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A Highly *Para*-Selective Copper(II)-Catalyzed Direct Arylation of Aniline and Phenol Derivatives**

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The ubiquity of the biaryl motif in natural products, medicines, and novel materials ensures a constant demand for their efficient and selective synthesis.[1] The most widespread biaryl-forming processes are cross-coupling reactions in which two prefunctionalized arene partners are connected by a transition-metal catalyst. Although selectivity in these cross-coupling reactions is not an issue, a compromise is made on efficiency; prior chemical transformations are required to obtain the coupling partners as the prefunctionalization events must be carried out regioselectively, and in some cases this can prove a significant challenge.[2] Much recent attention has been devoted to the development of new concepts to utilize a C–H bond in place of one or both of the cross-coupling partners.[3] The benefits of this strategy are considerable, but the crucial issue of selectivity is now relocated to the biaryl bond-forming step. Cyclometalation-based approaches constitute the most common strategy towards the arylation of C–H bonds, which results in functionalization *ortho* to a directing group.[3] Considering the wealth of electrophilic aromatic substitution reactions employed in synthesis, it is surprising that few *para*-selective direct arylation reactions are known.

Several research groups have reported methods to achieve direct metal-catalyzed arylation of electron-rich benzenes, but only moderate selectivity has been observed;[4] in most cases, all three possible isomers were obtained. Higher selectivity was reported by Buchwald and co-workers in a specific case during an oxidative coupling of anisole with anilides, wherein 1:2:12 *o*/*m*/*p* selectivity was achieved.[5] Kita et al. have reported a metal-free thiophenylation of some electron-rich arenes and heteroarenes with high selectivity.[6]

Recently, we reported a C3-selective copper-catalyzed direct arylation of indoles with diaryliodonium salts; this selectivity would be expected from an electrophilic substitution-type (S_EAr) mechanism (Figure 1).[7a] Intriguingly, we discovered that we were able to override this natural selectivity by using the coordinating ability of carbonyl groups to effect the C2 arylation of indoles. Similarly, we discovered that the carbonyl group of an anilide directed an unprecedented *meta*-selective arylation reaction.[7b] On the basis of these selectivity trends we speculated that electron-rich arenes without coordinating carbonyl groups should undergo direct arylation through a classical S_EAr-type mechanism, thereby leading to a *para*-selective process.

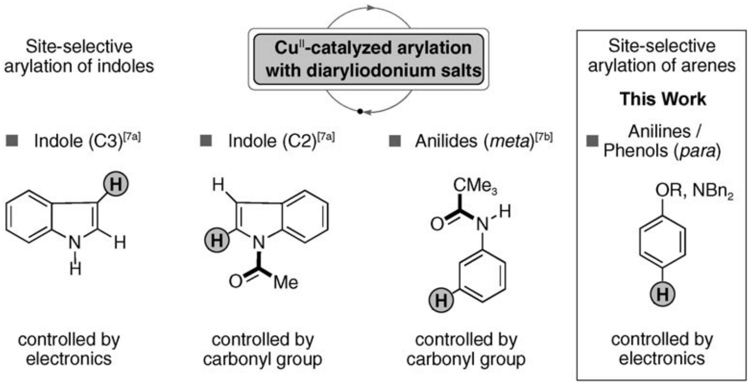

Figure 1. Selectivity trends in copper-catalyzed arylation.

Herein, we report the development of the first highly *para*-selective Friedel–Crafts-type arylation of phenol and aniline derivatives. This versatile copper-catalyzed method operates under mild reaction conditions, uses inexpensive catalysts, and tolerates diverse functionality on the arene-coupling partners (Figure 1). We have used this principle to demonstrate an iterative arylation of aniline, which enables us to selectively arylate the *para*, *ortho*, and then *meta* positions by using only our copper-catalyzed processes.

At the outset of our studies we submitted anisole to the standard conditions of our *meta*-selective pivanilide arylation reaction and were delighted to observe the *para* selectivity that we had predicted. A 62% yield of isolated *para*-phenylanisole (**3a**) was obtained, and the balance of the reaction consisted of separable starting material rather than any regioisomers arising from unselective arylation (Scheme 1). To the best of our knowledge, this represents the first highly selective *para*-arylation of anisole.

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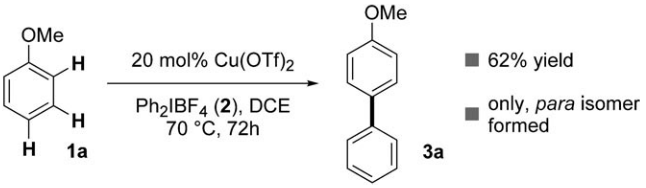
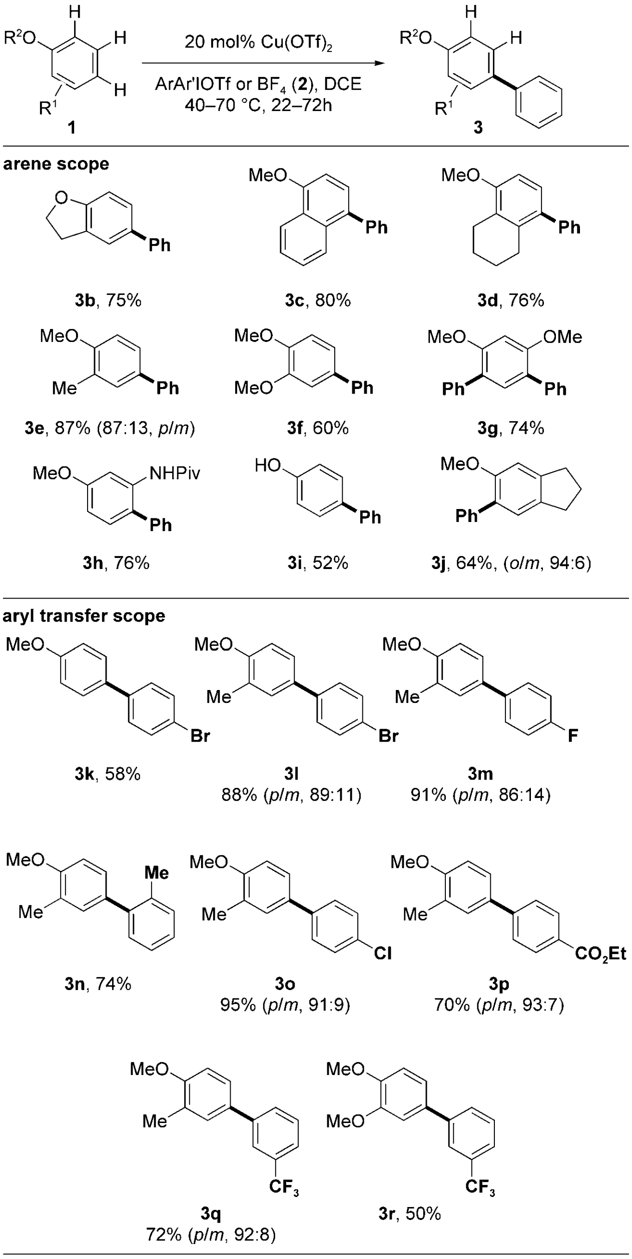


Scheme 1. Initial result for the *para* arylation of anisole.

We next investigated other phenol-derived substrates to survey the generality of this arylation (Scheme 2). 2,3-Dihydrobenzofuran, methoxynaphthalene, and a tetrahydronapthalene derivative all delivered the products resulting from arylation *para* to the oxygen atom with exquisite selectivity (**3b–d**). 2-Methylanisole was highly reactive, although a small amount of arylation *meta* to the oxygen atom was observed, presumably because of the competing electronic influence of the methyl group (**3e**). Molecules bearing two methoxy groups could also be monoarylated (**3f**) or diarylated (**3g**) depending on the arene substitution pattern. The methoxy group is capable of overpowering the *meta*-directing effect of the pivanilide, thereby resulting in arylation at the *para* position (**3h**), and a synthetically useful yield for the *para* arylation of phenol (**3i**) was observed by using our protocol. Interestingly, blocking the *para* position results in *ortho* selectivity (**3j**), and this reactivity pattern draws instructive parallels with the classical reactivity of anisole in standard S_EAr reactions. Importantly, the methoxy group can be used as an active functionality in nickel-catalyzed cross-coupling reactions with arylboronic esters, thus allowing further derivatization.[8] Diversely substituted and readily accessed diaryliodonium salts could be successfully used (Scheme 2).[9] Symmetrical iodonium salts were compatible, as were the mesityl- and tri(isopropylphenyl)-bearing unsymmetrical iodonium salts used in our previous studies.[7]

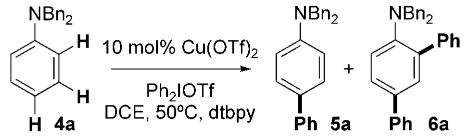


Scheme 2. Scope of the arylation of phenol derivatives. Tf = trifluoromethansulfonyl; DCE = 1,2-dichloroethane; Piv = *t*BuCO.

To increase the generality of this *para*-arylation process we next considered aniline derivatives. Numerous palladium(II)-catalyzed *ortho*-selective C–H arylations on acetanilides have been reported,[10] and we have developed a copper(II)-catalyzed *meta*-selective process.[7b] However, to the best of our knowledge, no *para*-selective process exists for anilines. We previously observed that *N*-methyl- and *N*,*N*-dimethylanilines resulted in *N*-arylation and decomposition, respectively, under our conditions, and that *N*-sulfonyl compounds are unreactive.[7b] Despite this, we hypothesized that judicious choice of an N-protecting group should permit *para*-selective arylation (Scheme 1).

Accordingly, we were pleased to find that *N*,*N*-dibenzylaniline was converted into the desired product **5a** after reaction at only 50 °C (Table 1, entry 1). Usefully, the benzyl groups are readily removed by hydrogenolysis. Optimization revealed the necessity of 2,6-di-*tert*-butylpyridine (dtbpy) as base to capture the TfOH generated in the reaction. At high conversions we also observed a deleterious *ortho* arylation of the desired product (to give **6a**; Table 1, entries 2 and 3); this was prevented by inverting the reaction stoichiometry (Table 1, entry 4).

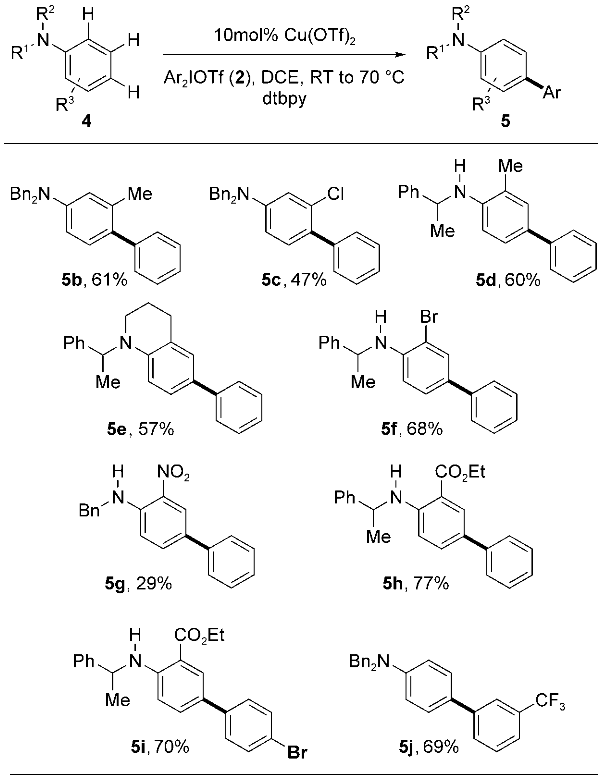
Table 1: Optimization of *para*-selective arylation of *N*,*N*-dibenzylaniline.[a]



Entry	Ph_2IOTf [equiv]	Ratio **5a**/**6a**	Conv., yield [**5a**, %]
1	1.1	9.0:1	75, –
2	1.3	4.2:1	91, 61
3	1.5	2.9:1	95, –
4	0.5	> 95:5	85, 77

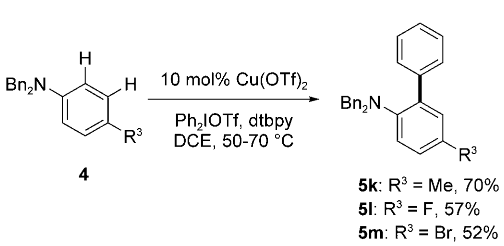
[a] dtbpy = 2,6-di-*tert*-butylpyridine.

A variety of substituted anilines are compatible with this process (Scheme 3). *Meta*-substituted anilines participated, with some diarylation being responsible for lower yields (**5b,c**). *Ortho*-substituted anilines work best with only one (modified) benzyl group, thus enabling electron-withdrawing and halogen-containing substrates to undergo the *para*-selective arylation process (**5d**,**f–h**). Arylation of a delicate tetrahydroquinoline showcased the potential for the construction of versatile heterocyclic biaryls (**5e**). The reaction still proceeds even in the presence of a strongly electron withdrawing nitro group, albeit in low conversion and yield (**5g**); additionally this product contains a versatile orthogonally protected 1,2-diamine.



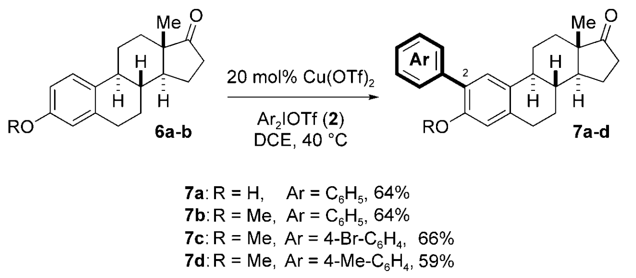
Scheme 3. *Para*-selective arylation of anilines.

When performing the reaction on *para*-substituted anilines, we obtained selective *ortho* arylation (Scheme 4). Notably, no di-*ortho*-arylation occurs, a drawback of many existing *ortho*-arylation procedures.[10] We speculate that the introduction of the *ortho*-aromatic group causes the nitrogen atom to twist out of plane with the aromatic ring, thus reducing conjugation of the lone pair of electrons and "switching off" the aniline to a second arylation.



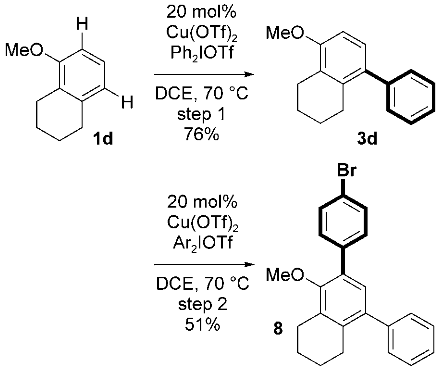
Scheme 4. *Ortho*-selective arylation of anilines.

To further explore its applicability we tested the new reaction on molecules containing complex architectures. Accordingly, the arylation of estrone and its methylated derivative proceeded at only 40 °C and included the transfer of aryl groups capable of further functionalization, thus demonstrating the mild and selective nature of our copper-catalyzed transformation (Scheme 5).[11]



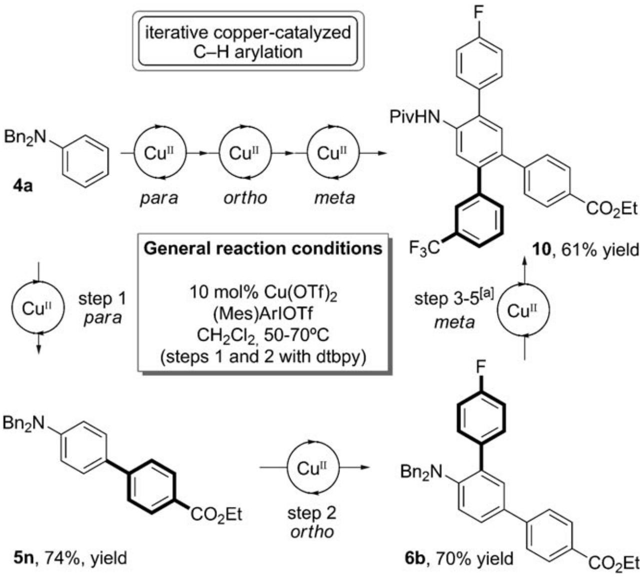
Scheme 5. Site-selective arylation of estrones.

We next sought to combine controllable *para* and *ortho* arylation of anisoles into an iterative process.[12] Starting from 5-methoxytetrahydronapthalene, *para*-phenylation delivered **3d** in 76% yield, and a second iteration added a 4-bromophenyl group in the *ortho* position, to give differentially diarylated product **8** (Scheme 6).



Scheme 6. Iterative arylation of phenol derivatives.

To extend this concept further, we showed that we can use our copper-catalyzed arylation methodology to functionalize all three positions of anilines—*ortho*, *meta*, and *para*. *N*,*N*-Dibenzylaniline first underwent *para*-selective arylation to **5n** (Scheme 7, step 1). The second iteration with a different diaryliodonium salt resulted in *ortho* arylation and led to the formation of differentially diarylated product **6b** (step 2). After a protecting-group switch (steps 3 and 4) from *N*,*N*-dibenzyl to *N*-pivaloyl, we performed a *meta*-selective arylation (step 5) by using a third diaryliodonium salt and the conditions detailed previously.[7b] This allowed the formation of the quateraryl compound **10** with exquisite control

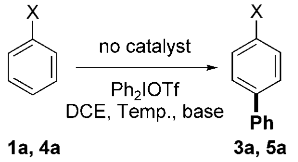


Scheme 7. Iterative arylation of aniline derivatives. [a] NBn$_2$ to NHPiv; step 3: Pd-C, H$_2$, MeOH then step 4; PivCl, Et$_3$N, THF (78 % yield over 2 steps). Mes = 2,4,6-trimethylbenzene.

of the regioselectivity, in high chemical yield, and crucially using only five chemical operations.

As part of our studies into the mechanism of this arylation process we tested the reaction in the absence of the copper catalyst.[13] Reaction occurred only at elevated temperature and, after three days at 90 °C, anisole produced (**3a**) in 23 % yield, while aniline (**4a**) gave **5a** in 59 % yield (determined by ^{1}H NMR spectroscopy; Table 2). In both cases this gives a significantly lower yield than obtained with the presence of the copper catalyst at lower temperature (Table 1).

Table 2: Copper-free arylation of electron-rich arenes.



X	*T* [°C]	Base	Ph$_2$IOTf [equiv]	Yield [%][a]
NBn$_2$	70	dtbpy	2.0	–
NBn$_2$	80	dtbpy	1.3	–
NBn$_2$	90	dtbpy	1.3	59% (**5a**)[b]
OMe	90	–	4.0	23% (**3a**)[c]

[a] Yield determined by NMR spectroscopy. [b] Ratio of monoarylation (**5a**) to diarylation (**6a**) is 4.5:1. [c] *para* only. Ph$_2$I-BF$_4$ gave only traces of **3a** at this temperature.

In regard to our original mechanistic proposal,[7] a pathway involving a copper(III)-aryl intermediate now seems less likely.[14] When considering alternative pathways we noted the hypervalent iodine mediated coupling of highly electron-rich arenes and thiophenes, which has been the focus of elegant work by Kita et al.[6] They also reported a reaction of in situ generated iodonium salts with electron-rich arenes and heteroarenes, which is proposed to proceed by single-electron transfer (SET) processes.[15] Whilst we cannot be certain that our reaction does not proceed by a similar mechanism, we think that it is unlikely because the phenol and aniline substrates exhibit selectivity patterns that are absolutely consistent with classical nucleophilic reactivity—reaction at the *para* position first, as in simple Friedel–Crafts processes or halogenation—whereas an SET mechanism would be expected to form regioisomeric mixtures of biaryl compounds.[16] This makes aryl radical cation intermediates seem less likely, a theory that is reinforced by the observation that radical-scavenging reagents do not affect our arylation process.

Although it is clear that the copper salt catalyzes the arylation reaction, the reaction in the absence of catalyst could be explained by a thermally induced dissociation of the counterion, thereby creating a highly electrophilic aromatic species that undergoes attack by the electron-rich arene. Moreover, it is possible that the copper catalyst also induces dissociation of the triflate anion to form a similar activated aryliodonium species.[13,17,18] This would rationalize the reactivity increase upon employing copper catalysts, whilst still delivering identical regioselectivity. Although we cannot be certain of the exact reaction mechanism, we believe that this transformation could be legitimately regarded as a “Friedel–Crafts arylation” reaction based on the observed *ortho*/*para* selectivity, and studies to elucidate the precise reaction pathway are currently underway.

In summary, we have developed the first highly *para*-selective arylation of aniline and phenol derivatives. This copper-catalyzed Friedel–Crafts-type strategy precludes the need for prefunctionalization of the nucleophilic arene component and represents a significant advance in direct arylation methodology to form valuable biaryl bonds. We have also shown that it is possible to use this method to iteratively functionalize arenes with exquisite selectivity, expediting access to complex polyaryls.

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