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Pd(0)-Mediated ^{11}C-Carbonylation of Aryl(mesityl)iodonium Salts as a Route to [^{11}C]Arylcarboxylic Acids and Derivatives

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Abstract: Pd(0)-mediated ^{11}C-carbonylation of aryl(mesityl)iodonium salts followed by aqueous quench provides a rapid room-temperature two-pot procedure for labeling arylcarboxylic acids and amide derivatives with the short-lived positron-emitter carbon-11 ($t_{1/2}$ = 20.4 min) in generally good to high yields (up to 71%). High product ring-selectivity (≥ 13) was achieved when using mesityl as a spectator group in the diaryliodonium salt precursors. This process has potential for preparing new radiotracers for molecular imaging with positron emission tomography.

Carboxylic acids and their derivatives, when labeled with the short-lived positron-emitter carbon-11 ($t_{1/2}$ = 20.4 min), are potential radiotracers for use in positron emission tomography (PET), a molecular imaging technology with expanding utility in biomedical research, drug development and clinical diagnosis.[1–3] Novel radiotracers are continuously in demand for biomedical research and for drug development. Generally, [^{11}C]arylcarboxylic acids have been synthesized from aryl halides, arylboronic acids or arylboronic esters with either [^{11}C]carbon monoxide or [^{11}C]carbon dioxide as a labeling synthon.[4–7] However, most of the known methods suffer drawbacks, such as air/moisture sensitivity[5], use of high temperatures,[6] or use of high amounts of precursor[4].

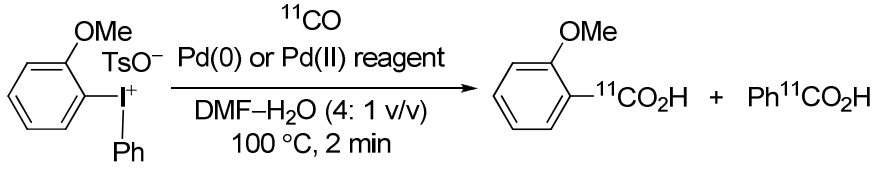
Carbon-11 is produced from biomedical cyclotrons as either [^{11}C]methane or [^{11}C]carbon dioxide through the $^{14}N(p,\alpha)^{11}C$ nuclear reaction on nitrogen in the presence of hydrogen (10%) or oxygen (1%), respectively.[8] Either labeled compound can be obtained in high yield and high molar activity [ratio of radioactivity (Bq) to amount of compound (mol)]. In addition, [^{11}C]carbon monoxide has been gaining importance as a labeling synthon because of: i) easy high-yield and high molar activity synthesis by passage of [^{11}C]carbon dioxide over heated molybdenum (875 °C);[9] (ii) the development of new apparatus[10–15] and techniques[16–20] for increasing [^{11}C]carbon monoxide availability in small volumes of organic solvents; (iii) the expansion of strategies for transition-metal mediated insertion of [^{11}C]carbon monoxide into radiotracers;[21–25] and (iv) the generally high functional group tolerance of the transition metal-mediated reactions.

Aryliodine(III) compounds are useful arylation reagents.[26] As examples, diaryliodonium salts ($ArI^+Ar^1X^-$) may be readily synthesized as quite stable but reactive compounds. Generally, diaryliodonium salts show greater reactivity than the corresponding iodoarenes. In fact, the phenyliodonio group (PhI^+-) has10^6 times higher nucleofugacity than the widely used triflate leaving group.[27] Diaryliodonium salts have become widely used as precursors for labeling arenes with [^{18}F]fluoride ion and other radioactive nucleophiles.[28–30] Salts with dissimilar aryl rings (unsymmetrical salts) are generally preferred as precursors for ease of synthesis and reagent economy. The possibility to use reactive unsymmetrical diaryliodonium salts for other types of labeling reaction has been little explored. Exceptionally, Al-Qahtani and Pike reported that the Pd-mediated ^{11}C-carbonylation of diaryliodonium salts ($ArI^+Ar^1X^-$) in the presence of arylstannanes (Ar^2SnR_3) at room temperature rapidly produces pairs of ^{11}C-labeled diaryl ketones i.e., $Ar^{11}COAr^2$ plus $Ar^1-{}^{11}COAr^2$.[31] In that study, [^{11}C]arylcarboxylic acids were

observed as minor byproducts due to high water content in the reaction medium (DME: H_2O; 4: 1 v/v). Therefore, we envisaged that diaryliodonium salts might also serve as effective precursors for the rapid synthesis of [^{11}C]arylcarboxylic acids and derivatives under mild conditions from [^{11}C]carbon monoxide, provided that high ring-selectivity for the desired product could be attained. Here we describe our progress towards developing the ring-selective Pd-mediated ^{11}C-carbonylation of substituted diaryliodonium salts as a rapid room-temperature route for producing [^{11}C]arylcarboxylic acids and derivatives. We report that aryl(mesityl)iodonium salts are especially effective precursors for this radiochemistry.

Al-Qahtani and Pike[31] reported that the electron-rich 2-anisyl ring introduces some ring-selectivity into the Pd-mediated ^{11}C-carbonylation of 2-anisyl(phenyl)iodonium tosylate (**1**) by directing [^{11}C]carbon monoxide incorporation preferentially to the phenyl ring. Thus, the 2-anisyl group acted as a weak 'spectator group'. To investigate whether the choice of palladium reagent might increase ring-selectivity in the ^{11}C-carbonylation of **1**, different palladium(0) and palladium(II) species were tested at 100 °C (Table 1).

Table 1. Screening of Palladium Reagents for the ^{11}C-Carbonylation of **1**.



1 [^{11}C]**2** [^{11}C]**3**

entry	Pd oxidation state	Pd reagent	*sonication time*[a] *(min)*	*I* (%)	Y_A of [^{11}C]acids (%)[b]	[^{11}C]3: [^{11}C]2 ratio
1	II	$PdCl_2$	0.5	48	39	1.4
2	II	$[PdCl(C_3H_5)]_2$	0.5	53	49	1.2
3	II	(NHC)Pd(allyl)Cl[c]	0.5	24	18	1.1
4	II	$Pd(OAc)_2$	0.5	42	27	0.8
5	II	$Pd(PPh_3)_2Cl_2$	0.5	47	38	1.7
6	0	$Pd(PPh_3)_4$	5	23	16	16

7	0	Pd[(*o*-tolyl)$_3$P]$_2$	5	62	49	3.6
8	0	Pd[P(Cy)$_3$]$_2$	5	27	12	2.5
9	0	Pd[(*t*-Bu)$_3$P]$_2$	5	12	9	1.4
10	0	Pd(dppe)$_2$	5	45	32	1.0
11	0	Pd(dba)$_2$	0.5	44	39	1.1
12	0	Pd$_2$(dba)$_3$	0.5	47	37	0.9

[a] Of **1** with Pd-reagent preceding ^{11}C-carbonylation.
[b] Aggregate yields (Y_A) are based on [^{11}C]CO incorporation (I) and HPLC analysis, as described in the text.
[c] NHC = bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

Briefly, [^{11}C]carbon monoxide was carried by helium into a sealed mini-autoclave.[12] Then a pre-sonicated[32] mixture of diaryliodonium salt (3.8 μmol; 1.5−2.3 mg) and Pd reagent (~ 0.5 mg), in DMF−water (4: 1, v/v; 100 μL), was pumped into the autoclave and allowed to react at a set temperature for 2 min. The reactor contents were then transferred to a vented V-vial (5-mL). The radioactivity in the vial was measured. The vial was then purged with helium (10 mL/min) for 2 min to remove unreacted [^{11}C]carbon monoxide, and the residual radioactivity was recorded. The percent incorporation of [^{11}C]carbon monoxide (I%) was measured as the ratio of the final and initial radioactivity multiplied by 100. Control experiments showed that negligible radioactivity was lost before the helium purge.

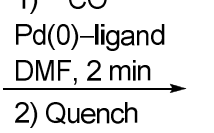
An aliquot of each quenched reaction mixture was analyzed with gradient reverse phase HPLC. No radioactivity was left on the HPLC column at the end of analysis. All radioactive peak areas were decay-corrected. The aggregate yield of [^{11}C]carboxylic acids (Y_A%) was measured as the sum of peak areas corresponding to the two expected [^{11}C]carboxylic acids divided by the sum of peak areas for all detected radioactivity, multiplied by I%. The yield of a single [^{11}C]carboxylic acid or [^{11}C]amide was measured analogously from its chromatographic peak area and I%. Ring-selectivity was defined as the ratio of the yield of the desired

[^{11}C]carboxylic acid divided by the yield of the [^{11}C]carboxylic acid derived from the spectator ring. Labeled products were identified by coinjection with non-radioactive standards.

In the screening reactions, except for that using an *N*-heterocyclic carbene (NHC)-based reagent (Table 1, entry 3), all the tested Pd(II) reagents (entries 1, 2, 4 and 5) gave 42−53% [^{11}C]carbon monoxide incorporation. In most cases, formation of [^{11}C]benzoic acid ([^{11}C]**3**) was slightly preferred over [^{11}C]2-methoxybenzoic acid ([^{11}C]**2**). Among Pd(0) reagents (entries 6−12), $Pd(PPh_3)_4$ uniquely showed very high selectivity for formation of [^{11}C]**3** (16-fold; entry 6), although [^{11}C]carbon monoxide incorporation was low (23%). The more bulky phosphines [e.g., tri(*o*-tolylphosphine)] gave much higher [^{11}C]carbon monoxide incorporation (62%) and about 4-fold ring-selectivity for [^{11}C]**3** (entry 7).

In view of the high ring-selectivity achieved with $Pd(PPh_3)_4$, we sought to improve yields with its use in the ^{11}C-carbonylation of **1**. Interestingly, when reactions were conducted in anhydrous DMF and quenched with water-MeCN in a 2-pot procedure, there were fewer and lower levels of unknown radioactive byproducts, and the aggregate yield of [^{11}C]carboxylic acids increased over two-fold (from 16 to 36%; Table entry 1 vs. entry 2). Basic (aq. 0.5 M NaOH or aq. 1 M NH_4OH in MeCN, 1: 1 v/v), or acidic (aq. 1 M HCl in MeCN, 1: 1 v/v) quenching agents were also examined. Neutral or basic quench conditions were well tolerated. NH_4OH gave the best reproducibility and ring-selectivity (entry 3).

Table 2. Effects of Pd-Ligand System, Temperature, and Quenching Agent on ^{11}C-Carbonylation of **1** in One-pot and Two-pot Procedures.



entry	Pd–ligand system	reaction temp. (°C)	*I* (%)[a]	quench method: agent[b]	quench method: temp. (°C)	Y_A of [^{11}C]acids[c] (%)[a]	[^{11}C]3: [^{11}C]2 ratio

1	$Pd(PPh_3)_4$[d]	100	23	-	-	16	16
2	$Pd(PPh_3)_4$	100	37	A	100	36	8
3	$Pd(PPh_3)_4$	100	37	B	RT	35	20
4	$Pd(PPh_3)_4$	RT	35 ± 0	A	100	30 ± 1	11
5	$Pd(PPh_3)_4$	RT	36	B	100	29	17
6	$Pd(PPh_3)_4$	RT	30 ± 4	B	RT	22 ± 1	10
7	$Pd(PPh_3)_4$–Xantphos	RT	57	A	RT	33	6
8	$Pd(PPh_3)_4$–Xantphos	RT	62 ± 3	A	50	43 ± 3	12
9	$Pd(PPh_3)_4$–Xantphos	RT	64 ± 3	B	50	51 ± 5	15
10	$Pd(PPh_3)_4$–Xantphos[d]	RT	36	-	-	10	7

[a] Values are means ± SEMs for $n \geq 2$ or otherwise $n = 1$.
[b] A: H_2O–MeCN (500 µL; 1: 1 v/v) for 2 min; B: 1 M NH_4OH–MeCN (500 µL; 1: 1 v/v) for 2 min.
[c] Aggregate yields (Y_A) are based on [^{11}C]CO incorporation (I) and HPLC analysis, as defined in the text.
[d] One-pot procedure. Other entries are two-pot.

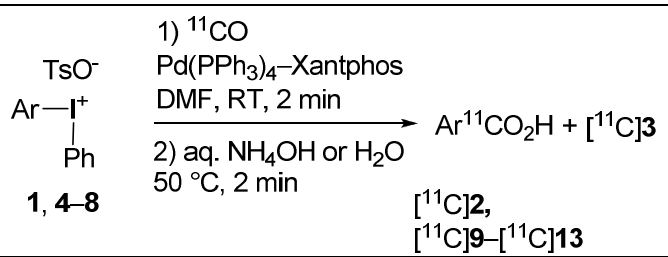
In general, lowering the reaction temperature from 100 °C to room temperature did not greatly affect the radioactive product outcome (Table 2, *c.f.*, entries 2 and 3 with entries 4 and 6, respectively). However, when radiosyntheses were performed at room temperature, a quench temperature of at least 50 °C was found to avoid some unknown radioactive byproducts.

Bidentate phosphines, particularly Xantphos with a large bite angle (110°), are efficient ligands in aminocarbonylation reactions.[19,33] Hence, we examined the $Pd(PPh_3)_4$–Xantphos pair for effect on [^{11}C]carbon monoxide incorporation. In the two-pot procedure with reaction at room temperature, addition of Xantphos gratifyingly gave almost 2-fold higher [^{11}C]carbon monoxide incorporation than when absent (Table 2, entries 4−6 vs entries 7−9). Surprisingly, Xantphos had little effect on [^{11}C]carbon monoxide incorporation in the one-pot process (entry 10).

In search of increased ring-selectivity, we examined different 'spectator groups' (Table 3). The best ring selectivities were obtained with 2,4,6-tri-substituted aryl groups. Despite giving a slightly lower aggregate yield of the [^{11}C]acids, a salt with a mesityl spectator group (**5**) gave complete conversion into the desired [^{11}C]benzoic acid ([^{11}C]**3**). A salt with a 2,4,6-

trimethoxyphenyl (TMP) group (**6**) gave comparable results, but required longer initial sonication of the reaction mixture (10 min vs 5 min) for complete dissolution of reagents. Notably, little ring-selectivity was observed in the reaction of the phenyl(2-thienyl)iodonium salt (**7**).

Table 3. Spectator Group Effect on Yields and Ring-Selectivities in the ^{11}C-Carbonylation of Aryl(phenyl)iodonium Salts with the RT Two-pot Procedure.



salt[a]	Ar (spectator group)	*I* (%)[b]	Y_A of [^{11}C]acids (%)[b,c]	[^{11}C]**3**: Ar^{11}CO$_2$H ratio
1	2-An	64 ± 3	51 ± 5	15
4	4-An	87	73	1.6
5	Mes	69 ± 1	56 ± 4	[^{11}C]**3** only
6	TMP[d]	70 ± 2	64 ± 3	20
7	2-Thi	61	58	0.8
8	DMU[e]	86	83	0.1

[a] All salts were tosylates, except **8** which was a triflate.
[b] *V*alues are means ± SEMs for $n = 2$ or otherwise $n = 1$.
[c] All reactions were quenched with Method B, except for those of **4** and **7** which were quenched with Method A. Aggregate yields (Y_A) are measured from [^{11}C]CO incorporation (*I*) and HPLC analysis, as defined in the text.

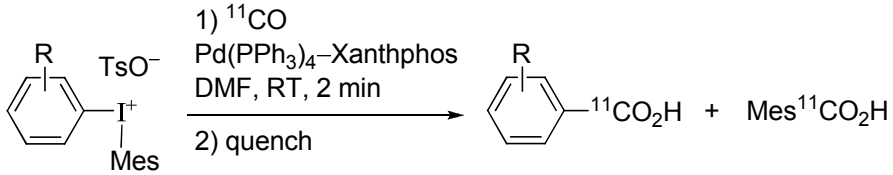
[d] Sonication time: 10 min; 5 min was used for other entries.
[e] DMU: 1,3-dimethyl-urac-5-yl.

A 1,3-dimethyl-urac-5-yl (DMU) ring has been used as a spectator group in arylation reactions.[34] However, here this group failed as a spectator group: the ^{11}C-carbonylation of DMU(phenyl)iodonium triflate (**8**)[35] gave mostly [^{11}C]1,3-dimethyl-uracil-5-carboxylic acid ([^{11}C]**13**) (Table 3, entry 8).

We investigated the substrate scope and limitations of the room temperature two-pot ^{11}C-carbonylation procedure with various substituted aryl(mesityl)iodonium salts (**5**, **14a**−**14n**) that

had been synthesized by known methods.[36,37] Electron-withdrawing or electron-donating groups in *meta* or *para* position gave good [^{11}C]carbon monoxide incorporation (> 60%) and moderate to high yields of the desired [^{11}C]carboxylic acids (47−71%), with the exception of 4-iodophenyl(mesityl)iodonium triflate, which gave [^{11}C]4-iodobenzoic acid ([^{11}C]**15e**) in low yield (11%). The mesityl group always acted as a highly effective spectator group, driving all the ^{11}C-carbonylation reactions almost exclusively to the desired aryl ring with ring-selectivities usually far exceeding 13 (Table 4).

Table 4. Substrate Scope for Substituted Aryl(mesityl)iodonium Salts.



5, 14a–**14n** [^{11}C]**2,** [^{11}C]**3,** [^{11}C]**9,** [^{11}C]**15a**–[^{11}C]**15n** [^{11}C]**10**

salt	R	desired product	*I* (%)[a]	ring-selectivity[b]	yield of desired product (%)[c]
5	H	[^{11}C]**3**	69 ± 1	[^{11}C]**3** only	56 ± 4
14a	3-SF_5	[^{11}C]**15a**	72 ± 3	13	55 ± 0
14b	3-CN	[^{11}C]**15b**	82 ± 1	[^{11}C]**15b** only	65 ± 7
14c	3-Me	[^{11}C]**15c**	78 ± 4	> 183	61 ± 4
14d	4-SF_5	[^{11}C]**15d**	77 ± 0	16	63 ± 1
14e[d,e]	4-I	[^{11}C]**15e**	80 ± 3	[^{11}C]**15e** only	11 ± 4
14f	4-OMe	[^{11}C]**9**	60 ± 3	> 61	47 ± 6
14g	4-Me	[^{11}C]**15g**	77 ± 3	> 40	60 ± 1
14h	4-CF_3	[^{11}C]**15h**	77 ± 8	> 72	71 ± 9
14i[e]	2-*i*Pr	[^{11}C]**15i**	53 ± 1	> 66	46 ± 3
14j	2-Me	[^{11}C]**15j**	72 ± 5	[^{11}C]**15j** only	59 ± 2
14k	2-OMe	[^{11}C]**2**	43 ± 1	> 23	23 ± 1
14l	2-CN	[^{11}C]**15l**	37 ± 10	33	12 ± 0
14m	2-CF_3	[^{11}C]**15m**	41 ± 11	n.d.[f]	1 ± 0
14n[d]	2-F	[^{11}C]**15n**	30 ± 2	[^{11}C]**15n** only	5 ± 2

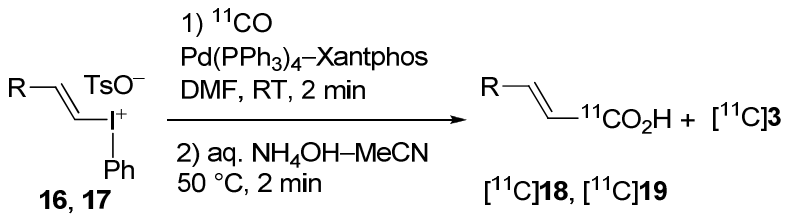
[a] Values are means ± SEMs for n = 2
[b] For desired product versus [^{11}C]**10**.
[c] Yields are based on [^{11}C]CO incorporation (*I*) and HPLC analysis, as defined in the text, and are means ± SEMs for n = 2.
[d] Triflate; other salts are tosylates.
[e] **14e, 14i**, and **14n** were quenched with method A; the remaining reactions were quenched

with method B.
[f] n.d. = not determined.

Substituent electronics, more so than size, dictated ^{11}C-carbonylation yield for *ortho* substituted aryl(mesityl)iodonium salts (Table 4). For example, moderate yields of [^{11}C]carboxylic acids were obtained from salts with an electron-donating *ortho* methyl or *ortho* isopropyl substituent ([^{11}C]**15j** and [^{11}C]**15i**; 59 and 46%; respectively). By contrast, salts with small electron-withdrawing substituents, such as nitrile or fluoro, gave low yields of the desired [^{11}C]carboxylic acids (12% for [^{11}C]**15l** and 5% for [^{11}C]**15n**). The salt with a bulkier and stronger electron-withdrawing *ortho* trifluoromethyl substituent gave only 1% of labeled acid ([^{11}C]**15m**). [^{11}C]Carbon monoxide incorporation into the Pd-iodonium center was low with *ortho* electron-withdrawing substituents; more than 60% of radioactivity was lost in the helium purging of the reaction mixtures. Moreover, many unidentified radioactive products formed.

^{11}C-Carbonylation at an sp^2 carbon proceeded smoothly in (*E*)-phenyl(styryl)iodonium tosylate[38] (**16**) to give [^{11}C](*E*)-cinnamic acid ([^{11}C]**18**) in good yield and selectivity (Table 5). This method was also effective for preparing a non-conjugated vinylic [^{11}C]carboxylic acid ([^{11}C]**19**) from **17** (Table 5).

Table 5. ^{11}C-Carbonylations at Vinylic Carbons.

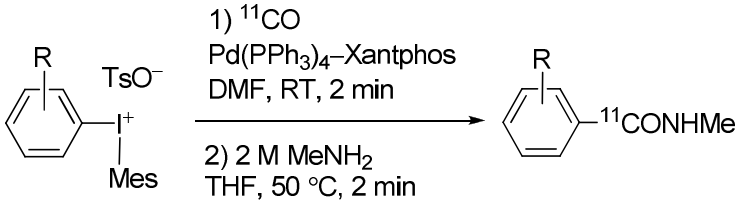


salt	R	[^{11}C]vinylic acid	*I* (%)[a]	[^{11}C]vinylic acid: [^{11}C]3 ratio	[^{11}C]vinylic acid yield (%)[a,b]
16	Ph	[^{11}C]**18**	92 ± 0	10	69 ± 5
17	cyclohexyl	[^{11}C]**19**	68 ± 1	1.4	32 ± 4

[a] Values are means ± SEMs for *n* = 2.
[b] Yields are based on [^{11}C]CO incorporation (*I*) and HPLC analysis, as defined in the text.

Finally, we explored the mild two-pot ^{11}C-carbonylation procedure for the synthesis of [^{11}C]*N*-methylamides (Table 6). When the probable intermediates (aryl-Pd-^{11}CO) from the reactions of [^{11}C]carbon monoxide with the diaryliodonium salts **14b**, **14g**, and **14i** were quenched with methylamine (2 M in THF), amides [^{11}C]**20a−c**, were obtained in moderate yields (25−30%) under non-optimized conditions. These results suggest that the ^{11}C-carbonylation of diaryliodonium salts may be applied readily to synthesize derivatives of [^{11}C]carboxylic acids thereby extending the scope of this methodology.

Table 6. Examples of the Syntheses of [^{11}C]Amides.



14b,**14g**,**14i** [^{11}C]**20a**–[^{11}C]**20c**

salt	R	[^{11}C]amide	*I* (%)	[^{11}C]amide yield (%)[a]
14b	3-CN	[^{11}C]**20a**	81	30
14g	4-Me	[^{11}C]**20b**	73	28
14i	2-*i*Pr	[^{11}C]**20c**	53	25

[a] Yields are based on *I* and HPLC, and are for *n* = 1.

In summary, the ^{11}C-carbonylation of diaryliodonium salts constitutes a new and viable method for the synthesis of [^{11}C]arylcarboxylic acids and derivatives.

Experimental Section

Materials and Methods

Arylcarboxylic acids, 4-iodophenyl(mesityl)iodonium triflate (**14e**), other chemicals, and solvents were purchased commercially. All other diaryliodonium salts were synthesized according to literature methods.[35–37] (*E*)-Phenyl(styryl)iodonium tosylate (**16**) and (*E*)-(2-cyclohexylvinyl)(phenyl)iodonium tosylate (**17**) were synthesized by treatment of the

corresponding boronic acids with Koser's reagent,[38] as described below. Some salts required additional purification by crystallization. In those cases, salts were dissolved in a minimal volume of MeCN or MeOH and precipitated by slow addition of diethyl ether and allowed to stand in a refrigerator for about 0.5 h. ^{1}H (400.13 MHz), ^{13}C (100.62 MHz), and ^{19}F (376.47 MHz) NMR spectra were recorded on an Avance 400 instrument (Bruker) at RT in deuterated solvents. ^{1}H and ^{13}C NMR signals are reported as δ (ppm) downfield from the signal for tetramethylsilane. ^{19}F NMR signals are reported as δ (ppm) downfield from the signal for trichlorofluoromethane. HRMS data (ESI-TOF) were obtained at the Bioorganic Chemistry Laboratory of NIDDK (NIH). Melting points were measured with a Digital SMP20 (Stuart) melting point apparatus. Radiochemistry was performed in a lead-shielded hot-cell for protection of personnel from radiation.

Synthesis of diaryliodonium salts

General method A. Koser's reagent (0.78 g, 2 mmol) was added in one portion to an arene (2 mmol) in DCM-CF_3CH_2OH (10 mL, 10: 1, v/v) at RT. The resulting mixture was stirred at RT for 24 h. Solvent was evaporated off and the crude mixture was triturated in diethyl ether (30 mL) for 30 min. The white solid was filtered off, washed with diethyl ether, and dried in vacuo.

General Method B. $TsOH·H_2O$ (0.38 g, 2 mmol) in MeCN (2 mL) was added to a solution of (diacetoxyiodo)arene (2 mmol) in DCM-CF_3CH_2OH (10 mL, 10: 1, v/v) at 0 °C or $CHCl_3$ (15 mL). In the case of reaction in DCM-CF_3CH_2OH, the obtained pale yellow solution was stirred for 10 min and an arene (5 mmol) was added. The mixture was then warmed to RT and stirred until it gave a negative KI-starch paper test result. In the case of reaction in $CHCl_3$, the mixture was heated at 60 °C for 3 h. At the end of reactions, solvent was evaporated off and the crude

mixture was triturated in diethyl ether (30 mL) for 30 min. The white solid was filtered off, washed with diethyl ether and dried in vacuo.

General Method C. TsOH·H_2O (0.38 g, 2 mmol) was added to a solution of iodoarene (2 mmol) and *m*CPBA (0.49 g, 2.2 mmol) in MeCN (10 mL) and the reaction mixture was heated at 77 °C for about 0.5 h. Mesitylene (0.5 mL) was added to the reaction mixture and heating was continued until the reaction mixture gave a negative KI-starch paper test result (0.5−4 h). Solvent was evaporated off and the crude mixture was triturated in diethyl ether (30 mL) for 30 min. The white solid was filtered off, washed with diethyl ether and dried in vacuo.

(2-Methoxyphenyl)(phenyl)iodonium tosylate (1). Method B, using phenyltributylstannane in place of arene, gave **1** as a white solid (0.67 g, 70%). mp = 119−121 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, *J* = 8.0 Hz, 2H), 7.65–7.73 (m, 1H), 7.58–7.65 (m, 2H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 7.6 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 3.90 (s, 3H), 2.32 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$), δ 156.8, 142.8, 139.2, 136.3, 135.3, 134.4, 131.7, 131.6, 128.4, 126.0, 123.8, 114.2, 112.4, 104.6, 56.8, 21.3. HRMS Calc'd. for $C_{13}H_{12}OI^+$[M–OTs]$^+$ 310.9933, found 310.9937.

(4-Methoxyphenyl)(phenyl)iodonium tosylate (4). Method A gave **4** as a white solid (0.9 g, 93%). mp = 163−166 °C; ^{1}H NMR (CD_3OD) δ 8.13–8.08 (m, 2H), 8.08–8.04 (m, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.67–7.61 (m, 1H), 7.53–7.46 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 9.1 Hz, 1H), 7.03 (q, *J* = 5.5 Hz, 1H), 3.82 (s, 3H), 2.35 (s, 3H). ^{13}C{^{1}H}NMR (CD_3OD) δ 164.5, 143.6, 141.7, 138.6, 136.0, 133.4, 133.0, 129.8, 127.0, 118.8, 116.6, 104.5, 56.4, 21.3. HRMS Calc'd. for $C_{13}H_{12}OI^+$ [M–OTs]$^+$ 310.9933, found 310.9935.

Mesityl(phenyl)iodonium tosylate (5). Method A gave **5** as a white solid (0.81 g, 82%). mp = 175−177 °C; ^{1}H NMR (CD_3OD) δ 7.91–7.86 (m, 2H), 7.69–7.60 (m, 3H), 7.52–7.46 (m, 2H),

7.24–7.17 (m, 4H), 2.64 (s, 6H), 2.36 (s, 3H), 2.35 (s, 3H). $^{13}C\{^{1}H\}$NMR (CD_3OD) δ 145.9, 143.7, 143.6, 141.8, 135.4, 133.4, 133.3, 131.4, 129.9, 127.1, 122.5, 114.3, 27.2, 21.5, 21.1. HRMS Calc'd. for $C_{15}H_{16}I^+$ $[M–OTs]^+$ 323.0297, found 323.0302.

Phenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (6). Method A gave **6** as a white solid (1 g, 92%). mp = 198−199 °C; ^{1}H NMR (CD_3OD) δ 7.94 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.48–7.41 (m, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 6.40 (s, 2H), 3.96 (s, 6H), 3.88 (s, 3H), 2.35 (s, 3H). $^{13}C\{^{1}H\}$NMR (CD_3OD) δ 168.9, 161.6, 143.8, 141.7, 135.9, 133.2, 132.9, 129.9, 127.1, 116.0, 93.0, 86.3, 57.9, 56.8, 21.5. HRMS Calc'd. for $C_{15}H_{16}O_3I^+$ $[M–OTs]^+$ 371.0144, found 371.0145.

Phenyl(thiophen-2-yl)iodonium tosylate (7). Method A gave **7** as a white solid (0.28 g, 61%, 1 mmol scale). mp = 141−143 °C; ^{1}H NMR (CD_3OD) δ 8.19–8.11 (m, 2H), 7.99 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.87 (dd, *J* = 5.4, 1.2 Hz, 1H), 7.71–7.63 (m, 3H), 7.54–7.47 (m, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.15 (dd, *J* = 5.4, 3.8 Hz, 1H), 2.35 (s, 3H). $^{13}C\{^{1}H\}$NMR (CD_3OD) δ 143.7, 142.3, 141.8, 138.7, 135.9, 133.8, 133.2, 131.0, 130.0, 127.1, 119.2, 99.2, 21.5. HRMS Calc'd. for $C_{10}H_8SI^+$ $[M–OTs]^+$ 286.9391, found 286.9393.

(1,3-Dimethyl-urac-5-yl)(phenyl)iodonium triflate (8). TfOH (0.36 mL, 4 mmol) was added dropwise to a solution of (diacetoxyiodo)benzene (0.66, 2 mmol) in DCM (10 mL) at – 40 °C and the resulting yellow solution was stirred for 0.5 h. 1,3-Dimethyluracil (0.28 g, 2 mmol) was added to this stirred solution which was further stirred at – 40 °C for 0.5 h. The mixture was warmed to RT and stirred for another 0.5 h. Solvent was evaporated off and the residue was triturated in diethyl ether (30 mL) for 30 min. The solid was filtered off, washed with diethyl ether (15 mL × 2) and dried in vacuo to give **8** as a white solid (0.85 g, 86%). mp = 168−170 °C; ^{1}H NMR (CD_3CN) δ 8.59 (s, 1H), 8.11–8.04 (m, 2H), 7.70 (tt, *J* = 7.1, 1.1 Hz, 1H), 7.57–7.50

(m, 2H), 3.41 (s, 3H), 3.26 (s, 3H). $^{13}C\{^{1}H\}$NMR (CD_3CN) δ 160.1, 156.1, 151.9, 136.4, 134.0, 133.1, 121.3 (q, J = 320.6 Hz), 114.9, 86.6, 38.6, 30.0. $^{19}F\{^{1}H\}$ NMR (CD_3CN) δ −79.34 (s). HRMS Calc'd. for $C_{12}H_{12}IN_2O_2^+$ $[M-OTf]^+$ 342.9944, found 342.9939.

3-Pentafluorosulfanylphenyl(mesityl)iodonium tosylate (14a). Method C gave **4** as a white solid (0.61 g, 53%). mp = 193−195 °C; ^{1}H NMR (CD_3OD) δ 8.42 (s, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.73–7.61 (m, 3H), 7.26 (s, 2H), 7.20 (d, J = 8.0 Hz, 2H), 2.64 (s, 6H), 2.37 (s, 3H), 2.35 (s, 3H). $^{13}C\{^{1}H\}$NMR (CD_3OD) δ 156.1 (quint, J = 19.2 Hz), 146.5, 143.8, 143.6, 141.8, 138.3, 134.2, 132.54 (quint, J = 4.5 Hz), 131.7, 130.7 (quint, J = 4.5 Hz), 129.9, 127.1, 122.8, 113.9, 27.2, 21.5, 21.2. $^{19}F\{^{1}H\}$ NMR (CD_3OD) δ 79.99 (quint, J = 150.6 Hz), 61.45 (d, J = 148.7 Hz). HRMS Calc'd. for $C_{15}H_{15}F_5IS^+$ $[M–OTs]^+$ 448.9859, found 448.9863.

(3-Cyanophenyl)(mesityl)iodonium tosylate (14b). Method B, from (4-diacetoxyiodo)benzonitrile and mesitylene gave **14b** as an off-white solid (0.65 g, 63%). mp = 177−178 °C; ^{1}H NMR (DMSO-D_6) δ 8.56 (t, J = 1.5 Hz, 1H), 8.23 (dq, J = 8.3, 1.0 Hz, 1H), 8.09 (dt, J = 7.8, 1.0 Hz, 1H), 7.66 (t, J = 8.0 Hz, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.21 (s, 2H), 7.10 (d, J = 7.8 Hz, 2H), 2.59 (s, 6H), 2.29 (s, 3H), 2.28 (s, 3H). $^{13}C\{^{1}H\}$NMR (DMSO-D_6) δ 145.4, 143.2, 141.7, 138.9, 137.6, 135.3, 132.3, 129.7, 127.9, 125.4, 122.8, 116.8, 114.5, 113.9, 26.3, 20.7, 20.4. HRMS Calc'd. for $C_{16}H_{15}IN^+$ $[M–OTs]^+$ 348.0249, found 348.0254.

Mesityl(*m*-tolyl)iodonium tosylate (14c). Method C gave **14c** as a white solid (0.77 g, 76%). mp = 159−161 °C; ^{1}H NMR (CD_3OD) δ 7.73 (s, 1H), 7.66 (d, J = 6.8 Hz, 2H), 7.65 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.21 (s, 2H), 7.19 (d, J = 7.9 Hz, 2H), 2.63 (s, 6H), 2.35 (s, 9H). $^{13}C\{^{1}H\}$NMR (CD_3OD) δ 145.7, 144.3, 143.6, 143.5, 141.6, 135.4,

134.0, 132.9, 132.2, 131.3, 129.8, 127.0, 122.2, 114.0, 27.1, 21.33, 21.27, 21.1. HRMS Calc'd. for $C_{16}H_{18}I^+$ $[M–OTs]^+$ 337.0453, found 337.0449.

4-Pentafluorosulfanylphenyl(mesityl)iodonium tosylate (14d). Method C gave **14d** as a white solid (0.33 g, 29%). mp = 162−163 °C; ^{1}H NMR (CD_3OD) δ 8.05 (d, J = 8.7 Hz, 2H), 7.94 (d, J = 9.0 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H), 7.26 (s, 2H), 7.20 (d, J = 8.0 Hz, 2H), 2.64 (s, 6H), 2.37 (s, 3H), 2.36 (s, 3H). ^{13}C{^{1}H}NMR (CD_3OD) δ 157.1 (quint, J = 18.5 Hz), 146.4, 143.7, 143.5, 141.7, 135.9, 131.6, 130.6 (quint, J = 4.6 Hz), 129.8, 127.0, 122.5, 117.6, 27.1, 21.3, 21.1. ^{19}F{^{1}H} NMR (CD_3OD) δ 80.10 (quint, J = 150.4 Hz), 61.11 (d, J = 148.5 Hz). HRMS Calc'd. for $C_{15}H_{15}F_5IS^+$ $[M–OTs]^+$ 448.9859, found 448.9857.

Mesityl(4-methoxyphenyl)iodonium tosylate (14f). Method B, using (diacetoxyiodo)mesitylene and anisole, gave **14f** as a white solid (0.6 g, 57%). mp = 191−192 °C; ^{1}H NMR (CD_3OD) δ 7.84 (q, J = 5.6 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.21 (d overlapped with singlet up field, J = 8.2 Hz, 2H), 7.18 (s, 2H), 7.02 (q, J = 5.6 Hz, 1H), 7.02 (d, J = 9.2 Hz, 1H), 3.82 (s, 3H), 2.65 (s, 6H), 2.35 (s, 3H), 2.33 (s, 3H). ^{13}C{^{1}H}NMR (CD_3OD) δ 164.3, 145.6, 143.8, 143.4, 141.7, 137.6, 131.3, 129.9, 127.1, 123.0, 119.0, 102.8, 56.5, 27.1, 21.5, 21.2). HRMS Calc'd. for $C_{16}H_{18}IO^+$ $[M–OTs]^+$ 353.0402, found 353.0403.

Mesityl(*p*-tolyl)iodonium tosylate (14g). Method C gave **14g** as a white solid (0.62 g, 61%). mp = 171−172 °C; ^{1}H NMR (CD_3OD) δ 7.76 (d, J = 7.9 Hz, 2H), 7.66 (d, J = 7.5 Hz, 2H), 7.30 (d, J = 7.7 Hz, 2H), 7.20 (s, 4H), 2.63 (s, 6H), 2.40–2.32 (m, 9H). ^{13}C{^{1}H}NMR (CD_3OD) δ 145.7, 144.6, 143.6, 143.4, 141.6, 135.3, 134.0, 131.3, 129.8, 127.0, 122.4, 110.4, 27.0, 21.3, 21.3, 21.1. HRMS Calc'd. for $C_{16}H_{18}I^+$ $[M–OTs]^+$ 337.0453, found 337.0447.

Mesityl(4-(trifluoromethyl)phenyl)iodonium tosylate (14h). Method C gave **14h** as a white solid (0.36 g, 64%). mp = 164−166 °C; ^{1}H NMR (CD_3OD) δ 8.05 (d, J = 8.0 Hz, 2H), 7.77 (d, J

= 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.24 (s, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.64 (s, 6H), 2.36 (s, 3H), 2.35 (s, 3H). $^{13}C\{^{1}H\}$NMR (CD_3OD) δ 146.2, 143.7, 143.6, 141.7, 135.9, 134.8 (q, *J* = 34.2 Hz), 129.8, 129.7 (q, *J* = 3.0 Hz), 126.9, 124.7 (q, *J* = 272.7 Hz), 122.5, 118.0, 27.1, 21.3, 21.1. $^{19}F\{^{1}H\}$ NMR (CD_3OD) δ – 64.7. HRMS Calc'd. for $C_{16}H_{15}F_3I^+$ $[M–OTs]^+$ 391.0171, found 391.0172.

(2-Isopropylphenyl)(mesityl)iodonium tosylate (**14i**)**.** Method C gave **14i** as a white solid (0.35 g, 33%). mp = 146−149 °C; ^{1}H NMR (CD_3OD) δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.69–7.63 (m, 3H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.28 (t, *J* = 7.1 Hz, 1H), 7.24–7.17 (m, 4H), 3.03 (sept, *J* = 6.8 Hz, 1H), 2.60 (s, 6H), 2.35 (s, 6H), 1.19 (d, *J* = 6.4 Hz, 6H). $^{13}C\{^{1}H\}$NMR (CD_3OD) δ 151.9, 145.8, 143.7, 143.6, 141.6, 137.7, 134.4, 131.6, 131.1, 130.1, 129.8, 127.0, 121.4, 118.0, 39.3, 26.8, 24.0, 21.3, 21.0. HRMS Calc'd. for $C_{18}H_{22}I^+$ $[M–OTs]^+$ 365.0766, found 365.0769.

Mesityl(*o*-tolyl)iodonium tosylate (14j). Method B, using (2-diacetoxyiodo)toluene and mesitylene in $CHCl_3$ at 60 °C with 3 h reaction time, gave **14j** as an off-white solid (0.67 g, 66%). mp = 172−173 °C; ^{1}H NMR (CD_3OD) δ 7.83 (d, *J* = 7.9 Hz, 1H) 7.66 (d, *J* = 8.2 Hz, 2H), 7.56–7.52 (m, 2H), 7.28–7.16 (m, 5H), 2.61 (s, 6H), 2.60 (s, 3H), 2.36 (s, 3H), 2.35 (s, 3H). $^{13}C\{^{1}H\}$NMR (CD_3OD) δ 145.8, 143.8, 143.7, 142.5, 141.7, 137.3, 134.1, 133.5, 131.6, 130.8, 129.9, 127.1, 121.7, 118.5, 27.1, 25.2, 21.5, 21.1. HRMS Calc'd. for $C_{16}H_{18}I^+$ $[M–OTs]^+$ 337.0453, found 337.0456.

Mesityl(2-methoxyphenyl)iodonium tosylate (**14k**). Method C was used with slight modification. Thus, $TsOH·H_2O$ (0.98 g, 4 mmol) was added to a solution of 2-iodoanisole (0.94 g, 4 mmol) and *m*CPBA (0.98 g, 4.4 mmol) in $CHCl_3$ (20 mL) at RT and stirred for 10 min. Mesitylboronic acid (0.66 g, 4 mmol) was added to the mixture and stirred for 1 h at RT. Work up was as in method C and gave **14k** as white crystals (1.44 g, 69%). mp = 178−179 °C. ^{1}H

NMR (CD_3OD) δ 7.87 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.63–7.60 (m, 1H), 7.25 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.16 (s, 2H), 7.06 (td, *J* = 7.9, 1.3 Hz, 1H), 3.91 (s, 3H), 2.63 (s, 6H), 2.34 (s, 3H), 2.33 (s, 3H). $^{13}C\{^1H\}$NMR (CD_3OD) δ 158.6, 145.5, 143.9, 143.8, 141.7, 137.4, 136.0, 131.2, 129.9, 127.1, 124.9, 121.1, 114.4, 103.3, 57.6, 26.9, 21.5, 21.1. HRMS Calc'd. for $C_{16}H_{18}OI^+$ $[M–OTs]^+$ 353.0402, found 353.0406.

(2-Cyanophenyl)(mesityl)iodonium tosylate (14l). Method C gave **14l** as a white solid (0.17 g, 16%). mp = 187−190 °C; ^1H NMR (CD_3OD) δ 8.25 (dd, *J* = 8.1, 0.9 Hz, 1H), 8.03 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.84 (td, *J* = 7.7, 1.1 Hz, 1H), 7.76 (td, *J* = 7.9, 1.7 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.22 (s, 2H), 7.21 (d overlapped with the down field singlet, *J* = 8.0 Hz, 2H), 2.69 (s, 6H), 2.36 (s, 3H), 2.35 (s, 3H). $^{13}C\{^1H\}$NMR (CD_3OD) δ 146.3, 143.9, 143.7, 141.7, 138.9, 137.3, 137.1, 134.4, 131.7, 129.9, 127.1, 123.4, 119.2, 118.6, 117.2, 27.3, 21.4, 21.1. HRMS Calc'd. for $C_{16}H_{15}IN^+$ $[M\text{-}OTs]^+$ 348.0249, found 348.0254.

Mesityl(2-(trifluoromethyl)phenyl)iodonium tosylate (**14m**). Method C gave **14m** as a white solid (0.53 g, 47%). mp = 150−152 °C; ^1H NMR (CD_3OD) δ 8.05–7.99 (m, 2H), 7.85 (t, *J* = 7.7 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.25 (s, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 2.61 (s, 6H), 2.37 (s, 3H), 2.35 (s, 3H). $^{13}C\{^1H\}$NMR (CD_3OD) δ 146.6, 144.0, 143.5, 141.7, 138.7, 137.0, 134.2, 132.1 (q, *J* = 32.6 Hz), 131.8, 130.6 (q, *J* = 5.1 Hz), 129.8, 126.9, 124.2 (q, *J* = 273.6 Hz), 123.3, 109.3, 27.0, 21.3, 21.1. $^{19}F\{^1H\}$ NMR (CD_3OD) δ -60.83 (s). HRMS Calc'd. for $C_{16}H_{15}F_3I^+$ $[M–OTs]^+$ 391.0171, found 391.0173.

(2-Fluorophenyl)(mesityl)iodonium tosylate (14n). Method C gave **14n** as a white solid (0.55 g, 54%). mp = 167−168 °C; ^1H NMR (CD_3OD) δ 8.12 (dd, *J* = 7.7, 5.9, 1.5 Hz, 1H), 7.73–7.68 (m, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.44 (td, *J* = 8.7, 1.3 Hz, 1H), 7.32 (td, *J* = 8.1, 1.3 Hz, 1H), 7.21 (d overlapped with up field singlet, *J* = 8.5 Hz, 2H), 7.18 (s, 2H), 2.66 (s, 6H), 2.35 (s, 3H),

2.32 (s, 3H). $^{13}C\{^{1}H\}$NMR (CD_3OD) δ 161.7 (d, J = 250.3 Hz), 145.8, 143.5, 141.7, 138.3, 136.9, 136.8, 131.3, 129.8, 128.8 (d, J = 3.2 Hz), 126.9, 122.6, 118.4 (d, J = 22.5 Hz), 100.9 (d, J = 23.3 Hz), 26.8 (d, J = 1.9 Hz), 21.3, 21.0. $^{19}F\{^{1}H\}$ NMR (376 MHz, CD_3OD) δ −98.34 (s). HRMS Calc'd. for $C_{15}H_{15}FI^+$ $[M–OTs]^+$ 341.0203, found 341.0206.

(*E*)-Phenyl(styryl)iodonium tosylate (**16**). Koser's reagent (0.392 g, 1 mmol) was added to a solution of (*E*)-styrylboronic acid (0.15 g, 1 mmol) in DCM-CF_3CH_2OH (10 mL; 9: 1 v/v) at 0 °C. The mixture was stirred overnight. Solvent was then evaporated off, and the residue was triturated in diethyl ether (25 mL). The solid was filtered off and recrystallized to give **16** as off-white crystals (0.38 g; 79%). mp = 147−148 °C. ^1H NMR (CD_3OD) δ 8.14 (d, J = 7.6 Hz, 2H), 7.92 (d, J = 14.4 Hz, 1H), 7.81 (d, J = 14.4 Hz, 1H), 7.65–7.73 (m, 3H), 7.55 (t, J = 8.0 Hz, 2H), 7.49–7.55 (m, 2H), 7.38–7.47 (m, 3H), 7.20 (d, J = 8.0 Hz, 2H), 2.34 (s, 3H), $^{13}C\{^{1}H\}$NMR (CD_3OD) δ 152.0, 143.6, 141.7, 136.6, 135.9, 133.6, 133.2, 132.2, 130.2, 129.9, 128.9, 127.0, 114.2, 99.9, 21.3. HRMS Calc'd for $C_{14}H_{12}I^+$ $[M−OTs]^+$ 306.9984, found 306.9987.

(*E*)-(2-Cyclohexylvinyl)(phenyl)iodonium tosylate (**17**). The method for **16** was applied to (*E*)-(2-cyclohexylvinyl)boronic acid (1.5 mmol) and gave **17** as a white solid (0.57 g; 79%). mp = 85−87 °C. ^1H NMR (CD_3OD) δ 8.05 (dd, J = 7.6 Hz, 2H), 7.75–7.66 (m, 3H), 7.55 (t, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.98–7.07 (m, 2H), 2.36 (s, 3H), 2.25–2.36 (m, 1H), 1.73 (d, J = 10.4 Hz, 4H), 1.65 (d, J = 12.8 Hz, 1H), 1.10–1.38 (m, 5H). $^{13}C\{^{1}H\}$NMR (CD_3OD) δ 160.4, 143.7, 141.7, 136.5, 133.5, 133.1, 129.9, 127.0, 113.7, 99.8, 45.2, 32.6, 26.8, 26.6, 21.4. HRMS Calc'd. for $C_{14}H_{18}I^+$ $[M−OTs]^+$ 313.0453, found 313.0455.

Synthesis of amides (20 a−c). $SOCl_2$ (1.1 eq) was added to an aryl acid (2-isopropylbenzoic acid, 3-cyanobenzoic acid or 4-toluic acid) in toluene (0.3 M) and the reaction mixture was heated at reflux for 3 h. The solvent and residual $SOCl_2$ were evaporated off in vacuo and the

residue was dissolved in anhydrous THF. A THF solution of *N*-methylamine (2 M, 2.3 eq) was added and the reaction mixture was stirred at RT for 16 h. The mixture was concentrated to dryness in vacuo and the crude product was purified with flash chromatography on normal phase silica gel with DCM and methanol as a gradient starting at 0% methanol and increased to 5%. Thus were prepared:

3-Cyano-*N*-methylbenzamide (**20a**). White solid. mp = 136−138 °C. ^{1}H NMR ($CDCl_3$) δ 8.09–8.04 (m, 1H), 8.01 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.77 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 6.41 (bs, 1H), 3.03 (d, *J* = 4.9 Hz, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$) δ 166.0, 135.8, 134.6, 131.3, 130.6, 129.6, 118.0, 112.9, 27.4. HRMS Calc'd. for $C_9H_9N_2O$ $[M+H]^+$ 161.0715, found 161.0717.

4-Methyl-*N*-methylbenzamide (**20b**). White solid. mp = 137−138 °C. ^{1}H NMR ($CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 6.17 (bs, 1H), 3.00 (d, *J* = 4.8 Hz, 3H), 2.38 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$) δ 168.2, 141.7, 131.8, 129.2, 126.8, 26.8, 21.4. HRMS Calc'd. for $C_9H_{12}NO$ $[M+H]^+$ 150.0919; found 150.0918.

2-Isopropyl-*N*-methylbenzamide (**20c**). Off-white solid (~ 90% pure by HPLC). mp = 73−75 °C. ^{1}H NMR ($CDCl_3$) δ 7.36 (s, 2H), 7.31–7.21 (m, 1H), 7.20–7.11 (m, 1H), 5.74 (bs, 1H), 3.31 (sept, *J* = 6.8 Hz, 1H), 3.00 (d, *J* = 4.8 Hz, 3H), 1.26 (d, *J* = 4 Hz, 6H). ^{13}C{^{1}H}NMR ($CDCl_3$) δ 171.3, 146.6, 136.2, 129.9, 126.5, 126.0, 125.6, 29.9, 26.7, 24.2. HRMS Calc'd. for $C_{11}H_{16}NO$ $[M+H]^+$ 178.1232; found 178.1233.

Radiochemistry

No-carrier-added [^{11}C]CO_2 was prepared with the ^{14}N(p,α)^{11}C nuclear reaction by bombarding a nitrogen-1% oxygen gas target (initial pressure 300 p.s.i.) with a proton beam (16 MeV, 5 or 10 μA) from a cyclotron (PETrace; GE) for 5 or 10 min. Radiochemistry was performed in a lead-

shielded hot-cell on a modified Synthia platform controlled by in-house developed software based on Labview.[39,40] [^{11}C]CO_2 was first collected in a stainless steel tube trap filled with molecular sieves (13X or 4Å) at RT. The trap was purged with helium at 80 mL/min for 45 s to remove oxygen. [^{11}C]CO_2 was then released in a helium stream (16 mL/min) at 270°C and concentrated in a cryogenic trap filled with silica gel. [^{11}C]CO_2 was then released from the cryotrap in helium (10 mL/min) by warming the trap with a halogen lamp and then passed over molybdenum wire (99.97%, 0.05 mm diameter, Strem Chemicals, Newburyport, MA) in a quartz tube (22 cm length, 0.7 cm i.d.) heated at 875 °C to produce [^{11}C]CO. The [^{11}C]CO was first concentrated cryogenically on silica gel in a stainless steel trap cooled with liquid nitrogen and then released in helium into the autoclave by warming the trap with a halogen lamp.

One-pot ^{11}C-carbonylation method: Diaryliodonium salt **1** (3.8 μmol; ~ 1.8 mg) and Pd reagent (~ 0.5 mg) in DMF–H_2O (4: 1 v/v, 100 μL) were sonicated for 30 s or 5 min and loaded into an autoclave. The mixture was allowed to react with [^{11}C]CO at a set temperature for 2 min, and then collected in a vented glass vial (5-mL). Radioactivity in the vial was measured before and after helium purge for 2 min. An aliquot (50 μL) was then diluted with MeCN-H_2O (1: 1 v/v; 500 μL) and analyzed with reverse phase HPLC.

Two-pot ^{11}C-carbonylation method: Precursor (**1**, **4**−**8**, **14a**–**14n**, **16**, or **17**; 3.8 μmol; ~ 1.5−2.3 mg, plus $Pd(PPh_3)_4$ (0.5 mg) with Xantphos (0.5 mg) or without in DMF (80 μL) were sonicated for 5 min and treated with [^{11}C]CO in an autoclave at a set temperature for 2 min. The reaction mixture was then transferred to a vented glass vial and purged with helium for 2 min. An aliquot (50 μL) was then mixed with aq. NH_4OH (1 M)–MeCN or water–MeCN and allowed to react at RT, 50 or 100 °C for 2 min preceding HPLC analysis.

Two-pot ^{11}C-amidation method: The reaction mixture containing precursors (**14b**, **14g**, or **14i**; 3.8 μmol), $Pd(PPh_3)_4$ (0.5 mg) and Xantphos (0.5 mg) in DMF (80 μL) was sonicated for 5 min and treated with [^{11}C]CO in an autoclave at ambient temperature for 2 min. The reaction mixture was then transferred to a vented glass vial and purged with helium for 2 min. *N*-Methylamine in THF (2 M, 100 μL) was added to an aliquot of the reaction mixtre (50 μL) and the mixture was heated at 50 °C for 2 min. The reaction mixture was cooled to RT and analysed with HPLC.

Radioactivity was measured with a calibrated Atomlab™ 300 dose calibrator (Biodex Medical Systems; Shirley, NY), and corrected for background and physical decay of carbon-11.

Radio-HPLC analysis

HPLC was performed on a system comprising a Gold 126 solvent module (Beckman Coulter; Fullerton, CA) coupled with a 166 or 168 UV absorbance detector plus a Flow-count radioactivity PMT detector (Bioscan, Washington, DC). An aliquot of the quenched reaction mixture was injected onto a reverse phase column (Luna C18, 10 μm, 100 Å, 250 × 4.6 mm i.d.; Phenomenex, Torrance, CA) eluted at 2 mL/min with a linear gradient of aqueous 0.1% TFA (A)–MeCN (B), starting with 10% B and increasing to 50% B in 10 min, held for 5 min, then increased to 80% B in 2 min and held for 5 min at 80% B. Eluate was monitored for radioactivity and absorbance at 231 or 254 nm. Radiochemical product identities were confirmed by comparison of HPLC retention times with non-radioactive standards. In some examples, labeled products were collected and co-injected with reference standards.

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Notes

The authors declare no competing financial interest.

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ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI: Examples of radio-HPLC chromatograms, and ^{1}H-, ^{13}C{^{1}H}-, ^{19}F{^{1}H)}-NMR spectra.

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