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Ru-Catalyzed C–H Hydroxylation of Tyrosine-Containing Di- and Tripeptides toward the Assembly of L-DOPA Derivatives

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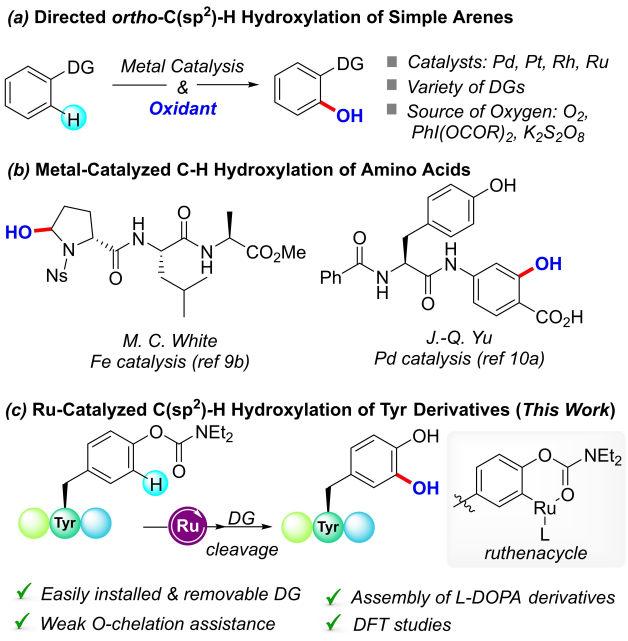
Abstract: The development of catalytic tools for the late-stage modification of amino acids within a peptide framework is a challenging task of capital importance. Herein, we report a Ru-catalyzed C-(sp^2)–H hydroxylation of a collection of Tyr-containing di- and tripeptides featuring the use of a carbamate as a removable directing group and $PhI(OCOCF_3)_2$ (PIFA) as oxidant. This air-compatible tagging technique is reliable, scalable and provides access to L-DOPA (L-3,4-dihydroxyphenylalanine) peptidomimetics in a racemization-free fashion. Density Functional Theory calculations support a Ru(II)/Ru(IV) catalytic cycle.

Keywords: hydroxylation; tyrosine; ruthenium catalysis; peptides; C–H functionalization

Introduction

The installation of small chemical entities such as trifluoromethyl, methyl or hydroxyl groups in a given bioactive molecule often ushers in higher binding affinity, different metabolism and improved pharmacokinetic properties of the resulting compound.[1] As a result, the appendance of those functional groups in a late-stage fashion represents a pressing goal of paramount chemical significance because it enables rapid lead diversification in the realm of drug discovery.[2] Hydroxylated aromatic compounds are ubiquitous in Nature and stand out as valuable feedstock in the chemical industry.[3] Among the existing phenol syntheses, the metal-catalyzed C(sp^2)–H hydroxylation of arenes upon chelation assistance poses the most streamlined and straightforward avenue (Scheme 1, *route a*).[4] In this respect, a variety of directing groups (DGs) have been reported to aid the practical oxidation of simple arenes in the presence of palladium,[5] rhodium,[6] ruthenium[7] or iron[8] catalysts, among others. However, despite the advances realized, the current synthetic toolbox remains essentially unexplored in more challenging settings such as amino acids and peptides. In 2016, the White group accomplished the site-selective and predictable C(sp^3)–H hydroxylation of aliphatic amino acids such as proline, leucine or valine in the presence of a strategically designed iron catalyst which resembled to an enzyme-type reactivity (Scheme 1, *route b*).[9] More recently, as part of their studies on the Pd-catalyzed *ortho*-hydroxylation of benzoic acids, Yu and co-workers disclosed the hydroxylation of a Tyr derivative in a remote position featuring a carboxylic acid as a weak DG.[10] Furthermore, the last years have witnessed the upsurge of a sheer number of biocatalytic techniques to perform C–H oxidation reactions in intricate scaffolds including amino acids.[11] However, the challenging site-selective C–H hydroxylation of tyrosine (Tyr) compounds upon metal catalysis remains elusive.

Tyr is the natural precursor of L-DOPA (L-3,4-dihydroxyphenylalanine), which is a potent drug for the clinical treatment of Parkinson's disease and can be



Scheme 1. Metal-catalyzed C–H hydroxylation reactions.

transformed into a wide range of neurotransmitters through biosynthetic pathways. Despite its tremendous medicinal relevance, there is currently no general method available to directly assemble L-DOPA from the corresponding amino acid in a practical fashion. Indeed, the most well-known protocols encompass Rh-catalyzed asymmetric hydrogenation reactions of enamides developed by Knowles[12] or lengthy routes from L-Tyr involving a classical Friedel-Crafts acetylation entailing corrosive acetyl chloride followed by subsequent reduction steps.[13] Likewise, those methods have not been tested in peptides to produce L-DOPA peptidomimetics. Despite the commercial availability of L-DOPA or its *N*-protected derivatives, they are rather expensive and often result in low yields of the corresponding peptide derivatives.[14] Accordingly, targeting a metal-catalyzed C–H hydroxylation of Tyr-containing compounds would arguably provide an excellent straightforward approach to forge L-DOPA derivatives, while expanding our chemical toolbox to diversify Tyr-containing peptides[15,16] and complementing enzymatic techniques.[17]

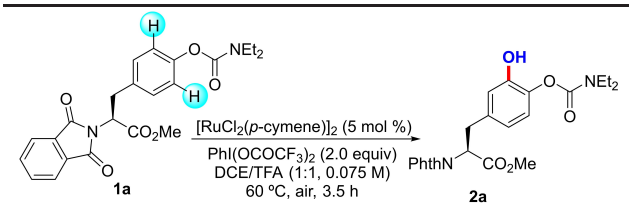
Although C–H hydroxylations within simple arenes have been well explored,[3–8] they rarely include substrates housing amides as functional groups. Therefore, their translation to the ever-growing field of bioconjugation is not a trivial task and poses several challenges: a) utilize a DG with superior coordinating ability to that of the peptide backbone, and b) select a catalyst with high tolerance for amides within peptide settings. Inspired by the attractive features of cost-effective ruthenium catalysis in the hydroxylations of simple arenes,[18] we envisaged that the phenol ring within Tyr could be easily transformed into a weak coordinating group[19] to further assist the corresponding hydroxylation upon the formation of a 6-membered ruthenacycle (Scheme 1, *route c*). Herein we describe a reliable Ru-catalyzed hydroxylation method upon assistance of a carbamate as removable DG,[18g] thus providing a general and less expensive method for the assembly of L-DOPA derivatives in a simple yet innovative manner.

Results and Discussion

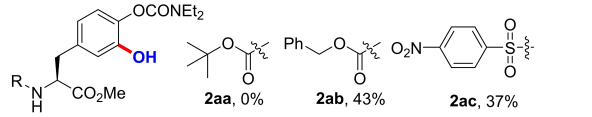
Building on precedents reported by Ackermann about the superior coordinating ability of amides to that of carbamates,[18f,g] we selected simple Tyr derivative **1a** devoid of a secondary amide as a model substrate to evaluate the feasibility of our hypothesis.

After systematic optimization,[20] we found that a combination of $[RuCl_2(p\text{-cymene})]_2$ as catalyst and hypervalent iodine reagent $PhI(OCOCF_3)_2$ (PIFA) as oxidant enabled the selective and rapid *ortho*-hydroxylation of Tyr compound **1a**, thereby affording exclusively mono-hydroxylated product **2a** in 73% yield after 3.5 hours (Table 1, entry 1). In line with our expectations, control experiments underpinned the crucial role of both the catalyst and oxidant in the hydroxylation reaction (entries 2 and 3). Likewise, the

Table 1. Ru-catalyzed C–H hydroxylation of **1a**.[a]



entry	change from standard conditions	**2a** (%)[b]
1	none	73
2	without $[RuCl_2(p\text{-cymene})]_2$	0
3	without $PhI(OCOCF_3)_2$	0
4	without TFA	39
5	under argon	73
6	$PhI(OCOCF_3)_2$ (1.2 equiv)	53
7	$PhI(OAc)_2$ as oxidant	45
8	at 50 °C	53
9	$[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %)	61
10	$Ru(OAc)_2(PPh_3)_3$ as catalyst	54
11	$RuCl_2(PPh_3)_3$ as catalyst	21
12	$RuCl_3$ as catalyst	0
13	DCE/TFA (8:2)	65
14	DCE/TFA (1:1, 0.15 M)	62



[a] Reaction conditions: **1a** (0.15 mmol), PIFA (0.45 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in a mixture of DCE/TFA (1:1, 2 mL) at 60 °C for 3.5 h under air.

[b] Yield of isolated product after column chromatography.

addition of TFA was key to ensure high yields (entry 4). Importantly, the reaction did not require an inert atmosphere and could be conducted under air (entry 5), which constitutes an additional bonus in terms of operational simplicity. The screening of oxidants revealed both the higher activity of PIFA, in comparison to other candidates such as $K_2S_2O_8$ or oxone,[20] and the requirement of adding 2 equivalents (entry 6). Closely related $PhI(OAc)_2$ (PIDA) could be also utilized, albeit **2a** was obtained in lower yields (entry 7). The performance of the process at lower temperature than 60 °C was found detrimental (entry 8), and degradation of the starting material was observed at higher temperatures.[20] The use of $[RuCl_2(p\text{-cymene})]_2$ as catalyst ushered in higher yields than other ruthenium catalysts, which delivered **2a** in comparatively lower yields (entries 9–12). The usage of higher amount of TFA (entry 13) or more diluted solutions (entry 14) did not improve the catalyst performance, thus showing the subtleties of our system. Importantly, the dihydroxylation reaction was never observed. Once the efficiency of utilizing a carbamate as DG in a fully protected compound was demonstrated, other Tyr compounds housing secondary amides were tested to evaluate the robustness of the method. As expected, Boc-protected Tyr compound (**1aa**) decomposed under the optimized conditions involving TFA, which is commonly used to effect the deprotection of Boc-amine derivatives. Other protecting groups such as benzyloxycarbonyl (**1ab**) and nosyl (**1ac**) could be employed, albeit the hydroxylation reaction occurred in 43% and 37% yields, respectively.

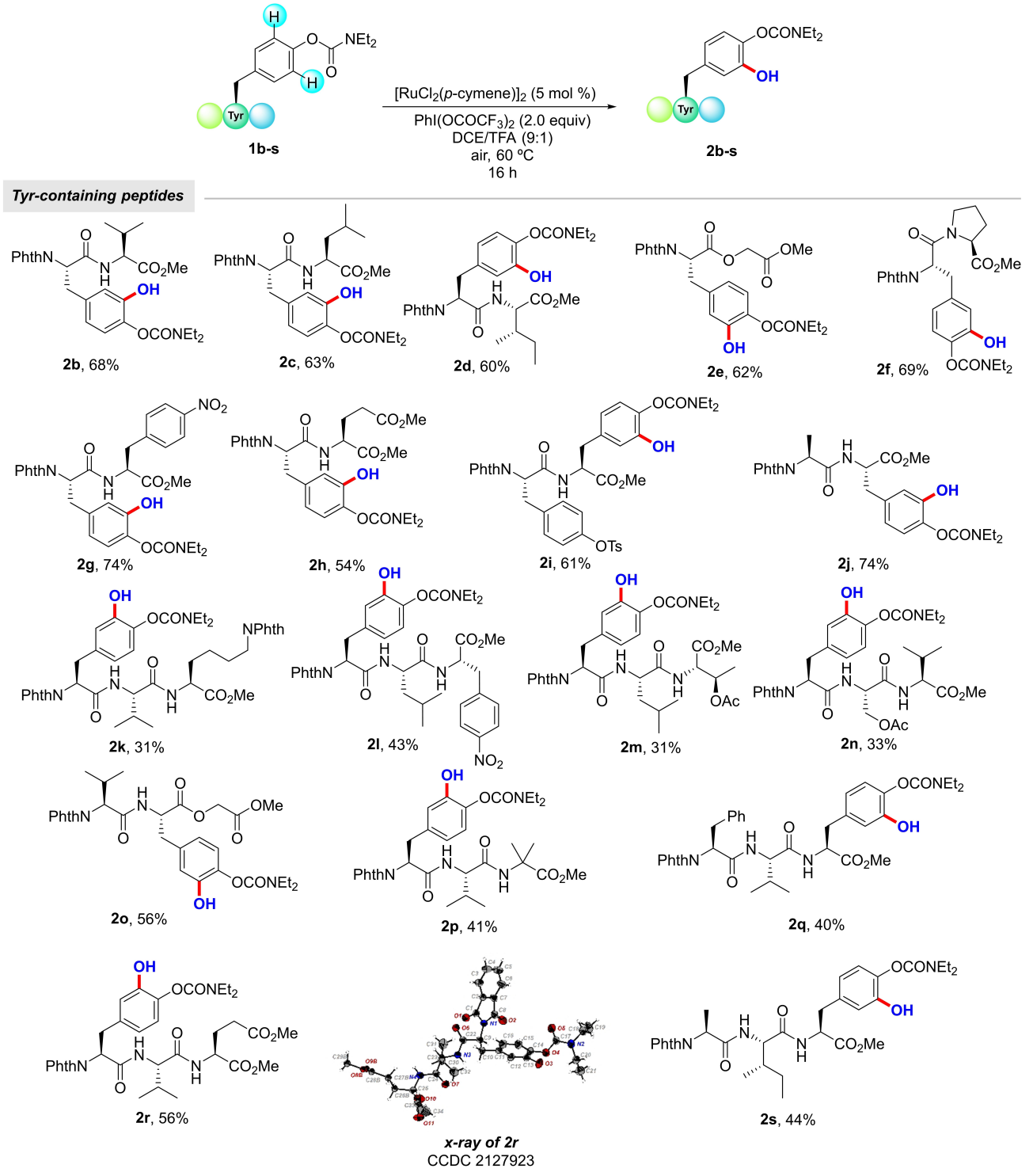
With these results in hand, we next tackled the hydroxylation reaction in more complex peptide settings to illustrate the generality of this platform to deliver L-DOPA derivatives in a simple fashion. As shown in Table 2, a wide number of previously inaccessible hydroxylated dipeptides could be assembled in moderate to excellent yields (up to 74%). A short family of Tyr-containing dipeptides incorporating Val (**2b**), Leu (**2c**), Ile (**2d**), Pro (**2f**), Phe (**2g**), Glu (**2h**), Tyr (**2i**) and Ala (**2j**) residues underwent the *ortho*-hydroxylation reaction in a site-selective manner under slightly modified conditions featuring the use of lower amount of TFA and longer reaction times than those used with the single Tyr compound **1a**.[20] These results clearly indicated that the *ortho*-hydroxylation of a Tyr residue can be efficiently directed by the weak coordination of the carbamate group in the presence of other competing O-chelating sites such as those amides of the peptide backbone.[18f] Encouraged by these promising results with dipeptide derivatives, we synthesized a variety of tripeptide compounds to evaluate our C(sp^2)–H hydroxylation manifold. Notably, the desired chemical modification of the Tyr unit could be achieved regardless of the position of the Tyr residue within the peptide sequence. Although the hydroxylated products were obtained in low to moderate yields in certain cases (up to 56%), it is worth noting that full conversion was not always achieved and unreactive starting material was sometimes observed. Owing to the use of a highly oxidizing system, residues bearing potentially oxidizable hydroxyl groups within Tyr[21] (**2i**), Thr (**2m**) and Ser (**2n**) as well as amino groups in Lys (**2k**) were protected to chemoselectively perform the corresponding C–H hydroxylation. Conversely, a dipeptide housing a methionine residue with a thioether motif resulted in the preferential oxidation of the sulfur atom. Likewise, the use of peptides bearing heterocyclic-containing amino acids such as histidine and tryptophan resulted in the entire inhibition of the process.[20] Importantly, biologically relevant depsipeptides **2e** and **2o** could be also hydroxylated in good yields.

The structure of **2r** was unambiguously assigned by X-ray diffraction and supported the appendance of the hydroxyl group at the *ortho* position of the Tyr unit.[22] Unfortunately, despite of our numerous attempts, the protocol could not be applied in tetra- or hexapeptides (Table S5 and Table S7).[20] We hypothesized that the high number of amide bonds in tetrapeptides could deeply compromise the required coordination of the Ru catalyst with the carbamate, thus outcompeting with the carbamate as weak O-coordinating groups. In fact, peptides have been used in Ru-catalyzed transformations as effective endogenous and exogenous ligands.[23] In this respect, we performed further studies to determine whether other DGs could be used in these endeavors to overcome this synthetic limitation.

As depicted on Table 3, a simple Tyr unit housing other DGs with carbonyl motifs as O-coordinating groups such as acetate (**2ag**), carbonates (**2ah**, **2ai**) or carbamates (**2aj**, **2ak** and **2al**) either inhibited the reaction or afforded hydroxylated compounds in much lower yields. Conversely, among the tested strong chelating heteroarene groups pyrimidine afforded a remarkable 50% yield of the corresponding *ortho*-hydroxylated product **2ae** under the standard conditions. Accordingly, we prepared the corresponding tetrapeptide incorporating a pyrimidine unit tethered with the oxygen atom of the phenol ring; however, after a wide variety of experiments with Ru and Pd catalysts (Table S6), we only obtained 15% yield of the desired product **2tb** when using $Pd(OAc)_2$ as catalyst.[20] Therefore, the hydroxylation of peptides with more than three amino acid residues still poses a daunting challenge and represents a task which deserves further analysis.

The robustness and synthetic utility was demonstrated by the performance of the hydroxylation of amino ester **1a** and dipeptide **1b** in higher scale (Scheme 2). Although the carbamate cleavage can be performed under a variety of conditions in simple

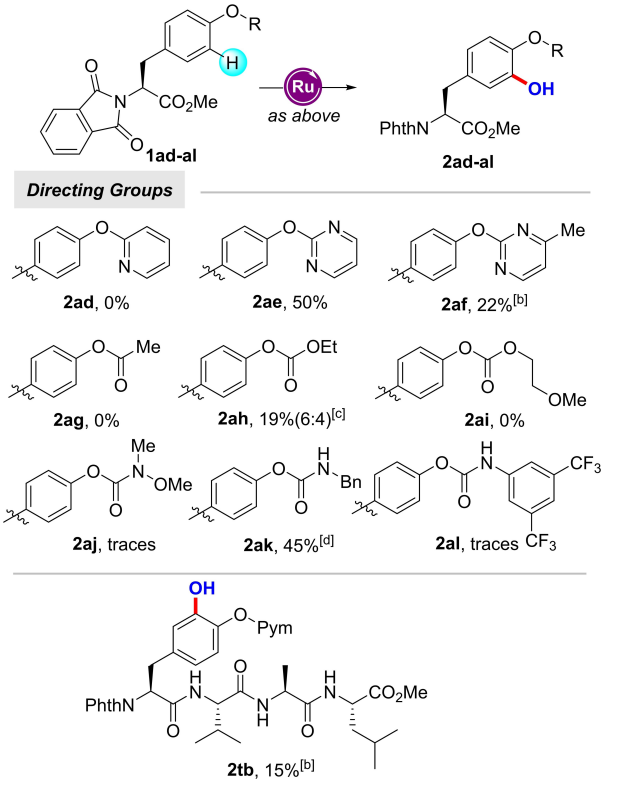
Table 2. Ru-catalyzed C–H hydroxylation of Tyr-containing peptides and depsipeptides.[a,b]



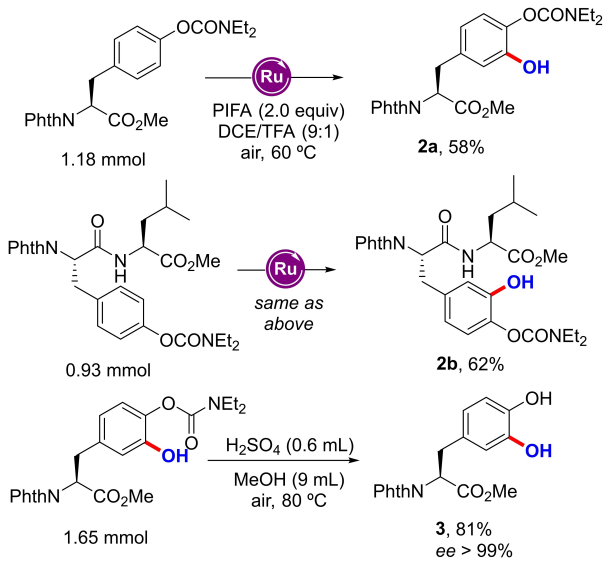
[a] As for Table 1, entry 1.
[b] Yield of isolated product after column chromatography, average of at least two independent runs with a variable yield by no more than 5% between runs.

phenols,[24] its removal within a peptide framework is not a trivial task; certain reagents such as $LiAlH_4$ or NaOH cannot be used without affecting the peptide structure and others such as hydrazine or the Schwartz reagent did not work. After a number of attempts, the cleavage of the carbamate in product **2 a** was achieved

Table 3. Influence of the directing group.[a]



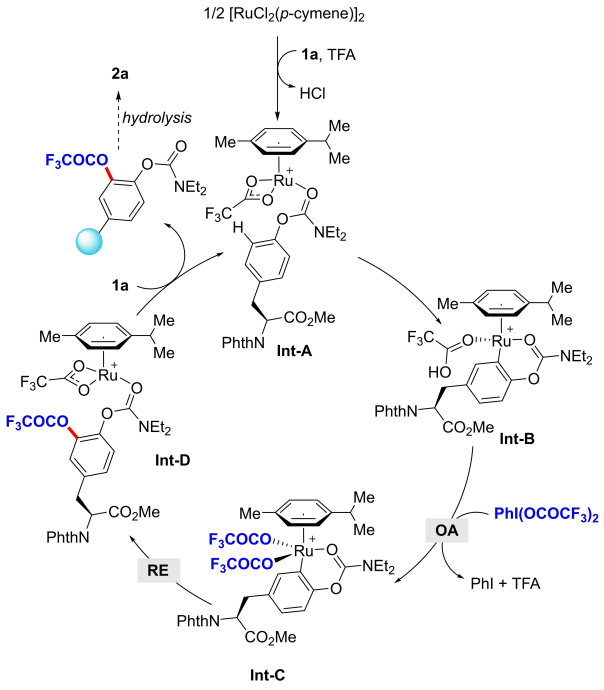
[a] Yield of isolated product after column chromatography, average of at least two independent runs with a variable yield by no more than 5% between runs.
[b] Reaction carried out with $Pd(OAc)_2$ (10 mol%), PIFA (0.30 mmol) and DCE (2 mL) at 80 °C under air.
[c] Ratio of mono- and dihydroxylated product.
[d] Reaction carried out with DCE (0.9 mL) and TFA (0.1 mL).



Scheme 2. High scale synthesis and DG cleavage to forge L-DOPA derivatives.

upon treatment with sulfuric acid in MeOH, which furnished the corresponding L-DOPA analog **3** in 81% yield. Remarkably, HPLC analysis of compound **3** verified that no racemization occurred neither along the hydroxylation nor the cleavage step.[20] Unfortunately, when dipeptide **2b** was submitted to those conditions compound **3** was formed, which resulted from a deprotection and amidolysis sequence. Although it seems a limitation at first sight, the access to fully decorated peptides housing a carbamate unit could offer interesting possibilities within drug discovery.[25]

In order to understand the reaction pathway as well as some of the observed experimental nuances, we further performed DFT studies. In particular, we focused our studies on the C–H hydroxylation of Tyr derivative **1a** and **1ad** bearing a carbamate and a pyridine as DG, respectively, which experimentally exhibited an entirely distinct reactivity profile. Assuming a similar reaction pathway to that described for the Ru-catalyzed C(sp^2)–H hydroxylation of arenes upon weak chelation assistance of secondary amides,[18b] we proposed the plausible mechanism depicted in Scheme 3. The reaction would start by complexation of the Ru catalyst and the Tyr compound assisted by TFA to deliver **Int-A**. The latter would likely undergo the *ortho*-C–H metalation aided by the trifluoroacetate anion to provide the 6-membered ruthenacycle **Int-B**. Then, oxidative addition of PIFA would result in the formation of highly reactive Ru(IV) **Int-C**, prone to



Scheme 3. Proposed reaction pathway for the Ru-catalyzed C–H hydroxylation of Tyr compounds.

undergo subsequent reductive elimination to deliver **Int-D**, which would eventually lead to hydroxylated product **2 a**. As commented above, experimental studies evidenced the profound effect of the nature of the DG in the reaction outcome: whereas substrate **1 a** bearing a carbamate as DG led to the target product in 73% yield, substrate **1 ad** with a strong pyridine DG remained unreactive.

Moreover, the lack of reactivity of tetrapeptides with multiple amide bonds also indicated that the nature of DG was of utmost importance within the hydroxylation of peptide derivatives. Accordingly, DFT calculations were undertaken with **1 a** and **1 ad** as model substrates to analyze the influence of using weak *vs* strongly coordinating groups in the three fundamental steps of the mechanism (Figure 1, black and blue reaction pathway, respectively). With the energy values in hand,[20] we can conclude that whereas both the C–H activation and the oxidative addition are endergonic events, the reductive elimination is exergonic for both substrates. As depicted in Figure 1, the higher stability of the ensuing *ortho*-hydroxylated compound **2 a** suggested that its formation may be the driving force to render the proposed mechanistic scenario thermodynamically favored. Indeed, all fundamental steps are thermodynamically and kinetically feasible under the optimized reaction conditions. The first step would consist of a C–H activation event of the tyrosine derivative, leading to the formation of **Int-B** through a CMD pathway with an energy penalty of 14.74 Kcal/mol.

The optimized structure of **TS1** reveals an elongation of the C–H bond of 0.3 Å and the approximation of the C atom to the metal center is verified by the value of the distance of the C–Ru bond, which decreased from 2.68 Å to 2.23 Å. The oxidative addition of PIFA to **Int-B** thereby delivering Ru(IV) species **Int-C** would not occur in a straightforward manner. As shown in Figure 1, the initial coordination of PIFA to **Int-B** upon a ligand exchange would deliver **Int-B'**, which would next undergo a formal oxidative addition through a concerted pathway leading to **Int-C'** with an energy barrier of 13.62 kcal/mol. This step could easily occur through a transition state (**TS2**) wherein a I–O bond is cleaved with the simultaneous formation of a new Ru–I bond. In fact, the I–O distance is lengthened from 2.28 Å to 3.03 Å, whereas the Ru–I distance is shortened from 3.76 Å to 2.98 Å. The so-formed **Int-C'** would furnish **Int-C** upon release of PhI and TFA. The latter could undergo a reductive elimination step with an energy barrier of 27.10 kcal/mol through a concerted transition state (**TS3**), in which the Ru–O distance is lengthened from 2.03 Å to 3.61 Å and the C–O distance is shortened from 2.64 Å to 1.38 Å. To our surprise, in sharp contrast with our experimental studies, the reaction pathway for substrate **1 ad** was shown also energetically feasible; whereas the C–H activation and the reductive elimination steps were slightly more favored than for substrate **1 a**, the oxidative addition of PIFA was shown more likely to happen with a substrate housing a weak coordinating group. Although merely speculative, we hypothesized that the transient ruthena-

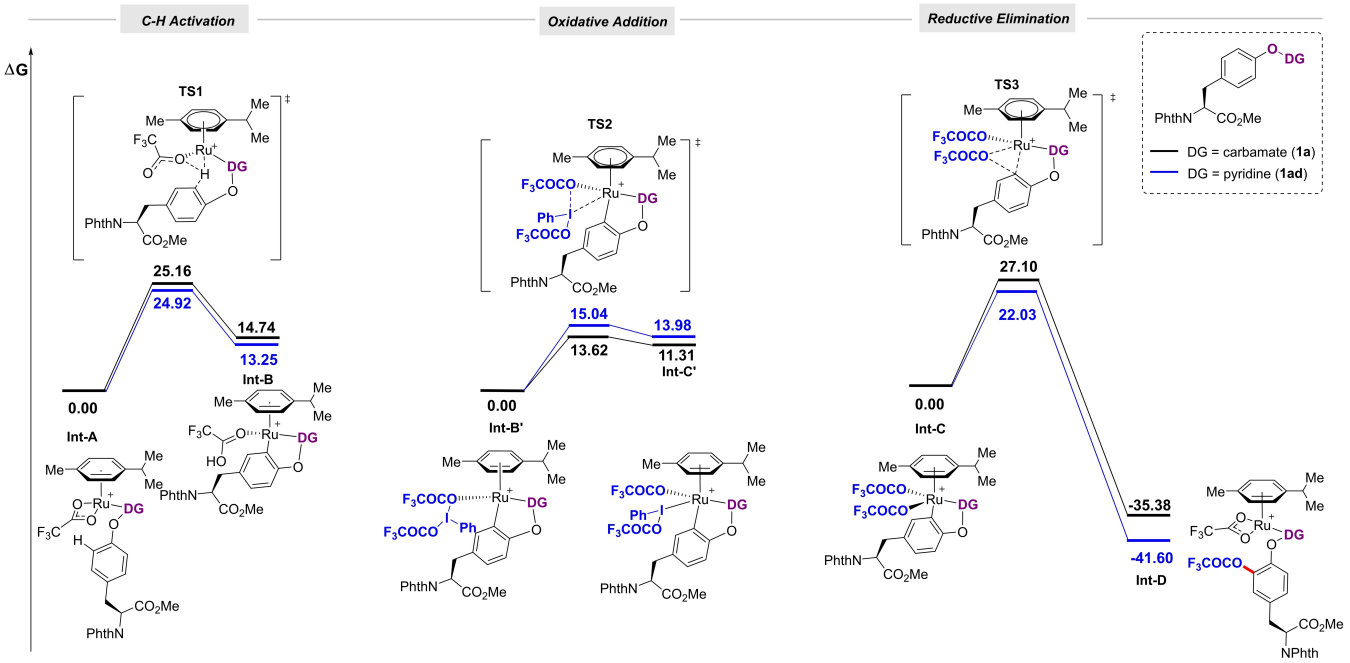


Figure 1. Comparison of the reaction energetics (ΔG in kcal/mol) of **1 a** and **1 ad**.

cycle species with a strong pyridine unit as supporting ligand may be much more stable than the parent species featuring a considerably weak coordination mode, thereby resulting in the entire inhibition of the process and likely evolving into dimers or unproductive reaction pathways.[26] In fact, a control experiment with an equimolecular mixture of **1a** and **1ad** under the standard conditions exclusively delivered **2a** in 41% yield, thus evidencing a partial inhibition of the process in the presence of a pyridine unit. Further studies are definitely required to conclude why tetrapeptides do not undergo the developed hydroxylation reaction.

Conclusion

In summary, we have developed a hydroxylation reaction for the modification of Tyr-containing peptides featuring the use of cost-effective and air-insensitive ruthenium catalysis. Unlike the methods available for the assembly of L-DOPA, this protocol enables the rapid installation of hydroxyl groups within existing peptides in a late-stage fashion. As a result, this labelling platform represents a reliable, yet scalable, means for the diversification of Tyr-containing compounds, thus providing access to L-DOPA peptidomimetics. Salient features of this unique strategy are the use of a carbamate as a weak O-coordinating group, mild reaction conditions, operational simplicity and retention of the chiral integrity of the existing stereocenters within the peptide framework. Computational studies supported a Ru(II)/Ru(IV) regime occurring upon the intermediacy of a challenging 6-membered ruthenacycle.

Experimental Section

General procedure for the Ru-catalyzed hydroxylation of 1a: A reaction tube containing a stirring bar was charged with tyrosine derivative **1a** (0.25 mmol, 106 mg), PIFA (0.50 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (5 mol%). Then, anhydrous 1,2-dichloroethane (1.0 mL) and TFA (1.0 mL) were added by syringe. The reaction tube was next warmed up to 60 °C in a heating block and stirred for 3.5 hours. The mixture was then allowed to warm to room temperature, the solvent was evaporated and the resulting crude was washed up with an aqueous solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (3×20 mL), dried over $MgSO_4$ and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford **2a** as a white solid (80 mg, 73% yield). Mp 70–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J=5.5, 3.1 Hz, 2H), 7.72 (dd, J=5.5, 3.1 Hz, 2H), 7.04–6.80 (m, 2H), 6.74 (dd, J=8.2, 2.1 Hz, 1H), 5.16 (dd, J=10.7, 5.7 Hz, 1H), 3.80 (s, 3H), 3.73–3.49 (m, 2H), 3.46–3.31 (m, 4H), 1.23 (dt, J=21.9, 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 167.4, 154.5, 147.6, 139.0, 135.3, 134.1, 131.5, 123.5, 122.0, 120.9, 119.8, 53.0, 52.8, 42.5, 42.2, 33.9, 14.0, 13.1. IR (cm^{-1}): 3373, 2968, 1995, 1709, 1427, 1386, 1236, 1113, 716, 439. HRMS *calcd.* for ($C_{23}H_{24}N_2O_7$): 440.1584, *found* 440.1595. This reaction was also performed in a higher scale: the use of **1a** (1.18 mmol, 500 mg), PIFA (2.36 mmol, 1.01 g) in a mixture of DCE (8 mL) and TFA (1 mL) provided 305 mg (58% yield) of **2a** as a white solid.

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