Iron-catalyzed thioetherification of thiols with aryl iodides†

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$FeCl_3$ in combination with bisphosphine ligands represents an efficient catalyst system for the cross-coupling of aryl- and alkyl thiols with aryl iodides, a broad spectrum of functional groups can be tolerated during the catalysis.

The transition-metal-catalyzed cross-coupling reaction is arguably one of the most powerful strategies for constructing carbon–carbon and carbon–heteroatom bonds.[1] This approach has been widely utilized in organic synthesis and materials science.[2]

Aryl thioethers are important skeletons for many biologically active compounds.[3] Palladium,[4–8] nickel,[9] cobalt,[10] copper,[11] indium[12] and iron[13] are known to serve as the metal sources in combination with appropriate ligands for the synthesis of aryl thioethers. Phosphines are a principal class of ligand for transition-metal-catalyzed reactions.[14] Monophosphines were reported as a ligand for the first palladium-catalyzed S-arylation of thiols with aryl halides by Migita *et al.* in 1980.[4] Recent studies suggested that bisphophines are more reactive than monophosphines for these reactions.[5] Josiphos ligand (1-dicyclohexylphosphino-2-di-*tert*-butylphosphinoethylferrocene, **L1**),[5] BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, **L2**), (*R*)-Tol-BINAP [(*R*)-(+)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl, **L3**],[6] Xantphos (9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, **L4**)[7] and DPEphos [bis(2-diphenylphosphinophenyl)ether, **L5**][8] have been investigated in palladium-catalyzed S-arylation of thiols with aryl halides (Fig. 1). Bisphospines were also utilized in nickel- and cobalt-catalyzed carbon–sulfur bond formation.[9,10] Although many metals catalysts have been explored, it is still desirable to develop an alternative strategy which uses cheaper and environmentally friendly metals. Cleaner and cheaper alternatives are especially valuable to the pharmaceutical industry.

Recently iron has been considered as an ideal choice not only because of its lower toxicity and cost compared to other metals but also because it possesses some unusual properties which have been utilized in many transformations.[15,16] Iron-catalyzed C–C,[17] C–N[18] and C–O[19] bond forming reactions have recently been developed. Despite the fact that iron was known to promote the formation of disulfides,[20] Bolm *et al.* reported that the first iron-catalyzed S-arylation of aryl thiols with aryl iodides uses $FeCl_3$–*N*,*N*′-dimethylethylenediamine as the catalyst.[13] However, this approach is limited as this system only works with aryl thiols and is completely ineffective for alkyl thiols. Thus, it is highly desirable to develop a new system to overcome this limitation. Herein we report the combination of $FeCl_3$ with bisphosphines that successfully catalyzes coupling of aryl- and alkyl thiols with aryl iodides in good to excellent yields.

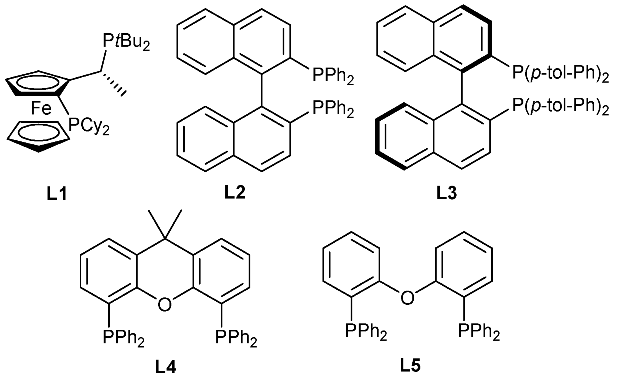
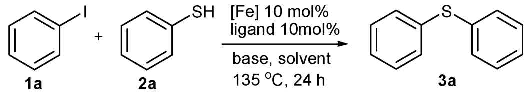


Fig. 1 Structures of the ligands **L1–L5**.

Initially, iodobenzene and thiophenol were selected as substrates to screen the optimized conditions. The results are summarized in Table 1. Various bisphosphines were examined. **L1** shows good activity with a 91% isolated yield (entry 1).

Table 1 Optimization of iron-catalyzed coupling of iodobenzene with thiophenol[a]



Entry	[Fe]	Ligand	Base	Solvent	Yield (%)
1	$FeCl_3$	**L1**	NaO*t*Bu	Toluene	91
2	$FeCl_3$	**L2**	NaO*t*Bu	Toluene	99
3	$FeCl_3$	**L3**	NaO*t*Bu	Toluene	99
4	$FeCl_3$	**L4**	NaO*t*Bu	Toluene	97
5	$FeCl_3$	**L5**	NaO*t*Bu	Toluene	29
6	$FeCl_3$	**L2**	KO*t*Bu	Toluene	98
7	$FeCl_3$	**L2**	K_2CO_3	Toluene	—
8	$FeCl_3$	**L2**	K_3PO_4	Toluene	—
9	$FeCl_3$	**L2**	Cs_2CO_3	Toluene	—
10	$FeCl_3$	**L2**	NaO*t*Bu	DMF	33
11	$FeCl_3$	**L2**	NaO*t*Bu	Dioxane	76
12	$FeCl_3$	**L2**	NaO*t*Bu	DME	38
13	FeF_3	**L2**	NaO*t*Bu	Toluene	63
14	Fe_2O_3	**L2**	NaO*t*Bu	Toluene	79[b]
15	$FeCl_3$	—	NaO*t*Bu	Toluene	—

[a] Reaction conditions: iron source (0.05 mmol, 10 mol%), ligand (0.05 mmol, 10 mol%), iodobenzene (0.75 mmol), thiophenol (0.5 mmol), base (1.0 mmol) in 0.5 mL solvent. [b] Fe_2O_3 (0.025 mmol).

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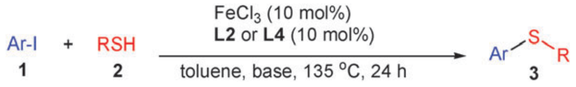
This ligand has demonstrated the greatest efficacy in palladium-catalyzed cross-coupling reactions of aryl halides and pseudo-halides with thiols.[5] However, we felt that the high cost of **L1** might limit its practical application. This positive result encouraged us to screen other cheaper and structurally simpler bisphosphines **L2–L5**. Surprisingly, **L2**, **L3** and **L4** also showed excellent activity, even better than **L1** (entries 2, 3 and 4). **L5** was previously used to couple aryl thiols with aryl iodides in the presence of palladium.[8] However, it could not provide a satisfactory result (entry 5). After screening bases and solvents (DMF = *N*,*N*-dimethylformamide; dioxane = 1,4-dioxacyclohexane; DME = dimethoxyethane), weak bases such as K_2CO_3, K_3PO_4 and Cs_2CO_3 did not show good results (entries 7–9); NaO*t*Bu and KO*t*Bu were equally active for this transformation.[5] Toluene was found to be superior to other solvents (entries 10–12). The moisture stable Fe_2O_3 was also active with a 79% yield (entry 14). When the reaction was carried out in the absence of a ligand, disulfide was detected as the sole product (entry 15).

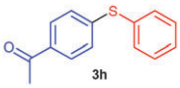
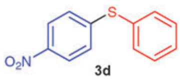
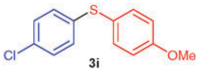
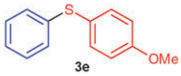
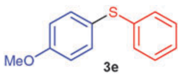
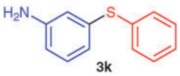
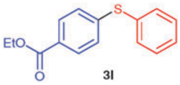
Using the previous optimizations, Table 2 summarizes the results of the iron-catalyzed S-arylation. A broad range of aryl iodides were tested. Electron-donating and electron-withdrawing aryl iodides all served as suitable partners for coupling with aryl thiols with good to excellent yields. It is important to note that functional groups such as chloro- (entries 1 and 9), free alcohol (entry 2), nitro- (entry 3), enolizable ketone (entry 8), bromo- (entry 10), unprotected amine (entry 11) and ester (entry 12) are all tolerated during the catalysis. Interestingly, when iodobenzene was coupled with 4-methoxythiophenol, **3e** resulted in an 83% yield (entry 4). The same compound was obtained in trace amounts by reacting electronically deactivated 4-iodoanisole with thiophenol under the same conditions. However, this can be dramatically improved by employing **L4** as ligand (entry 5). It implies that **L4** is more active than **L2** for this process.

Next we turned our attention to developing the coupling protocol for alkyl thiols. Unfortunately, when 1-dodecanethiol and iodobenzene were employed under the optimized conditions for aryl thiols (using ligands **L1** and **L2**) poor yields were observed (Table 3, entries 1 and 2, respectively). **L3** is more electron rich than **L2** and this modification resulted in a slightly higher yield. **L4** shows better results than **L2** but is still not sufficient (entry 4). After screening other parameters, including bases (entries 5–8) and solvents (entries 9–11), KO*t*Bu and dioxane were found to be the best base and solvent; in combination with $FeCl_3$–**L4** the product was obtained with a 98% yield (entry 11). A lower yield was observed when the reaction was carried out at 110 °C; in this trial disulfide was determined as the major product by GC-MS analysis (entry 12). Fe_2O_3 shows lower activity than $FeCl_3$ with a product yield of 24% (entry 13). Unsatisfactory results were also observed when the reaction was performed in the absence of a ligand (entry 14).

In order to test the scope of S-arylation using alkyl thiols, we utilized a wide array of aryl iodides, and the results are summarized in Table 4. Both long chain alkyl thiols, and sterically hindered thiols can be employed. For example, both

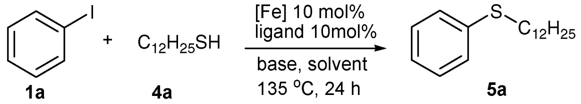
Table 2 Iron-catalyzed S-arylation of aryl iodides with aryl thiols[a]



Entry	Product	Yield (%)	Entry	Product	Yield (%)
1	 3b	91	7	 3g	91^b
2	 3c	85	8	 3h	95^b
3	 3d	77	9	 3i	77^b
4	 3e	83	10	 3j	87^b
5	 3e	93^b	11	 3k	92^b
6	 3f	94^b	12	 3l	72^{bc}

[a] Reaction conditions unless otherwise stated: $FeCl_3$ (0.1 mmol, 10 mol%), **L2** (0.1 mmol, 10 mol%), aryl iodide (1.5 mmol), aryl thiol (1.0 mmol), NaO*t*Bu (2.0 mmol) in toluene (1.0 mL). [b] **L4** was used. [c] KO*t*Bu was used.

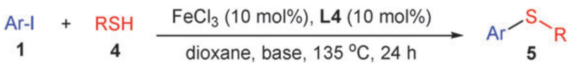
Table 3 Evaluation of iron-catalyzed coupling reaction of iodobenzene with 1-dodecanethiol[a]

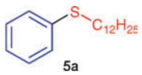
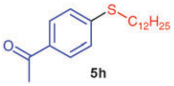
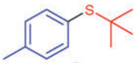
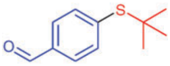
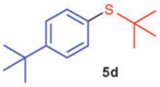
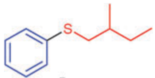
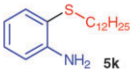


Entry	[Fe]	Ligand	Base	Solvent	Yield (%)
1	$FeCl_3$	**L1**	NaO*t*Bu	Toluene	21
2	$FeCl_3$	**L2**	NaO*t*Bu	Toluene	33
3	$FeCl_3$	**L3**	NaO*t*Bu	Toluene	41
4	$FeCl_3$	**L4**	NaO*t*Bu	Toluene	50
5	$FeCl_3$	**L4**	K_2CO_3	Toluene	62
6	$FeCl_3$	**L4**	K_3PO_4	Toluene	14
7	$FeCl_3$	**L4**	Cs_2CO_3	Toluene	64
8	$FeCl_3$	**L4**	KO*t*Bu	Toluene	70
9	$FeCl_3$	**L4**	KO*t*Bu	DMF	71
10	$FeCl_3$	**L4**	KO*t*Bu	DME	34
11	$FeCl_3$	**L4**	KO*t*Bu	Dioxane	98
12	$FeCl_3$	**L4**	KO*t*Bu	Dioxane	7^b
13	Fe_2O_3	**L4**	KO*t*Bu	Dioxane	24^c
14	$FeCl_3$	—	KO*t*Bu	Dioxane	16

[a] Reaction conditions: iron source (0.05 mmol, 10 mol%), ligand (0.05 mmol, 10 mol%), iodobenzene (0.75 mmol), 1-dodecanethiol (0.5 mmol), base (1.0 mmol) in 0.5 mL solvent. [b] 110 °C. [c] Fe_2O_3 (0.025 mmol).

Table 4 Iron-catalyzed S-arylation of aryl iodides with alkyl thiols[a]



Entry	Product	Yield (%)	Entry	Product	Yield (%)
1	 **5a**	97	7	 **5g**	64[b]
2	 **5b**	90	8	 **5h**	99[b]
3	 **5c**	88	9	 **5i**	77
4	 **5d**	72	10	 **5j**	66
5	 **5e**	62	11	 **5k**	75
6	 **5f**	75	12	 **5l**	75

[a] Reaction conditions unless otherwise stated: $FeCl_3$ (0.1 mmol, 10 mol%), **L4** (0.1 mmol, 10 mol%), aryl iodide (1.5 mmol), alkyl thiol (1.0 mmol), KO*t*Bu (2.0 mmol) in dioxane (1.0 mL). [b] Cs_2CO_3 was used.

*t*Bu- (entries 2–4, 7, 9 and 10) and 2-methylbutyl thiol (entry 5) yield satisfactory results. Benzyl mercaptan was ineffective in previous iron-catalyzed S-arylation,[13] but with our approach it can be coupled with iodobenzene to get **5f** in 75% isolated yield (entry 6). Functional groups such as enolizable ketone (entries 7 and 8), aldehyde (entry 9), free amine (entries 10 and 11) and nitrogen-containing heterocycle (entry 12) are all suitable as coupling partners.

In conclusion, we have demonstrated that the combination of $FeCl_3$ with bisphosphines **L2** or **L4** proves to be an efficient catalytic system for S-arylation of aryl- and alkyl thiols with aryl iodides. To the best of our knowledge, this is the first example of iron-catalyzed S-arylation of alkyl thiols with aryl halides. Understanding the origins of this novel system and applications to other cross-coupling reactions are in progress in our laboratory.

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