Anion **V** can undergo SET with aryl iodide to give the final arylated product **VI** and regenerate **II**, thereby propagating a radical chain reaction (pathway b). Alternatively, SET between **V** and oxidized donor **D(+1)** may give product **VI** and regenerate **D**, turning over a redox cycle (pathway a).[10]

Scheme 4. Mechanistic Studies[a]



[a](a) Proposed reaction pathways. (b) Calculated ΔG for SET reduction reaction of pCF$_3$C$_5$H$_4$−I with different electron donors. (c) Calculated ΔG for dissociation of Cs$_2$CO$_3$ in toluene. (d) Calculated energy profile for dppf and Cs$_2$CO$_3$-promoted C−H arylation of **1** with pCF$_3$C$_5$H$_4$−I. All energies are in kcal/mol. See the Supporting Information for a more detailed sequence of decarboxylation from **VIII** to **P7**.

As shown in Scheme 4B, DFT calculations suggest that dppf is a poor electron donor for SET reduction of ArI with a formidable energy barrier (68.1 kcal/mol).[19] In contrast, anionic CsCO$_3^-$ is a better SET reductant (forming Cs$^+$ and a bicarbonate radical[20]) with a ΔG of 11.7 kcal/mol, which is lower than ΔG for tBuO$^-$ (19.7 kcal/mol).[21] However, the dissociation of CsCO$_3^-$ from Cs$_2$CO$_3$ requires a considerable amount of energy (ΔG of 28.3 kcal/mol for a bimolecular process, 58.6 kcal/mol for a unimolecular process, Scheme 4C).[22] This dissociation penalty might diminish the overall reducing power of Cs$_2$CO$_3$. However, DFT calculations indicated dppf may form [dppf:CsCO$_3$]$^-$ complex **VII** with anion CsCO$_3^-$, promoting its SET reduction of ArI (ΔG 8.4 vs 11.7 kcal/mol, Scheme 4B, 4D).[23] Altogether, the overall energy barrier of dppf-promoted SET reduction of ArI by Cs$_2$CO$_3$ could be reduced to a level of 35.1 kcal/mol (as compared to 40 kcal/mol without dppf). Similar to CsCO$_3^-$, DFT calculations show that the reducing ability of tBuO$^-$ can be enhanced via formation of a [dppf:tBuO]$^-$ complex (16.3 vs 19.7 kcal/mol).[21] The functional role of TBAB is unclear. We suspect that Br$^-$ might facilitate the dissociation of CsCO$_3^-$ from Cs$_2$CO$_3$ via ion exchange.[24]

As shown in Scheme 4D, SET oxidation of **VII** gives **VIII**.[25] The process of dissociating CsCO$_3^-$ from **VIII** to generate the (dppf)$^+$ **IX**, a potential electron acceptor **D(+1)** for **V** to complete a redox cycle (pathway *a* in Scheme 4A), is thermodynamically challenging.[26] Instead, **VIII** might undergo decarboxylation and phosphine oxidation to generate Fe(I) dppf phosphine oxide **X**.[27] **X** then undergoes SET with ArI to give dppf(O) **P7**. We observe a small amount of dppf(O) **P7** (17% of dppf **P6** applied) in our reactions under O$_2$-free conditions.[28] The overall C−H arylation reaction likely proceeds through a radical-chain pathway (pathway *b* in Scheme 4A).[26]

In summary, we report the first radical C−H arylation reaction of oxazoles with (hetero)aryl iodides using Cs$_2$CO$_3$ as base/electron donor and dppf as a catalytic electron transfer mediator. This reaction offers an efficient and convenient method to prepare a wide range of 2-aryloxazoles from easily accessible precursors. The overall reaction likely follows the general BHAS mechanism through a radical-chain pathway. DFT calculations indicate that dppf forms a complex with CsCO$_3^-$ to enhance its SET reducing ability, thus promoting the formation of aryl radical from aryl iodides. This reducing ability of Cs$_2$CO$_3$ has been overlooked in the literature and might be responsible for other Cs$_2$CO$_3$-promoted radical reactions.[13] Application of dppf/Cs$_2$CO$_3$ and dppf/KOtBu protocols to other radical C−H arylation systems is currently under investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00530.

Additional experimental procedures and spectroscopic data for all new compounds are supplied (PDF)

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Notes

The authors declare no competing financial interest.

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(21) The ΔG of 19.7 kcal/mol is calculated for free anion $t\mathrm{BuO}^-$. KO*t*Bu and NaO*t*Bu exist as oligomers in solution. Their dissociation behavior can be strongly influenced by solvents and additives, which need to be taken into consideration when analyzing $t\mathrm{BuO}^-$-mediated SET reactions. Previous reports have shown that the use of ligand is critical to promote these SET processes (see ref 8). Dppf-mediated SET of KO*t*Bu is likely a complex process. A more comprehensive investigation of the dppf/KO*t*Bu system will be the subject of a future account.

(22) This value might be influenced by solvent and additives in the solution.

(23) DFT calculations indicate that **P7** dppf(O) is comparable to dppf in regard to forming complexes with $CsCO_3^-$ and undergoing SET with ArI. **P8** dppf(O_2) forms a stronger complex with $CsCO_3^-$, but the SET ability of the resulting complex is weaker. **P5** forms a weaker complex with $CsCO_3^-$ than dppf. **P1** cannot form a complex with $CsCO_3^-$. See the SI for more details.

(24) Like dppf, Br^- is also a poor electron door for SET reduction of ArI.

(25) DFT calculations showed that HOMO orbital of **VII** lies on the bicarbonate group. Thus, bicarbonate might be better viewed as the electron donor in this reaction system.

(26) Redox cycle pathway *a* in which **VIII** serves as **D(+1)** which accepts an electron from **V** cannot be completely ruled out.

(27) DFT calculations suggest that CsI, Cs_2CO_3, or $(Cs_2CO_3)Cs^+$ species are likely involved in the decarboxylation process. See the SI for more details.

(28) Control experiments show that heating dppf with Cs_2CO_3 in toluene at 110 °C for 24 h under O_2-free conditions leads to the formation of 9% of P-oxygenation product **P7** (a plausible reaction equation is shown below). Heating of **P7** with Cs_2CO_3 in toluene led to the formation of 17% of **P8**. In comparison, heating of **P5** with Cs_2CO_3 in toluene did not form any P-oxygenation product. See the SI for more details.

$$\begin{array}{c} Cs_2CO_3 + \text{dppf } \mathbf{P6} \\ + \text{ solvent (toluene)} \end{array} \xrightarrow[110\ ^\circ\mathrm{C}]{24\ \mathrm{h}} \begin{array}{c} CO_2 + \text{dppf(O) } \mathbf{P7} \\ Cs^+ + [\text{reduced solvent}]^- \end{array}$$