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Direct, visible light-sensitized benzylic C–H fluorination of peptides using dibenzosuberenone: selectivity for phenylalanine-like residues

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Dedicated to Professor Gary H. Posner on the occasion of his retirement.

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ABSTRACT

A visible light-sensitized benzylic sp^3 C–H fluorination protocol using dibenzosuberenone (5 mol %) and Selectfluor® is optimized for the direct functionalization of phenylalanine-like residues in short chain peptides. Amino acids, dipeptides, and tripeptides undergo benzylic fluorination with remarkable regioselectivity in the presence of protected basic, acidic, and nonpolar side chains (including those with tertiary sites). Additionally, protecting group compatibility, a gram scale application, and competition experiments were explored.

1. Introduction

The typical procession of *synthetic method development* passes through three arenas: 1) reaction discovery, 2) optimization and mechanistic understanding, and 3) application. In the world of modern fluorine chemistry, our laboratory[1] and others[2] have discovered some of the first mild ways to effect 'radical fluorination' of sp^3 C–H bonds – transformations of high interest in the fields of medicine and agrochemistry (*arena* 1).[3] Significant strides have been made in producing and beginning to understand these reactions; however, greater selectivity and more tangible applications to the synthesis of biologically relevant molecules remain promising goals (*arenas* 2 *and* 3). Toward these efforts, we report a discrete photochemical method optimized for the site-selective fluorination of peptides.[4]

Historically, chemists have gone to great lengths to access β-fluorinated amino acids.[5] Recently, a few examples regarding direct C–H fluorination of individual amino acids have materialized in the chemical literature. For instance, palladium catalysis has proven valuable in ligand-directed syntheses of β-fluoro-α-amino acids.[6] To a much lesser extent, photochemical benzylic fluorination tactics have also emerged that include a single derivative of β-fluorophenylalanine in the substrate scope.[7] Given our interest in the latter approach, we asked: does the innate benzylic selectivity drop off when phenylalanine is incorporated into peptide chains (Fig. 1)? Would we observe competitive fluorination on the tertiary sites of valine[8] and leucine,[9] for example? To our satisfaction, we found that our newly-developed photochemical approach using Selectfluor®, catalytic dibenzosuberenone, and visible light (14-Watt CFL) is remarkably selective for the benzylic sites of phenylalanine- and tyrosine-like residues in short chain peptides that incorporate a variety of aliphatic and protected basic or acidic side chains.

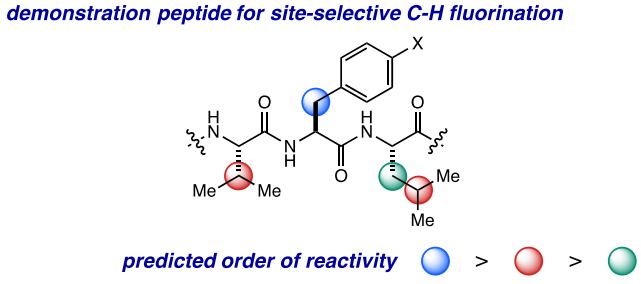

Fig. 1. Benzylic selectivity strategy toward 'directed' fluorination within peptide natural products.

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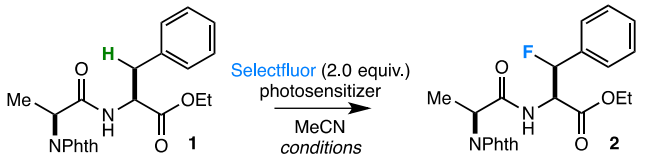
2. Results and discussion

Our initial screen included an evaluation of existing photochemical fluorination methods (developed in our laboratory[7b,10] and by others[11]) on a simple dipeptide – NPhth-Ala-Phe-OEt (**1**). Immediately, we found the methods that performed suitably in the fluorination of a single amino acid experienced a decline in product yield when applied to this dipeptide (Table 1). In some instances, increased loadings of the photosensitizers improved yields, but never above 50%. Accordingly, we expanded our survey to other potential ultraviolet and visible light photosensitizers. To our satisfaction, dibenzosuberenone[12] (5 mol %) and visible light from a 14-Watt CFL proved competent in the selective benzylic fluorination of NPhth-Ala-Phe-OEt using Selectfluor® (2.0 equiv) to provide **2** in 73% yield. We also noted that the diastereomeric ratio of the fluorinated product was ca. 2.1:1, regardless of photosensitizer.

Table 1
Photochemical fluorination optimized for dipeptides



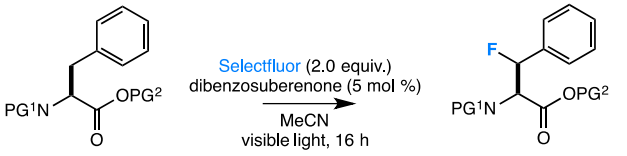
Entry	Photosensitizer	(mol %)	Light source	Yield (%)[a]
1	1,2,4,5-Tetracyanobenzene	5	300 nm	21
2		10	300 nm	33
3	Anthraquinone	10	300 nm	38
4		20	300 nm	42
5	1,4-Dicyanobenzene	10	300 nm	18
6		20	300 nm	42
7	1-Cyanonaphthalene	20	300 nm	trace
8	9,10-Phenanthrenequinone	10	300 nm	22
9		20	300 nm	21
10	Xanthone	10	300 nm	39
11		5	14-Watt CFL	39
12	2,7-Dichloro-9-fluorenone	10	300 nm	28
13		5	14-Watt CFL	29
14	9-Fluorenone	20	300 nm	10
15		5	14-Watt CFL	31
16	Benzophenone	20	300 nm	40
17		5	14-Watt CFL	46
18	2-Bromo-9-fluorenone	5	14-Watt CFL	22
19	2-Chlorothioxanthone	5	14-Watt CFL	28
20	**5-Dibenzosuberenone**	**5**	**14-Watt CFL**	**73[b]**

All reactions were irradiated in Pyrex microwave vials for 16 h while stirring, using either a 14-Watt CFL (visible light) or a Rayonet reactor (300 nm). In all cases, a 2.1:1 *dr* was observed. [a]Unless otherwise specified, ^{19}F NMR yields reported. [b]Isolated yield reported.

Control experiments revealed that 1) the reaction does not proceed in the absence of either light or dibenzosuberenone, 2) increasing the amount of Selectfluor® or dibenzosuberenone begins to have a negative impact on yield (though Selectfluor® may be decreased to 1.5 equiv in some cases with only a 5–10% decrease in yield), and 3) some benzylic fluorination is observed by heating the reaction mixture to reflux in the dark, albeit in poor yield (25%).[13] Furthermore, most photochemical fluorination methods require inert atmosphere, but this approach performs equally well in ambient air. Although anhydrous MeCN was used, rigorous exclusion of air and moisture (e.g., by degasification and Schlenck techniques) proved unnecessary – a testament to the robustness of the protocol.

Subsequently, we turned our attention to the scope of *N*- and *C*-termini protecting groups using phenylalanine derivatives (Table 2). Protecting group strategies are invaluable in peptide synthesis and may also be necessary to maintain compatibility with photochemical fluorination.[14] For instance, basic nitrogen sites have been particularly problematic in sp^3 C–H fluorination methods;[15] however, this may be circumvented through the installation of electron-withdrawing groups. Along these lines, phthalimido[16] (NPhth) and trifluoroacetate[17] (TFA) substituents at the N-terminus provided the best results (80% and 67%), and acetate groups were also competent (57%). On the other hand, Boc, Fmoc, and Cbz groups were not compatible with fluorination (0–10% yield). At the C-terminus, methyl and ethyl esters perform equally well,[18] but *tert*-butyl, trityl, and adamantyl esters decompose or undergo additional fluorination under the reaction conditions (accompanied with a decrease in yield). Moreover, we found that the C-terminus does not require a protecting group – photochemical benzylic fluorination can be achieved in good yields in the presence of carboxylic acids without competitive decarboxylative fluorination.[19]

Table 2
Protecting group compatibility



Entry	PG^1	PG^2	Yield (%)[a]
1	*tert*-butyloxycarbonyl (Boc)	-	10
2	fluorenylmethyloxycarbonyl (Fmoc)	-	0
3	carboxybenzyl (Cbz)	-	8
4	acetyl (Ac)	-	57
5	**trifluoroacetyl (TFA)**	**-**	**67**
6	**trifluoroacetyl (TFA)**	**methyl (Me)**	**74**
7	**trifluoroacetyl (TFA)**	**ethyl (Et)**	**60**
8	**phthalimide (Phth)**	**-**	**80[b]**
9	-	-	0
10	**phthalimide (Phth)**	**methyl (Me)**	**78**
11	**phthalimide (Phth)**	**ethyl (Et)**	**80**
12	phthalimide (Phth)	*tert*-butyl (*t*-Bu)	31
13	phthalimide (Phth)	trityl (Trt)	28
14	phthalimide (Phth)	1-adamantane (Ada)	20

[a]Unless otherwise specified, ^{19}F NMR yields reported. [b]Isolated yield reported.

In addition to phenylalanine, we envisioned that other benzylic residues could be targeted, such as tyrosine or other non-natural amino acids. The hydroxy substituent on tyrosine activates the aromatic ring toward background EAS with Selectfluor®, which substantially diminishes selectivity and the extent of benzylic fluorination.[20] Acetylation reduces ring fluorination, but still results in poor desired product yields. However, transformation of the hydroxy substituent to a trifluoroacetyl group makes tyrosine residues viable candidates for direct benzylic fluorination (71% yield).[21] What is more, the phthalimide-protected *p*-fluoro-phenylalanine, an isoelectronic and isosteric replacement for tyrosine, underwent benzylic fluorination in 84% yield (Table 3).

At this juncture, we had established a visible light protocol on a prototypical dipeptide, determined the compatibility of an array of protecting groups, and investigated the viability of other phenylalanine-like residues as targets for benzylic fluorination (**3**, **4**, and **5**). The next step was to examine the regioselectivity and reaction efficiency in the presence of other amino acids. Thus, we