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Iron/copper co-catalyzed highly selective arylation of sulfinamides with aryl iodides

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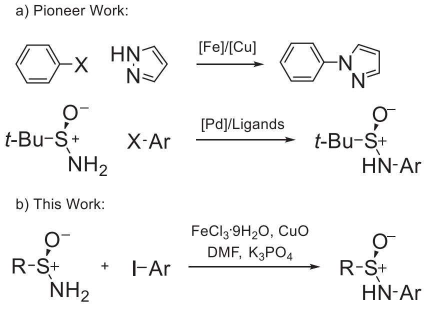
ABSTRACT

In the present study, an inexpensive but efficient Iron(III) and Copper(II) co-catalyst without ligands catalyzed arylation of sulfinamides with aryl iodide was primarily reported. In brief, in the presence of $Fe(NO_3)_3 \cdot 9H_2O$, CuO and K_3PO_4, the highly selective C–N cross coupling of several sulfinamides and aryl iodides was achieved in high chemical yield, while the aryl chlorides and bromides could not yield coupling products. It is noteworthy that through the arylation of chiral *tert*-butanesulfinamide with aryl iodides, *N*-aryl *tert*-butanesulfinamides are provided without racemization, even in gram-scale. The possible mechanism was that This oxidative addition process between copper catalyst and aryl-iodides might be significantly accelerated by active Fe(III) species. Moreover, using this synthetic method, a facile and efficient access was developed for the derivatives of *N*-phenyl sulfinamides, which might help to develop new drug molecules and material chemicals.

Sulfinamides are a crucial class of organic compounds in modern organic chemistry [1]. Enantiomer-pure sulfinamides and their derivatives have been widely employed in the synthesis of chiral drugs and natural products [1]; it has also been used as chiral ligands in catalytically asymmetric reactions [2]. Moreover, Sulfinamides are good precursors for the synthesis of sulfonamides, which are found in many drug molecules [2]. Recently, synthetic methodologies have been developed for transition metals catalyzed formation of chiral C–C bonds, using sulfinamides as chiral directing groups [3]. There were few facile methods developed for direct formation of C–N bond between various sulfiniamides and aryl halides. The arylations of sulfinamide derivatives from thionylanilines, sulfinylazides, sulfonyl chlorides and methyl sulfonates with Grignard reagents and amines have been investigated in several papers [4]. Recently, Zeng group and Cai & Guo Group have formulated the cross-coupling strategies to generate racemic and chiral sulfinamides, using Pd and Cu catalysts, respectively [5]. Inspired by the pioneer Fe-catalyzed cross-coupling reactions [6], especially Taillefer's report [7], an extremely simple Iron(III)-Copper(II) bimetallic catalytic system was demonstrated in this study for *N*-arylation of sulfinamides with aryl iodides (Scheme 1).

A racemic *tert*-butanesulfinamide **Rac-1** and 1-chloro-4-iodobenzene **2a** were taken as model substrates for the initial investigation. Taillefer's optimized conditions were first employed for the test. The desired product **3a** was isolated with 36% yield (Table 1, entry 1). As shown in entry 2, the reaction did not occur when $Cu(acac)_2$ replaced CuO. Note that the reactions led to clean conversion when they were catalyzed by inorganic iron(III) salts (e.g. $FeCl_3 \cdot 6H_2O$ and $Fe(NO_3)_3 \cdot 9H_2O$), and the isolated yields



Scheme 1. Overview.

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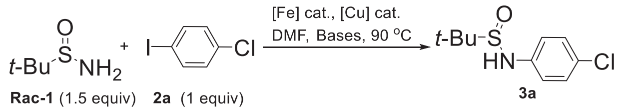
Table 1
Optimization of reaction conditions.



Entry	[Fe] cat. (0.15 eqv.)	[Cu] cat. (0.1 eqv.)	Bases (2 eqv.)	Yield[b]
1	$Fe(acac)_3$	CuO	Cs_2CO_3	36%
2	$Fe(acac)_3$	$Cu(acac)_2$	Cs_2CO_3	trace
3	$FeCl_3{\cdot}6H_2O$	CuO	Cs_2CO_3	79%
4	$Fe(NO_3)_3{\cdot}9H_2O$	CuO	Cs_2CO_3	85%
5	$Fe(NO_3)_3{\cdot}9H_2O$[a]	CuO	Cs_2CO_3	83%
6	$Fe(NO_3)_3{\cdot}9H_2O$[a]	CuO	KO*t*-Bu	30%
7	$Fe(NO_3)_3{\cdot}9H_2O$[a]	CuO	K_3PO_4	93%
8	$Fe(NO_3)_3{\cdot}9H_2O$[a]	CuO	NaOH	82%
9	–	CuO	K_3PO_4	NR
10	$Fe(NO_3)_3{\cdot}9H_2O$[a]	–	K_3PO_4	NR

[a] 0.1 eqv.
[b] Isolated yield.

reached 79% and 85%, respectively (Entry 3 and entry 4). Reduction of iron(III) catalyst loading to 0.1 eqv., the reaction was still efficient (Entry 5). Besides, several common inorganic bases were screened out for the reaction (entry 6, 7 and 8). The optimal result was achieved from the addition of K_3PO_4, with the cross-coupling product **3a** of 93% yield (Entry 7). However, there was no reaction without $Fe(NO_3)_3{\cdot}9H_2O$ or CuO catalysts (Entry 9 and 10).

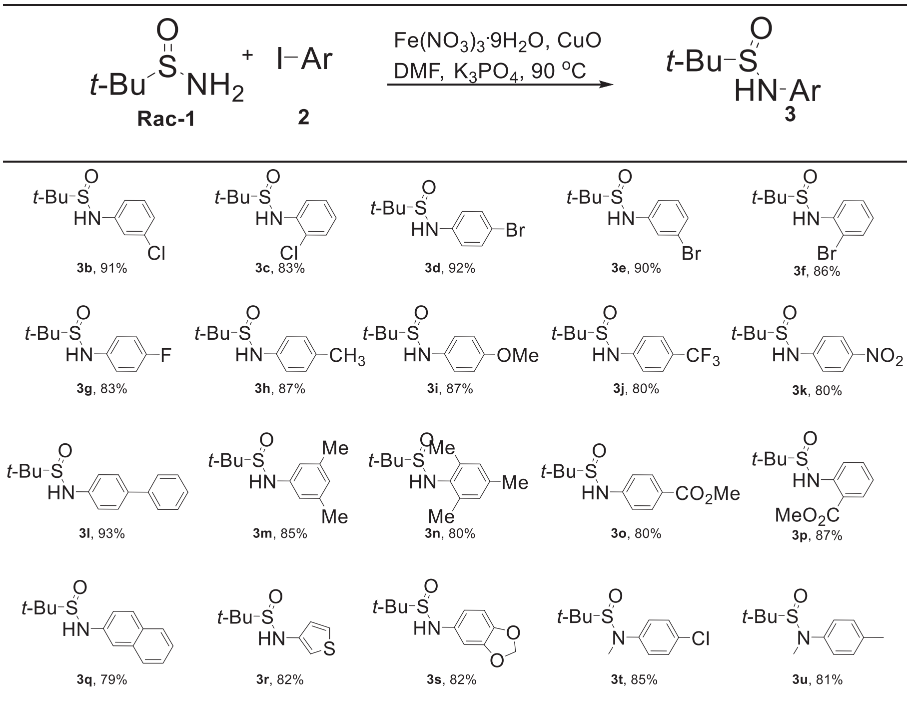
With the optimized conditions in hand (Table 1, Entry 7), the scope of substrates was further studied (Tables 2 and 3). As a result, the cross-coupling did not have any effect on aryl bromides and aryl chlorides. The products **3b**, **3c**, **3d**, **3e** and **3f** might be vital synthetic intermediates for further cross-coupling transformations to fabricate more complicated compounds. All the coupling products could be isolated with good to excellent yield, suggesting that the method exhibits a good tolerance of functional group. For instance, substrates **2** bearing electron-withdrawing or electron-donating at different positions of the aryl ring reacted efficiently to generate the corresponding products **3b-3p** of 79–93% yield (table 2). Even for the secondary sulfinamides substrates, the cross-coupling reactions could work excellently with high yield under the optimized conditions (products **3t** and **3u**, table 2). In the meantime, as shown in table 3, various patterns of substituted sulfinamides could also couple with aryl iodides to generate the products of good to excellent yield.

Based on these good results, enantiomeric pure (*R*)-*tert*-butanesulfinamide **R-1** has been adopted as the coupling precursor (as shown in table 4). High *ee* values of all coupling products were used, which reveals no significant epimerization under the optimized conditions. Moreover, gram-scale synthesis of chiral *N*-aryl-*tert*-butanesulfinamides with excellent yield and enantiomeric selectivity was also verified (Scheme 2).

To gain insights into the reaction mechanism, first, using excess TEMPO was found to have no significant inhibiting effect on the reaction, suggesting that the reaction did not undergo a radical process (Entry 1, Table 5). It is noteworthy that all of the reactions could occur smoothly and efficiently, when CuI and $FeSO_4{\cdot}7H_2O$ replaced CuO and $Fe(NO_3)_3{\cdot}9H_2O$, respectively (Entry 2, 3 and 6, Table 5). Bubbling air into the reaction could significantly stopped the reaction (Entry 4, Table 5). Interestingly, as catalyzed by CuI without $Fe(NO_3)_3{\cdot}9H_2O$, the reaction was dramatically moderated. 62% of **3a** was achieved over 60 h (Entry 5, Table 5). Using DMAc as solvent instead of DMF, led to low yield (37%, Entry 7, Table 5). The reaction did not occur when THF or DCE replaced DMF (Entry 8 and 9, Table 5). These results indicated that DMF played a crucial role in the process of the reaction.

However, the mechanism how iron interacts with copper catalysts and how to accelerate the reaction is still unknown [7,8]. Based on the limited observations, the plausible mechanism is proposed (Scheme 3) tentatively. Cu(II) might be firstly reduced by DMF in high temperature to generate Cu(I) [9], which occurred

Table 2
Investigation of scope of aryl iodide.



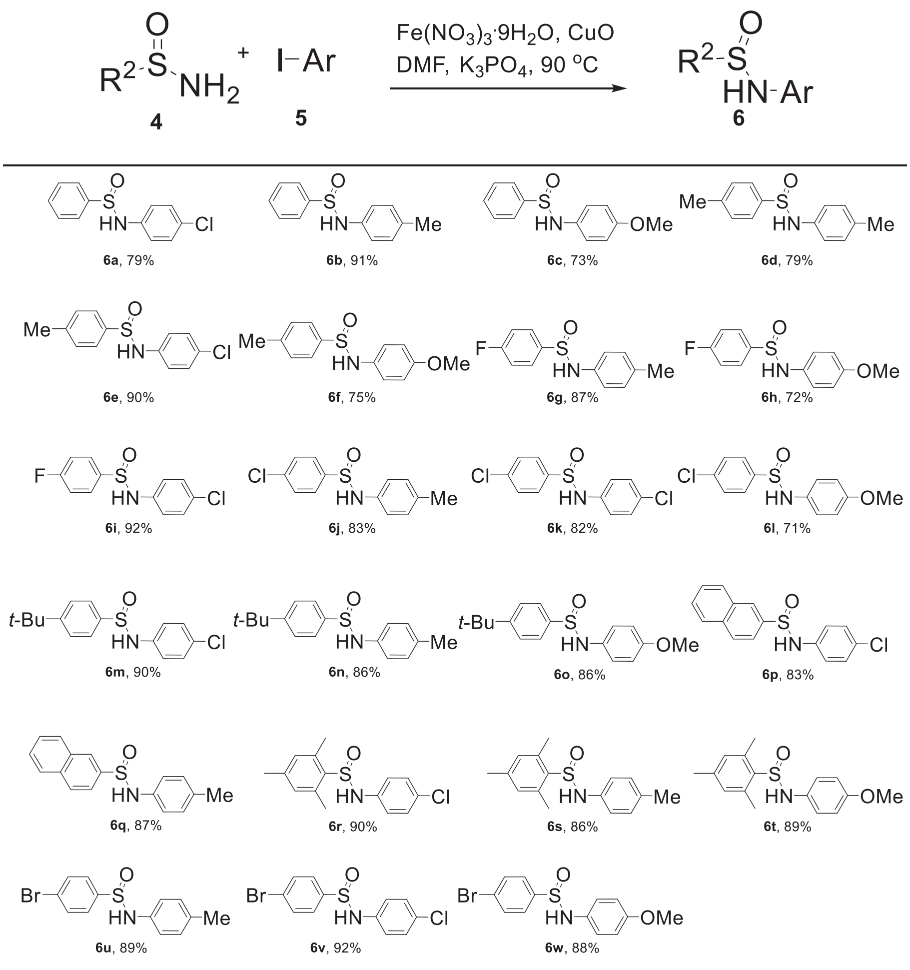
3b, 91% **3c**, 83% **3d**, 92% **3e**, 90% **3f**, 86%

3g, 83% **3h**, 87% **3i**, 87% **3j**, 80% **3k**, 80%

3l, 93% **3m**, 85% **3n**, 80% **3o**, 80% **3p**, 87%

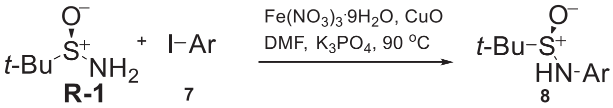
3q, 79% **3r**, 82% **3s**, 82% **3t**, 85% **3u**, 81%

Table 3
Cross-coupling reaction between more sulfiniamides with aryl iodides.

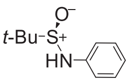
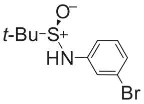
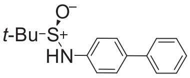
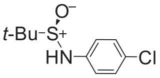


6a, 79%; **6b**, 91%; **6c**, 73%; **6d**, 79%; **6e**, 90%; **6f**, 75%; **6g**, 87%; **6h**, 72%; **6i**, 92%; **6j**, 83%; **6k**, 82%; **6l**, 71%; **6m**, 90%; **6n**, 86%; **6o**, 86%; **6p**, 83%; **6q**, 87%; **6r**, 90%; **6s**, 86%; **6t**, 89%; **6u**, 89%; **6v**, 92%; **6w**, 88%

Table 4
Cross-coupling reaction between (*R*)-*tert*-butanesulfinamide with aryl iodides.

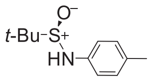
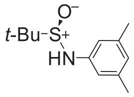


R-1 **7** **8**

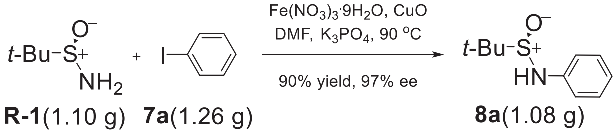
Entry	Products	Yield[a]	*ee*[b]
1[c]		91%	95%
2		90%	96%
3		93%	99%
4[d]		92%	97%

(*continued on next page*)

Table 4 (*continued*)

Entry	Products	Yield[a]	*ee*[b]
5		92%	99%
6[d]		93%	99%

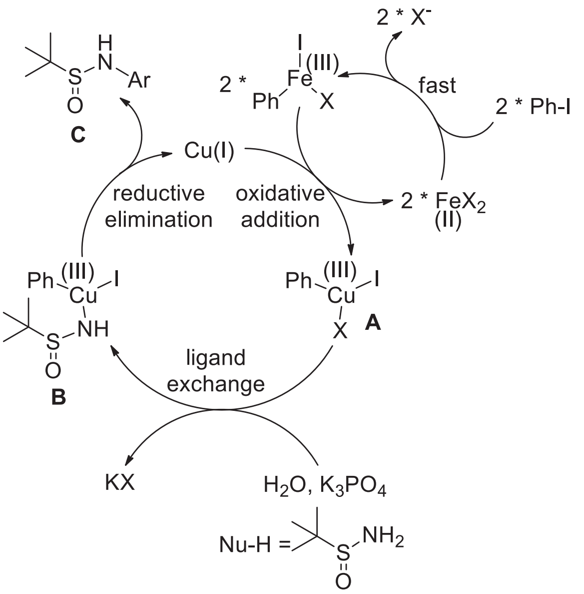
[a] Isolated yield.
[b] *ee* values were measured by chiral HPLC.
[c] The reaction was performed in gram-scale.
[d] The absolute configuration of **8d** and **8f** were determined by X-ray crystallographic analysis (**8d**, CCDC 1900195; **8f**, CCDC 1900194).



Scheme 2. Gram-scale coupling reaction to furnish chiral *N*-aryl-*tert*-butanesulfinamides **8a.**

oxidative addition with PhI affording the Cu(III) species **A**. Fe(III) or Fe(II) might play an essential role in stabilizing the deprotonated sulfinamides. After the standard ligand exchange, followed by reductive elimination, the cross-coupling product was finally furnished.

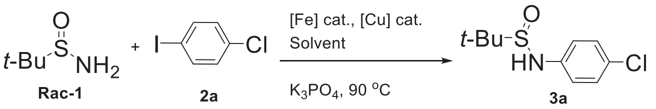
Based on the excellent selectivity between sulfinamides and aryl iodides, rather than aryl bromides, several derivatives of *N*-phenyl sulfinamides could be effectively furnished by "a two-step cross-coupling relay" (Scheme 4). To be specific, common intermediate **3d**, obtained from arylation of *tert*-butanesulfinamide with *p*-bromoiodobenzene, could directly deliver compounds **9** (Sonogashira), **10** (Suzuki), **11** (Buchwald-Hartwig) and **12** (Ullmann) through transition metal catalyzed C–C or C–N cross-coupling reactions. It would provide a quick method to furnish *N*-aryl sulfonamides (such as compound **13** and **14**).



Scheme 3. Plausible Mechanism.

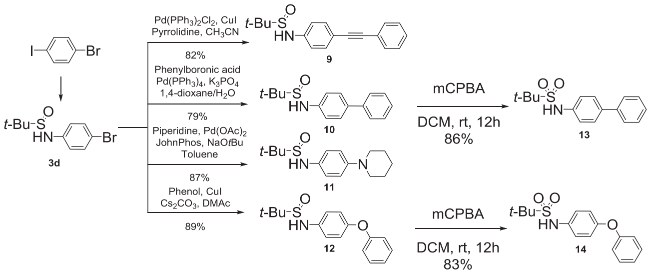
To sum up, in this study, a ligand-free Fe/Cu co-catalyzed C–N cross coupling of sulfinamides with aryl iodides was developed. Under the optimized conditions, $Fe(NO_3)_3·9H_2O$ and CuO were adopted as the co-catalytic system and K_3PO_4 as the base, and the cross-coupling reaction took place efficiently and cost-economically. Moreover, the chirality of (*R*)-*tert*-butanesulfinamides could be retained in *N*-aryl *tert*-butanesulfinamides without racemization under the optimized conditions. Besides, the gram-scale synthesis was also easily performed with excellent yield

Table 5
Reactions for exploration of possible mechanism.



Entry	[Fe] cat.	[Cu] cat.	Additive	Solvent	Time	Yield[a]
1	$Fe(NO_3)_3·9H_2O$	CuO	TEMPO[b]	DMF	8 h	62%
2	$Fe(NO_3)_3·9H_2O$	CuI	none	DMF	8 h	79%
3	$FeSO_4·7H_2O$	CuO	none	DMF	8 h	95%
4	$Fe(NO_3)_3·9H_2O$	CuO	Air	DMF	8 h	<5%
5	none	CuI	none	DMF	>60 h	62%
6	$FeSO_4·7H_2O$	CuI	none	DMF	8 h	76%
7	$Fe(NO_3)_3·9H_2O$	CuO	none	DMA[c]	8 h	37%
8	$Fe(NO_3)_3·9H_2O$	CuO	none	THF	8 h	NR
9	$Fe(NO_3)_3·9H_2O$	CuO	none	DCE	8 h	NR

[a] Isolated yield.
[b] 2 equiv. of TEMPO was used.
[c] DMAc = N,N-Dimethylacetamide.



Scheme 4. Facile construction of sulfinamides.

and *ee* value. Furthermore, a facile and efficient access was provided to the derivatives of *N*-phenyl sulfinamides. Hopefully, this method has a wide application in new drug molecules and material chemicals.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151167.

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