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Palladium(II)-Catalyzed *ortho*-C–H Arylation/Alkylation of *N*-Benzoyl α-Amino Ester Derivatives

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Abstract: The palladium-catalyzed arylation/alkylation of *ortho*-C–H bonds in *N*-benzoyl α-amino ester derivatives is described. In such a system both the NH-amido and the CO_2R groups in the α-amino ester moieties play a role in successful C–H activation/C–C bond formation using iodoaryl coupling partners. A wide variety of functional groups and electron-rich/deficient iodoarenes are tolerated. The yields obtained range from 20 to 95%.

The development of straightforward synthetic methodologies for the efficient and selective preparation of bioactive molecules is an important goal in drug discovery and in the production of pharmaceutical and agrochemical compounds.[1] In the last decades, transition-metal catalysis has become a powerful tool for the synthesis of a myriad of organic functionalities.[2] Among these catalytic reactions, direct regioselective C(sp^2,sp^3)–H activation/functionalization is a practical strategy for linking different building blocks in a one-step reaction in a cleaner fashion.[3] To achieve such selectivity, in most cases, the coordinating group must be associated with the substrate in a configuration that permits the metal centre to approach a specific C–H bond, and is subsequently removed after the target reaction.[4] In the last few years, we developed several chelation-assisted catalytic systems that led to excellent C–H bond activation and selective C–C and/or C–N bond formation by using commercially available but costly (Pd),[5] less costly (Ru),[6] and much less costly (Ni)[7] metal complexes. In our continuing pursuit of identifying new and more efficient directing-group moieties based on the regioselective arylation[8] and alkylation[6a,7a,9] of benzamides using well established reactions catalyzed by transition-metal catalysts, we hypothesized that an α-amino ester group might participate in the *ortho*-C–H activation/C–C coupling of carboxylic acid derivatives.

Functionalized molecules bearing amino acid moieties are of interest as potential bioactive substrates, because an amino acid can facilitate the diffusion of compounds through the wall of adnormal cells or bacterial cells, thus allowing them to reach the biological target.[10] In addition, bi(hetero)aryl compounds containing peptides are widespread and structurally diverse in natural products.[11] A survey of the literature indicates that studies of these types of molecules that present important biological activities have been reported (Figure 1).[12,13]

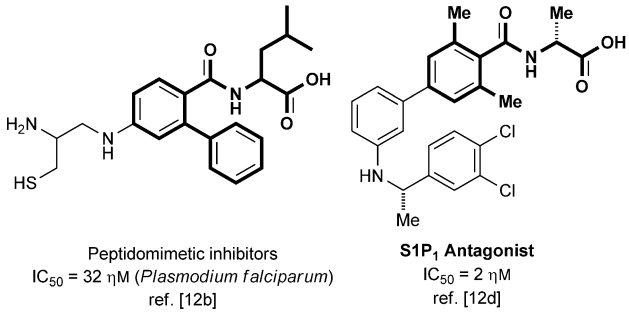

Figure 1. Bioactive *ortho*-substituted *N*-benzoyl α-amino acid compounds.

The *ortho*-functionalization of *N*-benzoyl α-amino esters through transition-metal catalysis might led to the synthesis of a great variety of potentially active molecules in which the amino ester arm plays, not only the role of a coordinating group, but also is an indispensable part of the reaction intermediate (functioning as the active region for further modifications) and the final product.

Our preliminary studies were focused on the reaction of the simple *N*-(2-methyl)benzoyl-glycine ester **1a** and iodobenzene using commercially available palladium(II) complexes in *t*-Amyl-OH as a solvent at 100 °C for 24 h (Table 1). All of the palladium complexes showed catalytic activity (**I**–**V**, entries 1–5). Among them, complexes **IV** and **V** resulted in better yields (70%). Several solvents were also evaluated for use (toluene, 1,2-DCE, and neat, Table 1, entries 6–8) in a search for a higher conversion using complex **V**, and only 0.1 mL of toluene showed a similar activity to that for *t*-Amyl-OH. When the reaction was carried out under atmospheric conditions the yield was slightly improved and better reproducibility was obtained (76%, entry 9). Other attempts to improve the conversion such as a higher temperature (110 °C, entry 10), more catalyst loading (15 mol%, entry 11), and more AgOAc (3 equiv, entry 12) failed to result in an improvement. In fact, under previous conditions, lower conversions were observed (entry 9 vs. 10–12). The use of larger amounts of PhI (2–4 equiv, entries 13 and 14) resulted in only a minor increase in yield (entry 9 vs. entries 13 and 14). Reducing the catalyst loading or the use of AgOAc

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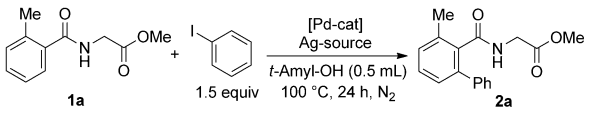
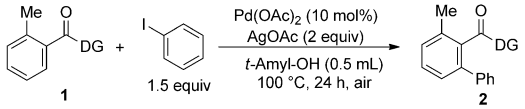
Table 1. Optimization of the *ortho*-C–H arylation of **1a** with iodobenzene.



Entry[a]	Catalyst ([mol%])	[Ag] ([equiv])	Yield **2a** [%][b]	Yield **1a** [%][b]
1	$PdCl_2(PPh_3)_2$ (10) **I**	AgOAc (2)	21	70
2	$Pd(TFA)_2$ (10) **II**	AgOAc (2)	59	34
3	$PdCl_2$ (10) **III**	AgOAc (2)	65	34
4	$PdCl_2(CH_3CN)_2$ (10) **IV**	AgOAc (2)	70	22
5	$Pd(OAc)_2$ (10) **V**	AgOAc (2)	70	28
6[c]	$Pd(OAc)_2$ (10)	AgOAc (2)	70	15
7[d]	$Pd(OAc)_2$ (10)	AgOAc (2)	47	29
8[e]	$Pd(OAc)_2$ (10)	AgOAc (2)	66	20
9[f]	**$Pd(OAc)_2$ (10)**	**AgOAc (2)**	**76 (71)**	**16**
10[g]	$Pd(OAc)_2$ (10)	AgOAc (2)	61	12
11[f]	$Pd(OAc)_2$ (15)	AgOAc (2)	67	14
12[f]	$Pd(OAc)_2$ (10)	AgOAc (3)	58	26
13[f,h]	$Pd(OAc)_2$ (10)	AgOAc (2)	77	20
14[f,i]	$Pd(OAc)_2$ (10)	AgOAc (2)	78	13
15	$Pd(OAc)_2$ (10)	AgOAc (1)	43	55
16	$Pd(OAc)_2$ (5)	AgOAc (2)	42	56
17	$Pd(OAc)_2$ (10)	–	3	95
18	–	AgOAc (2)	0	99
19[f]	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2)	9	82
20[f]	$Pd(OAc)_2$ (10)	Ag_2O (2)	2	67

[a] Conditions: **1a** (0.3 mmol), PhI (0.45 mmol), *t*-Amyl-OH (0.5 mL), N_2, 100 °C, 24 h. [b] ^{1}H NMR spectroscopic yield using 1,1,2,2-tetrachloroethane as the internal standard. Isolated yield in parenthesis. [c] Toluene (0.1 mL). [d] 1,2-DCE (0.5 mL). [e] Neat. [f] Charged in air. [g] 110 °C. [h] PhI (2 equiv). [i] PhI (4 equiv).

Table 2. Influence of the α-amino acid ester moiety on C–H arylation.[a]



Entry	DG	Yield **2** [%][b]	Entry	DG	Yield **2** [%][b]
1	**1a** (Gly)	**76**	7	**1g**	7
2	**1b**	66	8	**1h** (Met)	0
3	**1c**	0	9	**1i** (Asp)	60
4	**1d**	65	10	**1j** (Glu)	32
5	**1e** (Ala)	37	11	**1k**	42
6	**1f** (Leu)	25	12	**1l**	21

[a] Conditions: **1** (0.3 mmol), PhI (0.45 mmol), *t*-Amyl-OH (0.5 mL), air, 100 °C, 24 h. [b] ^{1}H NMR spectroscopic yield by using 1,1,2,2-tetrachloroethane as the internal standard.

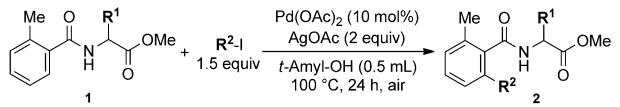
also resulted in lower conversions (entries 15 and 16). The roles of Pd^{II} and Ag were demonstrated when the reaction was carried out in the absence of Ag or Pd, in which the active catalyst involves the formation of Pd^{II} and Ag^+; Ag^+ might function as an iodide scavenger, facilitating the oxidative addition of the aryl iodide to the metal centre (entries 17 and 18).[14] Other Ag sources were also tested, but the yields obtained were quite poor (entries 19 and 20). In most cases, the remaining starting material did not extensively decompose and could be recovered. Many other attempts using different types of additives (bases, ligands, coordinating solvents, and O_2) were tested with no satisfactory improvement being realized (see the Supporting Information). To check whether or not the product **2a** was the cause of the low conversions, a test reaction was carried out under the optimized conditions, but with 0.5 equiv of **2a** being added the conversion was just 34% (vs. 76%, entry 9) showing that the product hampers the catalytic turnover in this reaction.

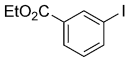
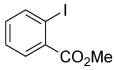
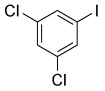
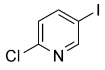
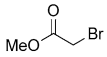
To study the influence of the α-amino ester moiety on the C–H arylation reaction, several *N*-benzoyl compounds bearing diverse natural and non-natural α and β-amino acid esters were synthesized **1b–l** (Table 2).

When the alkoxy group on the ester was exchanged for another longer or bulkier one, such as Et **1b** or *t*Bu **1d**, the conversion decreased to about 10%, showing that steric hindrance originating from the alkoxy group has only a small negative effect on the success of the reaction (entries 2 and 4 vs. entry 1). However, when a tertiary α-carbon amino ester was present on the substrate, the yield dramatically decreased as a function of the steric hindrance of the α-substituent (Me **1e** (Ala) < *i*Bu **1f** (Leu) < Ph **1g**, entries 5–7). Surprisingly, when the α-substituent was the CH_2CO_2Me group **1i** (Asp), the conversion increased, resulting in better yields (60%, entry 9). Nevertheless, when an additional methylene group was inserted in the α-substituent, such as $CH_2CH_2CO_2Me$ **1j** (Glu), the conversion dropped to 32% (entry 10). When the ethyl β-amino ester compound **1k** was treated under the same reaction conditions the conversion was moderate (42%, entry 11). Using the *N*-alkyl amide (*n*Bu) **1l**, only a 21% conversion was obtained (entry 12). It is possible that the ester group stabilizes some intermediates during the catalytic turnover by weak coordination to the metal centre. The importance of the NH-amide group was also confirmed when the tertiary amide **1c** was used and no conversion was detected (entry 3), as was previously observed in our group with other secondary-amide-type chelating-assisted catalytic systems.[5b,6a,b,7a]

To obtain additional information, the scope of compounds **1a** and **1i** were studied by using different halide-containing compounds (Table 3). For iodoarenes bearing *p*-substituted

Table 3. Scope for the *ortho*-C–H arylation of compounds **1a** and **1i**.[a]



Entry	R^2–I	R^3	R^1 = H yield **1a** [%][b]	R^1 = CH_2CO_2Me yield **1i** [%][b]
1		Me	58 (**2m**)	57 (**2ad**)
2		OMe	53 (**2n**)	52 (**2ae**)
3		NO_2	55 (**2o**)	83 (**2af**)
4		Ac	51 (**2p**)	56 (**2ag**)
5		F	55 (**2q**)	–
6		Cl	50 (**2r**)	–
7		Br	57 (**2s**)	71 (**2ah**)
8		OH	20[c] (**2t**)	–
9		CO_2Me	68 (**2u**)	71 (**2ai**)
10			60 (**2v**)	70 (**2aj**)
11			74 (**2w**)	60 (**2ak**)
12			55 (**2x**)	–
13			32[c] (**2y**)	28[c] (**2al**)
14[d]			28[c] (**2z**)	traces
15[d]	CH_3–I		67 (**2aa**)	–
16[d]			91 (**2ab**)	–
17[d]			72 (**2ac**)	–

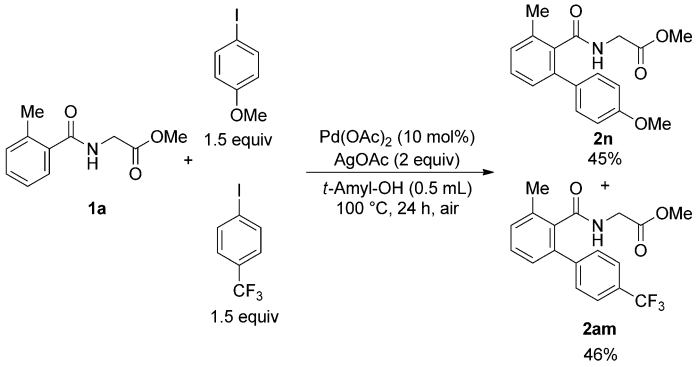
[a] Conditions: **1** (0.3 mmol), R^2–I (0.45 mmol), *t*-Amyl-OH (0.5 mL), air, 100 °C, 24 h. [b] Isolated yield. [c] ^{1}H NMR spectroscopic yield using 1,1,2,2-tetrachloroethane as the internal standard. [d] R^2–I (2 equiv).

electron-donating or -withdrawing groups, the yields obtained were similar and lower in the case of PhI (50–58%, entries 1–7, **1a**). However, this system tolerates different functional groups, such as nitro, ketone, and halides that are nearly ubiquitous in bioactive compounds and can be easily transformed into other functional groups. In the case of compound **1i**, the yields were also moderate, except for *p*-NO_2 and *p*-Br iodoarenes in which the yields were good (83 and 71%, entries 3 and 7, **1i**). The chemoselective coupling of this reaction in the presence of a C–Br bond is a very important point, since the C–Br bond can easily be functionalized, by Pd^0 catalysis, for example.[15] In both of the studied compounds, the *p*-ester iodoarene generated good yields (68% **1a** and 71% **1i**, entry 9). The *m*-ester iodoarene also resulted in good yields in both substrates (60% **1a** and 70% **1i**, entry 10). When *ortho*-electron-donating/-withdrawing group (EDG/EWG) iodoarenes, such as Me, OMe, and F, were used, no conversion was detected. Surprisingly, when the methyl 2-iodobenzoate was tested, the isolated yields obtained were good (74% **1a** and 60% **1i**, entry 11). This result shows that the ester also acts as a coordinating group facilitating C–I bond activation, a similar effect was recently observed by Fan and Ma in the direct C(sp^3)–H arylation of α-amino ester derivatives.[16] The reaction of **1i** with methyl 2-iodobenzoate generates two atropisomers, as evidenced by ^{1}H and ^{13}C NMR spectra, in a ratio of 2:1 (Supporting Information). A chiral HPLC analysis of the compound **2ah** (entry 7 in Table 3) showed that no racemization occurs under the reaction conditions.

Arylation with the 2-chloro-5-iodopyridine was also possible, but the conversion was only around 30% with both substrates (entry 13). This can be attributed to the fact that the coordinating ability of the pyridine to the metal centre slows down the catalytic turnover. This statement is based on an experimental result, when 1 equiv of pyridine was added under the optimized conditions for the reaction and no conversion was observed (Supporting Information).

To determine whether or not the electronic nature of the iodoarene has an effect on the catalytic C–C coupling reaction, compound **1a** was reacted under the same conditions with 1.5 equivalents of 4-iodoanisole and 4-iodobenzotrifluoride under the optimized conditions. Both iodoarenes afforded almost the same yield, which suggests that the electronic properties of the iodoarene has little affect on the catalytic reaction (Scheme 1).

When the same catalytic system was applied to the alkylation of substrates **1a** and **1i** by using 2 equivalents of *n*BuI, only a 28% yield was found for the case of **1a** and only traces for **1i** (entry 14). This is because the carboxylate ($^-$OAc) in the silver salt deactivates the alkyl halide through either esterification or decomposition by an E2 pathway.[17] When alkyl halides without a β-hydrogen, such as CH_3–I, ethyl iodoacetate, and methyl bromoacetate were used, good to excellent yields were obtained (67–91%, entries 15–17). It is important to note that

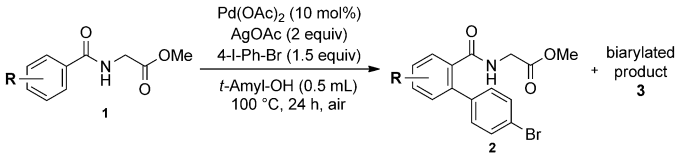


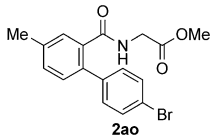
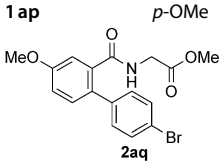
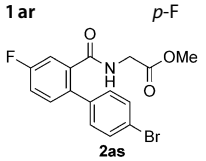
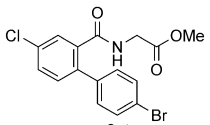
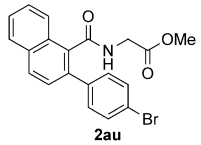
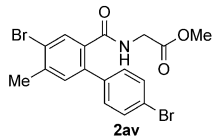
Scheme 1. Competition reaction between electron-rich and -deficient iodoarenes with **1a**.

the regioselective C–H methylation reaction is a very hot research topic in pharmaceutical chemistry due to the well-known "magic methyl effect" which, in many cases, greatly improves the biological activity of drugs.[12d,18]

The electronic and steric hindrance effects of the amide aromatic ring on the catalytic reaction were also studied (Table 4).

Table 4. Scope for the *ortho*-C–H arylation of *N*-benzoyl compounds.[a]



Entry	1	R	Conv. [%][c]	2 [%][b]	3 [%][c]	2/3[d]
1	**1an**	*p*-Me	63	51	11	83:17
2	 **2ao**		95	80	10	89:11
3	**1ap**	*p*-OMe	38	31	3	92:8
4	 **2aq**		64	60	0	100:0
5	**1ar**	*p*-F	56	46	7	89:11
6	 **2as**		45	39	3	93:7
7	 **2at**		77	73	0	100:0
8	 **2au**		25	21	0	100:0
9	 **2av**		55	51	0	100:0

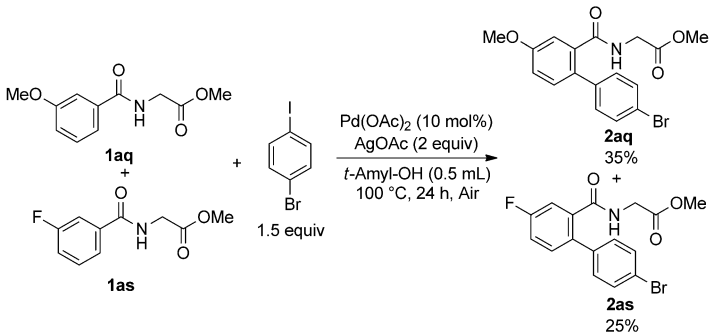
[a] Conditions: **1** (0.3 mmol), 4-iodobromobenzene (0.45 mmol), *t*-Amyl-OH (0.5 mL), air, 100 °C, 24 h. [b] Isolated yield. [c] ^{1}H NMR spectroscopic yield by using 1,1,2,2-tetrachloroethane as the internal standard. [d] Determined by ^{1}H NMR spectroscopy.

With both electron-withdrawing and -donating groups on the *meta*- and *para*-positions, the reaction proceeded well and with high regioselectivity, affording the monoarylated compound as the main product. The best results were obtained with *meta*-substituted aromatic amides (Me 95%, OMe 64%, Cl 77%; entries 2, 4, and 7) except for **1as** for which the conversion was low (F 45%, entry 6). In addition, the new C–C bond was formed through the less-hindered *ortho*-C–H bond and no evidence for the more-hindered *ortho*-monoarylated compound was detected. *Para*-substituted aromatic amides also afforded mainly the desired monoarylated product (**2**) in good yield (Me 63%, F 56%; entries 1 and 5) and low yield (OMe 38%; entry 3). The 3,4-disubstituted compound **1av** also furnished the *ortho* regioselective diaryl product in moderate yield (55%, entry 9). The 1-naphthyl amide **1au** provided the regioselective product **2au**; however, only in low yield (25%, entry 8). Unfortunately, when glycine heteroaromatic amides, such as thiophene, pyridine, and furan, were treated under the optimized reaction conditions, unsatisfactory results were obtained.

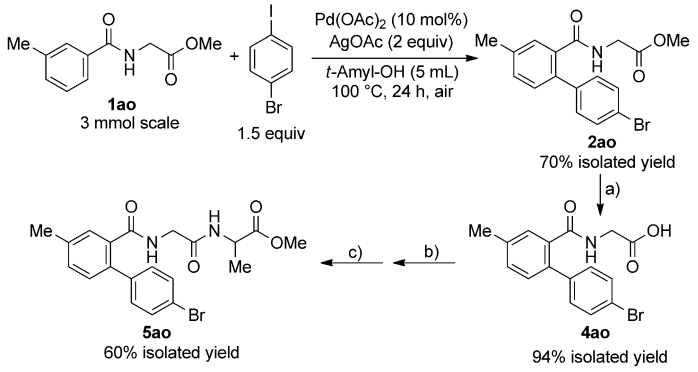
Similarly, in competition reactions of *meta*-substituted aromatic amides bearing an electron-rich (**1aq**) or -deficient group (**1as**), the electronic nature of the aromatic ring had a negligible effect on the course of the C–H arylation reaction (Scheme 2).

To evaluate the potential of the catalytic system and of this new family of compounds, **1ao** was reacted on a 3 mmol scale to give the arylated **2ao** in 70% yield (Scheme 3). Compound **2ao** can easily be transformed into the respective *N*-(2-aryl)benzoyl unprotected glycine **4ao** in 94% yield, and, by classical organic chemistry, another amino acid (or dipeptide) can be attached to give the biaryl peptide **5ao**, a richer amino acid compound.

The stoichiometric reaction of **1a** and **1i** with $Pd(OAc)_2$ in acetonitrile resulted in the produc-

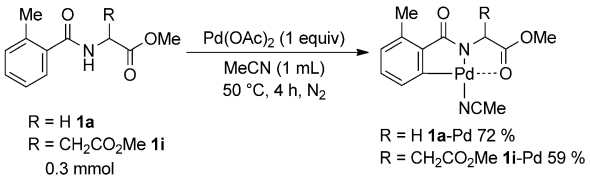


Scheme 2. Competition reaction between electron-rich and -deficient *N*-benzoyl amino esters **1aq** and **1as**.



Scheme 3. Arylation and further transformation of **1ao**. a) **2ao**/1,4-dioxane, 1.5 equiv $LiOH/H_2O$, RT, 30 min; b) 2.5 equiv *N*-ethylmorpholine/THF, 0 °C/1 equiv *i*-butylchloroformate, 1 h; c) 1.3 equiv, H-Ala-OMe.HCl, RT, 16 h.

tion of air-stable complexes that were characterized by ^1H and ^{13}C NMR spectroscopy and FAB-MS analysis (Supporting Information). These analyses showed one molecule of substrate per palladium atom and one coordinated acetonitrile (Scheme 4). Due to the impossibility of obtaining a suitable single crystal for X-ray analysis and based on NMR spectroscopy and mass analyses, we propose that the reaction proceeds by the tricoordination CNO of the substrate to the metal centre with one acetonitrile occupying the fourth site.



Scheme 4. Stoichiometric reaction of **1a** and **1i** with $Pd(OAc)_2$.

The reaction of **1a**–**Pd** with 1.5 equivalents of PhI and 2 equivalents of AgOAc, in *t*-Amyl-OH at 100 °C for 24 h, under air, afforded **2a** in 30% yield and and **1a** in 4% yield. Despite the lower yield of **2a**, the lower quantities of **1a** shows that **1a**–**Pd** reacts with PhI to generate **2a**, but **1a**–**Pd** also decomposes to other unidentified products under such conditions. It therefore appears that a similar intermediate palladium complex is involved in the catalytic cycle in which the NH-amido and α- or β-carbonyl ester aid in the regioselective C–H activation and concomitant C–C formation.

In summary, we report on findings that demonstrate that it is possible to use an α-amino ester moiety, such as glycine and aspartic derivatives, as directing groups for selective *ortho*-$C(sp^2)$–H activation and C–C bond formation with aryl iodides and bromo/iodo alkyl compounds that contain no β-hydrogen as coupling partners through palladium catalysis. Based on the experimental results and spectroscopic analyses, we propose that the NH-amido and carbonyl ester groups both play a major role in the catalytic reaction. This family of compounds bearing a biaryl and an amino acid ester group represent potential bioactive molecules.

Experimental Section

General procedure for the catalytic arylation of *N*-benzoyl amino ester derivatives (synthesis of compound 2a)

Methyl-2-(2-methylbenzamido)acetate (64 mg, 0.3 mmol), iodobenzene (52 μL, 0.45 mmol), palladium(II) acetate (6.8 mg, 0.03 mmol), silver(I) acetate (100 mg, 0.6 mmol), and 2-methyl-2-butanol (0.5 mL) were added to an oven-dried 5 mL screw-capped vial under an atmosphere of air. The mixture was stirred at 100 °C for 24 h followed by cooling to room temperature. The resulting solution was then filtered through a Celite pad and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc) to afford the desired arylated product **2a** in 72% yield.

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Keywords: alkylation · α-amino esters · arylation · C–H activation · palladium catalysis

[1] a) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651 – 2710; b) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092 – 9142; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960 – 9009; c) C. A. Busacca, D. R. Fandrick, J. J. Song, C. H. Senanayake in *Applications of Transition Metal Catalysis in Drug Discovery and Development*, John Wiley & Sons, New York, **2012**, pp. 1 – 24.

[2] M. Breuning, *Angew. Chem.* **2013**, *125*, 6704 – 6704; *Angew. Chem. Int. Ed.* **2013**, *52*, 6574 – 6574.

[3] a) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173 – 1193; b) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174 – 238; c) B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, *2008*, 949 – 957; d) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074 – 1086; e) G. P. McGlacken, L. M. Bateman, *Chem. Soc. Rev.* **2009**, *38*, 2447 – 2464; f) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196 – 5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094 – 5115; g) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976 – 10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792 – 9826; h) F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269 – 10310; i) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624 – 655; j) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147 – 1169; k) K. Hirano, M. Miura, *Synlett* **2011**, *2011*, 294 – 307; l) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315 – 1345; m) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788 – 802; n) B.-J. Li, Z.-J. Shi, *Chem. Soc. Rev.* **2012**, *41*, 5588 – 5598; o) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879 – 5918; p) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382 – 10401; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236 – 10254; q) M. C. White, *Synlett* **2012**, *23*, 2746 – 2748.

[4] a) C. Wang, Y. Huang, *Synlett* **2013**, *24*, 145 – 149; b) G. Rouquet, N. Chatani, *Angew. Chem.* **2013**, *125*, 11942 – 11959; *Angew. Chem. Int. Ed.* **2013**, *52*, 11726 – 11743; c) N. Chatani, *J. Synth. Org. Chem. Jpn.* **2013**, *71*, 406 – 416.

[5] a) Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984 – 12986; b) Y. Ano, M. Tobisu, N. Chatani, *Org. Lett.* **2012**, *14*, 354 – 357.

[6] a) S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 6898 – 6899; b) N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 8070 – 8073; c) K. Shibata, N. Hasegawa, Y. Fukumoto, N. Chatani, *ChemCatChem* **2012**, *4*, 1733 – 1736; d) Y. Ano, M. Tobisu, N. Chatani, *Synlett* **2012**, 2763 – 2767; e) N. Hasegawa, K. Shibata, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *Tetrahedron* **2013**, *69*, 4466 – 4472; f) Y. Aihara, N. Chatani, *Chem. Sci.* **2013**, *4*, 664 – 670; g) G. Rouquet, N. Chatani, *Chem. Sci.* **2013**, *4*, 2201 – 2208.

[7] a) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 14952 – 14955; b) Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2013**, *135*, 5308 – 5311; c) Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2014**, *136*, 898 – 901.

[8] a) Y. Kametani, T. Satoh, M. Miura, M. Nomura, *Tetrahedron Lett.* **2000**, *41*, 2655 – 2658; b) D. Shabashov, O. Daugulis, *Org. Lett.* **2006**, *8*, 4947 – 4949; c) D. Shabashov, J. s. R. M. Maldonado, O. Daugulis, *J. Org. Chem.* **2008**, *73*, 7818 – 7821; d) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886 – 9887; e) C. S. Yeung, X. Zhao, N. Borduas, V. M. Dong, *Chem. Sci.* **2010**, *1*, 331 – 336; f) M. Wasa, J.-Q. Yu, *Tetrahedron* **2010**, *66*, 4811 – 4815; g) G.-W. Wang, T.-T. Yuan, D.-D. Li, *Angew. Chem.* **2011**, *123*, 1416 – 1419; *Angew. Chem. Int. Ed.* **2011**, *50*, 1380 – 1383; h) X. Wang, D. Leow, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 13864 – 13867; i) L. Ilies, E. Konno, Q. Chen, E. Nakamura, *Asian J. Org. Chem.* **2012**, *1*, 142 – 145; j) D.-D. Li, T.-T. Yuan, G.-W. Wang, *J. Org. Chem.* **2012**, *77*, 3341 – 3347; k) F. Péron, C. Fossey, T. Cailly, F. Fabis, *Org. Lett.* **2012**, *14*, 1827 – 1829; l) K. Si Larbi, H. Y. Fu, N. Laidaoui, K. Beydoun, A. Miloudi, D. El Abed, S. Djabbar, H. Doucet, *ChemCatChem* **2012**, *4*, 815 – 823.

[9] a) S. J. Tremont, R. Hayat Ur, *J. Am. Chem. Soc.* **1984**, *106*, 5759 – 5760; b) Q. Chen, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 428 – 429; c) Q. Chen, L. Ilies, N. Yoshikai, E. Nakamura, *Org. Lett.* **2011**, *13*, 3232 – 3234.

[10] A. Gutiérrez, J. Bernal, M. D. Villacampa, C. Cativiela, A. Laguna, M. C. Gimeno, *Inorg. Chem.* **2013**, *52*, 6473 – 6480.

[11] a) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518 – 5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384 – 5427; b) L. Feliu, M. Planas, *Int. J. Pept. Res. Ther.* **2005**, *11*, 53 – 97.

[12] a) E. C. Lerner, Y. Qian, A. D. Hamilton, S. M. Sebti, *J. Biol. Chem.* **1995**, *270*, 26770 – 26773; b) D. Chakrabarti, T. Da Silva, J. Barger, S. Paquette, H. Patel, S. Patterson, C. M. Allen, *J. Biol. Chem.* **2002**, *277*, 42066 – 42073; c) J. Ohkanda, F. S. Buckner, J. W. Lockman, K. Yokoyama, D. Carrico, R. Eastman, K. de Luca-Fradley, W. Davies, S. L. Croft, W. C. Van Voorhis, M. H. Gelb, S. M. Sebti, A. D. Hamilton, *J. Med. Chem.* **2004**, *47*, 432 – 445; d) J. Quancard, B. Bollbuck, P. Janser, D. Angst, F. Berst, P. Buehlmayer, M. Streiff, C. Beerli, V. Brinkmann, D. Guerini, P. A. Smith, T. J. Seabrook, M. Traebert, K. Seuwen, R. Hersperger, C. Bruns, F. Bassilana, M. Bigaud, *Chem. Biol.* **2012**, *19*, 1142 – 1151.

[13] a) D. J. Burdick, K. Paris, K. Weese, M. Stanley, M. Beresini, K. Clark, R. S. McDowell, J. C. Marsters, Jr., T. R. Gadek, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1015 – 1018; b) D. J. Burdick, J. C. Marsters, Jr., I. Aliagas-Martin, M. Stanley, M. Beresini, K. Clark, R. S. McDowell, T. R. Gadek, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2055 – 2059.

[14] J. Powell, M. Horvath, A. Lough, *J. Chem. Soc. Chem. Commun.* **1993**, 733 – 735.

[15] D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27 – 50.

[16] M. Fan, D. Ma, *Angew. Chem.* **2013**, *125*, 12374 – 12377; *Angew. Chem. Int. Ed.* **2013**, *52*, 12152 – 12155.

[17] S.-Y. Zhang, Q. Li, G. He, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 12135 – 12141.

[18] a) C. S. Leung, S. S. F. Leung, J. Tirado-Rives, W. L. Jorgensen, *J. Med. Chem.* **2012**, *55*, 4489 – 4500; b) H. Schönherr, T. Cernak, *Angew. Chem.* **2013**, *125*, 12480 – 12492; *Angew. Chem. Int. Ed.* **2013**, *52*, 12256 – 12267.

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