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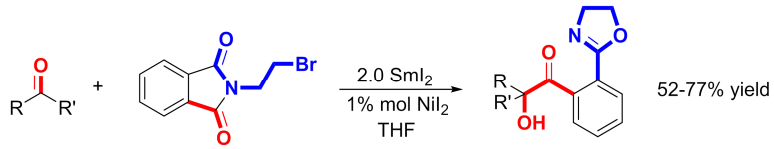

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SmI_2-promoted cross coupling reaction of *N*-2-bromoethylphthalimide and carbonyl compounds: synthesis of α-aryl-α'-hydroxy ketones[†]

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ABSTRACT

In this paper, we have disclosed the SmI_2-mediated carbonyl-imide reductive cross coupling between *N*-2-bromoethylphthalimide and different aldehydes and ketones in the presence of anhydrous catalytic NiI_2. This methodology provided an effective tool to prepare α-aryl-α'-hydroxy ketones under mild conditions which can be applied to various functionalised, aliphatic and aromatic aldehydes and ketones.

[†] *Dedicated to Prof. Steve G. Davies as a recognition for his many scientific achievements and for all his time.*

1. Introduction

Samarium diiodide[1] is unique when compared with other single electron transfer (SET) reagents due to its well-known versatility in providing different radicals in organic synthesis.[2] The use of samarium diiodide in different reductive processes,[3] including coupling reactions, has been widely covered in the literature.[4] In this regard, SmI_2 has been used to promote cross-coupling reactions of aldehydes,[5] ketones[6] and imines[7] under mild conditions. It has been reported that the ketyl-radical generated *in situ* after reaction of one equivalent of SmI_2 and the corresponding carbonyl compound affords, after hydrolysis, 1,2-diols or 1,2-diamines with excellent control of the selectivity.[8] In general, amides exhibit low reactivity in SmI_2-mediated cross coupling reactions,[9] however, cyclic imides have been reported to be much more reactive, undergoing intra- and intermolecular reactions in the presence of samarium diiodide at room temperature.[10]

α-Hydroxy ketones are compounds of great biological and chemical interest. For instance, the α-hydroxy ketone function is found in several pharmaceutical products such as antidepressants, anti-dementia drugs,[11] farnesyl transferase inhibitors,[12] and antitumorals.[13] In addition, α-hydroxy ketones are valuable building blocks for the synthesis of many other important structures of pharmacological interest such as amino ketones,[14] amino alcohols[15] or diols.[16] As a consequence, several procedures have been described for the preparation of these compounds including the α-oxidation of ketones, enol ethers or enolates,[17] the oxidation of alkenes,[18] the metal-catalyzed heteroatom transfer[19] and the acyloin condensation of aldehydes.[20] However, these reported methods have several drawbacks, including low yields, poor chemoselectivities and the generation of toxic waste.

The use of *N*-bromoethylphthalimide has additional value since it allows the incorporation of the 2-aryloxazoline moiety into the final products. Thus, the 2-aryloxazoline scaffold is present in the structure of many biologically relevant derivatives which exhibit cytotoxic,[21] antibacterial,[22] antitumoral,[23] antidepressant,[24] and antioxidant[25] activities. In addition, 2-aryloxazolines have a wide range of chemical applications, including: as chiral auxiliaries,[26] ligands in catalysis,[27] and synthetic intermediates.[28]

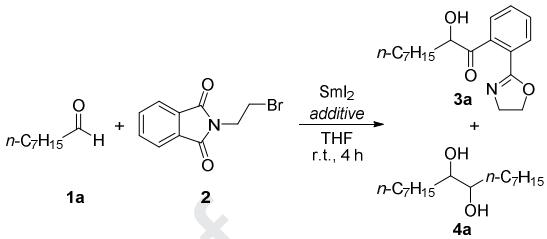
In view of the aforementioned synthetic and pharmacological importance of α-hydroxy ketone and oxazoline moieties, we envisioned the SmI_2-mediated aldehyde-imide reductive cross-coupling reaction as an effective tool to prepare these key intermediates. Thus, in connection with our long term interest in the study of highly selective and effective SmI_2-mediated processes,[29] herein we described a samarium-promoted reductive cross-coupling reaction of *N*-bromoethylphthalimide with different aldehydes and ketones in the presence of catalytic NiI_2 allowing access to the oxazoline-derived α-aryl-α'-hydroxy ketone moiety.

2. Results and Discussion

In our preliminary studies, the model reaction of *n*-octanal **1a** with *N*-2-bromoethylphthalimide **2** was studied (Table 1). Thus, when a mixture of *n*-octanal **1a** (1.0 equiv.), *N*-2-bromoethylphthalimide **2** (1.0 equiv.) and SmI_2 (2.0 equiv.) in THF was stirred for 4 h at room temperature, a crude was obtained, containing 15% of the octanal-derived α-aryl-α'-hydroxy ketone **3a**, along with diol **4a** derived from the homocoupling reaction of *n*-octanal **1a** (Table 1, entry 1).

It is well known that the reactivity of SmI_2 can be easily modulated by a judicious choice of different co-solvents or additives.[2c] In this regard, Fe(III) and Ni(II) salts are frequently used as additives in Sm(II)-mediated transformations.[30] With the aim of increasing the selectivity and efficiency of this reaction, we next investigated the reaction of *n*-octanal **1a** (1.0 equiv.), *N*-2-bromoethylphthalimide **2** (1.0 equiv.) and SmI_2 (2.0 equiv.) in the presence of different salts ($FeCl_3$, NaI and NiI_2) as additives (Table 1, entries 2-5).

Table 1. Screening of different additives for the samarium-promoted synthesis of **3a**.



Entry[a]	Additive	**3a**/**4a**[b]	Yield (%)[c]
1	-	1/3.7	15
2	$FeCl_3$ (5 mol%)	1/4	18
3	NaI (5 mol%)	1/1.2	37
4	NiI_2 (5 mol%)	6/1	75
5	NiI_2 (1 mol%)	6/1	76

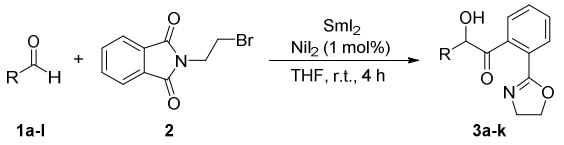
[a] All reactions were carried out with 1.0 equiv. of *n*-octanal, 1.0 equiv. of *N*-2-bromoethylphthalimide, 2.0 equiv. of SmI_2 and the corresponding additive. [b] **3a**/**4a** ratio was determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [c] Isolated yield of compound **3a** after column chromatography based on starting aldehyde **1a**.

Table 1 shows that the addition of $FeCl_3$ led to similar results to those obtained in the absence of any additive (Table 1, entry 2). The use of sodium iodide led to slightly improved results, affording an almost equimolar mixture of **3a** and diol **4a** from which the desired α-hydroxyketone **3a** was isolated in 37% yield (Table 1, entry 3). Finally, it was found that Ni(II) salts effectively promoted the reaction to afford α-hydroxyketone **3a** (Table 1, entries 4-5). The best results, with regard to both the yield and chemoselectivity, were obtained when SmI_2 (0.1 M in THF, 2.0 equiv.) and NiI_2 (1.0 mol%) were added to a solution of aldehyde **1a** (1.0 equiv.) and *N*-2-bromoethylphthalimide **2** (1.0 equiv.) in THF and the resulting mixture was stirred at r.t. for 4 h. Under these conditions, α-hydroxyketone **3a** was isolated in a 76% yield after flash column chromatography (Table 1, entry 5).

With the optimal conditions in hand, we tested the generality of this procedure for a variety of aldehydes in which the R group can be aliphatic (linear, cyclic and branched) **1a-e,** unsaturated **1f-g**, and aromatic **1h-l**. (Table 2). Thus, a mixture of the corresponding aldehyde **1a-l** (1.0 equiv.), *N*-2-bromoethylphthalimide **2** (1.0 equiv.), SmI_2 (0.1 M in THF, 2.0 equiv.) and NiI_2 (1.0 mol%) in THF were stirred at room temperature for 4 h. As shown in Table 2, when aliphatic aldehydes **1a-e** (Table 2, entries 1-5) were employed, α-aryl-α'-hydroxy ketones **3a-g** were isolated in good yields after flash column chromatography. No significant differences were observed when functionalized aldehydes **1f-g** were employed, with the desired compounds **3f-g** obtained in moderate to good yields. In contrast, aromatic aldehydes **1h-l** showed moderate or

low reactivity towards the reductive cross-coupling, which is in accordance with the reported facility of aromatic aldehydes to undergo SmI_2-mediated pinacol homocouplings.[31] Thus, benzaldehyde **1h** and other aromatic aldehydes substituted with electron-donating groups **1i** and **1j** afforded, in moderate yields, the desired α-hydroxy ketones **3h-j** (Table 2, entries 8-10). On the other hand, aldehydes containing electron-withdrawing groups **1k-l** afforded α-hydroxy ketone **3k** with very poor yield (Table 2, entry 11) or failed to give the desired cross-coupling compound **3l** (Table 2, entry 12). This behavior for aromatic aldehydes is also in accordance with results previously published in the literature. Thus, aromatic aldehydes bearing electron-withdrawing groups are generally known to facilitate formation of the pinacol homocoupling compound[32] resulting in lower yields of the cross-coupling adducts. It is noteworthy that this methodology would complement others previously reported by Yoda[10c] and Kise,[10h] in which the SmI_2-mediated pinacol-type cyclization of *N*-(γ-keto)phthalimides afforded α-hydroxylactams and/or 1,2-diols, respectively.

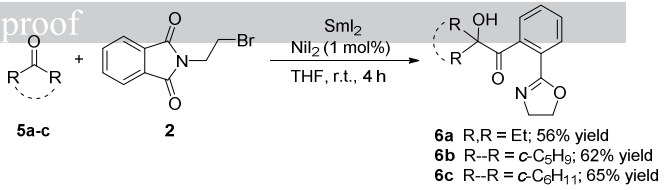
Table 2. Synthesis of α-aryl-α'-hydroxy ketones **3**.



Entry[a]	1	R	3	Yield (%)[b]
1	**1a**	*n*-C_7H_{15}	**3a**	76
2	**1b**	*n*-C_5H_{11}	**3b**	77
3	**1c**	*c*-C_6H_{11}	**3c**	71
4	**1d**	*i*-Pr	**3d**	69
5	**1e**	*s*-Bu	**3e**	65
6	**1f**	(*Z*)-EtCH=CH$(CH_2)_5$	**3f**	70
7	**1g**	(*E*)-PhCH=CH	**3g**	52
8	**1h**	Ph	**3h**	40
9	**1i**	*p*-MeC_6H_4	**3i**	48
10	**1j**	*p*-$MeOC_6H_4$	**3j**	55
11	**1k**	*p*-ClC_6H_4	**3k**	10
12	**1l**	*p*-$MeO_2CC_6H_4$	**3l**	*n.r.*

[a] All reactions were carried out with 1.0 equiv. of aldehyde, 1.0 equiv. of *N*-2-bromoethylphthalimide, 2.0 equiv. of SmI_2 and 1% mol of NiI_2. [b] Isolated yield of compounds **3** after flash column chromatography based on aldehydes **1**.

In order to increase the scope of this reaction, further studies were also carried out using ketones (3-pentanone **5a**, cyclopentanone **5b**, and cyclohexanone **5c**) as starting materials. Under the conditions reported above, ketones **5a-c** reacted with *N*-2-bromoethylphthalimide **2** to give the desired α-aryl-α'-hydroxy ketones **6a-c** in moderate yields (Scheme 1).

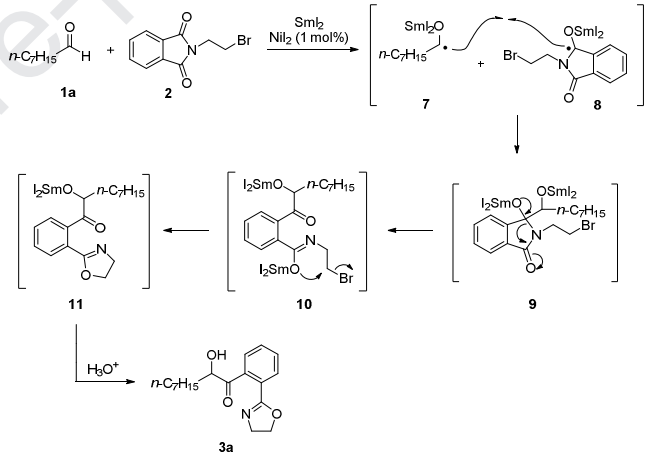


Scheme 1. SmI_2-promoted synthesis of ketone-derived α-aryl-α'-hydroxy ketones **6**.

In general terms, no significant differences were observed when this reaction was carried out using aldehydes **1** or ketones **5**.

α-Aryl-α'-hydroxy ketones **3** and **6** were fully characterized by ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), DEPT, HMBC and HSQC experiments, HRMS and other conventional techniques.

The formation of hydroxyl ketones **3** and **6** could be explained by assuming two SET reactions. Thus, after two samarium-promoted monoelectronic transferences to aldehyde **1a** and *N*-2-bromoethylphthalimide **2**, both samarium (III)-bound ketyl radical species **7** and **8** would be formed, respectively. Cross-coupling of both, ketyl radical **7** and imide-derived ketyl radical **8**, would afford intermediate **9** which then would give the dianionic species **10**. Intramolecular heterocyclization of **10**, followed by hydrolysis of the resulting intermediate **11**, would finally afford α-aryl-α'-hydroxy ketones **3** and **5** (Scheme 1).



Scheme 2. Proposed mechanism for the formation of **3a**.

3. Conclusion

In summary, we have herein disclosed the SmI_2-mediated carbonyl-imide reductive cross-coupling between *N*-2-bromoethylphthalimide and both aldehydes and ketones, in the presence of catalytic NiI_2, which provided an effective tool to prepare functionalized α-aryl-α'-hydroxy ketones under mild conditions. Taking into account the potential chemical and biological interest of α-hydroxy ketones, this procedure may eventually find application in the synthesis of bioactive products. Studies directed towards the synthesis of α-amino-α'-aryl ketones and other related compounds, including the asymmetric version, are currently under investigation in our laboratory.

4. Experimental Section

All reactions were conducted under dry nitrogen atmosphere. The glassware was oven dried (120 °C). THF was distilled from sodium/benzophenone ketyl immediately prior to use. All reagents were purchased in the highest quality available and were used without further purification. Flash column chromatography

was carried out on silica gel 230-400 mesh. Compounds were visualized on analytical thin layer chromatograms (TLC) by UV light (254 nm). ^{1}H NMR spectra were recorded at 300 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 75 MHz. Chemical shifts are given in ppm relative to tetramethylsilane (TMS), which is used as an internal standard, and coupling constants (*J*) are reported in Hz. High Resolution Mass Spectra (HRMS) were recorded using electrospray ionization in negative ion mode or TOF MS in positive ion mode.

*4.1. General procedure for the synthesis α-hydroxy ketones **3** and **6**:*

A 0.1 M solution of SmI_2 in THF (2.0 mmol, 2.0 equiv., 20 mL) was slowly added into a solution of the corresponding distilled aldehyde **1** or ketone **5** (1.0 mmol, 1.0 equiv.) and *N*-2-bromoethylphthalimide **2** (1.0 mmol, 1.0 equiv.) in dry THF (15 mL), followed by the addition of NiI_2 (1 mol%, 2.5 mg). The mixture was stirred at room temperature for 4 h. After that time, the mixture was hydrolysed with an aqueous solution of HCl 1.0 M (15 mL). The final product was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, filtered, dried over Na_2SO_4 and concentrated under reduced pressure. α-Hydroxy ketones **3** and **6** were purified by flash column chromatography (hexane/EtOAc ranging between 3/1 and 5/1).

*4.1.1. 1-[2-(4,5-Dihydrooxazol-2-yl)phenyl]-1-hydroxynonan-2-one **3a***: 0.23 g, 76%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89-7.85 (m, 1 H), 7.60-7.43 (m, 3 H), 5.57-5.55 (m, 1 H), 4.51 (dt, *J* = 11.2, 5.6 Hz, 1 H), 3.70-3.61 (m, 1 H), 3.58-3.51 (m, 1 H), 3.44-3.35 (m, 1 H), 2.38-2.17 (m, 2 H), 1.51-1.41 (m, 2 H), 1.27-1.02 (m, 8 H), 0.81 (t, *J* = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.6 (C), 169.0 (C), 138.8 (C), 132.3 (CH), 131.3 (C), 129.3 (CH), 124.3 (CH), 122.4 (CH), 70.5 (CH), 43.9 (CH_2), 33.2 (CH_2), 31.4 (CH_2), 29.3 (CH_2), 28.7 (2 x CH_2), 23.1 (CH_2), 22.4 (CH_2), 13.9 (CH_3). MS (ESI-TOF, *m/z*, %): 302 ([M-H]$^-$, 20), 286 (100), 240 (4). HRMS (ESI$^-$): calcd. for $C_{18}H_{24}NO_3$ [M-H]$^-$ 302.1750, found 302.1748; R_f = 0.38 (hexane/EtOAc 3:1).

*4.1.2. 1-[2-(4,5-Dihydrooxazol-2-yl)phenyl]-1-hydroxyheptan-2-one **3b**:* 0.21 g, 77%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87-7.84 (m, 1 H), 7.58-7.42 (m, 3 H), 5.35-5.33 (m, 1 H), 4.49 (dt, *J* = 14.6, 5.6 Hz, 1 H), 3.68-3.60 (m, 1 H), 3.57-3.50 (m, 1 H), 3.43-3.34 (m, 1 H), 2.34-2.16 (m, 2 H), 1.50-1.40 (m, 2 H), 1.21-0.99 (m, 4 H), 0.80 (t, *J* = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5 (C), 169.0 (C), 138.8 (C), 132.2 (CH), 131.3 (C), 129.2 (CH), 124.2 (CH), 122.4 (CH), 70.5 (CH), 43.8 (CH_2), 37.2 (CH_2), 30.8 (CH_2), 29.3 (CH_2), 22.8 (CH_2), 22.1 (CH_2), 13.6 (CH_3). MS (ESI-TOF, *m/z*, %): 274 ([M-H]$^-$, 35), 258 (100), 205 (2). HRMS (ESI$^-$): calcd. for $C_{16}H_{20}NO_3$ [M-H]$^-$ 274.1443, found 274.1439; R_f = 0.34 (hexane/EtOAc 3:1).

*4.1.3. 1-Cyclohexyl-2-[2-(4,5-dihydrooxazol-2-yl)phenyl]-2-hydroxyethanone **3c**:* 0.20 g, 71%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91-7.88 (m, 1 H), 7.61-7.46 (m, 3 H), 5.54-5.53 (m, 1 H), 4.54 (dt, *J* = 14.8, 5.4 Hz, 1 H), 3.73-3.65 (m, 1 H), 3.59-3.52 (m, 1 H), 3.38-3.28 (m, 1 H), 2.62-2.52 (m, 1 H), 1.80-1.42 (m, 6 H), 1.29-1.09 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.7 (C), 169.0 (C), 138.8 (C), 132.1 (CH), 131.4 (C), 129.2 (CH), 124.3 (CH), 122.2 (CH), 69.7 (CH), 46.8 (CH_2), 44.0 (CH), 30.0 (CH_2), 29.7 (CH_2), 27.5 (CH_2) 25.5 (CH_2), 25.3 (CH_2), 24.8 (CH_2). MS (ESI-TOF, *m/z*, %): 286 ([M-H]$^-$, 100), 270 (9). HRMS (ESI$^-$): calcd. for $C_{17}H_{20}NO_3$ [M-H]$^-$ 286.1437, found 286.1436; R_f = 0.38 (hexane/EtOAc 3:1).

*4.1.4. 1-[2-(4,5-Dihydrooxazol-2-yl)phenyl]-1-hydroxy-3-methylbutan-2-one **3d**:* 0.17 g, 69%. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92-7.88 (m, 1 H), 7.60-7.46 (m, 3 H), 5.57-5.55 (m, 1 H), 4.56 (dt, *J* = 14.8, 5.3 Hz, 1 H), 3.74-3.66 (m, 1 H), 3.60-3.53 (m, 1 H), 3.38-3.29 (m, 1 H), 2.92-2.79 (m, 1 H), 1.07 (d, *J* = 6.6 Hz, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.9 (C), 169.1 (C), 139.0 (C), 132.2 (CH), 131.5 (C), 129.3 (CH), 124.4 (CH), 122.2 (CH), 69.8 (CH), 44.1 (CH_2), 36.7 (CH_2), 29.8 (CH), 19.3 (CH_3), 17.8 (CH_3). MS (ESI-TOF, *m/z*, %): 246 ([M-H]$^-$, 100), 230 (18). HRMS (ESI$^-$): calcd. for $C_{14}H_{16}NO_3$ [M-H]$^-$ 246.1124, found 246.1119; R_f = 0.28 (hexane/EtOAc 3:1).

*4.1.5. 1-[2-(4,5-Dihydrooxazol-2-yl)phenyl]-1-hydroxy-3-methylpentan-2-one **3e**:* 0.17 g, 65%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91-7.85 (m, 2 H), 7.61-7.45 (m, 6 H), 5.58 (s, 1 H), 5.56 (s, 1 H), 4.55 (dt, *J* = 14.8, 5.4 Hz, 2 H), 3.75-3.67 (m, 2 H), 3.60-3.53 (m, 2 H), 3.41-3.27 (m, 2 H), 2.80-2.64 (m, 2 H), 1.77 (s, 2 H), 1.75-1.42 (m, 2 H), 1.45-1.22 (m, 2 H), 1.05 (d, *J* = 6.7 Hz, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H), 0.82 (t, *J* = 7.4 Hz, 3 H), 0.77 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4 (2 x C), 169.1 (2 x C), 138.9 (C), 138.7 (C), 132.2 (CH), 132.1 (CH), 131.6 (2 x C), 129.3 (2 x CH), 124.5 (2 x CH), 122.4 (CH), 122.3 (CH), 70.5 (CH), 70.0 (CH), 44.5 (CH), 44.3 (CH), 44.2 (CH_2), 43.5 (CH_2), 30.1 (CH_2), 29.9 (CH_2), 26.9 (CH_2), 25.1 (CH_2), 17.6 (CH_3), 15.4 (CH_3), 11.9 (CH_3), 11.3 (CH_3). MS (ESI-TOF, *m/z*, %): 260 ([M-H]$^-$, 100), 244 (22). HRMS (ESI$^-$): calcd. for $C_{15}H_{18}NO_3$ [M-H]$^-$ 260.1287, found 260.1284; R_f = 0.31 (hexane/EtOAc 3:1).

*4.1.6. (Z)-1-[2-(4,5-Dihydrooxazol-2-yl)phenyl]-2 hydroxyundec-8-en-1-one **3f**:* 0.24 g, 70%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.45 (m, 4 H), 5.38-5.18 (m, 3 H), 4.62-4.45 (m, 1 H), 3.97-3.71 (m, 1 H), 3.64-3.41 (m, 2 H), 2.38-2.15 (m, 2 H), 2.04-1.94 (m, 4 H), 1.51-1.18 (m, 6 H), 0.81 (t, *J* = 7.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5 (C), 168.9 (C), 138.92 (C), 133.1 (CH), 132.1 (CH), 131.4 (C), 129.4 (CH), 124.4 (CH), 122.6 (CH), 91.9 (CH), 70.4 (CH_2), 42.1 (CH_2), 37.3 (CH_2), 30.5 (CH_2), 29.5 (CH_2), 27.3 (CH_2), 25.0 (CH_2), 20.9 (CH_2), 14.8 (CH_3). HRMS (ESI+): calcd. for $C_{20}H_{28}NO_3$ [M+H]$^+$ 330.2069, found 330.2066; R_f = 0.36 (hexane/EtOAc 3:1).

*4.1.7. (E)-1-[2-(4,5-Dihydrooxazol-2-yl)phenyl]-2-hydroxy-4-phenylbut-3-en-1-one **3g**:* 0.16 g, 52%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02-7.21 (m, 10 H), 6.41-6.34 (m, 1 H), 5.63-5.62 (m, 1 H), 4.17-3.93 (m, 1 H), 3.75-3.41 (m, 2 H), 3.33-3.29 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.3 (C), 169.5 (C), 149.1 (CH), 143.9 (C), 133.8 (C), 133.0 (CH), 131.9 (CH), 131.2 (CH), 129.5 (2 x CH), 129.2 (2 x CH), 124.6 (CH), 123.0 (CH), 116.3 (CH), 91.5 (C), 69.2 (CH), 42.5 (CH_2), 28.2 (CH_2). HRMS (TOF MS ES+): calcd. for $C_{19}H_{18}NO_3$ [M+H]$^+$ 308.1287, found 308.1287; R_f = 0.34 (hexane/EtOAc 3:1).

*4.1.8. 1-[2-(4,5-Dihydrooxazol-2-yl)phenyl]-2-hydroxy-2-phenylethanone **3h**:* 0.11 g, 40%. Yellow oil. Data for the major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68-6.92 (m, 9 H), 5.30 (s, 1 H), 4.30-3.99 (m, 2 H), 3.88-3.63 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.6 (C), 169.5 (C), 137.5 (C), 139.8 (C), 134.9 (C), 132.4 (CH), 129.9 (CH), 129.7 (2 x CH) 129.4 (2 x CH), 124.9 (CH), 123.9 (CH), 123.1 (CH), 67.0 (CH), 44.3 (CH_2), 32.1 (CH_2). HRMS (TOF MS ES+): calcd. for $C_{17}H_{16}NO_3$ [M+H]$^+$ 282.1130, found 282.1127; R_f = 0.30 (hexane/EtOAc 3:1).

*4.1.9. 1-[2-(4,5-Dihydrooxazol-2-yl)phenyl]-2-hydroxy-2-(p-tolyl)ethanone **3i**:* 0.14 g, 48%. Yellow oil. Data for the major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10-7.84 (m, 3 H), 7.62-7.03 (m, 5 H), 6.51 (s, 1 H), 4.63-4.41 (m, 1 H), 3.81-3.61 (m, 1 H), 3.66-3.31 (m, 2 H), 2.49 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.7 (C), 169.2 (C), 143.9 (C), 140.1 (C), 133.4 (C), 132.3 (C), 131.9 (CH) 130.4 (2 x CH), 129.5 (2 x CH), 124.6 (CH), 123.0 (CH), 122.3 (CH), 66.8 (CH), 44.1

(CH_2), 31.0 (CH_2), 21.3 (CH_3). HRMS (ESI$^-$): calcd. for $C_{18}H_{16}NO_3$ $[M-H]^-$ 294.1130, found 294.1129; R_f = 0.28 (hexane/EtOAc 3:1).

4.1.10. 1-[2-(4,5-Dihydrooxazol-2-yl)phenyl]-2-hydroxy-2-(4-methoxyphenyl)ethanone ***3j****:* 0.17 g, 55%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.1 Hz, 2 H), 7.92 (d, *J* = 7.0 Hz, 1 H), 7.48 (q, *J* = 7.7 Hz, 2 H), 7.31-7.19 (m, 1 H), 7.06 (d, *J* = 9.3 Hz, 2 H), 6.46 (s, 1 H), 4.64-4.41 (m, 1 H), 3.95 (s, 3 H), 3.82-3.71 (m, 2 H), 3.65-3.45 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.8 (C), 169.7 (C), 165.0 (C), 140.3 (C), 132.3 (CH), 131.8 (2 x CH), 129.5 (CH) 128.7 (C), 124.8 (CH), 123.0 (CH), 114.9 (2 x CH), 66.7 (CH), 56.1 (CH_3) 44.3 (CH_2), 31.0 (CH_2). HRMS (TOF MS ES+): calcd. for $C_{18}H_{18}NO_4$ $[M+H]^+$ 312.1236, found 312.1234; R_f = 0.25 (hexane/EtOAc 3:1).

4.1.11. 2-(4-Chlorophenyl)-1-[2-(4,5-Dihydrooxazol-2-yl)phenyl]-2-hydroxyethanone ***3k****:* 0.03 g, 10%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99-7.90 (m, 2 H), 7.57 (dd, *J* = 8.7 Hz, 2.3 Hz, 2 H), 7.53-7.43 (m, 2 H), 7.35-7.28 (m, 1 H), 7.21-7.14 (m, 1 H), 6.43 (s, 1 H), 4.74-4.41 (m, 1 H), 3.80-3.34 (m, 3 H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.6 (C), 169.5 (C), 141.6 (C), 139.4 (C), 134.2 (C), 134.0 (C), 132.5 (CH), 130.7 (2 x CH) 130.1 (2 x CH), 129.8 (CH), 125.0 (CH), 123.0 (CH), 67.1 (CH), 44.5 (CH_2), 31.2 (CH_2). R_f = 0.28 (hexane/EtOAc 3:1). HRMS (TOF MS ES+): calcd. for $C_{17}H_{15}ClNO_3$ $[M+H]^+$ 316.0740, found 316.0737; R_f = 0.25 (hexane/EtOAc 3:1).

4.1.12. [2-(4,5-Dihydrooxazol-2-yl)phenyl]-2-ethyl-2-hydroxybutan-1-one ***6a***. 0.15 g, 56%. Yellow oil. Data for the major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.69 (m, 2 H), 7.58-7.56 (m, 2 H), 4.27-4.20 (m, 1 H), 4.17-4.09 (m, 1 H), 3.91-3.82 (m, 1 H), 3.56-3.44 (m, 1 H), 1.64-1.25 (m, 4 H), 1.23 (t, 3 H, *J* = 7.2 Hz), 0.85 (t, 3 H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.6 (C), 147.4 (C), 133.4 (CH), 133.1 (C), 130.3 (CH), 124.7 (CH), 124.5 (CH) 104.9 (C), 78.3 (C), 70.4 (CH_2), 46.1 (CH_2), 39.1 (CH_2), 21.3 (CH_3), 16.7 (CH_2), 15.1 (CH_3). HRMS (TOF MS ES+): calcd. for $C_{15}H_{19}NNaO_3$ $[M+Na]^+$ 284.1257, found 284.1257; R_f = 0.40 (hexane/EtOAc 1:1).

4.1.13. [2-(4,5-Dihydrooxazol-2-yl)phenyl](1-hydroxycyclopentyl)methanone ***6b***. 0.16 g, 62%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88-7.85 (m, 1 H), 7.78-7.75 (m, 1 H), 7.62-7.49 (m, 2 H), 4.28-4.19 (m, 2 H), 4.00-3.91 (m, 1 H), 3.57-3.47 (m, 1 H), 1.89-1.52 (m, 4 H), 1.34-1.27 (m, 2 H), 0.96-0.91 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.6 (C), 147.3 (C), 133.2 (CH), 132.2 (C), 129.9 (CH), 124.6 (CH), 123.9 (CH) 102.8 (C), 77.2 (C), 69.5 (CH_2), 45.6 (CH_2), 36.6 (CH_2), 35.2 (CH_2), 23.8 (CH_2), 23.2 (CH_2). HRMS (TOF MS ES+): calcd.for $C_{15}H_{18}NO_3$ $[M+H]^+$ 260.1281, found 260.1281; R_f = 0.28 (hexane/EtOAc 3:1).

4.1.14. [2-(4,5-Dihydrooxazol-2-yl)phenyl]-1-hydroxycyclohexyl)methanone ***6c***. 0.18 g, 65%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, 1 H, *J* = 7.5 Hz), 7.76 (d, 1 H, *J* = 7.4 Hz), 7.58 (td, 1 H, *J* = 7.5, 1.4 Hz), 7.50 (td, 1 H, *J* = 7.4, 1.2 Hz), 4.25-4.14 (m, 2 H), 3.88 (ddd, 1 H, *J* = 11.2, 8.0, 6.8 Hz), 3.50 (ddd, 1 H, *J* = 11.2, 9.9, 7.2 Hz), 1.86-1.81 (m, 1 H), 1.68-1.44 (m, 5 H), 1.38-1.22 (m, 3 H), 1.13-1.04 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5 (C), 147.0 (C), 133.0 (CH), 132.4 (C), 129.8 (CH), 124.9 (CH), 124.0 (CH) 104.2 (C), 76.7 (C), 69.6 (CH_2), 46.0 (CH_2), 32.6 (CH_2), 31.0 (CH_2), 25.5 (CH_2), 21.2 (CH_2), 21.0 (CH_2). HRMS (TOF MS ES+): calcd. for $C_{16}H_{20}NO_3$ $[M+H]^+$ 284.1438, found 274.1433; R_f = 0.25 (hexane/EtOAc 3:1).

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: