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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Overriding Ortho−Para Selectivity via a Traceless Directing Group Relay Strategy: The Meta-Selective Arylation of Phenols

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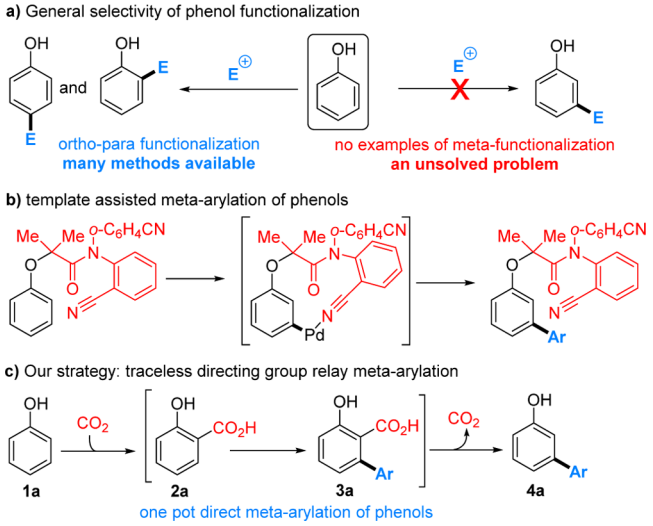
Supporting Information

ABSTRACT: The direct functionalization of phenols at the ortho and para position is generally facilitated by the electron-donating nature of the hydroxyl group. Accessing meta-functionalized phenols from the parent phenols, on the other hand, generally requires lengthy synthetic sequences. Here, we report the first methodology for the one-pot direct meta-selective arylation of phenols. This methodology is based on a traceless directing group relay strategy. In this process carbon dioxide is used as a transient directing group which facilitates a palladium catalyzed arylation meta to the phenol hydroxyl group with iodoarenes. This transformation proceeds with complete meta-selectivity and is compatible with a variety of functional groups both in the phenol and in the iodoarene coupling partner.

Phenols are important structural motifs found in natural products, pharmaceuticals, and polymers, as well as common versatile building blocks for synthesis.[1] Thus, methods for the efficient synthesis of phenols selectively functionalized at specific ring positions are of high interest. Due to the well-known ortho/para directing ability of the electron-donating hydroxyl group, a great many methodologies for the ortho- and para-functionalization of phenols have been reported and are commonly exploited (Scheme 1a).[1,2] However, this same strong directing effect prevents the selective direct functionalization of phenols at the meta position. Consequently, over the past decade, a variety of indirect methodologies have been developed based on the oxidation of substituted cyclohexanones,[3] cycloaddition reactions,[4] or the late installation of the OH functionality.[5] Given the wide availability of cheap phenol starting materials, the development of a methodology capable of using those building blocks to directly produce meta-functionalized phenols would be highly desirable. Ideally, such methodology would proceed in one step and be operationally simple and scalable. To date, only a handful of methodologies able to perform a direct meta-functionalization of substituted benzenes have been reported but none allow for the direct meta-selective functionalization of phenols.[6,7] A recent groundbreaking report by Yu and co-workers described a strategy for the meta-olefination[8] and arylation[9] of phenols that involves the installation at the hydroxyl of an innovatively designed moiety containing a strategically positioned nitrile group able to coordinate a Pd catalyst and therefore direct the functionalization at the meta-position (Scheme 1b). However, this approach requires five independent synthetic operations/purifications. Herein we report the first strategy allowing the direct selective meta-arylation of phenols.[10] Our methodology uses CO_2 as a traceless relay directing group in order to facilitate direct meta-arylation of phenols in a single synthetic operation. This versatile process is easily scalable and allows fast access to meta-arylphenols, important structural motifs contained in biologically active compounds, natural products, and organic electronic materials.

Scheme 1. Strategies for Regioselective C−H Functionalization of Phenols



We hypothesized that the meta-functionalization of phenols may be accessible via a traceless directing group relay strategy (Scheme 1c). We envisioned that, instead of transforming the hydroxyl group into a meta-directing group, we could use it to direct the ortho-installation of a secondary removable directing group. This second group would then facilitate an ortho-arylation (meta to the hydroxyl group) and, when cleaved, reveal the desired meta-arylated phenol. Further, we envisaged that by carefully selecting this traceless relay directing group,[11] it should be possible to carry out this transformation *in a single synthetic operation*. Based on the well-known reactivity of phenols toward ortho-carboxylation with CO_2 (i.e., Kolbe−Schmitt reaction),[12] recent work on the transition-metal-

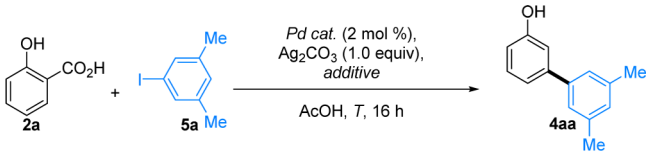
Received: January 15, 2014
Published: March 11, 2014

dx.doi.org/10.1021/ja500457s | J. Am. Chem. Soc. 2014, 136, 4109−4112

catalyzed decarboxylation of benzoic acids,[13,14] and the suitability of carboxylic acids to act as directing groups to mediate ortho-C−H arylations,[15] we anticipated that CO_2H would be an ideal traceless directing group candidate for testing our hypothesis (Scheme 1c).

We started our investigation by exploring the reactivity of salicylic acid (**2a**) with iodoarene **5a** toward the tandem arylation/decarboxylation process (Table 1). Examination of

Table 1. Optimization of the Tandem Arylation/Decarboxylation of Salicylic Acid 2a[a]



entry	Pd cat.	additive	T (°C)	yield[b]
a	$Pd(OAc)_2$	–	130	29%
b	$Pd(PPh_3)_4$	–	130	26%
c	PEPPSI-IPr	–	130	59%
d	PEPPSI-IPr	–	120	48%
e	PEPPSI-IPr	–	150	70%
f[c]	PEPPSI-IPr	–	150	83%
g[c]	PEPPSI-IPr	K_2CO_3 (0.5 equiv)	150	92%

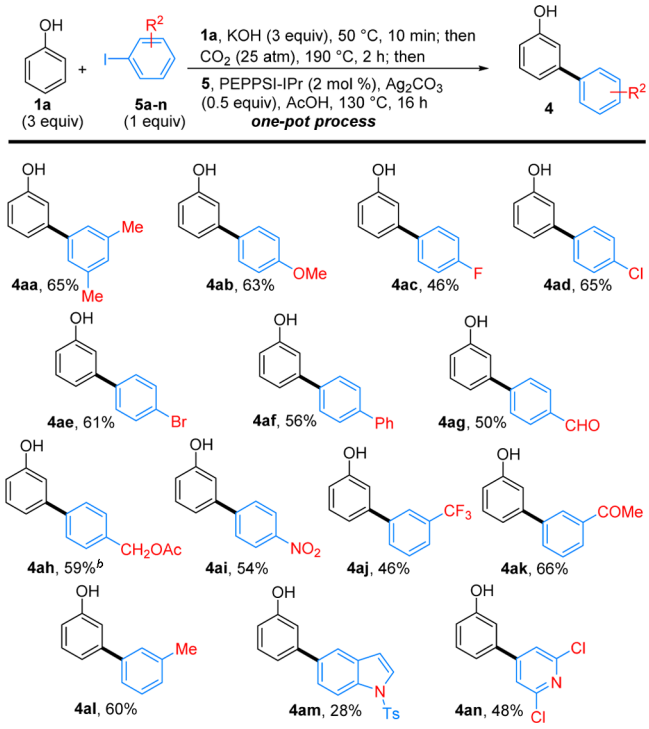
[a]Reactions were carried out with **2a** (1.0 equiv), **5a** (3.0 equiv), Pd cat. (2 mol %), Ag_2CO_3 (1.0 equiv) in AcOH (1.0 M) for 16 h. [b]Yields were calculated by ^1H NMR analysis using an internal standard. [c]0.5 equiv of Ag_2CO_3 was used.

reaction conditions previously developed for a different class of benzoic acids led to formation of the desired meta-arylated product **4aa** in 29% yield (Table 1, entry a).[11k] The source of the Pd catalyst (Table 1, entries a−c) proved crucial, with PEPPSI-IPr[16] leading to the best yields. The temperature of the reaction and the addition of K_2CO_3 as an additive were also found to improve the performance of the system, leading to the formation of **4aa** in 92% yield (Table 1, entries d−g).

Having developed suitable conditions for the arylation/decarboxylation tandem process we studied the development of a compatible carboxylation reaction, in order to access the desired one-pot meta-arylation process. Whereas the Kolbe−Schmitt carboxylation would traditionally require the synthesis and isolation of the sodium or potassium phenoxide from phenol prior to reaction with CO_2, we investigated the *in situ* deprotonation and carboxylation of phenol (**1a**) in order to develop a truly operationally simple process. After extensive optimization we found that treating **1a** with KOH under 25 atm of CO_2 at 190 °C for 2 h, followed by addition of the iodoarene **5a**, the Pd catalyst, Ag_2CO_3, and AcOH, and further reaction at 130 °C for 16 h allowed the selective direct meta-arylation of **1a** to **4aa** in 65% isolated yield after column chromatography (Scheme 2, **4aa**). This represents an average of 87% for each of the three steps in the carboxylation/arylation/decarboxylation overall sequence. The process is completely selective for the meta position, with no arylation in ortho or para being detected.[17] Further, unlike most direct arylations of mono-substituted arenes, the reaction is completely selective for mono- versus bis-arylation.[10]

Gratifyingly, our traceless directing group relay meta-arylation of phenol **1a** is very general (Scheme 2), with both electron-donating and -withdrawing groups being well tolerated in para and meta positions of the iodoarene coupling partner

Scheme 2. Scope of the Meta-Arylation of Phenol (1a) with Iodoarenes[a]



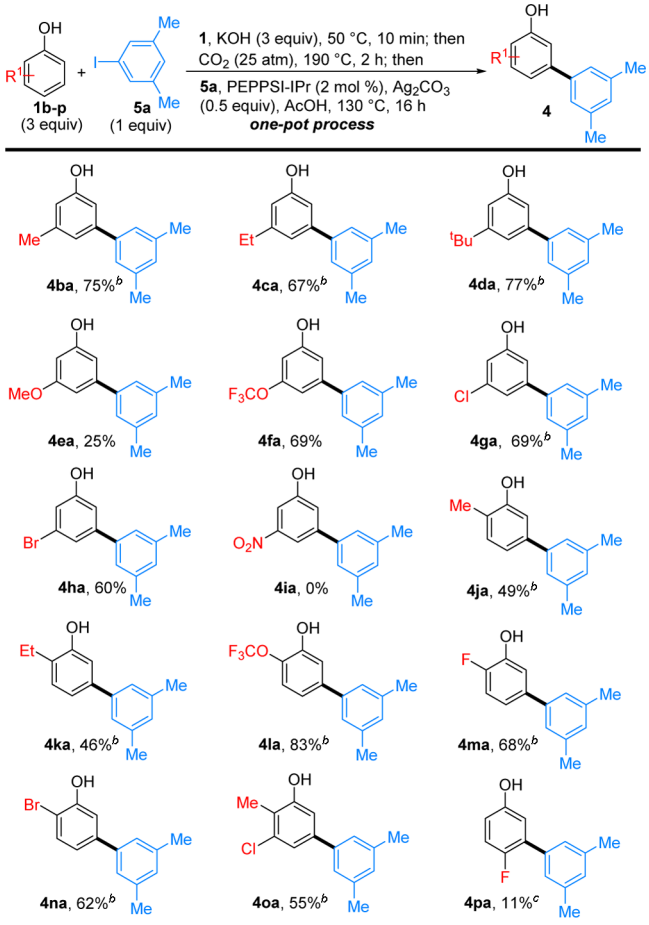
[a]Yields are of pure isolated product. [b] *para*-Iodobenzyl alcohol was used as starting material.

(for example, *p*-OMe **4ab** and *p*-NO_2 **4ai** were obtained in 63% and 54% isolated yield, respectively). The reaction conditions are compatible with Cl and Br, which are convenient handles for further functionalization (**4ad**, **4ae**, and **4an**). Interestingly, aldehyde functionality (**4ag**), despite its sensitivity to oxidation, is also compatible with the reaction without requiring the use of protecting groups. On the other hand, when *para*-iodobenzyl alcohol was used as the coupling partner, an *in situ* acetylation occurred leading to the acetyl ester **4ah**. Ortho-substituents at the iodoarene are not tolerated, suggesting a sterically crowded intermediate is being formed during the coupling. Finally, heteroarenes such as iodoindole and iodopyridine can be used as coupling partners leading to the corresponding meta-heteroarylphenol products **4am** and **4an**.

We then explored the applicability of this novel strategy for phenol meta-arylation to ortho and meta substituted phenol starting materials **1b−o** (Scheme 3). Gratifyingly, a wide variety of substituted phenols smoothly underwent meta-arylation without any modification to the standard conditions developed. On the other hand, a number of substituted phenols were found to afford higher yields if 4 mol % of the Pd catalyst were added in two batches (2 mol % each) during the reaction, indicating that for some substrates catalyst decomposition can be a problem. In this case there was no advantage using PEPPSI-IPr over the cheaper $Pd(OAc)_2$. Moderately electron-donating substituents at C3 led to good yields of meta-arylation (**4ba**, **4ca**, and **4da**). On the other hand, the more electron-donating MeO group afforded a low yield of the desired product **4ea**, due to fast protodecarboxylation of the salicylic acid intermediate. This side reaction could be prevented by using a CF_3O group instead which allowed the arylation to proceed in good yield (**4fa**). Electron-withdrawing groups at

dx.doi.org/10.1021/ja500457s | J. Am. Chem. Soc. 2014, 136, 4109−4112

Scheme 3. Scope of the Meta-Arylation of Phenols (1b–p) with Iodoarene 5a[a]



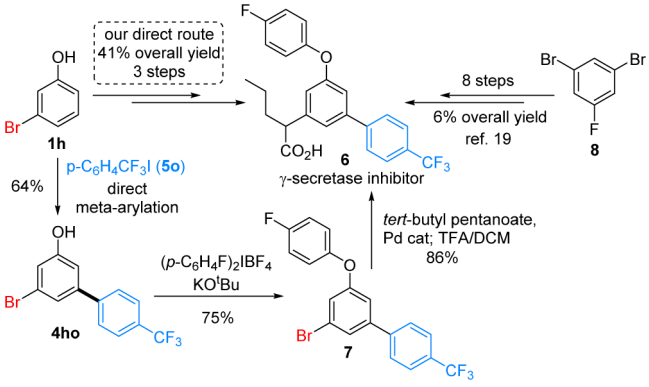
[a]Yields are of pure isolated product. [b] 4 mol % $Pd(OAc)_2$, added in two batches, was used instead of PEPPSI-IPr, and the reaction was stirred for 40 h. [c] Yield determined by ^1H NMR analysis using an internal standard.

C3, including Cl and Br, were also compatible with the reaction (**4ga** and **4ha**), but the strongly electron-withdrawing NO_2 group led to no reaction, by preventing the initial carboxylation step. A variety of substituents at C2 were also tolerated, affording the corresponding meta-arylated phenols in good yields (**4ja–oa**). As was the case with phenol (**1a**), in all cases the arylation reaction was completely selective for the meta position, with no other arylation products being observed.[18] On the other hand, substitution at C4 of the phenol was found incompatible with the arylation step: *para*-fluorophenol afforded arylation product **4pa** in only 11% yield, whereas *para*-methylphenol led to no coupling (both underwent carboxylation in 50% and 61% yield, respectively). Similarly to the lack of tolerance for ortho-substituted iodoarenes, this result confirms that steric hindrance next to the reacting C–H bond is deleterious, suggesting a highly sterically encumbered intermediate is being formed in the reaction.

This methodology is easily scalable. Applying our standard conditions, without any modification to the meta-arylation of **1b** with **5a** in a 5.0 mmol (1.2 g) scale of the iodoarene, afforded the corresponding biaryl **4ba** in 70% isolated yield (0.73 g, 3.5 mmol).

Because this methodology provides easy access to meta-arylphenols from cheap and readily available phenol starting materials, it allows streamlined access to molecules that would otherwise require many more steps for their synthesis. For example, the synthesis of γ-secretase inhibitor **6** (Scheme 4),

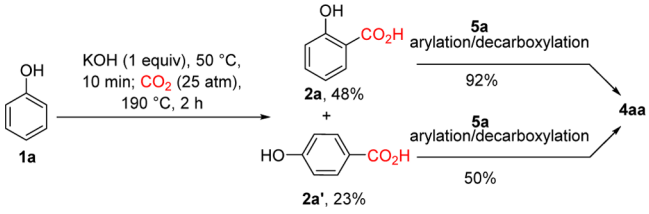
Scheme 4. Fast and Efficient Synthesis of γ-Secretase Inhibitor 6



under study for treatment of Alzheimer's disease, was accomplished in only three steps from 3-bromophenol (**1h**), with the key meta-arylation step forming **4ho** in 64% isolated yield. A subsequent O-arylation[19] and α-alkylation[20] afforded **6**, with 41% overall yield after only three steps. The previous synthesis of **6** required eight separate reaction steps and purifications starting from 1,3-dibromo-5-fluorobenzene (**8**), with 6% overall yield.[21]

In order to better understand the present transformation we stopped and analyzed the reaction of **1a** after the carboxylation step (Scheme 5). Contrary to our initial hypothesis,

Scheme 5. Mechanistic Investigation



carboxylation of **1a** was found to proceed at both the ortho and para position leading to a 48:23 mixture of acids **2a** and **2a′**. We then tested **2a** and **2a′**, separately, in the tandem arylation/decarboxylation process. Interestingly, both hydroxybenzoic acids afforded the meta-arylation product **4aa**, indicating the CO_2H group is able to direct the arylation meta to OH, and the resulting biaryl protodecarboxylates regardless of the regiochemistry of the initial carboxylation. This regioconvergence results in a more robust process, consistent with the complete meta-regioselectivity of arylation observed in all reactions. The ortho-arylation step is consistent with a Pd(II/IV) process as initially proposed by Daugulis, where the role of the Ag(I) salt would be as an iodide scavenger.[15a] Finally, the decarboxylation step of the electron-rich hindered intermediates **3** is likely mediated by Pd(II) as previously demonstrated for 2,6-disubstituted benzoic acids.[11k]

In conclusion, we report the first example of a one-pot direct meta-functionalization of phenols. This process is based on a strategy that involves the use of CO_2 as a traceless directing group. Upon carboxylation, the hydroxyl group relays the

dx.doi.org/10.1021/ja500457s | J. Am. Chem. Soc. 2014, 136, 4109–4112

directing power to the newly installed carboxylate which is then able to facilitate a tandem arylation/decarboxylation process that affords meta-arylphenol products and leaves no trace of the participation of CO_2 in the overall process. This transformation is completely regioselective, and compatible with a variety of substituents in both coupling partners. We envisage that this traceless directing group strategy will be applicable to the development of other useful one-pot meta-functionalization processes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the European Research Council for a Starting Grant (to I.L.), the China Scholarship Council and Queen Mary University of London for a studentship (to J.L.), the Marie Curie Foundation for an Intra-European Fellowship (to S.P.), and the EPSRC National Mass Spectrometry Service (Swansea).

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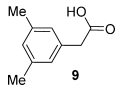
(17) The full mass balance of the reaction as determined by ^{1}H NMR crude analysis showed 73% of **4aa**, 15% of **5a**, 11% of **9**, 0.8 equiv of **1a**, and 0.8 equiv of *ortho*- and *para*-salicylic acid (**2a** and **2a′**).



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(18) As a representative example, ^{1}H NMR crude analysis of the arylation of **1b** showed 81% **4ba**, 13% of **5a**, <5% of **9**, 1.3 equiv of **1b**, and 0.1 equiv of 2-hydroxy-4-methylbenzoic acid, **2b**.

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