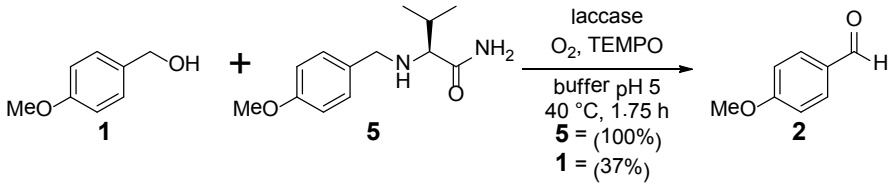
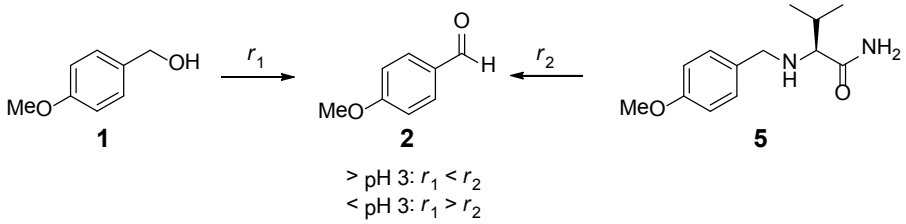
Supplementary Information

General information. Solvents were distilled from appropriate drying agents prior to use and stored under nitrogen. Chemicals were purchased from Sigma-Aldrich and used as received. Laccase from Trametes Versicolor (12.6 U/mg) was purchased from Sigma-Aldrich. Laccase mediated oxidations and iridium catalyzed reductions were performed in citric acid/Na citrate 25 mM buffer pH 5.0 through which was bubbled pure oxygen for at least 15 minutes. The preparations of substrates were followed with thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254). IR spectra were recorded on a Thermo Mattson IR 300 FTIR spectrometer. NMR spectra were recorded on a Bruker DMX 300 (300 MHz) or a Varian 400 (400 MHz). Chemical shifts are given in ppm with respect to tetramethylsilane (TMS) as internal standard. Coupling constants are reported as *J*-values in Hz. Flash column chromatography was carried out using Silicycle SilicaFlash P60 gel (40–63 μm). High resolution mass spectra were recorded on a JEOL AccuTOF (ESI), or a MAT900 (EI, CI, and ESI). The oxidations and reductive aminations were monitored with an Agilent 1120 Compact LC equipped with an Agilent Eclipse Plus C18 column.

Competitive oxidation under various pH values.
For a successful cascade reaction with a simultaneous reduction and oxidation step, the alcohol must be easier oxidized than the amine. We assumed that at lower pH the alkylated valinamide **5** was less prone to oxidation as more amine was protonated. However, the p-methoxy benzyl group might be unstable under these conditions, as valinamide turns into a better leaving group if the amine is protonated. Therefore, we first tested the stability of p-MeOBnValNH$_2$ (**5**) at pH values between 5 and 2.5. No decomposition of compound **5** was observed under any of these pH values. Next, the experiment described in Scheme 1 was repeated under pH conditions between 4.5 – 2.5. Indeed, the relative rate of oxidation became more favorable at decreasing pH values (Figure 1), and at pH 2.5, more benzylic alcohol was oxidized than amine **5**, which is a prerequisite for a successful transformation (Scheme 2) However, below pH 3 no full oxidation was observed. This can be explained by inactivation of the laccase, which optimal pH for these kind of reactions is around 3.5 – 5.0.[25,26] Hence, it was not possible to perform both transformations at the same time, as either the target compound was more reactive than the starting alcohol (> pH 3) or the enzyme was rapidly inactivated (< pH 3).



Scheme 1 Competitive oxidation between alkylated valinamide **5** and anisyl alcohol (**1**).



Scheme 2 pH dependent competitive oxidation

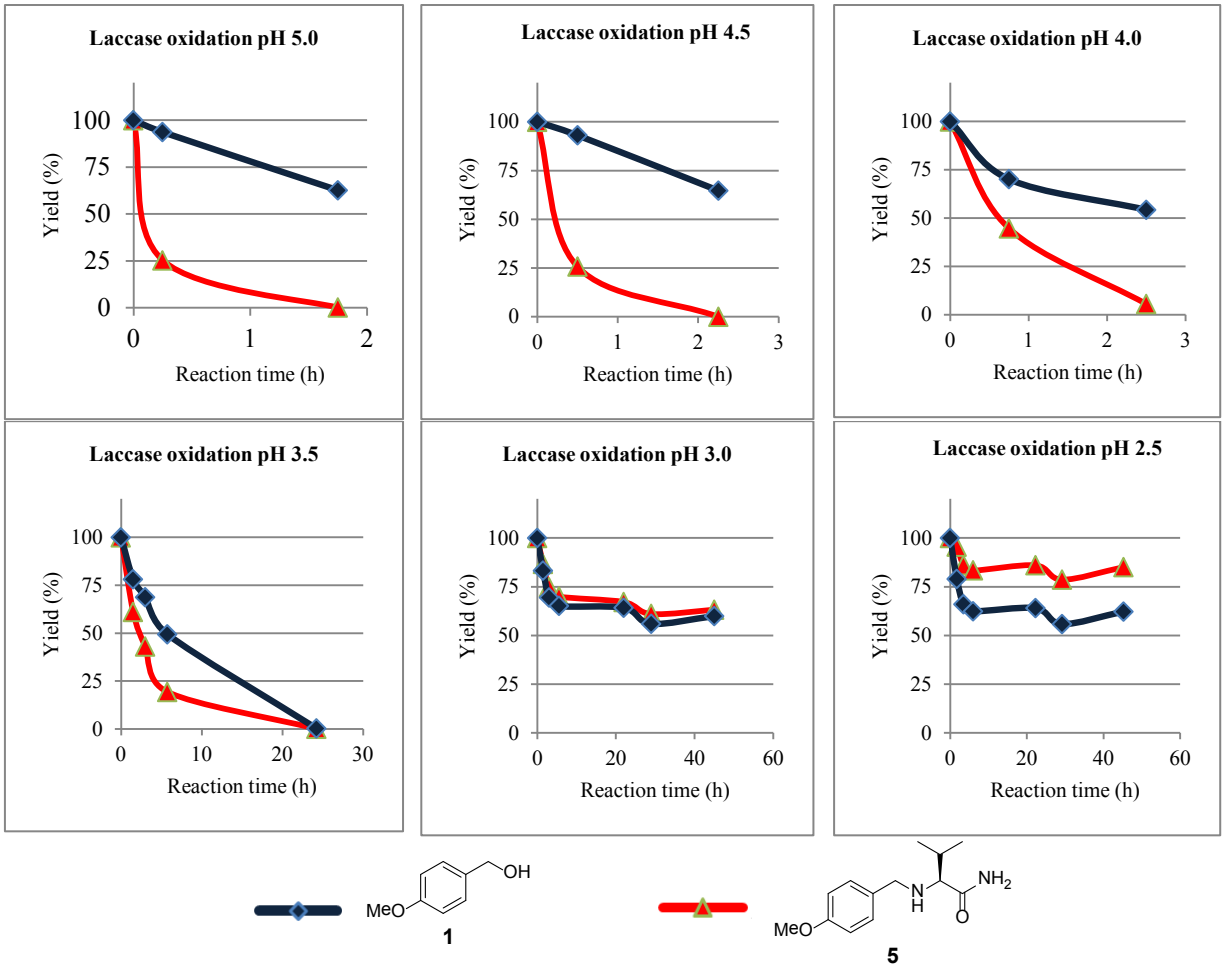


Figure 1 Competitive oxidation between alkylated valinamide **5** and anisyl alcohol (**1**) under different pH values.

General procedure for the oxidation. Laccase (25.0 U) and TEMPO (3.00 mg, 19.2 µmol, 0.3 equiv) were added via a stock solution in oxygenated citric acid/Na citrate 25 mM buffer pH 5.0. Anisyl alcohol (**1**) (7.97 µL, 64 µmol) was directly added via a pipette. The total reaction volume was 10.000 mL. The mixtures were shaken at 40 °C.

General procedure for the reductive amination. Iridium complex **6** (0.143 mg, 0.213 µmol, 0.05 equiv.), valinamide hydrochloride (**3**) (0.652 mg, 4.27 µmol), and HCO_2K (3.59 mg, 0.043 mmol, 10 equiv.) were added via a stock solution in oxygenated citric acid/Na citrate 25 mM buffer pH 5.0. Anisaldehyde (**2**) (5.14 µL, 0.043 mmol, 10 equiv.) was directly added via a pipette. The total reaction volume was 1.000 mL. The mixtures were shaken at 40 °C.

General procedure for the oxidation/reduction sequence. The amounts of the reagents differ and are stated in table 3. Laccase, TEMPO, iridium complex **6** and valinamide hydrochloride (**3**) were added via a stock solution in oxygenated citric acid/Na citrate 25 mM buffer pH 5.0. Anisyl alcohol (**1**) (26.69 µL, 0.214 mmol, 5 equiv.), was directly added via a pipette. The total reaction volume was 10.000 mL. The alcohol conversion was followed with HPLC and after the conversion reached about 80%, HCO_2K was added via a stock solution in oxygenated citric acid/Na citrate 25 mM buffer pH 5.0.

Optimised procedure for the oxidation reduction sequence (Table 3, entry 11). Laccase (5.0 U), TEMPO (6.00 mg, 38.4 µmol, 0.3 equiv), iridium complex **6** (0.58 mg, 0.86 µmol, 0.01 equiv.) and valinamide hydrochloride (**3**) (13.04 mg, 85.4 µmol) were added via a stock solution in oxygenated citric acid/Na citrate 25 mM buffer pH 5.0. Anisyl alcohol (**1**) (15.94 µL, 0.128 mmol) was directly added via a pipette. The total reaction volume was 10.000 mL. The mixtures were shaken at 40 °C. After 40h, 3.51 equiv. anisaldehyde (**2**) were formed. Next, HCO_2K (71.8 mg, 0.854 mmol, 10 equiv.) was added and the mixture shaked at 40 °C. A conversion of 91% was observed after a total reaction time of 65h. Afterwards, a saturated $NaHCO_3$ solution was added and the product extracted with DCM (3×). The combined organic extracts were dried over $MgSO_4$, concentrated and purified by column chromatography on silica (DCM/MeOH, 99:1 to 97:3), affording 10.0 mg (42.3 µmol, 50%) of the desired product.

Cp*Ir(4,4'-dimethoxy-2,2'-bipyridine)SO_4 (6) The procedure described by Francis[1] was used: To a solution of pentamethylcyclopentadienyliridium(III) chloride dimer (100 mg, 0.126 mmol, 0.5 equiv.) in MeOH (12 mL) was added

4,4'-dimethoxy-2,2'-bipyridine (54 mg, 0.252 mmol). The mixture was stirred for 4 h, followed by evaporation of the volatiles under reduced pressure. The residue was dissolved in as less as possible DCM. The product precipitated after the addition of heptane. Filtration and washing with heptane afforded 155 mg (0.252 mmol, 100%) of a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, J = 2.7 Hz, 2H), 8.37 (d, J = 6.5 Hz, 2H), 7.08 (dd, J = 6.5, 2.7 Hz, 2H), 4.42 (s, 6H), 1.65 (s, 17H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.36, 158.17, 149.94, 117.34, 111.52, 88.14, 77.16, 59.55, 8.86, 1.16.

To the complex obtained in the previous step (165 mg, 0.27 mmol) in 20 mL water was added Ag_2SO_4 (85 mg, 0.27 mmol, 1.01 equiv.). The mixture was stirred at ambient temperature overnight. The mixture was filtered and concentrated under reduced pressure, yielding 165 mg (0.26 mmol, 96%) of **6** as a yellow solid. ^{1}H NMR (400 MHz, D_2O) δ 8.88 (d, J = 6.6 Hz, 2H), 7.97 (d, J = 2.7 Hz, 2H), 7.41 (dd, J = 6.6, 2.7 Hz, 2H), 4.11 (s, 6H), 1.66 (s, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.44, 156.88, 151.81, 114.10, 110.15, 87.68, 56.35, 7.21.

Synthesis for HPLC analysis:

***N*-p-Methoxybenzyl-(S)-valinamide (5):**

To vacuum-dried 3A molecular sieves was added 5 mL MeOH (S)-valinamide hydrochloride (**3**) (250 mg, 1.64 mmol) and anisaldehyde (**2**) (0.197 mL, 1.64 mmol, 1 equiv.). The mixture was stirred at ambient temperature for 1.5h, after which $NaBH_4$ (248 mg, 6.55 mmol, 4 equiv.) was added. Gas formation was observed. The mixture was heated to 50 °C after 2.5h, but no further conversion was observed after 4h. More $NaBH_4$ (248 mg, 6.55 mmol, 4 equiv.) was added. Still, starting material was observed after a total reaction time of 6h. The mixture was filtered and concentrated in vacuo. Purification by column chromatography on silica yielded 83 mg (0.35 mmol, 21%) of a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, J = 8.8 Hz, 2H), 7.03 (br s, 1H) 6.86 (d, J = 8.8 Hz, 2H), 5.74 (br s, 1H), 3.80 (s, 3H), 3.76 (d, J = 12.8 Hz, 1H), 3.59 (d, J = 13.2 Hz, 1H), 2.95 (d, J = 4.8 Hz, 1H), 2.07 (dh, J = 7.2, 4.4 Hz, 1H) ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.9, 158.9, 131.9, 129.4, 114.0, 67.9, 55.4, 52.9, 31.4, 19.6, 18.1 IR (ATR): 3360, 3256, 2941, 1666, 1614, 1523, 1251, 806 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{21}N_2O_2Na$ $[M+Na]^+$ 259.14225; found 259.14214.

References

1 J. M. McFarland and M. B. Francis, *J. Am. Chem. Soc*. 2005, **127**, 13490–13491.