meta *Functionalization*

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Copper(II)-Catalyzed *meta*-Selective Direct Arylation of α-Aryl Carbonyl Compounds**

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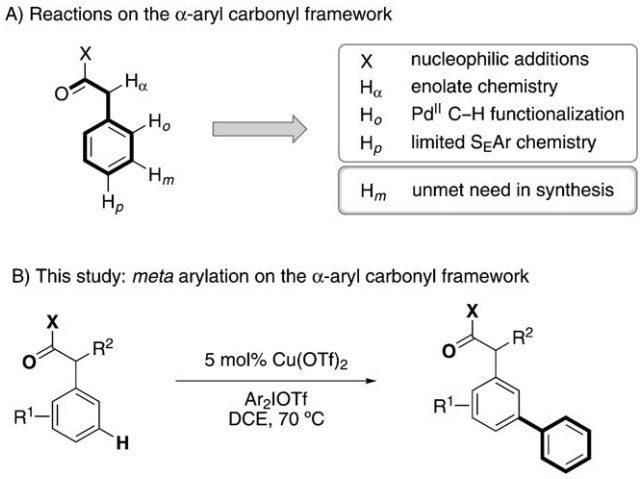
Substituted arenes dominate the properties of many natural products, medicines, and materials.[1] Therefore, the development of new methods for direct and selective aromatic functionalization is a persistent challenge for synthetic chemists.[2] A particularly important class of substituted aromatic compounds is the α-aryl carbonyl structure. These molecules represent broadly useful starting materials for complex molecule synthesis, and the basic structural framework is present in a wide range of medicinally relevant molecules.[3] Despite the importance of these structures, surprisingly few direct methods are available to selectively functionalize the arene nucleus in the absence of other groups: aromatic substitution reactions require directing functionality to control reactivity and selectivity; cross coupling processes need pre-installed functional groups; and while the acidity of the C–H bonds between the arene and carbonyl groups facilitates a wealth of enolate chemistry, it precludes the use of directed *ortho*-lithiation reactions.[4]

A potential solution to some of these limitations has recently been presented through the development of *ortho*-selective Pd^{II}-catalyzed C–H bond functionalization reactions.[5,6] The cyclometalation strategy employed in these transformations, however, cannot be used to facilitate *meta*- or *para*-functionalization of these molecules due to restrictive geometric constraints.[7,8] The synthetic utility of the generic α-aryl acetic acid motif would be significantly expanded by a methodology that provides direct access to isomeric molecules of potentially beneficial therapeutic value (Scheme 1 A). Herein, we report a copper-catalyzed *meta*-selective arylation of the α-aryl carbonyl scaffold with diaryliodonium salts that is directed by a remote and versatile Weinreb amide group (Scheme 1 B). This method provides a novel synthetic route to arenes displaying diverse substitution, benzylic chirality and quaternary centers. Its potential is further enhanced through its compatibility with iterative C–H bond functionalization methods that will have broad utility in the synthesis of highly functionalized arenes.



Scheme 1. The utility of the α-aryl carbonyl framework.

As part of our studies towards *meta*-selective functionalization processes,[8d] we postulated that the location of a carbonyl group plays a key role in determining the selectivity of our Cu^{II}-catalyzed *meta*-arylation of pivanilides. To test this hypothesis, we speculated that the α-aryl carbonyl would also provide a similar reactivity platform because the carbonyl motif is displayed in a similar position relative to the arene nucleus. Notably, the arene nucleophilicity of the electronically neutral α-aryl carbonyl motif is drastically different to the electron-rich pivanilide.

To test whether α-aryl carbonyl compounds could be functionalized at the *meta*-position, we prepared diethylamide **1a** and treated it with diphenyliodonium triflate and 20 mol% $Cu(OTf)_2$ in dichloroethane at 70 °C, conditions that are identical to those used for the arylation of pivanilides.[8d] After reaction for 24 h we were delighted to isolate a 72% yield of the *meta*-arylation product **2a**, importantly this was the only arylation product observed in the reaction (Table 1, entry 1). Not only does this result confirm that the carbonyl group is indeed responsible for the selectivity of this reaction, it also demonstrates that aromatic groups that lack any strong electronically or sterically directing substituents are still compatible with this *meta*-selective process. To the best of our knowledge, only Ir-catalyzed borylation of 1,3-disubstituted arenes[8b,c] is capable of achieving this type of transformation.

Having identified this new reactivity of α-aryl acetamides, we next assessed the nature of the carbonyl moiety by testing a range of substrates with our standard Cu^{II}-catalyzed

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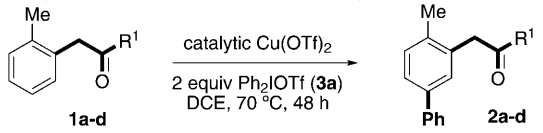
Table 1: Optimization of the *meta*-selective arylation reaction.[a]



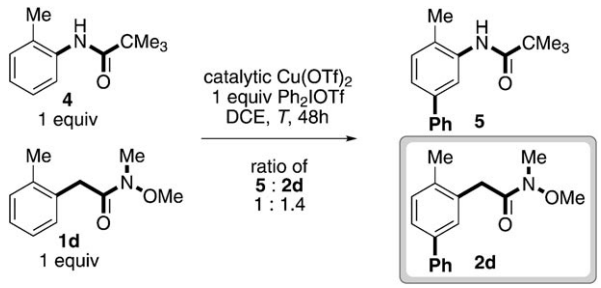
1a-d 2a-d

Entry	R^1	$Cu(OTf)_2$	NMR Yield (yield[b]) [%]
1	NEt_2 (**1a**)	20 mol%	75 (72)
2	OH (**1b**)	20 mol%	–
3	OEt (**1c**)	20 mol%	40 (38)
4	N(OMe)Me (**1d**)	20 mol%	76
5	N(OMe)Me (**1d**)	10 mol%	80
6	N(OMe)Me (**1d**)	5 mol%	93 (84)

[a] DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl. [b] Isolated yield after chromatography.

arylation conditions. We found that while α-arylacetic acid **1b** gave a complex mixture of undesired products, ester **1c** gave a moderate yield of arylated compound (**2c**) and was completely selective for the *meta*-position (Table 1, entries 2, 3).[5a] However, the superior performance of α-aryl acetamides (**1a**) led us to consider other amide functions, and we found that using Weinreb amide **1d** improved the yield in the arylation process (entries 4, 5). Using mild optimized reaction conditions, treatment of **1d** with 2 equivalents of diphenyliodonium triflate (**3a**) and 5 mol% $Cu(OTf)_2$ gave **2d** in 84% yield (Table 1, entry 6). Notably, the Weinreb amide motif also offers significant synthetic versatility in further transformations.

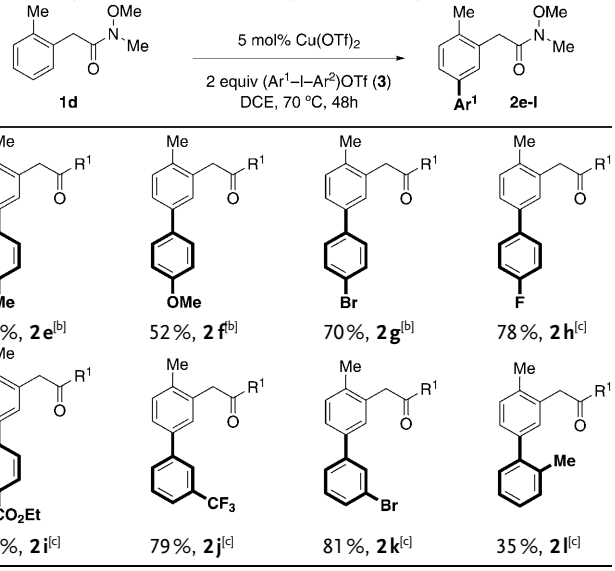
The improved reactivity of the α-aryl Weinreb amides may arise from the increased electron density on the carbonyl oxygen as a result of the α-heteroatom effect.[10] Indeed, a competition experiment between Weinreb amide **1d** and pivanilide **4** shows a preference for the formation of **2d** over **5** (Scheme 2). This is remarkable considering the drastically different electronic properties of these arenes and underlines the importance of the carbonyl group in this reaction.



Scheme 2. Competition experiment between **1d** and **4**. Ratio of **5**:**2d** determined by ^{1}H NMR spectroscopy.

We next explored the capacity of this useful *meta*-selective Cu^{II}-catalyzed arylation process (Table 2). Pleasingly, a range of aryl groups could be transferred through symmetrical or unsymmetrical diaryliodonium triflates in good yield with exquisite *meta*-selectivity. These salts are readily prepared in a one-step process from commercial materials.[11] Significantly, functionally diverse aryl groups displaying electron-rich (**2e,f**), electron-deficient (**2h–j**) and halogen-containing substituents (**2g,h,k**) were transferred in good yield; these latter groups can facilitate subsequent chemoselective processes.

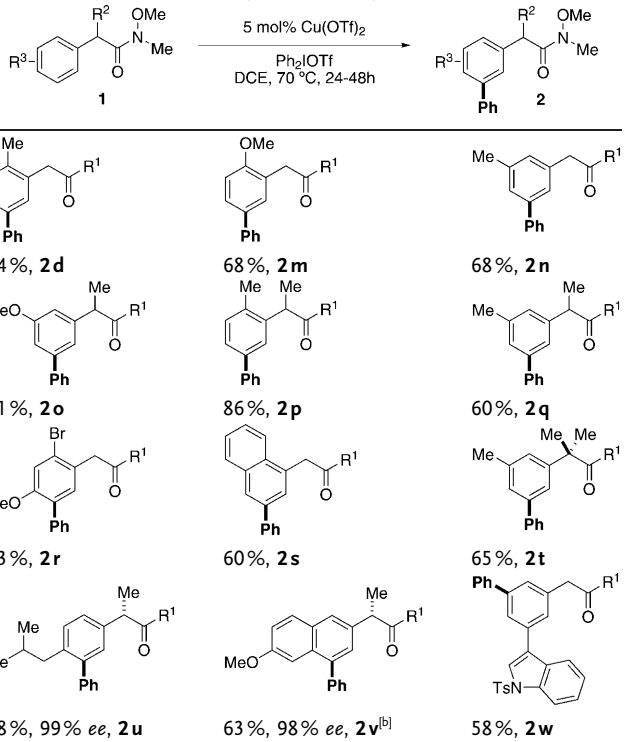
Table 2: Aryl transfer in the *meta*-arylation of α-arylacetamides.[a]



[a] R^1 = N(OMe)Me. [b] $Ar^1 = Ar^2$. [c] Ar^2 = mesityl.

The nature of the α-arylacetamide could also be varied. Alkyl groups are tolerated in all positions on the aromatic ring, with selective *meta*-arylation delivering complex 1,2,4- and 1,3,5-trisubstitued arenes (Table 3). When strongly elec-

Table 3: Scope of the *meta*-arylation of α-arylacetamides.[a]

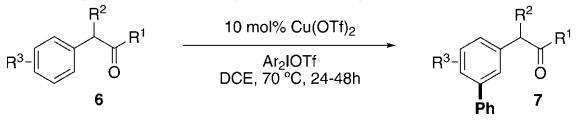


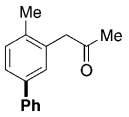
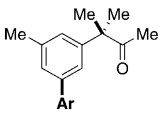
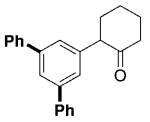
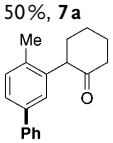
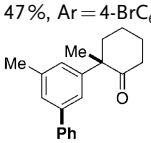
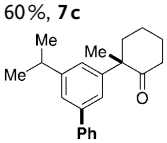
[a] R^1 = N(OMe)Me. [b] 10 mol% $Cu(OTf)_2$, 50 °C.

tron-donating substituents are located on the arene, the remote carbonyl group overrides these *para*-directing motifs to generate the isomer with the aryl group *meta* to both substituents (**2n**,**o**). The reaction tolerates molecules possessing orthogonal functionalities allowing access to complex arenes (**2r**), albeit in reduced yield due to incomplete conversion. The process works well for substrates displaying α-substitution (**2o–q**) providing the *meta*-arylated products in good yield. Moreover, enantiopure (*S*)-ibruprofen and (*S*)-naproxen derivatives underwent selective *meta*-arylation to **2u** and **2v** in 58% and 63% yield, respectively, leading to potential analogues of known nonsteroidal antiinflammatory drugs (NSAIDs). The mild reaction forms the product without loss of chiral integrity at the benzylic center, a result that rules out a mechanism involving enolization of the amide. α,α-Disubstitution can also be accommodated (**2t**), providing access to functionalized aryl motifs embedded within molecules that contain all carbon quaternary benzylic centers. An indole-containing substrate is tolerated under the mild reaction conditions and *meta*-arylation delivers the functionally rich 1,3,5-trisubstituted arene **2w**.

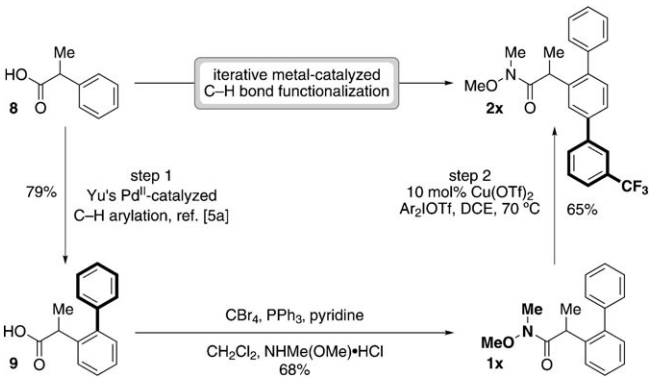
The *meta*-directing power of the remote carbonyl group was probed through the arylation of α-aryl ketones **6**, thereby significantly expanding the scope and generality of the process. Pleasingly, under our standard reaction conditions, methyl ketone **6a** underwent *meta*-arylation in reasonable yield to **7a** (Table 4). We also showed that a range of simple alkyl substituted α-arylketones work well in the *meta*-arylation, demonstrating the application of this transformation to even less reactive systems.

Table 4: Scope of the *meta*-arylation of α-arylketones.



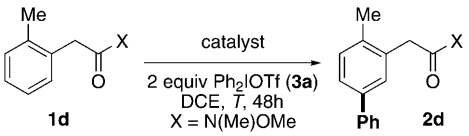
		
50%, **7a**	47%, Ar = 4-BrC_6H_4, **7b**	60%, **7c**
		
79%, **7d**	66%, **7e**	84%, **7f**

We next tested whether our new *meta*-arylation process could provide access to complex arene products through iterative metal-catalyzed C–H bond functionalization methods (Scheme 3).[12] For example, starting from arylacetic acid **8**, Yu's *ortho*-selective Pd^{II}-catalyzed C–H arylation would deliver **9**.[5a] Conversion to the Weinreb amide **1x**, followed by our Cu^{II}-catalyzed *meta*-selective arylation (65%) resulted in complex phenylacetic acid derivative **2x** in just three steps from a commercial building block. Such methods demonstrate the potential of iterative metal-catalyzed C–H bond functionalization for the rapid assembly of complex molecules.



Scheme 3. Iterative metal-catalyzed C–H bond functionalization.

As part of our ongoing studies to elucidate the origin of the *meta*-arylation reaction, we tested whether the selectivity was compromised at higher temperatures than our optimal conditions (Scheme 4), and we were extremely surprised to



Catalyst	*T* [°C]	Yield (conv.)
5 mol% $Cu(OTf)_2$	70	84 (93)%
no catalyst	70	0
no catalyst	80	(65)%
no catalyst	90	59 (64)%

Scheme 4. Metal-free *meta*-selective arylation reaction.

find that the *meta*-arylated product was still formed with the exquisite selectivity in the absence of the copper catalyst, albeit in moderate yield. A closer inspection of this result revealed an extremely narrow threshold temperature range for the copper-free reaction. While we observed reaction at 90 °C and 80 °C, no product was observed at 70 °C (our original operating temperature) in the absence of copper catalyst (Scheme 4). This suggests that the *meta*-selectivity may not be the result of a Cu^{III}–aryl intermediate that we had previously hypothesized in our original working model.[13] However, it does suggest that the copper salt must still be facilitating the reaction at 70 °C through an interaction with the diaryliodonium salt. In light of these observations, we are currently investigating the mechanism of this remarkable metal-free *meta*-arylation process, and these results will be published in due course.[14]

In conclusion, we have developed a method for the *meta*-selective arylation of the highly versatile α-aryl carbonyl motif with diaryliodonium salts. In this Cu^{II}-catalyzed process the remote carbonyl group is capable of overpowering even strongly directing functionalities to form the elusive *meta*-

products. Substitution is tolerated at all positions on the α-aryl carbonyl framework and the *meta*-arylation process can be linked with other cross coupling reactions through iterative C–H bond functionalization methods. We also discovered that a "metal-free" arylation process is also possible, providing a new angle for the origin of the remarkable *meta*-selectivity observed in this reaction.

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[14] 2-Me-pivanilide **4** (our standard substrate in Ref. [8d]) also undergoes metal-free *meta*-selective arylation to **5** at elevated temperature of 80 °C in 78% yield. In the absence of catalyst at 70 °C only trace amounts of product are observed.

