Articles

Microwave-Enhanced Copper-Catalyzed N-Arylation of Free and Protected Amino Acids in Water

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A microwave-enhanced copper-catalyzed protocol for N-arylation using water as the solvent is reported. This fast transformation allows the reaction between various amino acids or amino acid esters and a diverse set of substituted aryl bromides in less than 40 min, affording good yields of non-protected N-arylated amino acids with only minor racemization (6% or less). In addition, online ESI-MS and MS/MS analysis were used to "fish-out" an anionic Cu-containing amino acid complex directly from an ongoing N-arylation reaction.

Introduction

Modern drug discovery uses techniques such as combinatorial and parallel synthesis, as well as automated library production, to accelerate the lead identification process.[1] There is, however, an acute need to implement more sustainable methods, not only for large-scale production but also for lab-scale medicinal chemistry research.[2] A set of environmentally friendly approaches and technologies are available that can help to make progress in this somewhat forgotten research area.[3] One such "green" alternative concerns the use of water as an environmentally benign solvent. Water is cheap, nontoxic, and readily available.[4] In addition to these properties, the use of neat water helps to reduce the generation of organic solvent waste, which is normally produced during a synthesis or an optimization process.[5]

Beyond the development of environmentally friendlier synthetic methods, there is a need for decreased reaction times. Thus, high-density microwave heating has become a helpful processing tool because it allows rapid and convenient superheating to high temperatures in combination with excellent reaction control and low-energy consumption.[6,7,8,9] In addition, water increasingly behaves as a pseudo-organic solvent at temperatures above 140 °C, making the water−microwave combination even more interesting for organic synthesis.[10,11,12]

The research on palladium- and copper-catalyzed arylations of amines was pioneered by Buchwald and Hartwig.[13,14] Today, copper-catalyzed *N*-aryl bond formations rank among the most powerful methods in organic synthesis.[15] Although copper-catalyzed N-arylation of amino acids offers many advantages,[16] the reported transformations are in most cases both sluggish and time-consuming.[15,17]

The use of water as a nontoxic reaction medium, together with the employment of energy-efficient microwave heating[9] and catalytic methods, must be considered to be a promising and enabling green alternative. Herein, we report (a) the development of a fast racemization-free protocol for N-arylation of amino acids and amino acid esters in neat water, (b) applications in the synthesis of target structures, and (c) on-line ESI-MS detection of an anionic copper−amino acid complex.

Results and Discussion

Glycine (**1a**) was chosen as the first model amino acid, and L-phenylalanine (**1b**) was selected as a second substrate because of its limited water solubility. Inspired by Ma's elegant approaches for N-arylation,[16] 10 mol % of CuI was used without an external ligand to catalyze the process. Aryl iodides are known from the literature to be more reactive in N-arylations compared to aryl bromides, but they are also scarcely available and are more expensive.[15a] Hence, bromobenzene (**2a**) was selected as the aryl-Cu precursor in the first stage of the method development. To obtain reproducible results, Millipore water was selected as a consistent source of pure, deionized water. All reactions were performed with 1 mmol of the amino acid, and the reaction mixtures were sealed under air. Under these conditions with a 300 W single-mode microwave cavity, the heating of the samples to

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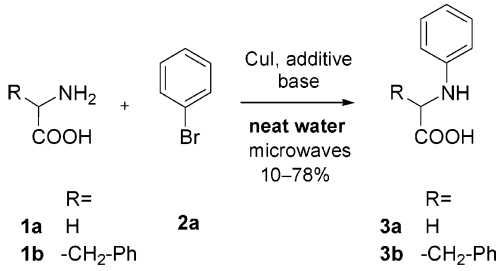


No	Amino acid	Additive	T (°C)	Time (min)	Yield (**3**) (%)
1	**1a**	-	140	15	-
2	**1a**	NaCl	160	20	10 (**3a**)
3	**1a**	KI	160	20	14 (**3a**)
4	**1a**	KI	185	20	22 (**3a**)
5	**1b**	KI	185	30	32 (**3b**)
6	**1b**	KI	185	40	78 (**3b**)
7	**1b**	KI	185	50	65 (**3b**)
8	**1b**	KI	185	60	66 (**3b**)

Figure 1. Impact of different additives and heating parameters on the microwave-assisted Cu(I)-catalyzed N-phenylation of glycine or L-phenylalanine in neat water. Reactions were carried out with 1.0 mmol of amino acid, 3 equiv of phenyl bromide, 2 equiv of K_2CO_3, 10 mol % CuI, 1.8 mL of water, and 0.2 mL of saturated salt solution with microwave irradiation at 140−185 °C for 20−40 min. Isolated yield of **3a** and **b** is >95% pure by LC-MS.

temperatures 140 °C was slow and unpredictable and resulted in low yields and vessel ruptures (below 5%, Figure 1, entry 1). Therefore, two salt additives (NaCl and KI) were evaluated to enhance the ionic strength of the reaction mixture to rapidly and safely reach high reaction temperatures and, hopefully, to provide both better aryl bromide solubility and improved amino acid conversion (Figure 1, entries 2−8).[18]

Initial test reactions indicated that sodium chloride could be a productive additive, and 10% of the added water volume was exchanged with a saturated sodium chloride solution. This modification increased the yield of **3a** to 10% after it was heated at 160 °C for 20 min (Figure 1, entry 2). Furthermore, when 0.2 mL of 10% saturated KI was used in place of the 0.2 mL of saturated 10% NaCl, the yield of **3a** improved to 14% at 160 °C (entry 3). For the best conversion, the temperature was increased to 185 °C.[19] Higher reaction temperatures provided lower yields.

The outcome of the N-arylations displayed a clear dependence on reaction time, as demonstrated by the reactions with L-phenylalanine **1b** and bromobenzene **2a** (Figure 1, entries 5−8). At 185 °C, full conversion and the highest yield was obtained after 40 min reaction time (78%, entry 6), while shorter reaction times did not furnish full conversion. Most likely, longer reaction times lead to product decomposition, although no obvious degradation products were detected by LC-MS. In comparison with the long reaction times of similar arylations presented in literature using traditional heating, the achieved acceleration must be considered noteworthy.[16,20,21] Additionally, only trace amounts of possible biaryl side-products were detected under these reaction conditions.[22]

Table 1. Impact of Different Reaction Parameters on Microwave-Assisted N-Phenylation of L-Phenylalanine with Bromobenzene in Neat Water[a]

no.	bromide (**2a**) (equiv)	K_2CO_3 (equiv)	K_3PO_4 (equiv)	yield (**3b**) (%)[b]
1	1	2		44
2	2	2		66
3	5	2		74
4	10	2		49
5	5	1.2		74
6	5	2		75
7	5	3		78
8	5	5		74
9	5		2	61
10	5		3	58

[a] Reactions were carried out with 1.0 mmol of L-Phenylalanine, 1−10 equiv of bromobenzene, 1.2−5 equiv of base, 10 mol % CuI, 1.8 mL of water, and 0.2 mL of saturated KI solution. Microwave irradiation at 185 °C for 40 min. [b] Isolated yield. **3b** is >95% pure by LC-MS.

Table 2. Cu(I)-Catalyzed N-Phenylation of Various Amino Acids in Neat Water[a]

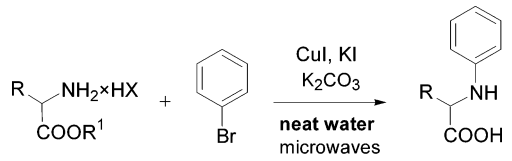
				yield of **3** (%)[b]		
				equiv K_2CO_3		
no.	amino acid	phenyl halide		1.2	2	3
1	L-Phe (**1b**)	**2a**	**3b**	75	75	78
2	D-Phe (**1c**)	**2a**	**3c**			77
3	L-Trp (**1d**)	**2a**	**3d**	66	64	65
4	Gly (**1a**)	**2a**	**3a**	66	41	29
5	L-Val (**1e**)	**2a**	**3e**	58	45	35
6	L-Leu (**1f**)	**2a**	**3f**	71	56	63
7	L-Leu (**1f**)	**2b**	**3f**		88	92
8	L-Pro (**1g**)	**2a**	**3g**	52	60	59
9	Boc-L-Phe-OH	**2a**	**3c**			58

[a] Reactions were carried out with 1.0 mmol of amino acid, 5 equiv of **2a** or **2b**, 1.2−3 equiv of base, 10 mol % CuI, 1.8 mL of water, and 0.2 mL of saturated KI solution. Microwave irradiation at 185 °C for 40 min. [b] Isolated yield. **3a**−**g** are >95% pure by LC-MS.

The results obtained using different substrate ratios of phenylalanine and bromobenzene and two appropriate inorganic bases are presented in Table 1. As illustrated, an excess of the bromide was beneficial and 5 equiv of **2a** provided the highest yield (Table 1, entries 1−4). In previous reports on Cu-mediated amino acid arylations, various bases have been used.[20] In our aqueous protocol, potassium carbonate or potassium phosphate were both found to be suitable, although higher yields were consistently obtained using potassium carbonate (Table 1, entries 5−10). With phenylalanine (**1b**), no significant difference in outcome using 1.2, 2, 3, or 5 equiv of potassium carbonate were found: yields of 74−78% of **3b** (Table 1, entries 5−8).

To further evaluate our N-arylation protocol, a set of amino acids was treated with bromobenzene with K_2CO_3 as base (Table 2). The selected reaction conditions turned out to be suitable for both free and protected amino acids, including the highly lipophilic **1b**, **c**, and **f**, although the amount of base proved to be highly critical. For aromatic amino acids such as phenylalanine or tryptophan, the concentration of base was less important, and the differences in yield were rather small (Table 2, entries 1 and 3). In contrast, only a small excess of base (1.2 equiv) was preferred for arylating

Table 3. N-Phenylation of Amino Acid Esters to Directly Afford the Free N-Phenylated Amino Acid[a]



4 **2a** **3**

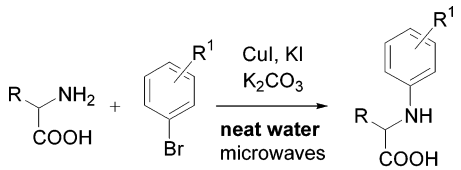
no.		amino acid ester	R^1	HX		yield of **3** (%)[b] K_2CO_3 (equiv) 1.2	2	3
1	**4a**	L-Leu	Me	HCl	**3f**	27	60	60
2	**4b**	L-Phe	Et	HCl	**3b**		96	69
3	**4c**	L-Leu	*t*-Bu	HCl	**3f**		6[c]	64
4	**4d**	L-Phe	*t*-Bu	HCl	**3b**		60	66
5	**4e**	L-Phe	Bz	HCl	**3b**		76	67
6	**4f**	L-Phe	Allyl	HCl	**3b**		57	52
7	**4g**	L-Leu	Allyl	HOTs	**3f**		93	69
8	**4h**	Boc-L-Phe-OH	Me		**3b**			81

[a] Reactions were carried out with 1.0 mmol of amino acid ester, 5 equiv of bromobenzene, 1.2−3 equiv of K_2CO_3, 10 mol % CuI, 1.8 mL of water, and 0.2 mL of saturated KI solution. Microwave irradiation at 185 °C for 40 min. [b] Isolated yield. **3** is >95% pure by LC-MS. [c] Incomplete conversion.

aliphatic amino acids like glycine and valine (Table 2, entries 4−6). Proline provided the highest yields of the corresponding product **3g** in the presence of 2−3 equiv of potassium carbonate (Table 2, entry 8). As expected, iodobenzene (**2b**) also served as a useful phenyl metal precursor, which was exemplified by the high yield (92%) obtained by reacting **2b** with L-leucine (Table 2, entry 7). No pronounced base dependence was observed with **2b,** and the desired product **3f** was obtained in an impressive 88−92% yield. Interestingly, it could also be demonstrated that in situ deprotection and subsequent N-arylation of an *N*-Boc-protected amino acid could be achieved in an isolated yield of 58% (Table 2, entry 9).[22,24]

The scope of the deprotection−N-arylation tandem procedure was further explored using a number of different amino acid esters (**4a**−**h**) in the described microwave procedure. Further, since most of the starting esters were available as salts of strong acids, we were interested in using them directly as N-nucleophiles. Rewardingly, all N-arylations were rapidly executed with concomitant ester deprotection affording a two-step one-pot synthesis of free **3b** and **3f** in 57−96% yields (Table 3). We were surprised to find that different kinds of esters (methyl, ethyl, *t*-butyl, benzyl, and allyl esters) could be phenylated with this method and that free arylated amino acids **3b** and **f** were produced under one, general condition. Here, the use of water as solvent not only possessed environmental and safety advantages but also preparative benefits. In most cases, the best results were obtained using 2 equiv of K_2CO_3, although in case of the *t*-butyl ester **4c**, 2 equiv did not allow full conversion. However, 3 equiv of base yielded complete conversion and a 64% yield of the desired product (Table 3, entry 3). A different result was obtained with allyl-protected **4g** and *para*-toluene-sulfonate as the counterion. With this salt, 2 equiv of potassium carbonate proved advantageous in the combined deprotection−N-arylation process to afford the desired product **3f** in a 93% yield (Table 3, entry 7).

Table 4. Copper (I)-Catalyzed N-Arylation with Different Aryl Bromides[a]



1b,e,g **2c-i** **5**

no.	amino acid	aryl bromide **2** R^1	position	yield **5** (%)[b]
1	**1b**	OMe	*m* (**2c**)	79 (**5a**)
2	**1e**	OMe	*m* (**2c**)	80 (**5b**)
3	**1g**	OMe	*m* (**2c**)	76 (**5c**)
4	**1b**	CH_2OH	*m* (**2d**)	87 (**5d**)
5	**1b**	CN	*m* (**2e**)	53 (**5e**)
6	**1b**	$COCH_3$	*m* (**2f**)	94 (**5f**)
7	**1b**	*t*-Bu	*p* (**2g**)	41 (**5g**)
8	L-Phe-OAllyl HCl	*t*-Bu	*p* (**2g**)	64 (**5g**)[c]
9	**1b**	COPh	*p* (**2h**)	18 (**5h**)
10	L-PheO-Allyl HCl	COPh	*p* (**2h**)	36 (**5h**)[c]
11	**1b**	CH_3	*o* (**2i**)	29 (**5i**)
12	**1b**	CH_3	*o* (**2i**)	43 (**5i**)[d]

[a] Reactions were carried out with 1.0 mmol of amino acid or amino acid ester salt, with 5 equiv of aryl bromide, 3 equiv of K_2CO_3, 10 mol % CuI, 1.8 mL of water, and 0.2 mL of saturated KI solution. Microwave irradiation at 185 °C for 40 min. [b] Isolated yield. **5** is >95% pure by LC-MS. [c] In H_2O/MeCN 4/1. [d] 2 h reaction time.

Furthermore, arylations using the diverse aryl bromides **2c**−**2i** as coupling partners were studied. The results are presented in Table 4. In this series of N-arylations, different substitution patterns were found to be important, while electronic properties proved to be less influential. The sterically hindered ortho-functionalized *o*-tolyl bromide furnished a moderate 29% yield of **5i**, which, however, was improved to 43% by prolonging the heating time to 2 h (Table 4, entries 11−12). Interestingly, meta-substituted aryl bromides seemed to deliver the highest yields of product anilines **5**.

Next to high yields and prevention of byproduct formation, it is of high importance to avoid racemization when functionalizing enantiomerically pure amino acids. Hence, a chiral HPLC system was used to analyze all final products. The L- and D-enantiomers of all N-arylated products were carefully analyzed with a chiral AGP column in combination with 2-propanol/phosphate buffer (pH = 5.5) as the mobile phase, confirming less than 6% racemization in all cases.[24] The least racemization was obtained with the amino acid ester salts, since the results obtained from the chiral HPLC measurements showed <3% racemization.

Furthermore, the developed N-arylation method was applied to synthesis of interesting target molecules in the field of angiotensin AT_1 and AT_2 receptor ligand research. Angiotensin II (Ang II, Asp-Arg-Val-Tyr-Ile-His-Pro-Phe) is believed to be the most important peptide hormone in the renin−angiotensin system (RAS) where it activates two major receptors: AT_1R and AT_2R.[23,24,25] However, while the

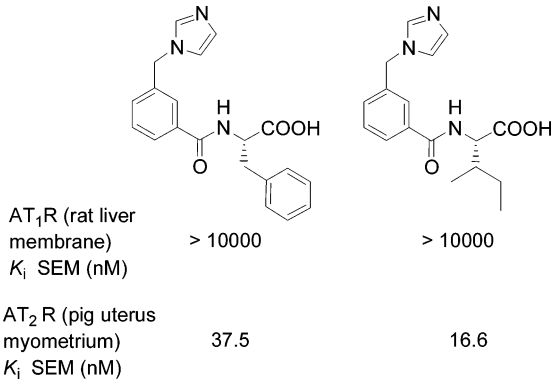


Figure 2. Highly selective AT_2R ligands.[26]

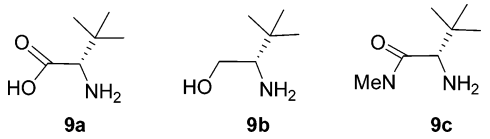


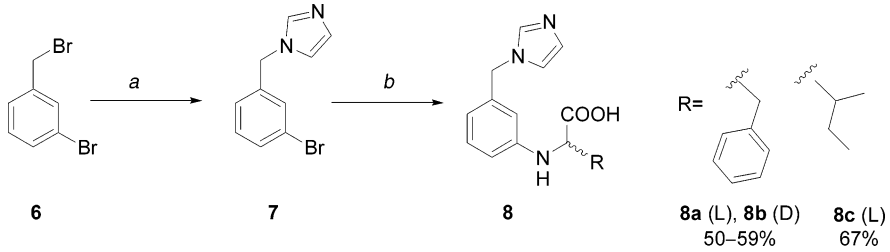
Figure 3. L-*t*-Leucine, L-*t*-leucinol, and L-*t*-leucinemethylamide for evaluation as copper(I) ligands.

AT_1 receptor has become a valuable target for hypertension therapy, the AT_2 receptor has been much less studied. Because of the therapeutic interest, the identification of truly selective ligands of each receptor is of great importance. Small, druglike peptidomimetic compounds with nanomolar affinity for the AT_2R and with full selectivity against the AT_1R were recently reported by Hallberg et al. (Figure 2).[26] Among the investigated amino acid derivatives, L-phenylalanine or L-isoleucine residues gave the best selectivity and activity.[26]

A further reduction of the peptidic character of the ligands in Figure 2 was of interest to possibly identify a novel carbonyl-free aniline-type AT_2R ligands. The investigated preparation strategy for these new compounds is depicted in Scheme 1. The imidazole moiety in **7** was easily introduced by substituting the benzylic bromide in **6**. Here, the published synthetic yield of **7**[27] could be improved from 81 to 94% by changing the reaction temperature and time. In the next step, the selected amino acids (phenylalanine and isoleucine) were N-arylated using the conditions from Table 4, furnishing the aniline products **8a**−**c** in 50−67% yields (Scheme 1). Disappointingly, compounds **8a**−**c** were all found to be inactive in both the AT_1R and AT_2R assays (K_i > 10000 nM), highlighting the importance of the carbonyl group for receptor binding.

D. Ma and co-workers have suggested two different plausible mechanisms for the Cu(I)-catalyzed N-arylation.[16a] In both cases, the amino acid plays a dual role: acting both as an O,N-chelating ligand to the metal center and as the nucleophilic substrate. Interestingly, both hypothesized catalytic pathways start with a bis-coordinated copper−amino acid intermediate [$Cu^+ \times {}^-NH\text{-}CHR\text{-}CO_2{}^-$], a species that is negatively charged with additional, neutral copper ligands (e.g., solvent molecules).

Scheme 1. N-Arylation Approach to Produce Potential Ligands for the AT_1 and AT_2 Receptors



[a] 1.0 equiv of *m*-bromobenzyl bromide, 4.4 equiv of imidazole in DMF, 100 °C, 6 h, then room temp, 94%. [b] 1.0 equiv of amino acid, 5 equiv of **7**, 3 equiv of K_2CO_3, 10 mol % CuI, 0.9 mL of water and 0.1 mL of saturated KI solution, microwave irradiation at 185 °C for 40 min.

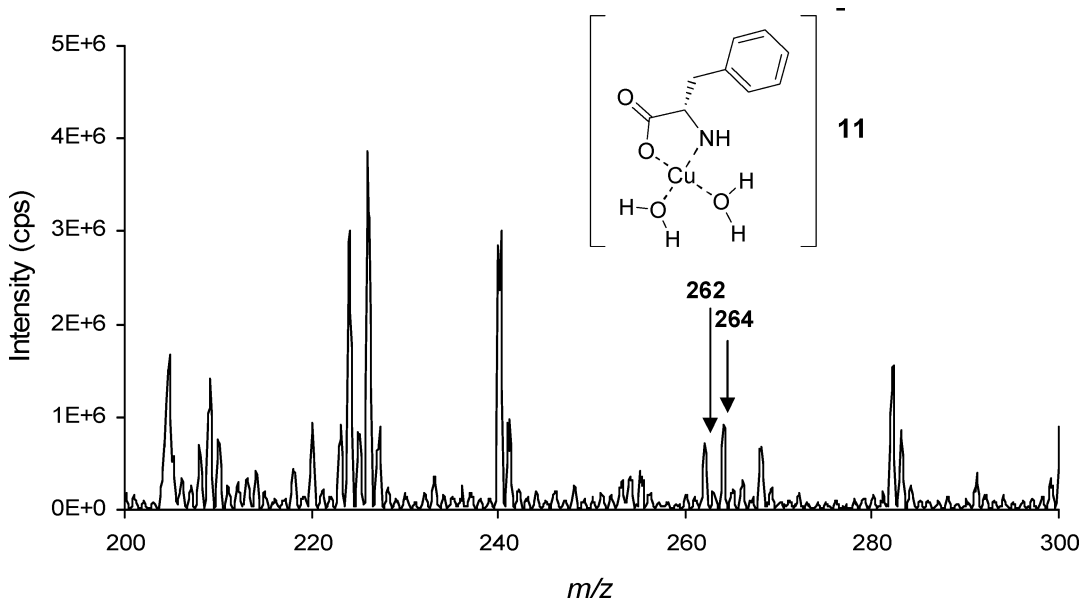


Figure 4. Copper(I)-containing L-phenylalanine complex **11** detected by (−)-ESI-MS.

To further investigate the role of the amino acid as a metal ligand, L-*t*-Leucine **9a** and nonacid derivatives **9b** and **9c** were reacted with bromobenzene **2a** (Figure 3). Interestingly, only the amino acid **9a** and the corresponding amino alcohol **9b** could be transformed into the corresponding N-arylated compounds **10a** and **10b**, where the acid provided a better yield (**10a**, 35%) than the analogous alcohol (**10b**, 15%, see Supporting Information). No traces of the arylated product could be detected with *N*-methylamide **9c**. These first results suggest that productive ligands should chelate the copper via both an amino and an hydroxy functionality.

Electrospray ionization (ESI) is used for transferring ionic species from the condensed phase to the gas phase, making them available for mass spectrometric detection (MS). The ESI-MS technique has previously been used to probe the mechanism of various Pd(0)-catalyzed coupling reactions[28] and is well demonstrated as a unique method for the analysis of homogeneous metal-catalyzed reactions.[29] Compared to palladium, copper has only two stable isotopes (100% ^{63}Cu and 45% ^{65}Cu), but they are both detectable and distinguishable, especially when using ESI-MS/MS. Inspired by previous ESI-MS achievements in homogeneous catalysis,[28,29] we initiated ESI-MS measurements of ongoing reaction systems for potential detection of copper−amino acid complexes during the arylation of **9a**, **9b**, and L-phenylalanine (**1b**). Since the reaction may proceed via anionic intermediates, we decided to study the reaction in negative detection mode.

As a starting point, we first conducted an ESI-MS analysis of a typical microwave reaction mixture. Under these conditions, ESI-MS detection showed mostly iodide ions, which made spectrometric interpretation difficult. Thus, the reaction cocktail was modified to contain no KI. The N-arylated products were instead formed using 1 equiv of amino acid, 5 equiv of bromobenzene, and only 2 equiv of the base (K_2CO_3) at 90 °C in water (**1b**) or in a 4/1 water−acetonitrile system to increase the solubility (**9a** and **9b**). The mixture was then heated in a standard heating block for several days (60 h). In all cases, the desired product could be detected by LC-MS and isolated, even though the total yields after 60 h of reaction time were lower than with microwave heating.[30] Samples were periodically removed during the reaction and diluted 100 times with water prior to (−)-ESI-MS analysis. A distinct copper complex was observed by (−)-ESI-MS only in the N-arylation of **1b**. In this case, the anionic copper−phenylalanine−water complex **11** with a *m*/*z* signal of 262 (^{63}Cu) was detected after 4 h (Figure 4). In addition, the corresponding *m*/*z* ratio of 264 (for ^{65}Cu) was found in the same reaction mixture. For both species, (−)-ESI-MS/MS measurements showed analogous copper-containing daughter fragments with the expected isotopic *m*/*z* difference of 2, together with the deprotonated L-phenylalanine anion. In all observations, ESI-MS measurements from the beginning of the reaction (after ∼4−6 h reaction time) gave higher signal-to-noise ratios than experienced in the end phase of the reaction (>20 h). The observation of catalytic complex **11** is in good agreement with either of the Ma-suggested alternative N-arylation mechanisms.[16]

Conclusion

In summary, we have successfully developed a general method for the microwave-induced N-arylation of amino acids in water providing moderate to high yields and less than 6% racemization. A diverse set of amino acids and differently substituted aryl bromides were fully reacted after 40 min of microwave radiation. In addition, various amino acid esters could be N-arylated with simultaneous deprotection, generating the free acid as product. On-line ESI-MS and MS/MS measurements of the reaction mixture were used for the detection of a copper−amino acid complex, supporting the dual role of the amino acids as both reagent and metal ligand.

Acknowledgment. This manuscript is dedicated to Prof. Anders Hallberg to mark his election as vice chancellor of Uppsala University. We gratefully acknowledge the Swedish Research Council, The Swedish Foundation for Strategic Research, Dr. Anders Karlsson (AstraZeneca R&D, Mölndal, Sweden), Dr. Prasad Appukkuttan, Dr. Luke Odell, Dr. Jenny Ekegren, Mr. Shane Peterson, and Mr. Milad Botros.

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

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