Metal-Free Synthesis of Aryl Esters from Carboxylic Acids and Diaryliodonium Salts
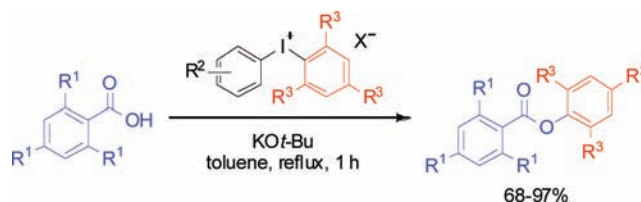
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ABSTRACT

An efficient arylation of carboxylic acids with diaryliodonium salts has been developed, giving aryl esters in high yields within short reaction times for both aromatic and aliphatic substrates. The transition-metal-free conditions are compatible with a range of functional groups, and good chemoselectivity is observed with unsymmetric diaryliodonium salts. Furthermore, steric hindrance in the *ortho* positions is well tolerated both in the carboxylic acid and in the diaryliodonium salt, yielding aryl esters that cannot be obtained via other esterification protocols.

Aryl esters are prevalent subunits in pharmaceuticals, agrochemicals, and polymers, as well as in naturally occurring compounds and building blocks for organic synthesis. Despite the plethora of synthetic methods available toward this compound class, sterically congested aryl esters remain difficult to obtain.[1]

Efficient esterification of carboxylic acids with phenols requires activation of the substrate(s) and removal of 1 equiv of water.[2] Both of these issues can be addressed utilizing acid halides or anhydrides, but such reagents limit the functional group tolerance and usually require separate preparation (Scheme 1, path a).[3] Modern coupling reagents can generate the activated intermediate in situ, but stoichiometric amounts of multiple reagents are typically needed.[4]

Scheme 1. Synthesis of Aryl Esters from Carboxylic Acids
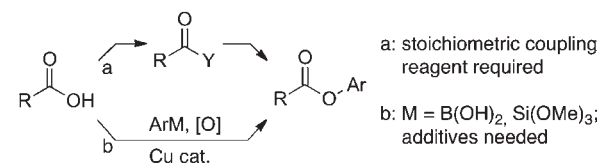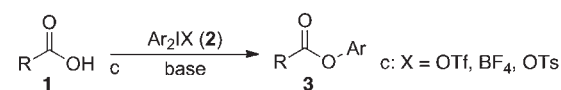
Transition-metal-catalyzed alternatives include the copper-mediated Chan—Lam reaction[5] (Scheme 1, path b) or Pd-catalyzed coupling of aryl halides and phenols under carbonylative conditions.[6] Synthesis of aryl esters via C—H activation of arenes often requires internal directing groups and has focused on formation of aryl acetates.[7] Metal-catalyzed oxidative arylation of

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(4) (a) Neises, B.; Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522–524. Mitsunobu reactions:(c) Fitzjarrald, V. P.; Pongdee, R. *Tetrahedron Lett.* **2007**, *48*, 3553–3557. (d) Iranpoor, N.; Firouzabadi, H.; Khalili, D.; Motevalli, S. *J. Org. Chem.* **2008**, *73*, 4882–4887.

(5) (a) Zhang, L.; Zhang, G.; Zhang, M.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 7472–7474. (b) Luo, F.; Pan, C.; Qian, P.; Cheng, J. *Synthesis* **2010**, 2005–2010. (c) Kim, S.; Lee, J. I. *J. Org. Chem.* **1984**, *49*, 1712–1716. (d) For a Cu-catalyzed coupling of an aryl halide with a carboxylic acid, see: Thasana, N.; Worayuthakarn, R.; Kradanrat, P.; Hohn, E.; Young, L.; Ruchirawat, S. *J. Org. Chem.* **2007**, *72*, 9379–9382.

aldehydes has been established almost exclusively for aromatic aldehydes.[8]

Metal-free oxidative esterifications can be performed with hypervalent iodine reagents.[9] The reaction of diaryliodonium salts with sodium carboxylates was briefly reported in the 1950s,[10] and one diaryliodonium salt has also been utilized as benzyne precursor in the synthesis of phenyl esters.[11]

The preparation of diaryliodonium salts has recently been facilitated by the development of efficient one-pot routes to these hypervalent iodine compounds.[12] They can be utilized as electrophilic arylating agents both in metal-catalyzed[13,14] and metal-free[13,15] protocols and can often replace organometallic reagents with less benign profiles.

In the course of our continued investigation of the synthesis[12a−d] and applications[16] of diaryliodonium salts, we have examined the arylation of carboxylic acids. Herein, we present our preliminary results on this reaction, which proved to be tolerant of steric hindrance as well as a range of functionalities.

The early reports on this transformation utilized excess sodium benzoate and diaryliodonium halides or hydrogen sulfates in refluxing protic solvents.[10] These conditions are potentially problematic for a number of functional groups, e.g., enolizable carbonyls. We sought to develop a general synthesis of aryl esters using aprotic solvents and diaryliodonium triflates or tetrafluoroborates, as these conditions allowed for lower reaction temperatures in the efficient arylation of phenoxides.[16b]

The conditions were optimized using benzoic acid (**1a**) and diphenyliodonium triflate (**2a**) as model substrates. An initial screening of solvents with several bases revealed that the conversion to phenyl benzoate (**3a**) was much higher in toluene than in THF, acetonitrile, or DMF. Further studies were thus carried out in toluene, and the results are summarized in Table 1.

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(9) (a) For a review, see: Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, 517–538. For catalytic systems (no aryl esters), see: (b) Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005**, *127*, 12244–12245. (c) Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Kita, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 6193–6196. (d) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 5331−5334.

(10) (a) Beringer, F. M.; Brierley, A.; Drexler, M.; Gindler, E. M.; Lumpkin, C. C. *J. Am. Chem. Soc.* **1953**, *75*, 2708–2712 (arylation of sodium benzoate, 5 equiv, with three different salts in 40–85% yield). (b) Nesmeyanov, A. N.; Makarova, L. G.; Tolstaya, T. P. *Tetrahedron* **1957**, *1*, 145–157 (no details given). (c) Fuson, R. C.; Albright, R. L. *J. Am. Chem. Soc.* **1959**, *81*, 487–490 (Cu-catalyzed synthesis of 2-acetoxy-2'-iodobiphenyl).

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(15) (a) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668–1669. (b) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Angew. Chem. Int. Ed.* **2010**, *49*, 3334–3337. (c) Morimoto, K.; Yamaoka, N.; Ogawa, C.; Nakae, T.; Fujioka, H.; Dohi, T.; Kita, Y. *Org. Lett.* **2010**, *12*, 3804–3807. (d) Ackermann, L.; Dell'Acqua, M.; Fenner, S.; Vicente, R.; Sandmann, R. *Org. Lett.* **2011**, *13*, 2358–2360.
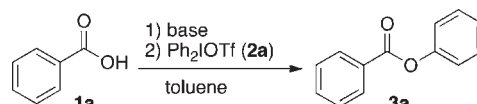
(16) (a) Norrby, P.-O.; Petersen, T. B.; Bielawski, M.; Olofsson, B. *Chem.—Eur. J.* **2010**, *16*, 8251–8254. (b) Jalalian, N.; Ishikawa, E. E.; Silva, L. F.; Olofsson, B. *Org. Lett.* **2011**, *13*, 1552–1555.

Table 1. Optimization of the Model Reaction[a]

entry	base	equiv of base	temp[b] (°C)	time (h)	yield[c] (%)
1	NaOH	1.1	130	1	<5
2	NaO-*t*-Bu	1.1	130	1	<5
3	NaO-*t*-Bu	1.1	130	16	78
4	KOH	1.1	130	1	79
5	K₃PO₄	1.1	130	1	85
6	K₂CO₃	1.1	130	2	89
7	**KO*t*-Bu**	**1.1**	**130**	**1**	**95**
8[d]	KO*t*-Bu	1.1	130	1	87
9	Cs₂CO₃	1.1	130	0.5	92
10	Cs₂CO₃	0.55	130	1	95
11	KO*t*-Bu	1.1	100	4	83
12	KO*t*-Bu	1.1	70	16	<5
13	Cs₂CO₃	0.55	100	2	93
14	Cs₂CO₃	0.55	70	16	63

[a] Base and benzoic acid (1.1 equiv) were mixed in toluene (3 mL) at rt before addition of **2a** (0.50 mmol) and heating to the tabulated temperature. [b] Oil bath temperature. [c] Isolated yield. [d] Toluene not dried.

The rate of the reaction shows strong dependence on the cation of the base: sodium bases effected almost no conversion to **3a** in 1 h at reflux (entries 1 and 2), while potassium and cesium bases resulted in good yields (entries 4−9).

Cesium carbonate proved most efficient, as 0.55 equiv of this diprotic base was sufficient to obtain **3a** in high yield (entry 10), but the price difference between Cs₂CO₃ and KO*t*-Bu does not justify the use of this base in general. The reaction was slow or absent at lower temperatures,

although cesium carbonate enabled significant conversion also at 70 °C (entries 11−14).

With the optimized conditions in hand, the influence of different diaryliodonium anions was investigated. As expected, tetrafluoroborate **2b** works just as efficiently as triflate **2a** (Table 2, entries 1 and 2). Tosylate **2c** also furnished **3a** in high yield (entry 3), whereas bromide **2d** gave poor results (entry 4).

The modest yield obtained with **2d** appears not to be caused by radical side reactions, as addition of the radical trap 1,1-diphenylethene had no effect (entry 5). The low yield can instead be explained by the moderate solubility of **2d** and the formation of bromobenzene from intramolecular coupling with the bromide anion, as previously reported.[17]

Table 2. Influence of the Diphenyliodonium Anion[a]
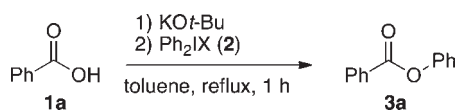
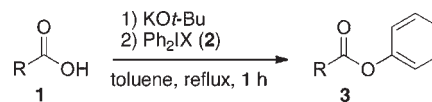| entry	salt **2**	X	yield[b] (%)
1	**2a**	OTf	95
2	**2b**	BF$_4$	97
3	**2c**	OTs	90
4	**2d**	Br	19
5[c]	**2d**	Br	19
6[d]	**2d**	Br	21

[a] KOt-Bu (1.1 equiv) and benzoic acid (1.1 equiv) were mixed in toluene (3 mL) at rt before addition of **2** (0.50 mmol) and heating to reflux. [b] Isolated yields. [c] With 1,1-diphenylethene (1.0 equiv). [d] In DMF.

The reaction scope was initially explored by phenylating carboxylic acids **1** with diphenyliodonium triflate (**2a**) and tetrafluoroborate (**2b**) (Table 3). As expected, the nucleophilicity of the carboxylic acid influenced the outcome of the reaction, and 2,4-dimethoxybenzoate was phenylated in better yield than 4-nitrobenzoate (entries 1 and 2). On the other hand, steric bulk of the carboxylic acid does not affect the reaction greatly and even highly hindered ester **3f** was formed in 90% yield (entries 3−5).

In contrast to classical esterification protocols, the presence of a primary alcohol moiety did not hamper the ester formation, and hydroxy ester **3g** was obtained as the only product (entry 6). *N*-Boc-phenylglycine could also be arylated to give amino acid derivative **3h** (entry 7).[18]

Further exploration of the reaction scope involved arylation with substituted diaryliodonium salts, which are easily available via one-pot reactions (see the Supporting

Table 3. Phenylation of Carboxylic Acids[a]

entry	**2** (X)	phenyl ester **3**	yield (%)[b]
1	**2a** (OTf)	**3b**	88
2	**2a** (OTf)	**3c**	59
3	**2a** (OTf)	**3d**	87
4	**2a** (OTf)	**3e**	86
5	**2a** (OTf)	**3f**	90
6[c]	**2b** (BF$_4$)	**3g**	68
7	**2b** (BF$_4$)	**3h**	79

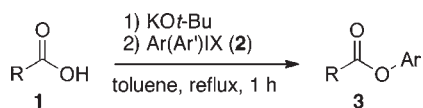[a] See Table 2 for conditions. [b] Isolated yields. [c] No etherification products detected.

Information).[12] Aryl groups with substituents ranging from electron-donating to electron-withdrawing could be transferred efficiently, as demonstrated with the symmetric salts **2e** and **2f** (Table 4, entries 1 and 2). The unsymmetric salt **2g** selectively transferred the nitro-substituted aryl moiety to the carboxylate, delivering product **3k** (entry 3).

Steric bulk in the *ortho* positions was very well tolerated, as demonstrated by arylations with salts **2h** and **2i** to yield highly congested products, including the novel esters **3m−p** (entries 4−8). Excellent chemoselectivity was observed with the unsymmetric salt **2i**, which transferred the tri(isopropyl)phenyl group (TRIP) in high yield (entries 5−8). Thus, unsymmetric diaryliodonium salts can be used with advantage when the symmetric reagent is expensive or cumbersome to prepare.

(17) Carroll, M. A.; Wood, R. A. *Tetrahedron* **2007**, *63*, 11349−11354.
(18) Racemic *N*-Boc-phenylglycine was used. Arylation of enantiomerically enriched carboxylic acids will be investigated for the full paper.

(19) Oh, C. H.; Kim, J. S.; Jung, H. H. *J. Org. Chem.* **1999**, *64*, 1338−1340.
(20) This so called *ortho*-effect varies with the nucleophile and is sometimes overriden by electronic properties, so that aryl groups with electron-donating *ortho*-substituents are not transferred; see refs 17 and 19 and: Ochiai, M.; Kitagawa, Y.; Takayama, N.; Takaoka, Y.; Shiro, M. *J. Am. Chem. Soc.* **1999**, *121*, 9233−9234.

Table 4. Arylation of Carboxylic Acids[a]

entry	salt 2	aryl ester 3	yield[b] (%)
1	2e	3i	81
2[c]	2f	3j	82
3[d]	2g	3k	92
4	2h	3l	96
5[e]	2i	3m	94
6[f]	2i	3n	88
7[e]	2i	3o	88
8[e]	2i	3p	92

[a] See Table 2 for conditions. [b] Isolated yield. [c] 1-Bromo-4-iodobenzene isolated in 92% yield. [d] No **3i** detected. [e] No phenyl ester detected. [f] 3% **3e** isolated as byproduct.

The observed chemoselectivity trends with diaryliodonium salts **2g** and **2i** follow previously reported selectivities for metal-free reactions, i.e., that electron-poor aryl groups are transferred more readily than electron-rich aryl groups (entry 3)[19] and that *ortho*-substituted aryl groups are transferred preferentially over aryl groups lacking such substituents (entries 5−8).[20]

Interestingly, the opposite chemoselectivity trends are observed with diaryliodonium salts used in the presence of a transition-metal catalyst. Then the more electron-rich, or least bulky, aryl group is generally transferred and the TRIP group is often used as a dummy ligand to increase the selectivity toward transfer of the other group.[13,14]

Finally, the carboxylic acid scope was further investigated, and aliphatic substrates were arylated without problems (entries 2, 7, and 8; see also Table 3, entry 6). Furthermore, a keto substituent posed no problem, as ester **3o** was obtained in high yield without formation of detectable amounts of byproducts via base-catalyzed condensation reactions (entry 7).

For reasons of atom economy, it should be stressed that the equivalent of iodoarene formed in the reaction can be isolated and utilized to regenerate the diaryliodonium salt, as demonstrated by the isolation of 1-bromo-4-iodobenzene in entry 2.

In conclusion, a fast synthesis of aryl esters directly from carboxylic acids and diaryliodonium salts has been developed. Good to excellent yields are obtained without the use of metal catalysts, halogenated solvents or excess reagents. Aryl esters can be synthesized in the presence of primary alcohols, *N*-Boc substituents and ketones, and both aromatic and aliphatic substrates are tolerated. The scope includes synthesis of remarkably hindered esters, which are impossible to obtain via direct esterification.

With the recent advances in efficient diaryliodonium salt synthesis, these reagents are now readily available. Continued investigations on the arylation of heteroatoms with diaryliodonium salts are underway, and the results will be reported in due course.

Supporting Information Available. Synthesis of diaryliodonium salts **2**, experimental procedures, analytical data, and ¹H and ¹³C NMR spectra of products **3**. This material is available free of charge via the Internet at http://pubs.acs.org.