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Palladium-Catalyzed Three-Component Coupling Reaction of *o*-Bromobenzaldehyde, *N*-Tosylhydrazone, and Methanol

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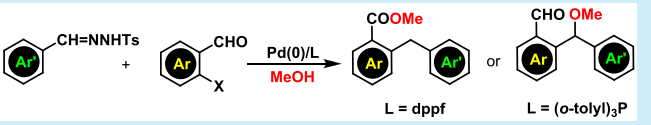
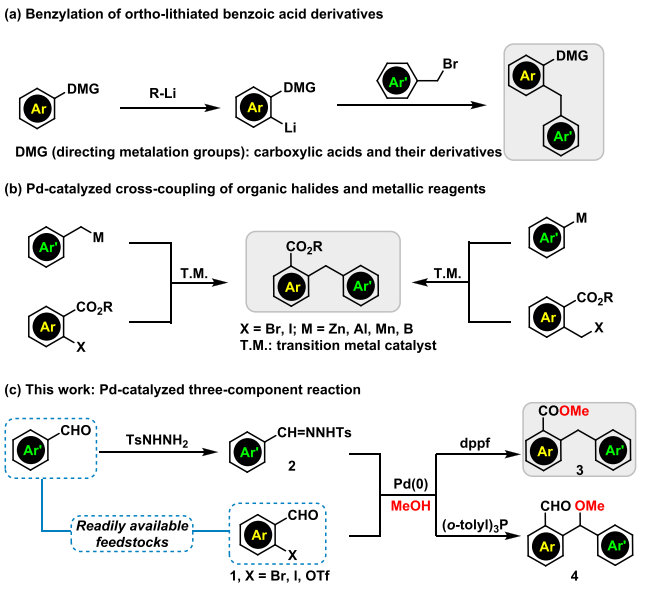
ABSTRACT: A ligand-controlled palladium-catalyzed three-component reaction of *o*-bromobenzaldehyde, *N*-tosylhydrazone, and methanol is described. This reaction uses readily available compounds as starting materials while displaying a broad substrate scope and good functional group compatibility.



2-Benzylbenzoic acid derivatives are highly valuable building blocks for organic synthesis.[1] A variety of bioactive compounds could be prepared by using these acid derivatives as key intermediates. Among known procedures for these deceptively simple-looking yet useful building blocks, the seemingly straightforward approach involves benzylation of *ortho*-lithiated benzoic acid derivatives (Scheme 1a). While this method was efficient for methylation of simple benzoic acid derivatives, the benzylation of corresponding *ortho*-lithiated arenes was suffered from low to moderate yields.[2] Furthermore, the preparation of analogues with structural complexity through this method could be problematic. Because multiple equivalents of strong base organolithium agents were required during the lithiation process, a mixture of regioisomers could be obtained when other coordinating groups were decorated on the aryl ring.[2b] Transition metal-catalyzed cross-coupling reaction of organic halides with organometallic agents is a modern optional approach (Scheme 1b).[3] However, the need to manipulate moisture sensitive organometallic reagents restricts the synthetic potential and functional group compatibility. Other methods, including reduction of *ortho*-benzoylated aromatic carboxylic acids or the oxidation of *ortho*-benzylated benzyl alcohols, may be not suitable for establishing a library of products with rich structural diversity, as the corresponding reactants were not readily accessible. In this context, the development of a new strategy[3h] that allows simultaneous setup benzyl and carboxyl functionalities via a single-step transformation of abundant feedstocks will be of high value to the synthetic and medicinal chemistry fields. Herein, we describe an unprecedented protocol by using palladium-catalyzed cross-coupling of 2-bromobenzaldehydes and *N*-tosylhydrazones as a versatile platform for accessing 2-benzylbenzoic esters (Scheme 1c). This reaction uses readily available materials as reactants and exhibits a broad substrate scope and good functional group compatibility, which may render our protocol practical and synthetically useful. Moreover, we found that the backbone of phosphine ligands exerted profound effects on altering the reaction pathways. Bidentate ligands mainly lead to the formation of desired diarylmethane **3**, and bulky monodentate ligands give methyl ether **4** as the major product while leaving the pendant aldehyde moiety intact.

Scheme 1. Selected Strategies for the Synthesis of 2-Benzylbenzoic Acid Derivatives



As pioneered by Van Vranken,[4] and later developed well by Barluenga,[5] Wang,[6] and others,[7] the migratory insertion of a palladium carbene intermediate has been proven to be versatile for the construction of carbon−carbon and carbon−heteroatom bonds. Recently, we have developed a palladium carbene[8] that participated in bridging C−H bond activation.[9] In these events,

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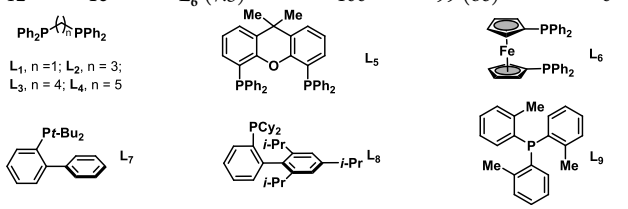
the carbene precursor acted as a bridging arm to deliver the palladium catalyst to the reacting site; the oxygen anion also acted as an internal nucleophile to accomplish the acylation. Illuminated by this discovery, we have conceived a palladium-catalyzed three-component reaction as a potential platform for the construction of 2-benzylbenzoic acid derivatives (Scheme 1c). Compared with our previous work, a number of obvious pitfalls must be kept in mind: (i) O−H bond insertion[10] of alcohol to the diazo compound generated in situ from *N*-tosylhydrazone and (ii) C−O bond formation through the coupling reaction of alcohol with aryl halide in the presence of a palladium catalyst.

At the outset of the study, readily available *o*-bromobenzaldehyde **1a** and *N*-tosylhydrazone **2b** were selected as the model substrates. Fortunately, when the reaction was carried out in MeOH at 60 °C for 3 h using $Pd(OAc)_2$ and dppm as the precatalyst and K_2CO_3 as the base, the desired diarylmethane **3b** was obtained, albeit in 15% GC yield (Table 1, entry 1).

Table 1. Evaluation of Reaction Conditions

entry[a]	1	ligand (mol %)	temp (°C)	3b (%)[b]	4b (%)[b]
1	1a	L_1 (7.5)	60	15	trace
2	1a	L_3 (7.5)	60	54	0
3	1a	L_7 (15)	60	4	30
4	1a	L_3 (7.5)	100	93 (85)	0
5	1a	L_2 (7.5)	100	80	1
6	1a	L_4 (7.5)	100	56	1
7	1a	L_6 (7.5)	100	99 (88)	0
8	1a	L_9 (15)	100	13	61
9[c]	1a	L_9 (15)	100	9	80 (72)
10	1a	L_8 (15)	100	28	18
11	1b	L_6 (7.5)	100	99 (86)	0
12[d]	1c	L_6 (7.5)	100	99 (86)	0



[a]Reaction conditions: **1** (0.3 mmol), **2b** (0.45 mmol), $Pd(OAc)_2$ (5 mol %), ligand (*x* mol %), K_2CO_3 (3.0 equiv) in MeOH (3.0 mL), stirring under an argon atmosphere. [b]GC yields using *n*-decane as an internal standard. Numbers in parentheses refer to isolated yields. [c]*t*-BuOK was used as a base. [d]$NaHCO_3$ was used as a base.

Switching the ligand to dppb enhanced the yield of **3b** to 54% (Table 1, entry 2). Intriguingly, when monodentate ligand JohnPhos was employed, the chemoselectivity was switched. 2-[Methoxy(*p*-tolyl)methyl]benzaldehyde **4b** was obtained as the major product (Table 1, entry 3). After the extensive evaluation of other reaction parameters,[11] we have identified a set of optimal conditions for the synthesis of **3b**, namely, carrying out the reaction at 100 °C, and using dppf (L_6) as a ligand, affording **3b** in 88% yield upon isolation (Table 1, entry 7). Gratifyingly, the three-component coupling that yields **4b** could also be increased by altering the ligand to L_9 (Table 1, entry 8). Replacing the base K_2CO_3 with *t*-BuOK could further enhance the yield of **4b** to 72% after isolation (Table 1, entry 9). *o*-Iodobenzaldehyde also worked well under the optimal condition (Table 1, entry 11). The reaction of triflate **1c** derived from salicylaldehyde under the optimal condition was not ideal. However, a brief examination of the effects of the base showed that $NaHCO_3$ was superior to others, affording **3b** in 86% isolated yield (Table 1, entry 12).

With the optimal conditions established, we next focused on exploring the scope of aldehydes and *N*-tosylhydrazones with different substituents on the aromatic rings (Scheme 2). With respect to aldehydes, a series of substituents, including electron-donating or electron-withdrawing groups on the phenyl ring of *o*-bromobenzaldehyde, were all compatible (Scheme 2, **3c**−**3n**), giving the corresponding products in moderate to excellent yields. In general, aldehydes bearing electron-donating groups react better than those bearing electron-withdrawing groups. The reaction of *o*-bromobenzaldehyde with a tosylate functionality at position 4 could also proceed well, while giving free phenolic product **3k** in 58% isolated yield, together with a 17% yield of **3d**. The heteroaromatic furan ring (**3o**), labile mom (**3n**) group, and alkynyl moiety (**3p**) were tolerated, as well.

For the scope of *N*-tosylhydrazones, the electron-donating and electron-withdrawing substituents at the *para*, *meta*, and *ortho* positions of the phenyl ring were all tolerated well. Notably, a potentially reactive bromo group was compatible (**3z** and **3aa**), which could be a useful handle for further cross-coupling reactions. *N*-Tosylhydrazones derived from thiophene-2-carbaldehyde and furan-2-carbaldehyde could also participate in the current transformation, while affording the corresponding products **3ag** and **3ah** in diminished yields. Pleasingly, hydrazones decorated by terminal alkenyl (**3an**), ferecenyl (**3ao**), ester (**3ap**), and amide (**3aq** and **3ar**) groups were good substrates for current three-component reactions. Dihydrazone could also couple with *o*-bromobenzaldehyde, giving the corresponding C_2-symmetric diester **3as** in 54% yield upon isolation. The current protocol was also amenable to late-stage modification of complex molecules. For instance, **3at**, **3au**, and **3ay** embedded with core structural motifs of approved drugs estrone, repaglinide, and mianserin were obtained in 68%, 52%, and 77% isolated yields, respectively.

As mentioned above, 2-benzylbenzoic acid derivatives are versatile building blocks. For example, **3i** has been applied for the synthesis of tricyclic benzothiazolo[4,5]azepine derivative **A**, which shows promising anxiolytic activity.[12] Product **3s** was used as a precursor to construct tetrahydroisoquinoline-3-carboxylic acid **B**, which could be a nonpeptide inhibitor of angiotensin II binding to the AT_2 site.[1c] According to very recent study, product **3w** bearing a fluoro atom could be applied for a straightforward synthesis of glucose-regulated protein 94 (Grp94) inhibitor **D**. **D** exhibits a 0.54 μm affinity and a 73-fold selectivity toward Grp94 and offers opportunities for inhibition of metastatic cancer.[1j] Product **3t** bearing two methoxyl groups on each phenyl ring provides an opportunity for the preparation of xanthene type dyes. Lavis and co-workers have used **3t** as a handle to synthesize carbofluorescein **C** and its derivative carborhodamine.[1i] Moreover, products **3ak** and **3am** could be applied for natural product synthesis, such as Justincidin E[1d,13] and Marosporin.[1h] It is worth mentioning that alcohols other than methanol are not suitable components under current conditions. As depicted, when ethanol was employed as a solvent, the desired adduct **3az** was produced in 23% NMR yield.

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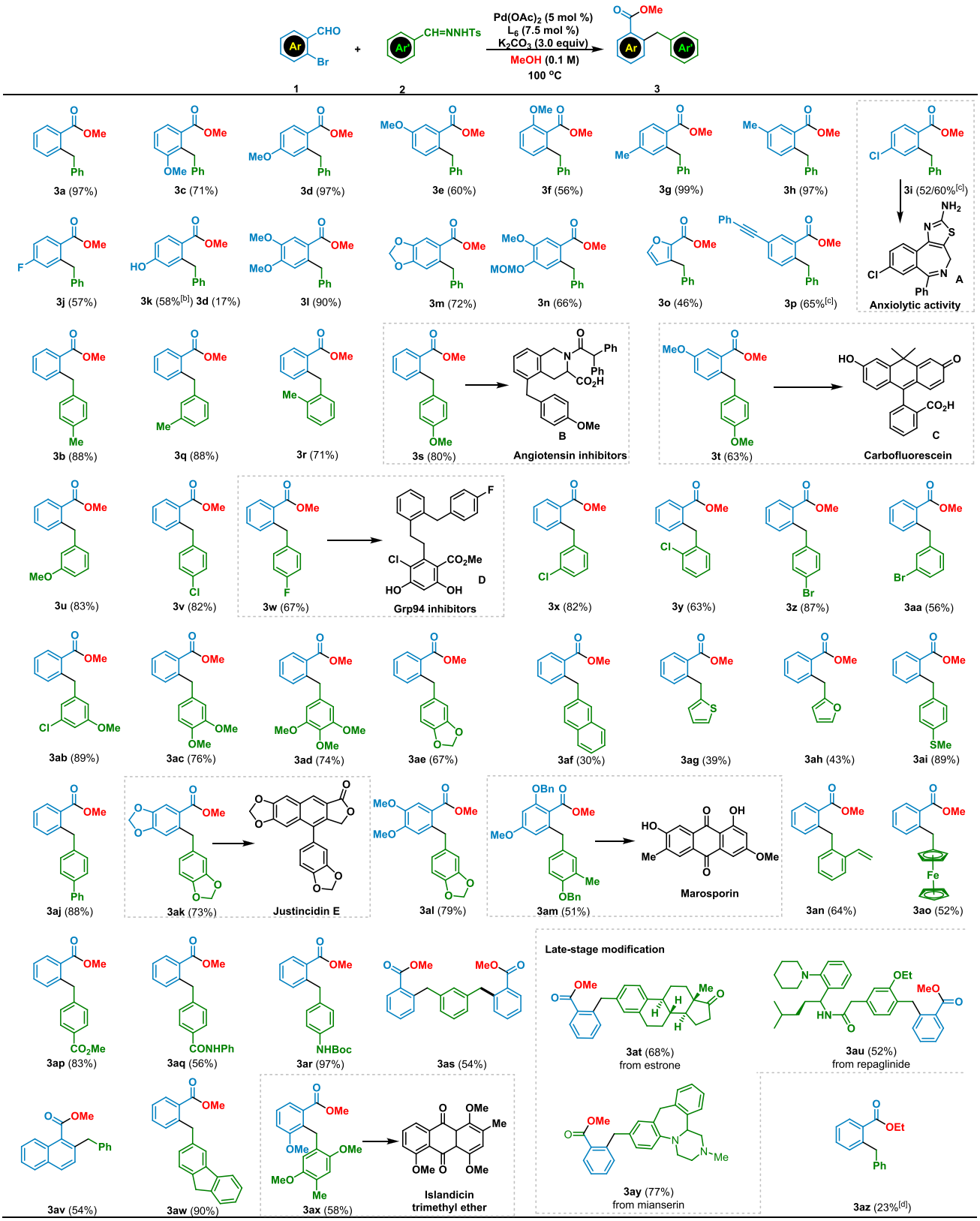
Scheme 2. Substrate Scope[a]



[a]For reaction conditions, see entry 7 of Table 1. [b]3-Bromo-4-formylphenyl 4-methylbenzenesulfonate was employed. [c]Aryl triflate was used instead of the corresponding aryl bromide. [d]NMR yield.

A one-pot, four-component, two-step reaction of benzaldehyde with tosyl hydrazide and *o*-bromobenzaldehyde in methanol was carried out on a 5 mmol scale (Scheme 3). To our delight, the desired product **3a** was obtained in 94% yield. Saponification of **3a** gave free carbolic acid **5** in excellent yield. According to the reported procedure, **5** could be easily

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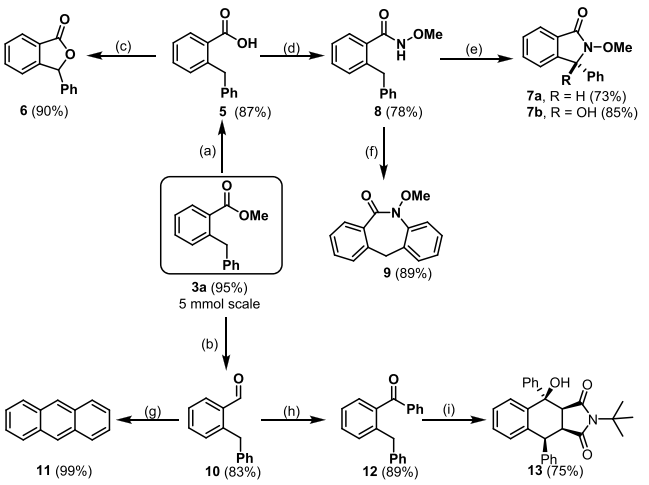
Scheme 3. Synthetic Application of 3a[a]

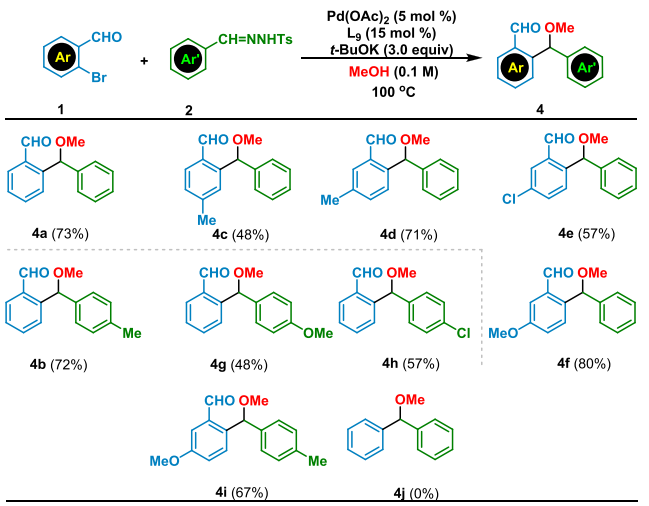


[a]Conditions and reagents: (a) KOH, MeOH/H_2O, reflux, 4 h, 87% yield; (b) (i) $LiAlH_4$, THF, rt, 4 h, 87% yield; (ii) IBX, DMSO, rt, overnight, 95% yield; (c) ref 12; (d) ref 1k; (e) ref 1k; (f) ref 15; (g) $TsNH_2$, $BF_3{\cdot}Et_2O$, PhMe, rt, 10 min, 99% yield; (h) (i) PhMgBr, THF, rt, 4 h; (ii) PCC, DCM, rt, 1 h; 89% yield over two steps; (i) ref 17.

converted to value-added heterocyclic compounds isobenzofuranone **6**,[14] substituted isoindolinone **7**,[1k] and dibenzo[*b*,*e*]-azepin-6-one **9**.[15] Following a two-step procedure, ester **3a** was converted to aldehyde **10** in high efficiency. Treatment of **10** with tosylamine in the presence of $BF_3{\cdot}Et_2O$ gave anthracene **11** in almost quantitative yield.[16] Additionally, upon irradiation under certain conditions, aldehyde **10** and its derivative ketone **12** could serve as hydroxy-*o*-quinodimethane precursors to participate in Diels–Alder reactions.[13] As described by Melchiorre and co-workers, 2-benzylbenzophenone **12** reacting with *N*-*tert*-butylmaleimide could produce **13** in a highly stereoselective manner.[17]

After establishing a reliable method for various 2-benzylbenzoic ester synthesis, we next briefly investigated the substrate scope for the synthesis of **4**. As one can see from the results compiled in Scheme 4, when $(o\text{-tolyl})_3P$ was used as ligand and *t*-BuOK was employed as base, a variety of 2-[methoxy(aryl)-methyl]benzaldehydes **4** could be selectively obtained. Although the generality of the current condition for this reaction is a bit limited at the moment, this represents a rare example on a palladium-catalyzed three-component reaction of aryl halides with simple *N*-tosylhydrazones and external nucleophiles to form new carbon–carbon and carbon–heteroatom bonds on the same carbenic carbon center.[7a] The aldehyde function is crucial for the current condition, as a simple phenyl bromide could not react to give **4j**. Further studies to enhance the utility of this transformation are ongoing.

Scheme 4. Substrate Scope for the Synthesis of 4



In conclusion, we have reported an unprecedented palladium-catalyzed three-component reaction of *o*-bromobenzaldehydes with *N*-tosylhydrazone and methanol. This transformation offers a modular approach to synthetically valuable building block 2-benzylbenzoic acid derivatives in a single step. The reaction displays a relatively broad substrate scope and good functional group compatibility and is amenable for late-stage modification of approved drugs. Moreover, the backbone of the phosphine ligands exhibits pronounced effects on controlling the chemoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00579.

Experimental procedures and analysis data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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