Advanced Synthesis & Catalysis

## Accepted Article

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**To be cited as:** *Adv. Synth. Catal.* 10.1002/adsc.201900564

**Link to VoR:** http://dx.doi.org/10.1002/adsc.201900564

10.1002/adsc.201900564

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

# Stereoselective Oxa-Michael Addition of Tyrosine to Propargyl Aldehyde/Esters: Formation of Benzofurans and Flavones

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

**Abstract.** The steroselective oxa-Michael addition of the phenol moiety present in tyrosine and 3-iodotyrosine to different propargyl aldehydes delivered products with predominantly *Z* stereochemistry, as evidenced by X-ray crystallography analysis. When ethyl propiolate was used as the propargyl ester source, the products were achieved with exclusively *E* stereochemistry with yields ranging from 17% to 91%. The oxa-Michael addition compounds served as substrates in the synthesis of 5- and 6-membered heterocyclic compounds. The atmosphere applied to the reaction medium directly influenced the formation of the products. When an inert atmosphere of nitrogen was applied, a 2-aryl-3-formyl-5-alanylbenzofuran core was selectively obtained via a Heck intramolecular reaction, while the reactions carried out under a carbon monoxide atmosphere led exclusively to 6-alanyl-2-arylflavone derivatives via reductive intramolecular acylation.

**Keywords:** Flavone; Heck reaction; oxa-Michael addition; Tyrosine.

## Introduction

Since the early days of synthetic organic chemistry, the formation of carbon-carbon bonds has been a challenge for chemists. Michael addition is a conjugate addition reaction between a carbon nucleophile and an *α,β*-unsaturated carbonyl compound and has gained prominence since its discovery in 1887 by Arthur Michael.[1] Today, this reaction represents one of the most versatile methods in chemical transformation.

Over time, several variations of the Michael reaction have emerged and soon gained ground as tools to build new molecules, for example, the aza-Michael,[2a] sulfa-Michael[2b] and oxa-Michael[2c] reactions, which involve the addition of amines, thiols, and alcohols, respectively, to α,β-unsaturated carbonyl compounds. The oxa-Michael reaction, in particular, provides access to building blocks used efficiently in the synthesis of oxygen-containing heterocyclic compounds, such as chromenes, tetrahydropyrans, benzofurans, flavones and so on.[3]

On this basis, the intramolecular Heck reaction[4] has been explored as an alternative to obtain heterocyclic rings and even macrocycles, from the building blocks generated in the oxa-Michael addition reaction.[2c] Since their first publication in 1977 by Mori and co-workers (Scheme 1a), intramolecular Heck reactions have been shown to be important tools in the synthesis of natural products with complex structures.[5,6] Frontier and co-workers[7–9] reported the sequential use of the oxa-Michael addition reaction between 2-iodophenol and ethyl propiolate, followed by intramolecular cyclisation to benzofuran under palladium catalysis (Scheme 1b).

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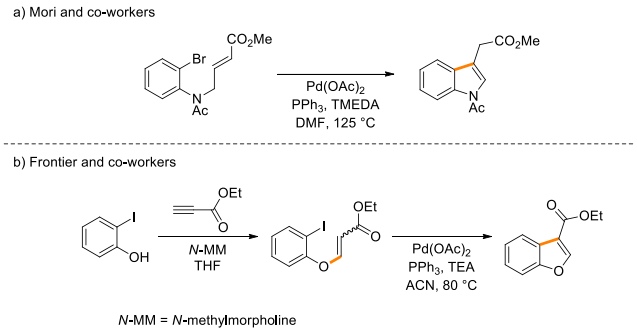
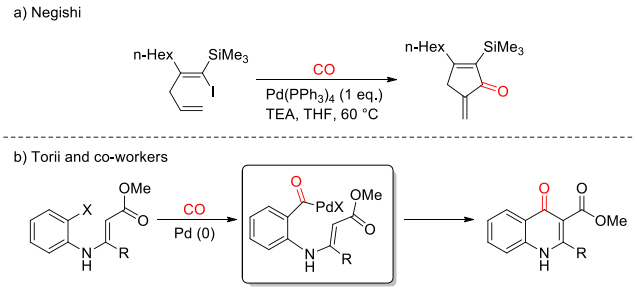



**Scheme 1.** Known intramolecular Heck reactions.

As an alternative, carbonyl coupling, employing carbon monoxide in intramolecular cyclisation reactions, is a promising strategy in the synthesis of heterocyclic rings, especially when a carbonyl as a structural ring member is desired. In 1983, Negishi[10,11] published the first example of an intramolecular carbonylative Heck reaction using stoichiometric amounts of palladium. The cyclised product was obtained in a moderate yield of 54% (Scheme 2a). Quinolone derivatives can also be conveniently prepared via carbonylation reaction, as demonstrated by Torii and co-workers.[12] The oxidative addition of the palladium to the carbon-halogen bond, followed by the carbon monoxide insertion provides the alkylpalladium, which after complexing with the π electrons of the double bond, *β*-elimination of the hydride and reductive elimination, leads to the carbonylative intramolecular cyclisation




product (Scheme 2b).

**Scheme 2.** Intramolecular carbonylative Heck reaction.

Based on the system described by Frontier and Torii[12] (Schemes 1b and 2b), here we present a mild method to achieve benzofuran and flavone-type heterocyclic rings derived from the amino acid tyrosine, thereby representing a strategy to obtain non-natural amino acid derivatives. For this, we reacted *α,β*-unsaturated aldehydes with tyrosine,[13] via an oxa-Michael addition reaction, with the products serving as substrates in intramolecular Heck reactions and carbonylative cyclisation.

## Results and Discussion

As a starting point, it was necessary to evaluate the optimum reaction conditions to form the oxa-Michael addition product. Different bases, solvents and additives or heating were investigated. 3-Iodotyrosine **1a** and phenylpropylaldehyde **2a** were our starting materials of choice in the optimisation of the reaction.

Inorganic bases combined with magnesium chloride provided products with 58% and 63% conversion and *Z/E* ratios of 53:47 and 73:27, respectively (Table 1, entries 1 and 2). The conversion rates, as well as the *Z/E* ratio, were obtained by $^1$H NMR from the crude material. By replacing the inorganic bases with triethylamine (TEA), the conversion was increased to 80% with a *Z/E* ratio of 83:17 (Table 1, entry 3). Surprisingly, we did not achieve any reaction product when the solvent was replaced by tetrahydrofuran (THF) (Table 1, entry 4).

By keeping TEA as the base and toluene as the solvent, the conversion was decreased to 19% (Table 1, entry 5). The use of microwaves as an alternative source of energy[14] was also investigated; however, it was not beneficial, with only a 15% conversion (Table 1, entry 6). Increasing the base amount two-fold in the absence of magnesium chloride as an additive resulted in a drastic improved the conversion rate to 85% with a *Z/E* ratio of 87:13 (Table 1, entry 7). We noticed that when we raised the temperature, as well as the exposure time to the microwaves, the conversion rate and the *Z/E* ratio were compromised (Table 1, entries 8, 10, 13 and 14).

Under ambient conditions of pressure (1 atm) and temperature (~20 °C), the product was isolated after 3 h with a 91% yield and *Z/E* ratio of 90:10 (Table 1, entry 9). When we replaced toluene with dichloromethane (DCM) or increased the amount of base to 5 eqv., we did not observe any improvement (Table 9, entries 11 and 12). Under sonication conditions,[15] the desired product was obtained with an 85% conversion and a *Z/E* ratio of 91:9 after 2 h (Table 9, entry 15).

The absence of β-hydrogen on the aldehyde made it impossible to distinguish the *E*-isomer of *Z* only with the NMR data. However, the crystal structure of **3d** was solved. The analysis indicated the formation of the *Z*-isomer (Figure 1). Therefore, we assume that the *Z*-isomer is the predominant product in the oxa-Michael addition reaction.

The optimised reaction conditions (Table 1, entry 9) allowed us to evaluate the scope of the oxa-Michael addition (Scheme 3). We observed that the iodine present in the aromatic ring of tyrosine positively affected the reaction yields of **3a-h**. We suggest that the p$K_a$ of the phenol group of 3-iodotyrosine is slightly more acidic than the phenol group of the tyrosine, thereby making the phenol deprotonation easier with the base.[16]

**Figure 1.** X-ray crystallography of product **3d**.[17]

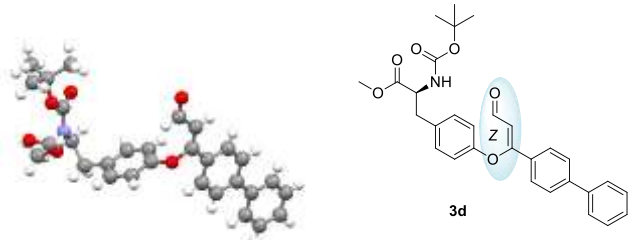


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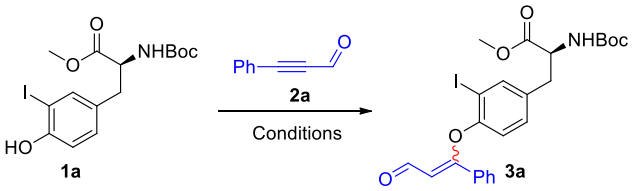
**Table 1.** Optimisation of oxa-Michael addition reaction.



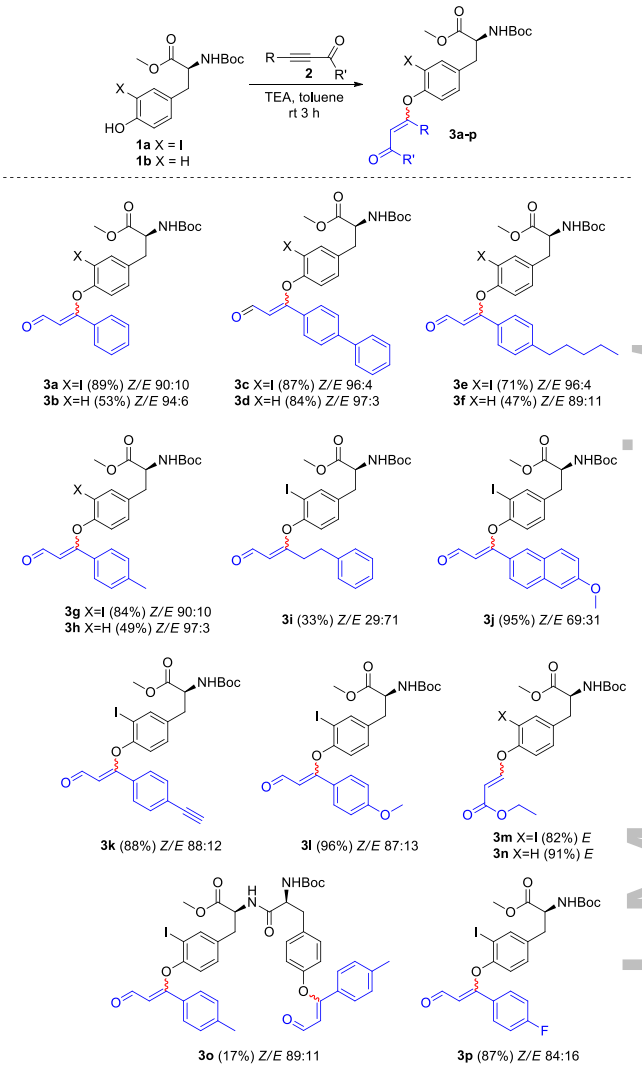

| # | Base (eq.) | Solvent | *Z*/*E*[a] | T (°C) | (%)[b] |
|---|---|---|---|---|---|
| 1 | $Cs_2CO_3$ (1) | DCM | 53:47 | rt | 58 |
| 2 | $Na_2CO_3$ (1) | DCM | 73:27 | rt | 63 |
| 3 | TEA (1) | DCM | 83:17 | rt | 80 |
| 4 | TEA (1) | THF | 0 | rt | 0 |
| 5 | TEA (1) | toluene | 84:16 | rt | 19 |
| 6 | TEA (1) | toluene | 85:15 | MW 50 | 15[c] |
| 7 | TEA (2) | toluene | 87:13 | MW 50 | 85[c] |
| 8 | TEA (2) | toluene | 88:12 | MW 50 | 87[d] |
| 9 | TEA (2) | toluene | 90:10 | rt | 91[e] |
| 10 | TEA (2) | DCM | 83:17 | MW 50 | 84[d] |
| 11 | TEA (2) | DCM | 86:14 | rt | 86[e] |
| 12 | TEA (5) | toluene | 88:12 | rt | 87[e] |
| 13 | TEA (5) | toluene | 86:14 | MW 50 | 87[c] |
| 14 | TEA (5) | toluene | 85:15 | MW 100 | 85[c] |
| 15 | TEA (2) | toluene | 91:9 | ))) | 85[f] |

Reaction time: 24 h. [a] *Z*/*E* ratio determined by $^1$H NMR. [b] Conversion determined by $^1$H NMR. [c] 20 minutes under irradiation of microwaves. [d] 60 minutes under irradiation of microwaves. [e] Reaction time: 3 h. [f] 2 hours under ultrasound irradiation. Entry 1 to 6 were used $MgCl_2$ as additive.

The reaction between 3-iodotyrosine **1a** and phenylpropylaldehyde **2a** led to the desired product in a 89% yield and a *Z*/*E* ratio of 90:10. In contrast, a lower yield was observed when using tyrosine without the iodine atom in its structure (53% yield and a *Z*/*E* ratio of 94:6). Similar results were obtained with the compounds **3g** (84%, *Z*/*E* 90:10) and **3h** (49%, *Z*/*E* 93:7).

Biphenyl propionaldehyde afforded products **3c** (87%, *Z*/*E* 96:4) and **3d** (84%, *Z*/*E* 97:3) with good yields and excellent Z/E ratios. When we analysed **3e** (71%, *Z*/*E* 96:4) and **3f** (47%, *Z*/*E* 89:11), we noticed differences in the reaction yields due to the presence or absence of iodine on the tyrosine ring. The same pattern was maintained in all cases presented in Scheme 3.

Propargyl aldehyde with an alkyl chain attached at the *sp* carbon provided the desired product **3i** with a low yield and stereoselectivity (33%, *Z*/*E* 29:71). A poor stereoselectivity was also observed for product **3j**, despite the high yield (95%, *Z*/*E* 69:31). The oxa-Michael addition product **3l** was isolated with a 96% yield and a *Z*/*E* ratio of 87:13. We correlated this high yield with the presence of the methoxy donating group. 4-Ethynylphenylpropylaldehyde gave the desired product **3k** in good yield and stereoselectivity (88%, *Z*/*E* 88:12).




**Scheme 3.** Scope of oxa-Michael addition between tyrosine and propargyl aldehydes/ester.

In addition to propargylic aldehydes, the scope of the reaction was extended to ethyl propiolate. The results of the reaction between ethyl propiolate and tyrosine were satisfactory, leading to the exclusive formation of *E* isomers. Based on the calculation of the coupling constant ($J$ = 12.3 Hz), products **3m** and **3n** were isolated with 82% and 91% yields, respectively.

The oxa-Michael addition between 4-toluylpropiolaldehyde and a dipeptide Tyr-Tyr was investigated, 2 eqv. of propargyl aldehyde were employed and product **3o** was obtained in only a 17% yield with a *Z*/*E* ratio of 89:11. Propargyl aldehyde containing electron withdrawing group, such as 4-fluorophenyl propiolaldehyde, the product **3p** was achieved in 87% yield and a Z/E ratio 84:16. The low yield can be influenced by the formation of several non-characterised by-products. Despite the low yield, the oxa-Michael addition between tyrosine-containing peptides and propargyl aldehydes or propargyl esters

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opens up a wide range of applications. The strategy could be useful, for example, in biological systems to target tyrosines covalently in the catalytic pocket of proteins.

Based on the crystal structure of **3d** (Figure 1), we believe that the reaction product between phenylpropargylaldehyde derivatives and tyrosine tends to assume a more stable configuration, which in this case is the *Z* stereoisomer. The system tends to keep planarity along the α,β-unsaturated aldehydes and the aromatic ring attached on *β*-C, otherwise, if the system assumes configuration *E*, it may not be stable due to the steric hindrance effect of the aromatic ring over the aldehyde. In contrast, when we used an alkyl substituent on *β*-C, product **3i** was isolated as a mixture of stereoisomers with predominantly the *E* configuration. To support our hypothesis, reaction products **3m** and **3n** with no substituent at *β*-C were isolated exclusively as *E* stereoisomers.

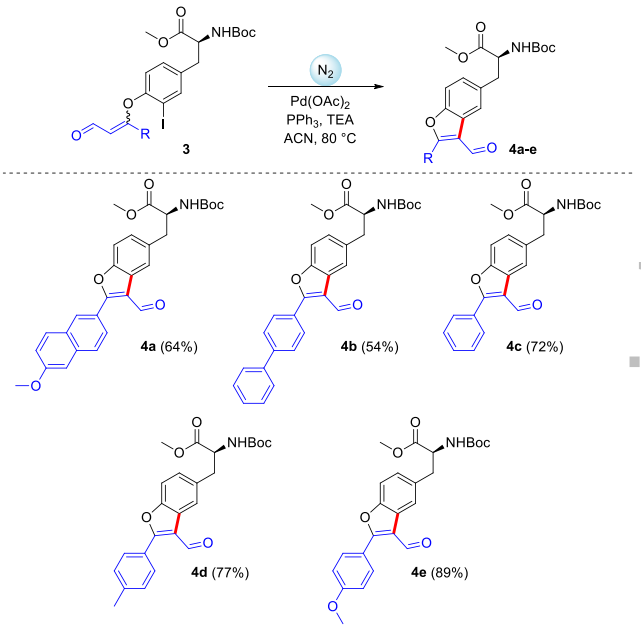
Once the oxa-Michael addition reaction was completed, we proceeded to the next stage of the work. In order to obtain benzofuran heterocycles, some of the products shown in Scheme 3 were reacted in the presence of palladium via a Heck intramolecular reaction.

Under these conditions and under a nitrogen atmosphere, we observed the total consumption of the aldehyde **3a** after 7 h. Benzofuran **4a** was isolated in a 64% yield (Scheme 4). The replacement of $PPh_3$ with $PCy_3$ or $PBu_3$ did not afford the desired cyclisation product. Instead, we observed a reverse conversion of aldehyde **3a** to 3-iodotyrosine **1a**. On the basis that alkyl phosphines are more nucleophilic than aromatic phosphines, we believe that a conjugate addition of the phosphine to the double bond occurred,[18–20] followed by a restoration of 3-iodotyrosine **1a** (see SI). The absence of a base and/or phosphine did not lead to the consumption of the starting material.

The aldehyde containing a biphenyl led to cyclisation product **4b** in a 54% yield, while the aldehyde substituted with a methoxy group led to benzofuran **4e** in an 89% yield. Closer yields were achieved when aldehydes bearing phenyl and tolyl groups were used, with **4c** and **4d** isolated in 72% and 77% yields, respectively (Scheme 4).

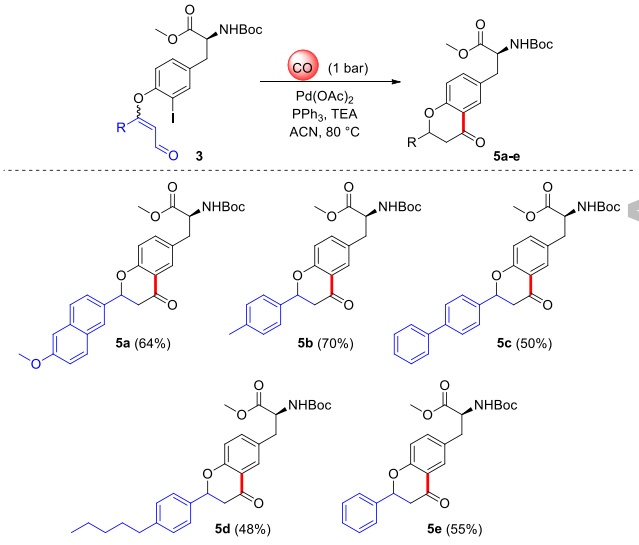
The intramolecular Heck reaction is shown to be sensitive to the groups attached to the *α,β*-unsaturated carbonyl system. Electron-donating groups led to the respective products in higher yields than those achieved with neutral groups attached to the same system. When we used aldehyde **3i** bearing an alkyl group, we did not observe the formation of the corresponding benzofuran.

In an attempt to form products via carbonylative coupling of α,β-unsaturated aldehydes, we replaced the nitrogen atmosphere with a carbon monoxide atmosphere. In a stainless-steel pressurised reactor under 1 bar of carbon monoxide, the mixture containing the reagents was heated to 80 °C for 3 h, followed by purification of the products. To our surprise, we did not observe the aldehyde signal in the $^1$H NMR spectrum. We did, however, see the appearance of a signal at 193.4 ppm in the $^{13}$C NMR spectrum, characteristic of a ketone, suggesting the formation of a reductive intramolecular acylation product instead of the intramolecular carbonylative coupling, as subsequently confirmed by NMR (Scheme 5).




**Scheme 4.** Examples of benzofuran derivatives.

Knowing the course of the reaction, we used different *α,β*-unsaturated aldehydes in order to achieve 6-alanyl-2-arylflavone derivatives via reductive intramolecular acylation reaction.[21] The starting aldehyde containing the 6-methoxynaphthalene group was converted to product **5a** in a 64% yield while the biphenyl **5c** and 4-pentyl **5d** derivatives were obtained in 50% and 48% yields, respectively, and the flavone **5e** in a 55% yield. The higher yield was achieved using an aldehyde containing a tolyl group. The respective flavone **5b** was isolated in a 70% yield (Scheme 5).




**Scheme 5.** Examples of 6-alanyl-2-arylflavones derivatives.

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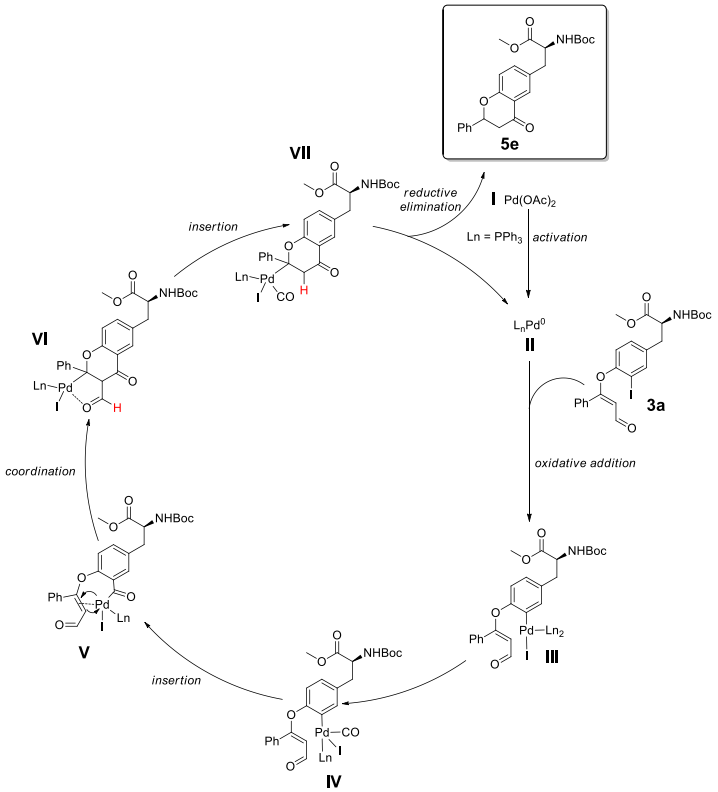


**Scheme 6.** Mechanistic proposal for reductive intramolecular acylation reaction.

Based on the results mentioned above and the data available in the literature,[22] a plausible mechanism was proposed for the reductive intramolecular acylation. The first step should involve palladium activation by an exchange of ligands in the presence of $PPh_3$, which after oxidative addition of Pd(0) to **3a** led to Pd(II) intermediate **III**. The carbon monoxide atmosphere may favour the formation of complex **IV**, followed by the migratory insertion of carbon monoxide to provide **V**. Palladium then forms a π-complex with the alkene followed by formation of alkyl palladium **VI**. The coordination between the palladium and aldehyde oxygen keeps the metal oxidation at Pd(II). After a decarbonylative insertion, followed by a reductive elimination, product **5e** was released. The reaction has been found to proceed with suppressed *β*-hydride elimination (Scheme 6).

## Conclusion

The oxa-Michael stereoselective addition of the phenol group present on tyrosine or 3-iodotyrosine to different propargyl aldehydes delivered products with predominantly *Z* stereochemistry, as evidenced by the analysis of X-ray crystallography. However, when ethyl propiolate was used as the propargyl ester source, the products were isolated with the stereochemistry exclusively *E* and the yields ranged from 17% to 91%. The oxa-Michael addition compounds were explored as substrates in the synthesis of 5- and 6-membered heterocyclic compounds. To our surprise, the atmosphere applied to the reaction medium directly influenced the formation of the products. When an inert atmosphere of nitrogen was applied, 2-aryl-3-formyl-5-alanylbenzofurans were selectively obtained via the Heck intramolecular reaction, while the reactions carried out under a carbon monoxide atmosphere exclusively gave 6-alanyl-2-arylflavone derivatives via reductive intramolecular acylation. A proposal mechanism for the reductive intramolecular acylation reaction based on experimental observations was disclosed.

## Experimental Section

To a vial equipped with a magnetic stirrer bar and sealed with a septum were added the 3-iodotyrosine or tyrosine (0.25 mmol), toluene (1 mL), TEA (70 µL, 0.5 mmol) and propargyl aldehyde or ethyl propiolate (0.25 mmol) at room temperature. The reaction mixture was stirred vigorously at room temperature for 3 h. The product was purified by silica flash chromatography and eluted with ethyl acetate/hexane 3:7. Further experimental details and product characterization are given in the Supporting Information.

**Tyrosine (3a)**. The Product was obtained as a yellow oil. Yield: 122 mg (89%). $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 38.1 °. **IR** (film) $cm^{-1}$: 3242, 2877, 1685, 1654, 1601, 1566, 1430, 1400, 1322, 1229, 1182, 1121, 1099, 1009, 978, 817, 672. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.03 (d, *J* = 7.6 Hz, 1H), 7.62 (s, 1H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.38 (q, *J* = 7.5, 6.5 Hz, 3H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 6.27 (d, *J* = 7.6 Hz, 1H), 5.12 – 4.97 (m, 1H), 4.56 – 4.40 (m, 1H), 3.66 (s, 3H), 2.94 (ddd, *J* = 38.0, 13.6, 5.8 Hz, 2H), 1.40 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 190.4, 171.9, 166.9, 155.2, 140.7, 133.3, 132.1, 131.6, 130.5, 129.1, 128.5, 127.4, 116.6, 116.0, 85.8, 80.1, 54.3, 52.3, 37.1, 28.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{24}H_{26}INO_6 + H]^+$: 552.0883, found: 552.0880.

**Tyrosine (3b)**. The Product was obtained as a yellow oil. Yield: 56 mg (53%). $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 35.0 °. **IR** (film) $cm^{-1}$: 3227, 2879, 1654, 1609, 1555, 1456, 1402, 1322, 1238, 1171, 1123, 1104, 981, 814, 747, 711, 674. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.06 (d, *J* = 7.7 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.43 – 7.31 (m, 3H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.24 (d, *J* = 7.7 Hz, 1H), 4.97 (d, *J* = 4.1 Hz, 1H), 4.57 – 4.45 (m, 1H), 3.64 (s, 3H), 2.98 (ddt, *J* = 19.6, 13.8, 6.0 Hz, 2H), 1.39 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 190.6, 172.2, 167.1, 156.3, 155.0, 132.8, 131.4, 131.1, 130.8, 130.0, 128.9, 128.6, 127.5, 121.3, 116.9, 116.5, 80.0, 54.4, 52.1, 37.7, 28.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{24}H_{27}NO_6 + H]^+$: 426.1917, found: 426.1915.

**Tyrosine (3c)**. The Product was obtained as a yellow foam. Yield: 136 mg (87%). **MP** 79-91 °C. $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 28.5 °. **IR** (solid) $cm^{-1}$: 3233, 2879, 1687, 1657, 1566, 1553, 1434, 1322, 1259,1188, 1128, 1011, 976, 821, 737, 678. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.03 (d, *J* = 7.7 Hz, 1H), 7.68 – 7.59 (m, 5H), 7.59 – 7.51 (m, 2H), 7.40 (dt, *J* = 13.2, 6.9 Hz, 3H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.32 (d, *J* = 7.6 Hz, 1H), 5.07 (d, *J* = 6.8 Hz, 1H), 4.54 – 4.43 (m, 1H), 3.65 (s, 3H), 2.95 (ddd, *J* = 39.5, 13.7, 5.8 Hz, 2H), 1.39 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 190.4, 171.9, 166.6, 155.3, 154.9, 144.4, 140.7, 139.5, 133.3, 130.9, 130.6, 129.0, 128.2, 127.9, 127.7, 127.0, 116.5, 116.0, 85.8, 80.1, 54.3, 52.3, 37.1, 28.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{30}H_{30}INO_6 + H]^+$: 628.1196, found: 628.1192.

**Tyrosine (3d)**. The Product was obtained as a yellow crystal. Yield: 105 mg (84%). **MP** 149-151 °C. $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 26.0 °. **IR** (solid) $cm^{-1}$: 3289, 2887, 1700, 1639, 1613, 1551, 1458, 1398, 1363, 1303, 1214, 1168, 1119, 1095, 1022, 994, 974, 819, 789, 741, 715, 668. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.07 (d, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 3H), 7.62 – 7.52 (m, 4H), 7.41 (dt, *J* = 13.4, 7.1 Hz, 3H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.30 (d, *J* = 7.7 Hz, 1H), 5.03 – 4.92 (m, 1H), 4.60 – 4.44 (m, 1H), 3.64 (s, 3H), 2.98 (ddt, *J* = 19.6, 14.0, 6.1 Hz, 2H), 1.38 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 190.6, 172.2, 166.8, 156.5, 144.2, 139.6, 131.5, 131.1, 130.8, 128.9, 128.2, 127.9, 127.6, 127.0, 116.8, 116.4, 80.0, 54.4, 52.2, 37.7, 28.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{30}H_{31}NO_6 + H]^+$: 502.2230, found: 502.2226.

**Tyrosine (3e)**. The Product was obtained as a yellow oil. Yield: 110 mg (71%). $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 31.7 °. **IR** (film) $cm^{-1}$: 3252, 2857, 2833, 2762, 1685, 1654, 1611, 1601, 1566, 1555, 1432, 1322, 1229, 1184, 1123, 1009, 978, 814. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.00 (d, *J* = 7.7 Hz, 1H), 7.62 (s, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.91 (d, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 6.26 (d, *J* = 7.7 Hz, 1H), 5.06 (d, *J* = 6.6 Hz, 1H), 4.54 – 4.42 (m, 1H), 3.66 (s, 3H), 2.95 (ddd, *J* = 36.6, 13.7, 5.5 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 1.58 (p, *J* = 7.3 Hz, 2H), 1.40 (s, 9H), 1.34 – 1.25 (m, 4H), 0.87 (t, *J* = 6.6 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 190.5, 171.9, 167.1, 155.4, 154.9, 147.4, 140.6, 133.1, 130.5, 129.4, 129.2, 127.3, 116.0, 115.8, 85.7, 80.1, 54.3, 52.2, 37.1, 35.8, 31.4, 30.6, 28.3, 22.4, 13.9. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{29}H_{36}INO_6 + H]^+$: 622.1666, found: 622.1661.

**Tyrosine (3f)**. The Product was obtained as a yellow oil. Yield: 58 mg (47%). $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 34.5 °. **IR** (film) $cm^{-1}$: 3250, 2857, 2833, 2762, 1687, 1655, 1611, 1553, 1454, 1322, 1240, 1173, 1127, 1106, 1022, 979, 810. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.03 (d, *J* = 6.0 Hz, 1H), 7.49 (d, *J* = 6.5 Hz, 2H), 7.16 (d, *J* = 6.6 Hz, 2H), 7.03 (d, *J* = 6.9 Hz, 2H), 6.91 (d, *J* = 6.7 Hz, 2H), 6.24 (d, *J* = 6.0 Hz, 1H), 5.00 (d, *J* = 8.5 Hz, 1H), 4.52 (d, *J* = 7.3 Hz, 1H), 3.64 (s, 3H), 2.98 (qd, *J* = 14.3, 6.0 Hz, 2H), 2.58 (t, *J* = 7.8 Hz, 2H), 1.59 (p, *J* = 7.6, 6.8 Hz, 2H), 1.39 (s, 9H), 1.35 – 1.21 (m, 4H), 0.88 (t, *J* = 6.1 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 190.7, 172.2, 167.3, 156.6, 155.0, 147.1, 131.0, 130.9, 130.7, 130.0, 129.0, 128.6, 127.4, 116.8, 115.9, 80.0, 54.4, 52.1, 37.7, 35.8, 31.4, 30.7, 28.3, 22.4, 13.9. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{29}H_{37}NO_6 + H]^+$: 496.2699, found: 496.2695.

**Tyrosine (3g)**. The Product was obtained as a yellow oil. Yield: 118 mg (84%). $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 20.6 °. **IR** (film) $cm^{-1}$: 3250, 2879, 1687, 1654, 1611, 1568, 1460, 1434, 1322, 1229, 1188, 1128, 1009, 979, 802. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.01 (d, *J* = 7.7 Hz, 1H), 7.62 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 6.24 (d, *J* = 7.7 Hz, 1H), 5.13 – 5.02 (m, 1H), 4.54 – 4.43 (m, 1H), 3.67 (s, 3H), 2.95 (ddd, *J* = 39.0, 13.3, 6.4 Hz, 2H), 2.34 (s, 3H), 1.40 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 190.4, 171.9, 167.1, 155.3, 154.9, 142.4, 140.6, 133.2, 130.5, 129.9, 129.2, 127.3, 116.0, 116.0, 85.7, 80.0, 54.3, 52.2, 37.1, 28.3, 21.5. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{25}H_{28}INO_6 + H]^+$: 566.1040, found: 566,1037.

**Tyrosine (3h)**. The Product was obtained as a yellow oil. Yield: 54 mg (49%). $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 22.4 °. **IR** (film) $cm^{-1}$: 3259, 2879, 2758, 1687, 1654, 1603, 1553, 1456, 1322, 1236, 1171, 1125, 1106, 1022, 979, 799, 713. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.03 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 6.5 Hz, 2H), 7.16 (d, *J* = 6.8 Hz, 2H), 7.03 (d, *J* = 6.7 Hz, 2H), 6.90 (d, *J* = 6.6 Hz, 2H), 6.22 (d, *J* = 7.7 Hz, 1H), 4.98 (d, *J* = 3.5 Hz, 1H), 4.59 – 4.44 (m, 1H), 3.65 (s, 3H), 2.99 (tt, *J* = 17.0, 9.7 Hz, 2H), 2.34 (s, 3H), 1.39 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 190.7, 172.2, 167.3, 156.4, 155.0, 142.1, 130.9, 130.7, 129.9, 129.7, 127.4, 116.8, 115.9, 80.0, 54.4, 52.1, 37.7, 28.2, 21.5. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{25}H_{29}NO_6 + H]^+$: 440.2073, found: 440.2068.

**Tyrosine (3i)**. The Product was obtained as a yellow oil. Yield: 48 mg (33%). $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 32.9 °. **IR** (film) $cm^{-1}$: 3242, 2879, 2836, 1685, 1648, 1566, 1432, 1391, 1322, 1184, 1121, 1024, 1007, 985, 814, 713, 680. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.02 (d, *J* = 7.8 Hz, 1H), 9.63 (d, *J* = 7.5 Hz, 1H), 7.64 (s, 1H), 7.30 (dq, *J* = 16.7, 7.5 Hz, 4H), 7.14 (ddd, *J* = 15.7, 8.2, 5.2 Hz, 2H), 6.86 (dd, *J* = 8.2, 4.1 Hz, 1H), 5.57 (d, *J* = 7.8 Hz, 1H), 5.07 (d, *J* = 5.7 Hz, 1H), 4.97 (d, *J* = 7.5 Hz, 1H), 4.61 – 4.47 (m, 1H), 3.72 (d, *J* = 8.2 Hz, 3H), 3.22 – 3.05 (m, 4H), 3.05 – 2.89 (m, 1H), 2.84 (t, *J* = 7.8 Hz, 1H), 2.54 – 2.45 (m, 1H), 1.43 (d, *J* = 5.9 Hz, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 190.2, 189.4, 176.7, 171.8, 155.0, 153.2, 151.5, 140.9, 139.9, 139.5, 136.5, 135.0, 130.9, 130.7, 128.7, 128.6, 128.6, 128.5, 128.3, 126.7, 126.6, 122.3, 119.2, 115.1, 108.4, 89.8, 88.5, 80.2, 52.4, 37.6, 34.6, 33.8, 32.8, 32.7, 28.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{26}H_{30}INO_6 + H]^+$: 580.1196, found: 580.1193.

**Tyrosine (3j)**. The Product was obtained as a yellow foam. Yield: 150 mg (95%). MP 85-87 °C. $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 31.0 °. **IR** (solid) $cm^{-1}$: 3229, 2875, 2753, 1685, 1654, 1601, 1560, 1430, 1346, 1322, 1300, 1229, 1179, 1158, 1127, 1086, 1054, 987, 901, 827, 789. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 9.62 (d, *J* = 7.6 Hz, 1H), 8.15 (s, 1H), 8.02 (s, 1H), 7.84 (s, 1H), 7.76 – 7.61 (m, 3H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.27 – 7.04 (m, 4H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.37 (d, *J* = 7.6 Hz, 1H), 5.35 (d, *J* = 7.7 Hz, 1H), 5.20 (d, *J* = 8.1 Hz, 1H), 5.08 (d, *J* = 8.4 Hz, 1H), 4.47 (s, 1H), 3.94 (s, 1H), 3.89 (s, 3H), 3.73 (s, 1H), 3.61 (s, 3H), 3.20 – 2.76 (m, 3H), 1.44 (s, 4H), 1.37 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 192.3, 190.4, 175.3, 171.9, 171.9, 167.2, 159.5, 159.4, 155.6, 154.9, 152.1, 141.0, 140.7, 136.6, 136.3, 136.2, 133.2, 131.0, 130.6, 130.3, 128.3, 128.1, 127.8, 127.8 127.2, 127.0, 126.9, 126.7, 124.0, 122.4, 120.0, 119.9, 116.2, 115.9, 109.4, 105.8, 105.8, 89.8, 85.7, 80.0, 55.4, 54.3, 52.4, 52.2, 37.3, 37.0, 28.3, 28.2. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{29}H_{30}INO_7 + H]^+$: 632.1145, found: 632.1143.

**Tyrosine (3k)**. The Product was obtained as a yellow foam. Yield: 126 mg (88%). **MP** 65-68 °C. $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 33.0 °. **IR** (solid) $cm^{-1}$: 3170, 2877, 1685, 1648, 1601, 1566, 1432, 1322, 1257, 1227, 1184, 1125, 1102, 1009, 978, 817. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.63 (s, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.27 (d, *J* = 7.5 Hz, 1H), 5.07 (d, *J* = 8.2 Hz, 1H), 4.49 (d, *J* = 7.4 Hz, 1H), 3.67 (s, 3H), 3.22 (s, 1H), 2.95 (ddd, *J* = 42.6, 14.2, 6.3 Hz, 2H), 1.40 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 191.5, 190.2, 173.9, 171.9, 171.8, 165.8, 155.0, 154.9, 151.8, 141.0,

140.8, 136.8, 133.5, 132.7, 132.6, 132.3, 132.2, 132.0, 131.1, 130.8, 130.6, 130.1, 127.2, 125.5, 122.3, 117.1, 116.8, 115.9, 109.7, 85.8, 82.6, 80.3, 80.1, 54.3, 52.3, 37.1, 28.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{26}H_{26}INO_6 + H]^+$: 576.0883, found: 576.0880.

**Tyrosine (3l)**. The Product was obtained as a yellow oil. Yield: 139 mg (96%). $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 28.5 º. **IR** (film) $cm^{-1}$: 3250, 2877, 2749, 1687, 1654, 1603, 1551, 1462, 1432, 1352, 1322, 1303, 1216, 1186, 1136, 1058, 996, 814. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 9.97 (d, *J* = 7.6 Hz, 1H), 7.63 (s, 1H), 7.58 – 7.47 (m, 2H), 6.98 – 6.83 (m, 3H), 6.61 (d, *J* = 8.3 Hz, 1H), 6.21 (d, *J* = 7.8 Hz, 1H), 5.16 – 5.01 (m, 1H), 4.57 – 4.41 (m, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.09 – 2.81 (m, 2H), 1.40 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 192.0, 190.3, 171.9, 171.8, 171.0, 166.9, 162.4, 162.3, 155.5, 154.9, 152.1, 140.9, 140.6, 136.5, 133.1, 131.9, 131.0, 130.5, 129.2, 124.2, 124.1, 122.4, 116.7, 115.8, 115.1, 114.6, 114.4, 114.0, 108.8, 89.7, 85.6, 80.0, 55.5, 55.4, 54.3, 53.4, 52.3, 52.2, 37.0, 28.3, 28.2. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{25}H_{28}INO_7 + H]^+$: 582.0989, found: 582.0986.

**Tyrosine (3m)**. The Product was obtained as a white crystal. Yield: 106 mg (82%). **MP** 95-97 °C. $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 34.5 º. **IR** (solid) $cm^{-1}$: 3224, 2875, 1683, 1652, 1629, 1596, 1542, 1479, 1434, 1391, 1322, 1249, 1197, 1153, 1117, 1078, 1020, 996, 964, 912, 814, 797. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 12.3 Hz, 1H), 7.62 (d, *J* = 2.1 Hz, 1H), 7.15 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.97 (s, 1H), 5.49 (d, *J* = 12.3 Hz, 1H), 5.10 (d, *J* = 8.1 Hz, 1H), 4.60 – 4.48 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 3.04 (ddd, *J* = 46.0, 13.9, 6.3 Hz, 2H), 1.43 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 171.8, 166.8, 158.7, 154.9, 154.2, 140.7, 135.4, 130.8, 118.8, 102.7, 87.7, 80.1, 60.1, 54.3, 52.4, 37.2, 28.3, 14.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{20}H_{26}INO_7 + H]^+$: 520.0832, found: 520.0829.

**Tyrosine (3n)**. The Product was obtained as a yellow oil. Yield: 89 mg (91%). $[\alpha]_D^{20}$ (*c* = 0.2, $CHCl_3$): + 36.7 º. **IR** (film) $cm^{-1}$: 3259, 2881, 1687, 1652, 1596, 1551, 1456, 1393, 1322, 1244, 1177, 1130, 1078, 1013, 985, 922, 810. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 12.2 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 5.54 (d, *J* = 12.2 Hz, 1H), 5.03 (d, *J* = 7.3 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 3.18 – 2.95 (m, 2H), 1.42 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 172.1, 167.13, 158.9, 154.9, 132.9, 130.8, 118.1, 102.2, 80.0, 60.0, 54.4, 52.2, 37.7, 28.3, 14.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{20}H_{27}NO_7 + H]^+$: 394.1866, found: 394.1862.

**Dipeptide (3o)**. The Product was obtained as a yellow oil. Yield: 37 mg (17%). $[\alpha]_D^{20}$ (*c* = 0.1, $CHCl_3$): + 23.0 º. **IR** (film) $cm^{-1}$: 3200, 2879, 2753, 1685, 1601, 1553, 1456, 1432, 1393, 1344, 1322, 1276, 1261, 1229, 1173, 1130, 1106, 1059, 1009, 991, 979, 866, 797, 771, 711, 681. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 9.97 (s, 2H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.45 (dd, *J* = 8.2, 6.0 Hz, 4H), 7.14 (t, *J* = 8.0 Hz, 4H), 7.07 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.42 (d, *J* = 7.5 Hz, 1H), 6.22 (dd, *J* = 7.7, 2.0 Hz, 2H), 4.86 (s, 1H), 4.73 – 4.62 (m, 1H), 4.22 (d, *J* = 7.6 Hz, 1H), 3.62 (s, 3H), 3.09 – 2.77 (m, 4H), 2.32 (s, 6H), 1.37 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 190.6, 190.4, 171.0, 170.6, 167.2, 167.1, 156.5, 155.5, 142.4, 142.1, 140.6, 132.8, 131.2, 130.7, 130.4, 129.9, 129.8, 129.7, 129.3, 127.4, 127.3, 121.4, 116.9, 116.2, 116.0, 115.8, 85.8, 80.5, 53.1, 52.3, 37.3, 36.7, 28.2, 21.5. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{44}H_{45}IN_2O_9 + H]^+$: 873.2248, found: 873.2243.

**Dipeptide (3p)**. The Product was obtained as a yellow oil. Yield: 124 mg (87%). [α]D 20 (c = 0.2, CHCl3): + 12.5 º. IR (film) cm−1 : 3244, 2879, 1685, 1646, 1611, 1549, 1458, 1432,1184, 1123, 1102, 1007, 1099, 979, 817, 728. 1H NMR (300 MHz, CDCl3) δ 1H NMR (300 MHz, CDCl3) δ 9.92 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 14.3 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.3 Hz, 1H), 6.52 (d, J = 8.3 Hz, 1H), 6.14 (d, J = 7.6 Hz, 1H), 4.98 (s, 1H), 4.43 (s, 1H), 3.60 (s, 3H), 3.05 – 2.73 (m, 2H), 1.32 (s, 9H). 13C NMR (75 MHz, CDCl3) δ 13C NMR (75 MHz, CDCl3) δ 190.2, 171.8, 166.3, 165.8, 162.9, 155.0, 140.8, 131.6 (d, J = 219 Hz), 130.8, 130.6, 129.6 (d, J = 8.7 Hz), 128.3 (d, J = 3.3 Hz), 116.6, 116.3, 116.1 (d, J = 23.7 Hz), 85.8, 80.1, 52.3, 37.1, 28.3. HRMS (ESI-TOF) m/z, calcd for [C24H25FINO7 + Na]$^+$ : 592.0603, found: 592.0598.

**General procedure for Heck intramolecular (4a-e):** The *α,β*-unsaturated aldehyde **3** (0.1 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol%), $PPh_3$ (5.2 mg, 20 mol%), TEA (70 µL, 0.5 mmol) and acetonitrile (5 mL) were added to a stainless steel vessel, equipped with a magnetic bar. The system was sealed and purged with nitrogen and maintained at 1 bar of pressure. The system was kept under stirring and heating at 80 °C for 3 hours. Then, the system was cooled to room temperature and opened. The resulting material was transferred to a flask, dried under vacuum and purified on chromatography column (using ethyl acetate / hexane 2:8).

**Benzofurane (4a)**. The Product was obtained as a yellow solid. Yield: 32 mg (64%). **MP** 83-85 °C. $[\alpha]_D^{20}$ (*c* = 0.1, $CHCl_3$): + 73.6 º. IR (solid) $cm^{-1}$: 3222, 2879, 1680, 1631, 1601, 1572, 1473, 1436, 1344, 1320, 1210, 1179, 1147, 1127, 1028, 992, 888, 868, 825, 778, 706, 687. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.26 (s, 1H), 8.05 (s, 1H), 7.88 (s, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.26 (s, 1H), 7.18 (d, *J* = 9.0 Hz, 2H), 5.05 (d, *J* = 6.7 Hz, 1H), 4.71 – 4.57 (m, 1H), 3.97 (s, 3H), 3.78 (s, 3H), 3.24 (qd, *J* = 13.9, 5.6 Hz, 2H), 1.43 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 186.6, 172.2, 166.1, 159.4, 155.1, 153.3, 135.9, 132.9, 130.4, 129.5, 128.4, 127.8, 127.2, 126.0, 125.7, 123.6, 123.1, 120.2, 117.1, 111.0, 105.9, 80.0, 55.5, 54.8, 52.3, 38.4, 28.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{29}H_{30}NO_7 + H]^+$: 504.2022, found: 504.2018.

**Benzofurane (4b)**. The Product was obtained as a yellow solid. Yield: 27 mg (54%). **MP** 148-150 °C. $[\alpha]_D^{20}$ (*c* = 0.1, $CHCl_3$): + 58.0 º. **IR** (solid) $cm^{-1}$: 3239, 2883, 1702, 1693. 1633, 1607, 1471, 1421, 1393, 1324, 1300, 1225, 1208, 1171, 1154, 1125, 1035, 1020, 966, 897, 829, 810, 788, 748, 709, 674. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.06 (s, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.72 – 7.64 (m, 2H), 7.51 (dt, *J* = 7.6, 3.0 Hz, 3H), 7.44 (d, *J* = 7.1 Hz, 1H), 7.20 (dd, *J* = 8.4, 1,7 Hz, 1H), 5.04 (d, *J* = 7.0 Hz, 1H), 4.65 (d, *J* = 6.6 Hz, 1H), 3.79 (s, 3H), 3.25 (qd, *J* = 13.9, 5.5 Hz, 2H), 1.44 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 186.4, 172.2, 165.3, 155.1, 153.3, 144.0, 139.7, 133.0, 129.5, 129.1, 128.3, 127.8, 127.4, 127.2, 125.9, 123.2, 117.4, 111.1, 80.0, 54.9, 52.3, 38.4, 28.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{30}H_{29}NO_6 + H]^+$: 500.2073, found: 500.2065.

**Benzofurane (4c)**. The Product was obtained as a yellow oil. Yield: 30 mg (72%). **MP** 125-127 °C. $[\alpha]_D^{20}$ (*c* = 0.1, $CHCl_3$): + 82.7 º. **IR** (solid) $cm^{-1}$: 3242, 2881, 1702, 1693, 1637, 1609, 1475, 1423, 1393, 1326, 1300, 1210, 1171, 1156, 1127, 1033, 1020, 998, 966, 899, 864, 829, 786, 750, 674. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.04 (s, 1H), 7.85 (dd, *J* = 6.5, 2.8 Hz, 2H), 7.62 – 7.53 (m, 3H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.18 (dd, *J* = 8.5, 1.5 Hz, 1H), 5.03 (d, *J* = 6.4 Hz, 1H), 4.69 – 4.57 (m, 1H), 3.77 (s, 3H), 3.23 (qd, *J* = 13.6, 5.6 Hz, 2H), 1.42 (s, 9H). **$^{13}$C NMR** (75 MHz $CDCl_3$) δ 186.5, 172.2, 165.7, 155.1, 153.3, 132.9, 131.1, 129.2, 129.1, 128.6, 127.3, 125.8, 123.2, 117.4, 111.1, 80.0, 54.9, 52.3, 38.3, 28.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{24}H_{25}NO_6 + H]^+$: 424.1760, found: 424.1752.

**Benzofurane (4d)**. The Product was obtained as a yellow solid. Yield: 33 mg (77%). **MP** 114-116 °C. $[\alpha]_D^{20}$ (*c* = 0.1, $CHCl_3$): + 79.5 º. **IR** (solid) $cm^{-1}$: 3237, 2881, 2833, 2751, 1700, 1691, 1633, 1607, 1475, 1421, 1391, 1324, 1305, 1298, 1210, 1171, 1154, 1145, 1127, 1035, 1020, 966, 897, 864, 830, 797, 784, 754, 700. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.03 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 1H), 5.10 – 4.98 (m, 1H), 4.70 – 4.56 (m, 1H), 3.78 (s, 3H), 3.23 (qd, *J* = 13.7, 5.5 Hz, 2H), 2.47 (s, 3H), 1.43 (s,

9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 186.5, 172.2, 166.0, 155.1, 153.2, 141.8, 132.8, 129.9, 129.0, 127.1, 125.9, 125.8, 123.1, 117.0, 111.0, 79.9, 54.8, 52.3, 38.3, 28.3, 21.5. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{25}H_{27}NO_6 + H]^+$: 438.1917, found: 438.1912.

**Benzofurane (4e)**. The Product was obtained as a yellow solid. Yield: 40 mg (89%). **MP** 105-107 °C. $[\alpha]_D^{20}$ (*c* = 0.1, $CHCl_3$): + 82.0 º. **IR** (solid) $cm^{-1}$: 3229, 2881, 2745, 1702, 1691, 1631, 1616, 1557, 1475, 1460, 1411, 1393, 1326, 1305, 1212, 1173, 1127, 1071, 1032, 1022, 996, 966, 897, 832, 812, 793, 765. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.02 (s, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.19 – 7.11 (m, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 5.05 (s, 1H), 4.63 (s, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.23 (tt, *J* = 19.6, 9.5 Hz, 2H), 1.43 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 186.4, 172.2, 165.9, 162.1, 155.1, 153.0, 132.8, 130.7, 126.9, 126.0, 123.0, 121.0, 116.4, 114.7, 110.9, 79.9, 55.5, 54.9, 52.3, 38.3, 28.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{25}H_{27}NO_7 + H]^+$: 454.1866, found: 454.1860.

**General procedure for reductive intramolecular acylation (5a-e):** The *α,β*-unsaturated aldehyde **3** (0.1 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol%), $PPh_3$ (5.2 mg, 20 mol%), TEA (70 µL, 0.5 mmol) and acetonitrile (5 mL) were added to a stainless steel vessel, equipped with a magnetic bar. The system was sealed and purged with carbon monoxide and maintained at 1 bar of pressure. The system was kept under stirring and heating at 80 °C for 3 hours. Then, the system was cooled to room temperature and opened. The resulting material was transferred to a flask, dried under vacuum and purified on chromatography column (using ethyl acetate / hexane 2:8).

**Flavone (5a)**. The Product was obtained as a yellow foam. Yield: 32 mg (64%). **MP** 84-86 °C. $[\alpha]_D^{20}$ (*c* = 0.1, $CHCl_3$): + 38.0 º. **IR** (solid) $cm^{-1}$: 3240, 2875, 2836, 1685, 1654, 1631, 1624, 1568, 1436, 1393, 1344, 1322, 1255, 1225, 1207, 1156, 1125, 989, 953, 884, 827, 786, 758. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.87 (d, *J* = 9.0 Hz, 1H), 7.84 – 7.72 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.22 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.17 (s, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.32 (q, *J* = 4.7 Hz, 1H), 5.06 (d, *J* = 6.5 Hz, 1H), 4.57 (s, 1H), 3.95 (s, 3H), 3.92 – 3.77 (m, 2H), 3.75 (s, 3H), 3.10 (ddd, *J* = 45.2, 13.9, 5.6 Hz, 2H), 1.42 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 193.4, 171.9, 161.6, 160.2, 157.3, 137.7, 137.3, 131.9, 131.7, 131.3, 130.6, 130.2, 127.7, 127.4, 124.3, 120.0, 117.0, 114.4, 105.9, 98.8, 80.2, 55.5, 54.4, 52.4, 42.5, 37.6, 28.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{29}H_{31}NO_7 + H]^+$: 506.2179, found: 506.2172.

**Flavone (5b)**. The Product was obtained as a white solid. Yield: 31 mg (70%). **MP** 70-72 °C. $[\alpha]_D^{20}$ (*c* = 0.1, $CHCl_3$): + 36.5 º. **IR** (solid) $cm^{-1}$: 3248, 2879, 2831, 1689, 1631, 1568, 1555, 1445, 1393, 1374, 1344, 1322, 1255, 1207, 1184, 1169, 1125, 1024, 963, 944, 810, 789, 758. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 2H), 7.75 (s, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.27 (q, *J* = 4.4 Hz, 1H), 5.03 (d, *J* = 6.4 Hz, 1H), 4.57 (s, 1H), 3.74 (s, 3H), 3.73 – 3.60 (m, 2H), 3.10 (ddd, *J* = 44.4, 13.6, 5.5 Hz, 2H), 2.44 (s, 3H), 1.42 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 193.4, 171.8, 161.6, 157.2, 144.9, 137.4, 137.3, 133.8, 131.9, 130.7, 130.6, 129.5, 128.4, 116.9, 114.4, 98.7, 80.2, 54.4, 52.4, 42.5, 37.6, 28.3, 21.7. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{25}H_{29}NO_6 + H]^+$: 440.2073, found: 440.2067.

**Flavone (5c)**. The Product was obtained as a yellow oil. Yield: 25 mg (50%). **MP** 94-96 °C. $[\alpha]_D^{20}$ (*c* = 0.1, $CHCl_3$): + 39.2 º. **IR** (solid) $cm^{-1}$: 3259, 2879, 1691, 1629, 1568, 1551, 1445, 1391, 1374, 1346, 1322, 1257, 1205, 1179, 1125, 1013, 955, 806, 741, 672. **$^1$H NMR** (300 MHz, CDCl3) δ 7.91 (d, *J* = 7.9 Hz, 2H), 7.75 (s, 1H), 7.37 – 7.26 (m, 3H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.36 – 6.23 (m, 1H), 5.13 – 4.95 (m, 1H), 4.57 (s, 1H), 3.75 (s, 3H), 3.72 – 3.61 (m, 2H), 3.10 (ddd, *J* = 44.6, 13.7, 4.5 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 1.64 – 1.60 (m, 2H), 1.42 (s, 9H), 1.37 – 1.23 (m, 4H), 0.90 (t, *J* = 6.4 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 193.4, 171.8, 157.2, 149.8, 137.3, 134.0, 131.9, 130.6, 128.9, 128.4, 124.7, 117.0, 114.4, 98.7, 80.2, 54.3, 52.4, 42.5, 37.6, 36.0, 31.4, 30.7, 28.3, 22.5, 13.9. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{30}H_{31}NO_6 + H]^+$: 502.2230, found: 502.2227.

**Flavone (5d)**. The Product was obtained as a brown oil. Yield: 24 mg (48%). $[\alpha]_D^{20}$ (*c* = 0.1, $CHCl_3$): + 32.4 º. **IR** (film) $cm^{-1}$: 3257, 2859, 2833, 2764, 1689, 1654, 1631, 1568, 1553, 1445, 1393, 1374, 1346, 1322, 1255, 1205, 1181, 1125, 1024, 950, 806, 758. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 7.4 Hz, 2H), 7.51 – 7.35 (m, 5H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.30 (q, *J* = 4.4 Hz, 1H), 5.03 (d, *J* = 6.1 Hz, 1H), 4.64 – 4.50 (m, 1H), 3.85 – 3.67 (m, Hz, 5H), 3.10 (ddd, *J* = 44.9, 13.7, 5.4 Hz, 2H), 1.43 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 193.4, 171.8, 157.2, 155.0, 146.6, 139.6, 137.4, 137.3, 135.0, 132.0, 130.7, 130.7, 129.0, 128.9, 128.4, 127.5, 127.3, 117.0, 114.4, 98.7, 80.3, 54.3, 52.5, 42.7, 37.7, 28.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{29}H_{37}NO_6 + H]^+$: 496.2699, found: 496.2695.

**Flavone (5e)**. The Product was obtained as a yellow oil. Yield: 23 mg (55%). $[\alpha]_D^{20}$ (*c* = 0.1, $CHCl_3$): + 35.7 º. **IR** (film) $cm^{-1}$: 3559, 2879, 1687, 1654, 1633, 1568, 1546, 1445, 1402, 1374, 1346, 1322, 1255, 1207, 1175, 1125, 1022, 968, 948, 810, 760, 734, 713, 668. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.5 Hz, 2H), 7.76 (s, 1H), 7.66 – 7.59 (m, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.38 (s, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.28 (q, *J* = 4.4 Hz, 1H), 5.04 (d, *J* = 5.8 Hz, 1H), 4.65 – 4.48 (m, 1H), 3.83 – 3.63 (m, 5H), 3.10 (ddd, *J* = 44.9, 14.2, 6.0 Hz, 2H), 1.42 (s, 9H). **$^{13}$C NMR:** (75 MHz, $CDCl_3$) δ 193.8, 171.8, 161.5, 157.2, 137.3, 136.3, 133.9, 131.9, 130.6, 128.8, 128.3, 124.8, 116.9, 114.4, 98.6, 80.2, 54.4, 52.4, 42.6, 37.6, 28.3. **HRMS** (ESI-TOF) *m/z*, calcd for $[C_{24}H_{27}NO_6 + H]^+$: 426.1917, found: 426.1911.

## Acknowledgements

*The authors gratefully acknowledge financial support from the São Paulo Research Foundation (FAPESP - 2013/17960-7 to S.N.S.V., 2016/04289-3 to I.M.O.), The National Council for Scientific and Technological Development (CNPq) for a fellowship (302418/2018-0 to HAS) and Coordination for the Improvement of Higher Education Personnel (CAPES) (303207/2017–5 to J.Z-S)- Finance Code 001. Prof. Regina H. A. Santos from IQSCUSP for the X-ray data collection.*

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FULL PAPER

# Stereoselective oxa-Michael Addition of Tyrosine to Propargyl Aldehyde/Esters: Formation of Benzofurans and Flavones

*Adv. Synth. Catal.* **Year**, *Volume*, Page – Page

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