Microwave-Promoted Aminocarbonylation of Aryl Iodides, Aryl Bromides, and Aryl Chlorides in Water

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Fast and direct methods have been developed for the small-scale carbonylative preparation of benzamides from aryl iodides, bromides, and chlorides in pure water. The reactions proceed by palladium catalysis using noninert conditions, solid $Mo(CO)_6$ as the CO source, and controlled microwave superheating. Within 15 min of microwave processing, more than 90 aminocarbonylations were successfully performed in useful to excellent yields employing both primary and secondary amines. Using appropriate ratios of starting amines and aryl halides, the competing hydroxycarbonylation reaction was suppressed and only trace amounts of the corresponding carboxylic acids were detected. Based on this aqueous carbonylation, a facile preparation of a novel HIV-1 protease inhibitor was achieved.

Introduction

The similar polarity of classic organic solvents and high-temperature water has encouraged chemists to investigate not only biocatalyzed but also metal-catalyzed organic transformations in aqueous media.[1−4] In addition to being a safe and readily available environmentally friendly solvent,[5] water has also been recognized as an effective reaction medium with unique properties and possibilities for palladium-catalyzed coupling reactions.[6−8] Simultaneously, high-density microwave irradiation has matured into a reliable and useful methodology for accelerated processing of small-scale reactions.[9−12] Thus, gradually it has become clear that the combined approach of microwave superheating, homogeneous catalysis, and aqueous conditions offers a nearly synergistic strategy in the sense that the combination in itself offers greater potential than the three parts in isolation.

In modern drug discovery a number of solutions for how to increase the output of unique chemical entities have been presented, e.g., combinatorial synthesis, parallel synthesis, and automated library production.[13] Even though many of these small-scale techniques in themselves are productive, they altogether generate significant quantities of chemical waste.[14,15] In large, the development of new methods that reduce the environmental impact is of increasing importance, not only for pharmaceutical production but also in the medicinal or combinatorial chemistry research laboratory. The use of water as a nontoxic reaction medium, together with the employment of energy-efficient microwave heating[16] and catalytic methods, must be considered to be both promising and enabling green alternatives.

Palladium(0)-catalyzed carbonylations of aryl halides are among the most important carbon−carbon bond forming reactions that proceed via crucial arylpalladium intermediates.[17−19] While this class of reactions has been extensively used in large-scale productions, its true potential has not been fully utilized in lab-scale synthesis due to the cumbersome handling of the toxic CO gas.[20] In the course of our quest for carbonylative procedures suitable for microwave-accelerated high-speed chemistry, we identified $Mo(CO)_6$ as a convenient and reliable solid CO source.[21−23] In addition and contrary to the general belief,[24−27] we also found that aminocarbonylation reactions with aryl bromides in pure water were quite general, with the amine being a better nucleophile than water.[28] Thus, using noninert conditions, Herrman's palladacycle[29] as a thermostable pal-

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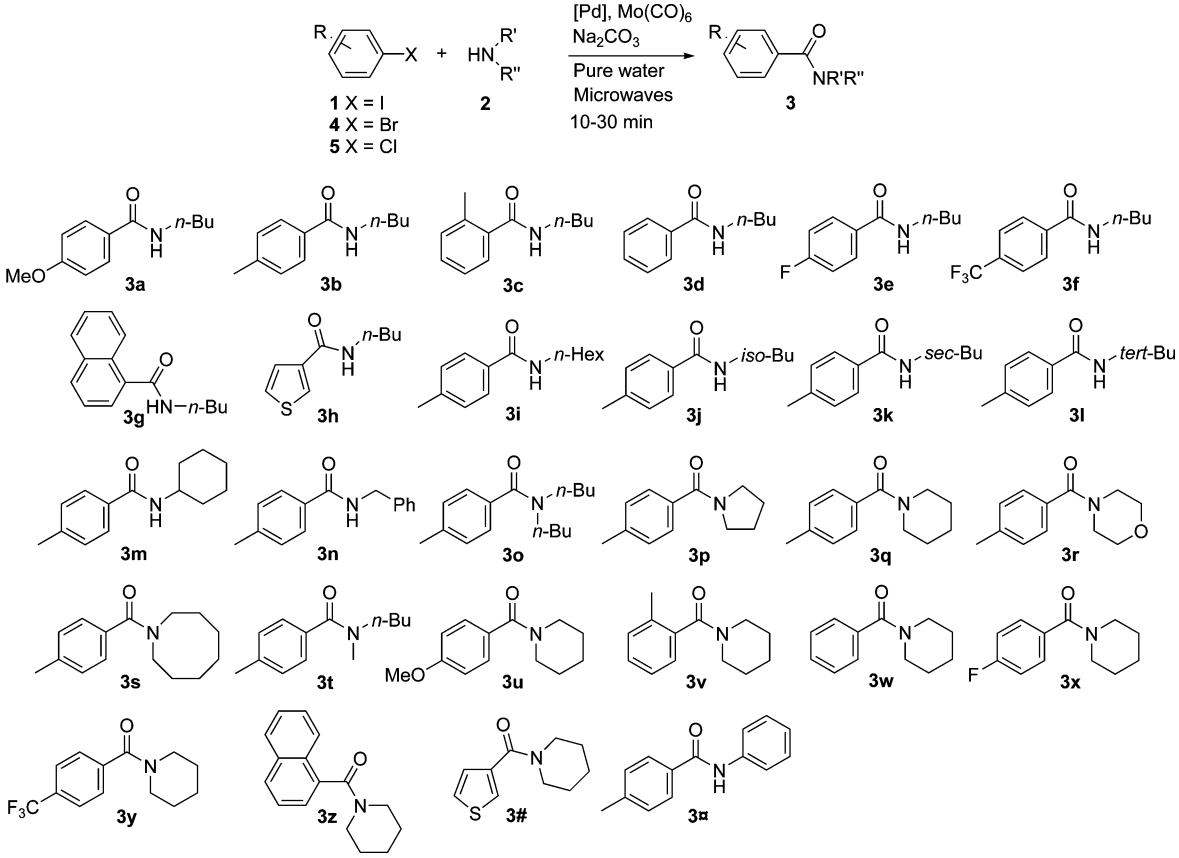
Scheme 1. Microwave-Promoted Aminocarbonylations in Pure Water and Product Structures



ladium source, and optimized reagent stoichiometry only minor amounts of the corresponding benzoic acid were formed.[28] Herein, we report a detailed and full description of the development of aqueous aminocarbonylation protocols not only for aryl bromides but also for aryl iodides and aryl chlorides. Furthermore, the synthesis of a potent HIV-1 protease inhibitor using this amidation technology is presented.

Results and Discussion

Conventionally, aminocarbonylations have been performed with aryl iodides or bromides and amines under CO pressure in non-nucleophilic organic solvents employing standard ligand-free or phosphine-based catalytic palladium systems.[18] Unfortunately, electron-rich trialkylphosphine ligands, which have proved highly successful in a number of related palladium-catalyzed couplings with sluggish aryl chlorides, cannot readily be handled and used under noninert conditions.[30] A new strategy to replace air-sensitive trialkylphosphines with phosphonium salts (acting as convenient trialkylphosphine precursors) was recently disclosed by Gregory Fu.[31] The scope of this elegant approach included cross-couplings, Heck arylations, and Sonogashira reactions of both electron-poor and electron-rich aryl chlorides, although long reaction times and argon atmosphere were utilized. The first general aminocarbonylation procedure using aryl chlorides as arylating agents was not published until 2006.[32]

Table 1. Formation of Aromatic Amide (3g) or Acid by Fast Carbonylation of 1-Iodonaphthalene (1g) with *n*-Butylamine (2a) in Water[a]

1-iodonaphthalene (**1g**) (mmol)	*n*-butylamine (**2a**) (mmol)	isolated yield **3g** (%)[b]
1.0	0	0[c]
1.0	2.0	74
1.0	**5.0**	**83**
1.2	1.0	54
2.0	1.0	73
5.0	1.0	72

[a] 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % $Pd(OAc)_2$, 2.0 mL of H_2O, microwave irradiated at 110 °C for 10 min, >95% conversion of yield-limiting reactant according to GC-MS. [b] >95% purity by GC-MS, yield based on the limiting reactant. [c] Incomplete conversion of **1g**, isolated yield of 1-naphthyl carboxylic acid 6%.

Against this background, we decided to begin our study of in situ carbonylations in water by first focusing on aryl iodides (**1**) and aryl bromides (**4**), before starting to work with the more demanding aryl chlorides (**5**, Scheme 1). Efforts were directed toward identification of efficient procedures using either the aryl halide or nucleophilic amine as the yield-determining reaction participant. All carbonylations described were conducted sequentially in reaction vessels sealed under air using thermocontrolled microwave heating.

Aryl Iodides as Coupling Partners. A straightforward phosphine-free protocol with 0.05 equiv of $Pd(OAc)_2$ as precatalyst and different amounts of 1-iodonaphthalene (**1g**) and *n*-butylamine (**2a**), 0.5 equiv of $Mo(CO)_6$, and 3.0 equiv of Na_2CO_3 in water was selected as the first model system. The temperature was set to 110 °C and the reaction time to 10 min. As shown in Table 1, **2a** competed favorably with water in trapping the acylpalladium intermediate under these conditions, providing 54−83% of benzamide **3g** and no or only trace

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Table 2. Fast Aminocarbonylation of Aryl Iodides with *n*-Butylamine (2a) in Water[a]

no.	aryl-I R-group	aryl amide	yield (%)[b]
1	**1a** 4-MeO−	**3a**	81
2	**1b** 4-Me−	**3b**	88
3	**1c** 2-Me−	**3c**	65
4	**1d** H−	**3d**	88
5	**1e** 4-F−	**3e**	88
6	**1f** 4-CF_3−	**3f**	92
7	**1g** 1-naphthyl−	**3g**	83
8	**1h** 3-thionyl−	**3h**	84

[a] Method A: 1.0 mmol of aryl iodide (**1**), 5.0 equiv of *n*-butylamine (**2a**), 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % $Pd(OAc)_2$, 2.0 mL of H_2O, microwave irradiated at 110 °C for 10 min. [b] Isolated yield, >95% purity by GC-MS.

Table 3. Fast Aminocarbonylation of *p*-Tolyl Iodide (1b) with Miscellaneous Amines in Water[a]

no.	amine	method	aryl amide	yield (%)[b]
1	**2b** *n*-hexylamine	A	**3i**	88
2	**2c** *iso*-butylamine	A	**3j**	83
3	**2d** *sec*-butylamine	A	**3k**	61
4		B	**3k**	64
5	**2e** *tert*-butylamine	A	**3l**	35
6		B	**3l**	43
7	**2f** cyclohexylamine	A	**3m**	68
8	**2g** benzylamine	A	**3n**	78
9	**2h** dibutylamine	A	**3o**	52
10		B	**3o**	63
11	**2i** pyrrolidine	A	**3p**	68
12	**2j** piperidine	A	**3q**	61
13	**2k** morpholine	B	**3r**	15
14	**2l** azocine	A	**3s**	66

[a] Method A: 1.0 mmol of *p*-tolyl iodide (**1b**), 5.0 equiv of amine (**2**), 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % $Pd(OAc)_2$, 2.0 mL of H_2O, microwave irradiated at 110 °C for 10 min. Method B: 2.0 equiv of **1b**, 1.0 mmol of amine (**2**), 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % $Pd(OAc)_2$, 2.0 mL of H_2O, microwave irradiated at 110 °C for 10 min. [b] Isolated yield, >95% purity by GC-MS.

amounts of 1-naphthylcarboxylic acid. It was of interest to note the minor influence on the reaction outcome by switching the aryl iodide/primary amine stoichiometry, although an excess of either reactant increased the yield with a **1g**/**2a** ratio of 1:5 as the top combination.

Preparative examples of aminocarbonylations using 5 equiv of *n*-butylamine (**2a**) and different aryl iodides are presented in Table 2. In general, isolated yields of products **3a**,**b**,**d**−**h** were high (81−92%), regardless if electron-rich or electron-deficient aryl iodides were used as arylpalladium precursors. The hindered **1c** was the only exception to this trend, furnishing a moderate 65% yield of aromatic amide **3c** with hydrodehalogenation as the dominant side reaction. Despite the relatively low reaction temperature (110 °C), no reaction retardation due to potential solubility problems in water was experienced.[1−4]

The reactions of *p*-tolyl iodide (**1b**) and a variety of amines forming secondary and tertiary benzamides are presented in Table 3. Aminocarbonylation of the relatively unhindered, primary amines **2b**−**d**,**f**,**g** proceeded smoothly in 61−88% yield, while reactions with the more bulky *tert*-butylamine (**2e**) were less efficient (entries 5 and 6, Table 3). Secondary amines coupled with **1b** in moderate to good yields (52−78%) with the exception of morpholine (**2k**, entry 13, Table 3). Interestingly, improved yields were realized with all reluctant amines by changing the **1b**/**2** ratio from 1:5 to 2:1 (from method A to method B), avoiding product loss as a consequence of concomitant deiodination.

Aryl Bromides as Coupling Partners. Carbonylative reactions of the representative aryl bromide, 1-bromonaphthalene (**4g**), with different concentrations of *n*-butylamine (**2a**) employing Herrman's palladacycle[29] as a phosphine-containing and thermostable catalyst are summarized in Table 4. In general, palladium(0)-catalyzed reactions with aryl bromides are easily performed under microwave conditions with this precatalyst.[29] High-density microwave irradiation smoothly raised the temperature of the aqueous reaction cocktail to 170 °C, indicating a significant contribution of heating by ionic conduction.[33] However, the higher reaction temperature necessary with bromides made the hydroxycarbonylation pathway more efficient, and without **2a**, 1-naphthyl carboxylic acid was isolated in 67% yield (Table 4). In fact, this reaction must be considered to be a straightforward alternative for synthesizing benzoic acids compared to more sophisticated methods.[18] Even in the presence of the amine, detectable amounts of acid were formed in all processed reactions (Table 4). On the basis of this challenge and on the choice of the synthetic target structure, a bromo-substituted HIV-1 protease inhibitor, we decided to perform a more extensive optimization study using either the amine (Tables 5 and 6) or the aryl bromide (Tables 7 and 8) as the limiting reactant.

Table 4. Formation of Aromatic Amide (3g) or Acid by Fast Carbonylation of 1-Bromonaphthalene (4g) with *n*-Butylamine (2a) in Water[a]

1-bromonaphthalene (**4g**) (mmol)	*n*-butylamine (**2a**) (mmol)	isolated yield **3g** (%)[b]	isolated yield (%) or amount of acid
1.0	0	0	67
1.0	2.0	62	10
1.0	**5.0**	**67**	10
1.2	1.0	63	0.12 mmol
2.0	**1.0**	**79**	0.29 mmol
5.0	1.0	81	0.38 mmol

[a] 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 2.0 mL of H_2O, microwave irradiated at 170 °C for 10 min, >95% conversion of yield limiting reactant according to GC-MS. [b] >95% purity by GC-MS.

Table 5. Fast Aminocarbonylation of Aryl Bromides with Excess of *n*-Butylamine (2a) in Water[a]

no.	aryl-Br R-group	method	aryl amide	yield (%)[b]
1	**4a** 4-MeO−	B	**3a**	60
2	**4b** 4-Me−	B	**3b**	74
3		A	**3b**	80
4		C	**3b**	70
5		D	**3b**	78
6	**4c** 2-Me−	B	**3c**	71
7		A	**3c**	67
8	**4d** H−	B	**3d**	72
9	**4e** 4-F−	B	**3e**	62
10		A	**3e**	59
11	**4f** 4-CF_3−	B	**3f**	60
12	**4g** 1-naphthyl−	B	**3g**	67
13		A	**3g**	66
14	**4h** 3-thionyl−	B	**3h**	55

[a] Method A: 1.0 mmol of aryl bromide (**4**), 5.0 equiv of *n*-butylamine (**2a**), 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 2.0 mL of H_2O, microwave irradiated at 170 °C for 15 min. Method B: 0.8 mmol of aryl bromide (**4**), 3.0 equiv of **2a**, 0.75 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 2.0 mL of H_2O, microwave irradiated at 170 °C for 15 min. Method C: 1.0 mmol of aryl bromide (**4**), 5.0 equiv of **2a**, 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 2.0 mL of H_2O, 0.50 equiv of imidazole, microwave irradiated at 140 °C for 15 min. Method D: 1.0 mmol of aryl bromide (**4**), 5.0 equiv of **2a**, 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 10 mol % $[(t\text{-}Bu)_3PH]BF_4$, 2.0 mL of H_2O, microwave irradiated at 140 °C for 20 min. [b] Isolated yield, >95% purity by GC-MS.

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Table 6. Fast Aminocarbonylation of *p*-Tolyl Bromide (4b) with Excess of Miscellaneous Primary and Secondary Amines in Water[a]

no.	amine	method	aryl amide	yield (%)[b]
1	**2b** *n*-hexylamine	E	**3i**	82
2	**2c** *iso*-butylamine	E	**3j**	71
3	**2d** *sec*-butylamine	E	**3k**	60
4	**2e** *tert*-butylamine	F	**3l**	44
5	**2f** cyclohexylamine	F	**3m**	56
6		G	**3m**	67
7		H	**3m**	59
8	**2g** benzylamine	E	**3n**	50
9	**2m** methylbutylamine	E	**3t**	77
10	**2n** dibutylamine	E	**3o**	47
11	**2i** pyrrolidine	E	**3p**	60
12	**2j** piperidine	E	**3q**	57
13	**2k** morpholine	E	**3r**	55
14	**2l** azocine	E	**3s**	66

[a] Method E: 1.0 mmol of *p*-tolyl bromide (**4b**), 5.0 equiv of amine (**2**), 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 2.0 mL of H_2O, microwave irradiated at 170 °C for 10 min. Method F: 1.0 mmol of **4b**, 3.0 equiv of amine (**2**), 0.75 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 2.0 mL of H_2O, microwave irradiated at 180 °C for 15 min. Method G: 1.0 mmol of **4b**, 5.0 equiv of amine (**2**), 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 2.0 mL of H_2O, microwave irradiated at 180 °C for 15 min. Method H: 1.0 mmol of **4b**, 5.0 equiv of amine (**2**), 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 0.50 equiv of imidazole, 2.0 mL of H_2O, microwave irradiated at 150 °C for 15 min. [b] Isolated yield, >95% purity by GC-MS.

Table 7. Fast Aminocarbonylation with *n*-Butylamine (2a) or Piperidine (2j) and Excess of Aryl Bromides in Water[a]

no.	aryl-Br R-group	*n*-butylamide/ yield (%)[b]	piperidineamide/ yield (%)[b]
1	**4a** 4-MeO−	**3a**/75	**3u**/84
2	**4b** 4-Me−	**3b**/86	**3q**/88
3	**4c** 2-Me−	**3c**/74	**3v**/70
4	**4d** H−	**3d**/78	**3w**/87
5	**4e** 4-F−	**3e**/63	**3x**/80
6	**4f** 4-CF_3−	**3f**/83	**3y**/74
7	**4g** 1-naphthyl	**3g**/79	**3z**/78
8	**4h** 3-thionyl	**3h**/43	**3#**/76
9		**3h**/54[c]	

[a] Method I: 1.0 mmol of *n*-butylamine (**2a**) or piperidine (**2j**), 2.0 equiv of bromide (**4**), 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 2.0 mL of H_2O, microwave irradiated at 170 °C for 10 min. [b] Isolated yield, >95% purity by GC-MS. [c] Method J: As method I but with microwave irradiation at 180 °C for 10 min.

Table 8. Fast Aminocarbonylation with Miscellaneous Amines and Excess of *p*-Tolyl Bromide (4b) in Water[a]

no.	amine	aryl amide	yield (%)[b]
1	**2b** *n*-hexylamine	**3i**	97
2	**2c** *iso*-butylamine	**3j**	82
3	**3h** *sec*-butylamine	**3k**	74
4	**2e** *tert*-butylamine	**3l**	60
5	**2f** cyclohexylamine	**3m**	68
6	**2g** benzylamine	**3n**	81
7	**2o** aniline	**3**-☼-	70
8	**2h** dibutylamine	**3o**	53
9	**2i** pyrrolidine	**3p**	92
10	**2k** morpholine	**3r**	73
11	**2l** azocine	**3s**	70

[a] Method I: 1.0 mmol of amine (**2**), 2.0 equiv of *p*-tolyl bromide (**4b**), 0.5 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 2.0 mL of H_2O, microwave irradiated at 170 °C for 10 min. [b] Isolated yield, >95% purity by GC-MS.

Aminocarbonylation of a diverse set of aryl bromides with an excess of *n*-butylamine (**2a**) proceeded in 15 min at 170 °C, affording the corresponding aromatic amides in 55−80% isolated yield (methods A and B, Table 5). Neither electronic nor steric properties of the carbocyclic aromatic group were of much importance for the reaction efficiency, but the thiophene derivative **4h** furnished the lowest yield (55%, entry 14, Table 5). Decreasing the reaction temperature to 140 °C in the presence of a nucleophilic catalyst, imidazole,[34] gave a slightly lower yield of **3b** compared to the reactions at elevated temperatures (entries 3 and 4, Table 5). However, at 140 °C addition of the $(t\text{-Bu})_3$P-liberating $[(t\text{-Bu})_3PH]BF_4$ phosphonium salt gave the benzamide product in comparable yield (78%) to the reaction at 170 °C (entries 3 and 5, Table 5).

In the complementary carbonylations of *p*-tolyl bromide (**4b**) with a surplus of different primary amines the product yields increased as the bulkiness of the alkyl amines diminished (Table 6). Going from *tert*-butylamine (**2e**) to *n*-hexylamine (**2b**), the yield increased from 44 to 82%. The reaction with cyclohexylamine (**2f**) constituted an example of a relatively sluggish transformation with incomplete consumption of the aryl bromide at 170 °C. Thus, an increase of reaction temperature to 180 °C and a prolonged irradiation time provided complete conversion and 67% isolated yield of **3m** (method G, Table 6). With secondary amines, both cyclic and noncyclic structures served as productive nucleophiles in the carbonylations of **4b**, the best one being methylbutylamine (**2m**), rendering product **3t** in an isolated yield of 77% (entry 9, Table 6).

Results obtained when the reactant stoichiometry was switched to a 2 equiv excess of aryl bromide, using microwave irradiation at 170 °C for 10 min, are summarized in Tables 7 and 8. In most of the 28 cases, and with no regard to the electronic properties of the aromatic ring, both *n*-butylamine (**2a**) and piperidine (**2j**) provided high yields of the different benzamide products. With the sluggish 3-thionyl bromide (**4h**), piperidine (**2j**) acted as the better nucleophile, providing **3#** in 76% yield (entry 8, Table 7), while *n*-butylamine (**2a**) delivered disappointing 43−54% product. The overall best result with an aryl bromide was achieved in the reaction of *n*-hexylamine (**2b**) with *p*-tolyl bromide (**4b**), which displayed complete suppression of the hydroxycarbonylation reaction, producing the aminocarbonylated product **3i** in 97% isolated yield (entry 1, Table 8). The flash heated aqueous aminocarbonylation also worked with reluctant aniline (**2o**), yielding 70% product (entry 7, Table 8).[23] Altogether, slightly improved yields were obtained using an excess of aryl bromide compared to the opposite combination used in Tables 4−6.

To summarize our efforts utilizing aryl bromides, we have developed a number of efficient, high-yielding aqueous protocols producing benzamides with acceptable amounts of side products (benzoic acids and arenes). Competing side-reactions were minimized by adjustment of reaction temperatures and either by using an excess of the nucleophilic amine (Tables 5 and 6) or, alternatively, by employing the amine as the yield-limiting reactant (Tables 7 and 8).

Aryl Chlorides as Coupling Partners. Most aryl chlorides have been generally unreactive under previously employed aminocarbonylation conditions.[17,18,30,35] In fact, only a few examples of the complete range of carbonylative transformations have been reported using either electron-poor or metal-carbonyl-activated aryl chlorides.[35−42] Encouraged by the work of

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Table 9. Formation of Aromatic Amide (3g) or Acid by Fast Carbonylation of 1-Chloronaphthalene (5g) with *n*-Butylamine (2a) in Water[a]

1-chloronaphthalene (**5g**) (mmol)	*n*-butylamine (**2a**) (mmol)	isolated yield **3g** (%)
1.0	0	0[b]
1.0	5.0	trace[c]
1.0	**5.0**	**82**[d]
2.0	1.0	79[d]
5.0	1.0	81[d]

[a] 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 10 mol % $[(t\text{-}Bu)_3PH]BF_4$, 2.0 mL of H_2O, microwave irradiated at 170 °C for 10 min. [b] Incomplete conversion of **5g**, isolated yield of acid 56%. [c] Without $[(t\text{-}Bu)_3PH]BF_4$, incomplete conversion of **5g**. [d] >95% conversion of yield limiting reactant according to GC-MS.

Table 10. Fast Aminocarbonylation of Aryl Chlorides with *n*-Butylamine (2a) in Water[a]

no.	aryl-Cl R-group	method	aryl amide	yield (%)[b]
1	**5a** 4-MeO−	B	**3a**	74
2	**5b** 4-Me−	A	**3b**	44
3		B	**3b**	79
4		C	**3b**	70
5		D	**3b**	69
6	**5c** 2-Me−	A	**3c**	47
7		B	**3c**	77
8	**5d** H−	B	**3d**	76
9	**5e** 4-F−	B	**3e**	79
10	**5f** 4-CF_3−	A	**3f**	84
11	**5g** 1-naphthy−-	A	**3g**	82
12	**5h** 3-thionyl−	B	**3h**	64

[a] Method A: 1.0 mmol of aryl chloride (**5**), 5.0 equiv of *n*-butylamine (**2a**), 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 10 mol % $[(t\text{-}Bu)_3PH]BF_4$, 2.0 mL of H_2O, microwave irradiated at 170 °C for 10 min. Method B: As method A but with microwave irradiation at 170 °C for 30 min. Method C: As method A but with microwave irradiation at 180 °C for 20 min. Method D: As method A but with microwave irradiation at 180 °C for 30 min. [b] Isolated yield, >95% purity by GC-MS.

Gregory Fu, we decided to investigate whether the use of the $[(t\text{-}Bu)_3PH]BF_4$ salt in combination with microwave heating could enable a general acceleration of the $Mo(CO)_6$-mediated aminocarbonylation of reluctant aryl chlorides in water.

The valuable properties of the $(t\text{-}Bu)_3P$-releasing $[(t\text{-}Bu)_3PH]BF_4$ salt in the aminocarbonylation reactions were established as the reactions of *n*-butylamine (**2a**) and 1-chloronaphthalene (**5g**) in different concentrations were investigated (Table 9). Without the $(t\text{-}Bu)_3P$ source, only trace amounts of **3g** were obtained, but in the presence of 10 mol % $[(t\text{-}Bu)_3PH]BF_4$ the product was isolated in up to 82% yield. Reduced reaction temperature provided incomplete conversions and lower yields. Notably, **5g**/**2a** ratios of 1:5, 2:1, and 5:1 all afforded the benzamide product **3g** in a narrow yield interval of 79−82%.

The synthetic results using aryl chlorides **5a**−**h** and *n*-butylamine (**2a**) are summarized in Table 10. Significantly increased yields of sluggish, electron-rich aryl chlorides such as the tolyl chlorides **5b** and **5c** were obtained in the carbonylation reactions with *n*-butylamine (**2a**) when the reaction time was prolonged from 10 to 30 min at 170 °C (method B, Table 10). Even harsher conditions provided no preparative advantage (entries 4 and 5, Table 10). Using method B, the scope of the procedure was further investigated employing aryl chloride **5b** in combination with different primary and secondary amines, including aniline (**2o**) (Table 11). In most cases, the product yields were significantly improved by switching the concentration of the reactants to a 2 or 5 equiv excess of *p*-tolyl chloride (**5b**) (methods E and F, up to 99% isolated yield).

Table 11. Fast Aminocarbonylation of *p*-Tolyl Chloride (5b) with Miscellaneous Amines in Water[a]

no.	amine	method	aryl amide	yield (%)[d]
1	**2b** *n*-hexylamine	B	**3i**	32
2		E	**3i**	99
3	**2c** *iso*-butylamine	B	**3j**	74
4	**2d** *sec*-butylamine	B	**3k**	69
5	**2e** *tert*-butylamine	B	**3l**	24
6		E	**3l**	52
7	**2f** cyclohexylamine	B	**3m**	64
8	**2g** benzylamine	B	**3n**	81
9	**2o** aniline	B	**3**-☼	52
10		F	**3**-☼	67
11	**2n** dibutylamine	B	**3o**	44
12		F	**3o**	50
13	**2i** pyrrolidine	B	**3p**	78
14	**2j** piperidine	B	**3q**	79
15	**2k** morpholine	B	**3r**	48
16		F	**3r**	86
17	**2l** azocine	B	**3s**	46
18		F	**3s**	72

[a] Method B: 1.0 mmol of *p*-tolyl chloride (**5b**), 5.0 equiv of amine (**2**), 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 10 mol % $[(t\text{-}Bu)_3PH]BF_4$, 2.0 mL of H_2O, microwave irradiated at 170 °C for 30 min. Method E: 1.0 mmol of amine (**2**), 5.0 equiv of **5b**, 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 10 mol % $[(t\text{-}Bu)_3PH]BF_4$, 2.0 mL of H_2O, microwave irradiated at 170 °C for 30 min. Method F: 1.0 mmol of amine (**2**), 2.0 equiv of **5b**, 0.50 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 10 mol % $[(t\text{-}Bu)_3PH]BF_4$, 2.0 mL of H_2O, microwave irradiated at 170 °C for 30 min. [b] Isolated yield, >95% purity by GC-MS.

Synthesis of a HIV-1 Protease Inhibitor. HIV protease inhibitors (PIs) are important in HIV/AIDS therapy as components of the successful HAART (highly active antiretroviral therapy) regimen.[43,44] However, low oral bioavailability of most clinically used inhibitors and the increasing number of PI-resistant HIV strains have created a need for new chemical entities within this class of drugs.[45,46] The core structure of **9**, comprising a tertiary alcohol as part of the transition-state mimic, has been shown to yield efficient HIV-1 protease inhibitors with excellent membrane permeation properties (Scheme 2).[47] By optimizing the scaffold, compounds inhibiting the HIV-1 protease enzyme at low nanomolar concentrations have been reported. As deduced from X-ray crystallographic data obtained from an inhibitor within this class cocrystallized with HIV-1 protease, we found that the P1′ side chain of the inhibitor did not fully penetrate the S1′ pocket of the enzyme.[47] We were therefore interested to further explore this scaffold by elongating the P1′ side chain of the inhibitors via the aqueous carbonylative amidation protocol.

The conditions for aminocarbonylation of aryl bromides at 140 °C identified above using either imidazole as a nucleophilic catalyst or $[(t\text{-}Bu)_3PH]BF_4$ as $(t\text{-}Bu)_3P$ liberator (methods C and D, Table 5) were applied to **8**, prepared according to a modified literature procedure[47] (Scheme 2). With 2.5 equiv of imidazole

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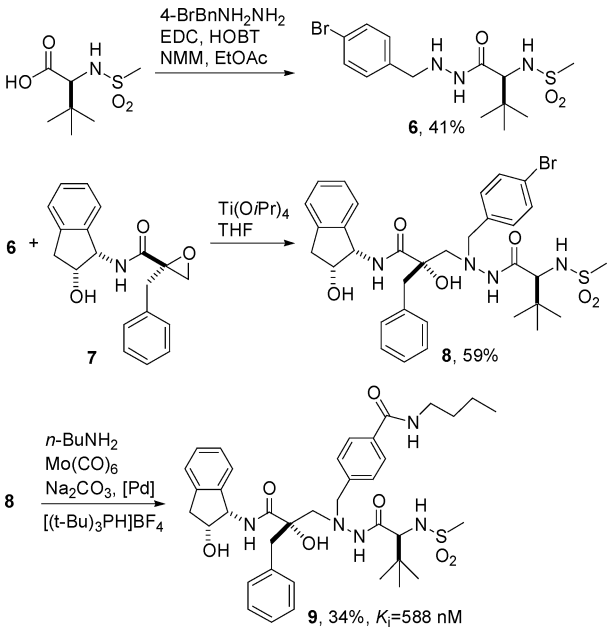
Scheme 2. Synthesis of HIV-1 Protease Inhibitor 9



and 10 equiv of *n*-butylamine, almost complete conversion after 20 min at 130 °C was furnished. Disappointingly, the amidated product **9** was obtained in a complex product mixture. In the presence of $[(t\text{-Bu})_3\text{PH}]\text{BF}_4$, the carbonylation of **8** proceeded smoothly with 10 equiv of *n*-butylamine at 140 °C with 20 min of microwave irradiation, although product **9** could be isolated only in a 34% yield after LC-MS purification. In addition, a substantial amount of the corresponding acid (15%) was isolated. The relatively low yield was however in accordance with results from preliminary attempts to use this scaffold in palladium-catalyzed cross-couplings and could also partly be explained by the rigorous LC/MS purification of the reaction mixture. In a HIV-1 protease assay,[48,49] compound **9** exhibited a K_i value of 588 nM, establishing the potency of this P1′-modified inhibitor. In short, the synthesis of **9** is a rare example of a medicinal chemistry synthesis in pure water and exemplifies the usefulness of the developed aqueous method even when dealing with complex substrates.

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Conclusion

The important role of chemoselective palladium-catalyzed coupling reactions in small-scale organic, medicinal, and high-throughput chemistry encouraged our development of rapid and robust aminocarbonylation protocols in water. In this extended study we presented recent progress in small-scale aminocarbonylation methodologies leading to the following issues being addressed: (1) the use of neat water as solvent was possible by the application of microwave superheating, (2) the competing hydroxycarbonylation process was inhibited by careful fine-tuning of reaction parameters, (3) the requirement of gaseous carbon monoxide was avoided by applying $Mo(CO)_6$ as a solid CO liberator, (4) restrictions in the scope of the reactions were overcome as both the aryl halide and the amine could be used in excess, and finally, (5) the utilization of sluggish aryl chlorides was solved by the use of a thermostable palladacycle and a commercially available $P(t\text{-Bu})_3$ ligand source. Furthermore, from the large number of examples it is clear that this is a general method that tolerates electronically and sterically diverse coupling partners. In summary, useful to excellent yields of different benzamide products were obtained by controlled microwave heating under noninert conditions. By employing this in situ aminocarbonylation approach in pure water, we successfully prepared a novel HIV-1 protease inhibitor in a straightforward manner. Finally, we would like to emphasize the great convenience of this one-pot microwave protocol, enabling a rapid nongaseous opportunity for transformation of easily accessible aryl iodides, bromides, and chlorides into various benzamides.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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