Electrophilic Substitution

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Direct *ortho* Iodination of β- and γ-Aryl Alkylamine Derivatives**

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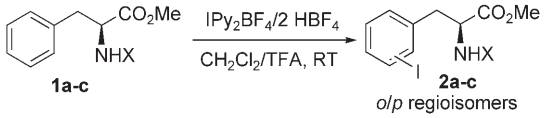
Selective C–H functionalization reactions allow the rapid modification of available molecular scaffolds. Organometallic and electrophilic processes serve as synthetic tools to this end. Selective electrophilic aromatic substitution at the *ortho* position remains elusive in the case of monosubstituted arenes. Therefore, *ortho*-substituted derivatives are prepared typically by indirect strategies. Arynes,[1] or the *ortho*-metalated species obtained upon the treatment of arenes with appropriate bases,[2] offer feasible alternatives. The metal-catalyzed activation of the *ortho* C–H bond is also useful in this context, and a number of approaches for the preparation of *ortho*-halogenated derivatives have recently been disclosed.[3] The recognition of controlling units that assist the delivery of the electrophile to the desired *ortho* position through standard electrophilic processes is crucial, and should lead to interesting opportunities.[4]

Herein, results on the controlled *ortho* iodination of phenylalanine and related β- and γ-aryl alkylamines are reported. The bonding of the amine to a small organic fragment able to weakly interact with the iodonium species was a key to this study from the outset.[5] The use of a trifluoroacetamide as an amine surrogate was investigated.[6] Our hypothesis was validated with the *O*-methyl ester derivatives of phenylalanine for the iodination of free amine, *N*-acetyl, and *N*-trifluoroacetyl substrates. The effect of the experimental conditions was also tested. Representative results are outlined in Table 1. Entries 1–3 show that the conversion of the amine into an amide modifies the regioselectivity of the reaction.[7] The use of the trifluoroacetamide derivative of the amine led to an unusual *ortho* iodination of the phenylalanine derivative.[5] Both the use of a mixture of CH_2Cl_2 and trifluoroacetic acid (TFA) as the solvent (Table 1, entries 3, 8, and 10) and the addition of HBF_4 (Table 1, entries 5 and 9) affect the selectivity in favor of the *ortho*-substituted isomer. The dependence of the regioselectivity on the concentration was tested. Thus, with a CH_2Cl_2/TFA ratio of 10:1, higher selectivity was observed for the iodination performed at 4.5×10^{-3} M than for the reaction in the more concentrated solution (5×10^{-2} M). Dilution to 3×10^{-3} M improved the selectivity, but the iodination did not proceed to conclusion, even after a longer reaction time (Table 1, entries 3, 5, and 7).

Table 1: Substrates and conditions for the *o*-iodination of α-phenylalanine derivatives.[a]



1a-c → **2a-c** *o*/*p* regioisomers

Entry	X	1	*t* [h]	CH_2Cl_2/TFA [mL/mL]	2 [%][b]	2 (*o*/*p*)[b]
1[c]	H	**1a**	5	100/10	53	**2a** (1:1)
2[c]	$COCH_3$	**1b**	4	100/10	32	**2b** (2:1)
3	$COCF_3$	**1c**	2	100/10	>95	**2c** (10:1)
4[d]	$COCF_3$	**1c**	6	100/10	>95	**2c** (10:1)
5	$COCF_3$	**1c**	0.5	10/1	>95	**2c** (5:1)
6	$COCF_3$	**1c**	4	100/1	50	**2c** (5:1)
7	$COCF_3$	**1c**	24	150/15	57	**2c** (12.5:1)
8	$COCF_3$	**1c**	0.1	–/10	>95	**2c** (4:1)
9[e]	$COCF_3$	**1c**	2.5	10/1	91	**2c** (1:1)
10	$COCF_3$	**1c**	4	10/–	60	**2c** (1:1)

[a] 0.5 mmol of **1**; ratio **1**/IPy_2BF_4/HBF_4 (1:1.5:3.1). [b] The conversion and the *o*/*p* ratio of **2** were determined by GC and/or ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] The reaction was carried out with a **1**/IPy_2BF_4/HBF_4 ratio of 1:1.05:2.1. [d] The reaction was carried out at −20 °C. [e] The reaction was carried out without HBF_4.

The conditions outlined in Table 1, entry 3 were then used routinely to investigate the generality of this *ortho* iodination. By this protocol, pure *o*-**2c**[8] was isolated in 80% yield, and *p*-**2c** in 5% yield. The iodination of trifluoroacetamides prepared from simpler amines showed that this method gives the desired selectivity for derivatives of β- and γ-aryl alkylamines (Scheme 1). In all cases, the conversion was higher than 95%, and the reaction furnished iodinated compounds as the only products.[9] The length of the tether between the arene ring and the trifluoroacetamide moiety drastically affects the selectivity. Excellent results were observed for the iodination when the spacer contained two or three methylene groups, for both secondary and tertiary amides. Compounds in which one or four methylene groups link the two active units were iodinated with 1:1 *o*/*p* selectivity. As expected, the reaction of the amide derived from aniline gave only the *p*-iodo regioisomer. Branching in the aliphatic spacer at the β position to the nitrogen atom led to poorer selectivity. This result probably reflects constraints

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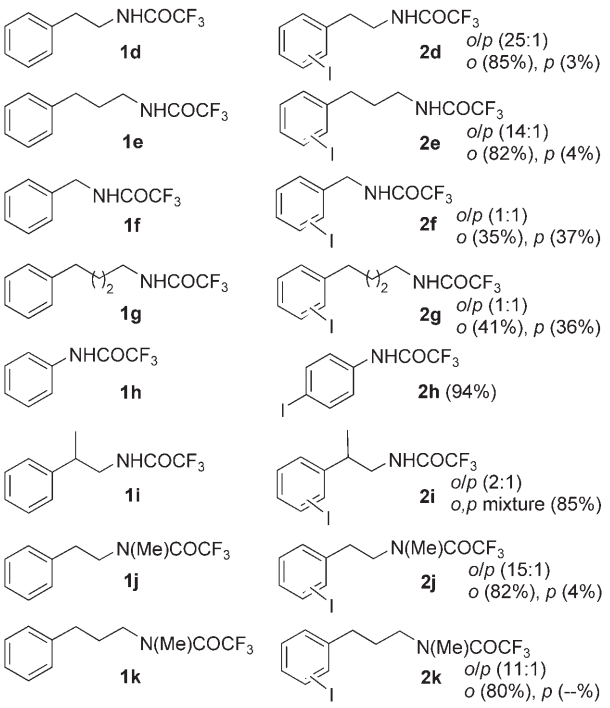
Supporting information for this article, including experimental procedures and spectral data for **2c–m**, **3**, **4**, **5**, and **6**, is available on the WWW under http://www.angewandte.org or from the author.

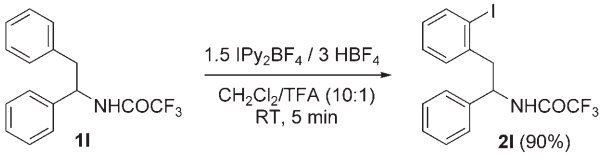


Scheme 1. Regioselectivity in the iodination of *N*-trifluoroacetylamides. The *o*/*p* ratios were determined by GC and/or ^{1}H NMR spectroscopic analysis of the crude reaction mixtures; the yields of the individual isomers after isolation by chromatographic separation are given.

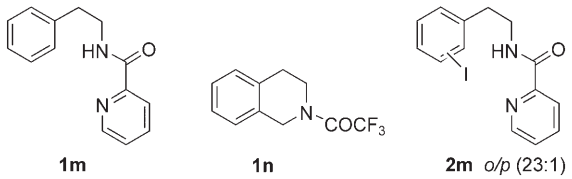
in the adoption of a conformation favoring *ortho* iodination. Interestingly, substitution in the α position to the nitrogen atom does not preclude the desired control over the regioselectivity, as evidenced in the iodination of compound **1l** (Scheme 2). This reaction is a significant example of a chemo- and regioselective iodination of the phenetylamine skeleton.[10]

The iodination of **1d** led with remarkable control to the formation of the target regioisomer. Full conversion into **2d** and a 25:1 ratio of the *ortho*- to the *para*-substituted regioisomer were observed after 2 h. The uniqueness of these reaction conditions for the successful *ortho* iodination was checked: In the absence of an acid, HBF_4 and/or TFA, a major drop in the *o*/*p* ratio was observed, and upon replacing TFA with acetic acid a 1:1 mixture of iodinated regioisomers was obtained.

A hypothesis was formulated to explain these results, although no compelling evidence had yet been gathered. Two model compounds were designed as substrates to provide more information about the reaction and were subjected to the iodination (Scheme 3). The additional results supported the proposed working model.

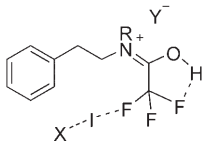


Scheme 2. Chemo- and regioselective iodination of **1l**.



Scheme 3. Model compounds.

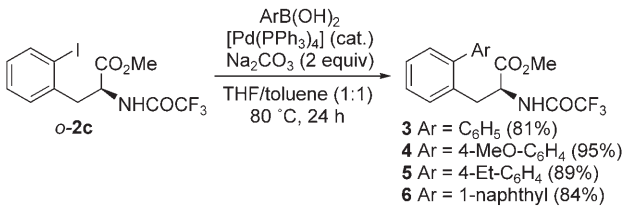
The amide **1m** prepared from β-phenylethylamine contains a strong coordinating fragment based on pyridine. This substrate was transformed under the standard conditions into the iodinated compound **2m**, with total conversion after 2 h. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy indicated a 23:1 ratio for the *o*/*p* selectivity; *o*-**2m** was isolated in 90% yield. On the other hand, the iodination of **1n** led to a complex mixture. Thus, a certain degree of freedom in the tethering chain seems to be necessary to allow for a selective *ortho* iodination. These results and the observed influence of the length of the tethering chain suggest that the *ortho* iodination might arise from an initial close contact between the electrophile and the trifluoroacetamide moiety. This interaction would ultimately precede an intramolecular delivery of the electrophile to the *ortho* position. The fluorine atoms should play a key role in this model, as their characteristics would make possible such a contact.[11] A tentative model for this interaction is proposed in Scheme 4.



Scheme 4. Proposed interaction that might control the *ortho* iodination of amides derived from aryl-substituted alkylamines.

We recognized the utility of our new method for the straightforward preparation of *o*-iodo derivatives of phenetylamines and phenylalanine. These *o*-iodo compounds were further elaborated into biaryl scaffolds by palladium-catalyzed cross-coupling reactions. This two-step sequence offers a convenient preparation of aryl-substituted constrained phenylalanine derivatives[12] in a synthetic scenario in which the potential of the metal-mediated arylation of the C–H bond has not yet been exploited.[13] The results of the Suzuki–Miyaura coupling of boronic acids with **2c** are summarized in Scheme 5.[14,9] Overall, this synthesis of constrained phenylalanine derivatives starting from the building block **1c** is a demanding option.[15]

In summary, an aromatic electrophilic substitution of monosubstituted arenes with the selective incorporation of iodine at the *ortho* position has been reported. The products are valuable reagents for the rapid generation of diversity by metal-mediated reactions. Further synthetic work and mechanistic studies should provide insight into the origin of this unusual reactivity. The transformation offers a promising alternative to the use of transition metals or strong bases to force the difficult iodination of *ortho* carbon atoms. It should prompt efforts to explore the reactivity of other electrophiles and starting scaffolds, and to search for alternative directing groups for electrophilic transformations.



Scheme 5. Synthesis of *ortho*-substituted biaryls derived from phenylalanine by selective iodination followed by palladium-catalyzed cross-coupling.

Experimental Section

Typical procedure: Compound **1c** (137 mg, 0.5 mmol) was dissolved in a mixture of anhydrous CH_2Cl_2 (100 mL) and TFA (10 mL). HBF_4 (54 wt% in diethyl ether; 0.21 mL, 1.5 mmol) was then added, followed by IPy_2BF_4 (0.28 g, 0.75 mmol; Py = pyridine), whereupon the solution turned pink. The mixture was stirred at room temperature for 2 h, then quenched with cold water. The organic layer was washed twice with water, once with 5% aqueous sodium thiosulfate, and again with water, then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 3:1; $R_f = 0.57$) to afford **2c** (160 mg, 80%).

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[9] For reaction times, experimental details, and characterization data, see the Supporting Information.

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[15] HPLC analysis of **3** on a chiral phase proved that it was formed as single enantiomer (>98% *ee*). Compound **6** was formed as a mixture of two diastereomers, each with >97% *ee*.

