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Palladium-Catalyzed Desulfitative Oxidative Coupling between Arenesulfinic Acid Salts and Allylic Alcohols: A Strategy for the Selective Construction of β-Aryl Ketones and Aldehydes

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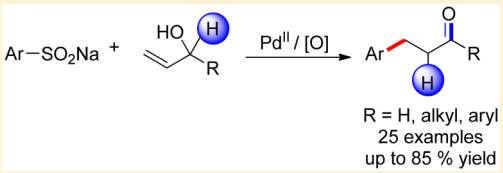
Supporting Information

ABSTRACT: An efficient palladium-catalyzed desulfitative oxidative coupling of sodium arylsulfinites for highly region-selective Heck-type reaction of allylic alcohols has been developed. The compatibility of the functionalities of −I, −Br, and −F would explore further postfunctionalization of the C−X bonds. This method provides a new and straightforward protocol for the synthesis of β-aryl ketones and aldehydes. The deuterium labeling experiments indicated that this transformation may proceed via a [1, 2-H] shift process.



The β-aryl carbonyl compounds have drawn much attention owing to the prevalence of the fundamental building blocks in pharmaceuticals and biologically active natural products.[1] Particularly, large numbers of β-aryl ketones have been recently discovered to have remarkable bioactivities, such as propafenone (**a**), neohesperidin dihydrochalcone (**b**), and nabumetone (**c**) (Figure 1).[2]

Due to their importance, various methods have been developed to construct the β-aryl carbonyl frameworks. Notably, in last decades, the traditional synthetic routes for β-aryl carbonyl by the redox isomerization of allylic alcohols with rhodium, ruthenium, palladium, iron-catalysts have been reported.[3] Among the reported oxidations, monodentated nitrogenous ligands in combination with $Pd(OAc)_2$ have been successfully employed to provide active catalyst mixtures.[3m−p] However, most of these oxidations suffer from relatively high catalyst loadings, high oxygen pressures, and an excess of ligand or base, which is still an imposing challenge for chemists. The Pd^{II}-catalyzed oxidation of alcohols using molecular oxygen as the terminal oxidant is potentially a powerful protocol with a single N-heterocyclic carbene (NHC) ligand.[3q] Besides, the use of Pd-catalyzed oxidative coupling of allyl alcohols with arenes in the regioselective synthesis of β-aryl ketones and aldehydes would constitute an efficient and straightforward approach.[4] In 1968, Heck reported the first example of the formation of arylated ketones with the reaction of allylic alcohols and organopalladium compounds.[5] Subsequently, various Pd-catalyzed Heck reaction systems using aryl halide reagents were developed (Scheme 1, eq 1).[6] On the other hand, the arylboron reagents have emerged in the past few years as alternative arylation sources due to their good functional group tolerance, commercial availability, and good reactivity (Scheme 1, eq 2).[7] Recently, our group also developed a facile Pd-catalyzed aerobic oxidative coupling of allylic alcohols with (hetero) aryl nucleophiles (aromatic carboxylic acids via decarboxylation and arylsulfonolydrazide via extrusion of SO_2) (Scheme 1, eq 2).[8]

Previously, it was known that sulfinic acid salts (or acids) could widely act as sulfonylation[9] and trifluoromethylation reagents,[10] owing to their highly stability and commercial availability. Besides, the arenesulfinite salts have a great potential to serve as ideal aryl sources for C−C bond formation via extrusion of SO_2 since they are cheap, stable, easy to handle, and easily prepared from their corresponding sulfonyl chlorides.[11] Therefore, they have been attracted considerable interest from organic chemists in pursuing synthetic efficiency. Recently, the use of various aromatic sulfinic salts as the arene sources promises an applicable and efficient protocol, such as the desulfitative Heck-type reactions,[12] homocoupling reactions,[13] addition reactions,[14] and cross-coupling reactions.[15] Our group has also realized the synthesis of β-ketosulfones,[16] sulphonamides,[17] vinyl sulfones,[18] and unsymmetrical internal alkynes[19] (via desulfitative arylation) with sodium arylsulfinates. As our continuous interest in sodium sulfinates as substrates and based on our previous work with allylic alcohols,[8,20] we wish to describe a concise and efficient desulfitative oxidative coupling reaction for synthesis of β-aryl ketones and aldehydes. Herein, we report a Pd-catalyzed desulfitative synthesis of β-aryl ketones and aldehydes from sodium aryl sulfinate and allylic alcohols (Scheme 1, eq 3). To the best of our knowledge, it is the first example to realize the highly regioselective Heck-type reaction of allylic alcohols using sodium aryl sulfinates as aryl sources for the construction of β-aryl ketones and aldehydes.

We initially studied our investigation by using sodium benzenesulfinate (**1a**) with oct-1-en-3-ol (**2a**) as the substrates in the presence of 10 mol % of $Pd(OAc)_2$ and 20 mol % of

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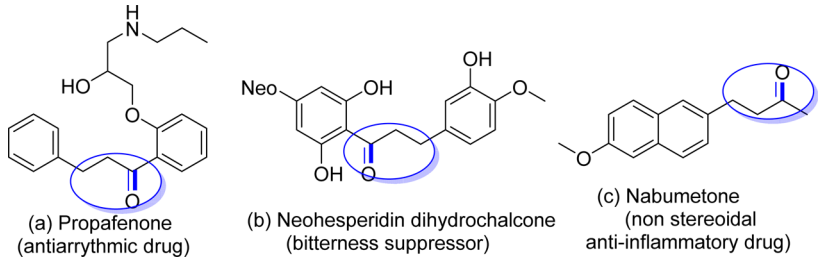
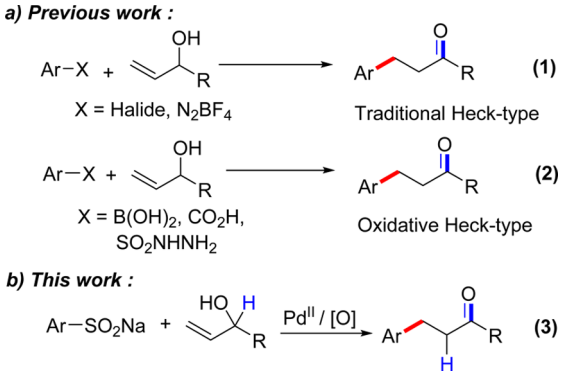


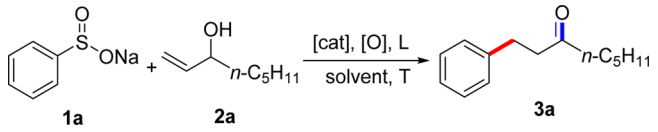
Figure 1. Structures of pharmaceutical importance encoded with β-aryl carbonyl skeleton.

Scheme 1. Reported Methods for the Synthesis of β-Aryl Ketones



1,10-phenanthroline under O_2 atmosphere in a dioxane solvent system. Not surprisingly, the yield of the desired product **3a** was only 25% (Table 1, entry 1). To improve the yield of **3a**, we screened various parameters including catalyst, ligand, oxidant, and solvent. Compared with $PdCl_2$ and $Pd_2(dba)_3$, the use of $Pd(TFA)_2$ as catalyst gave a little further increase in the yield of product for the reaction (Table 1, entries 2−4). Further investigation of the oxidants led to the discovery that $Cu(TFA)_2{\cdot}xH_2O$ was the best oxidant for this reaction (Table 1, entries 5−8). Then we explored the influence of several ligands which were routinely used in Pd-catalyzed oxidative Heck-type transformations. Fortunately, the use of the ligand of 4,7-dimethyl-1,10-phenanthroline, a bidentate nitrogenous ligand, gave a moderate yield (Table 1, entries 9−12). Meanwhile, various solvents were also tested (Table 1, entries 13−15). To our delight, the polar solvent of dioxane was

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	ligand	oxidant	solvent	yield[b] (%)
1	$Pd(OAc)_2$	Phen[c]	O_2	dioxane	25
2	$PdCl_2$	Phen	O_2	dioxane	20
3	$Pd_2(dba)_3$	Phen	O_2	dioxane	22
4	$Pd(TFA)_2$	Phen	O_2	dioxane	30
5	$Pd(TFA)_2$	Phen	Ag_2CO_3	dioxane	trace
6	$Pd(TFA)_2$	Phen	$Cu(OAc)_2{\cdot}xH_2O$	dioxane	n.d.
7	$Pd(TFA)_2$	Phen	BQ	dioxane	n.d.
8	$Pd(TFA)_2$	Phen	$Cu(TFA)_2{\cdot}xH_2O$	dioxane	60
9	$Pd(TFA)_2$	Bpy[d]	$Cu(TFA)_2{\cdot}xH_2O$	dioxane	30
10	$Pd(TFA)_2$	PPh_3	$Cu(TFA)_2{\cdot}xH_2O$	dioxane	10
11	$Pd(TFA)_2$	DPEPhos[e]	$Cu(TFA)_2{\cdot}xH_2O$	dioxane	45
12	**$Pd(TFA)_2$**	**Bphen[f]**	**$Cu(TFA)_2{\cdot}xH_2O$**	**dioxane**	**85**
13	$Pd(TFA)_2$	Bphen	$Cu(TFA)_2{\cdot}xH_2O$	PhMe	26
14	$Pd(TFA)_2$	Bphen	$Cu(TFA)_2{\cdot}xH_2O$	CH_3CN	32
15	$Pd(TFA)_2$	Bphen	$Cu(TFA)_2{\cdot}xH_2O$	DMSO	30
16	–	Bphen	$Cu(TFA)_2{\cdot}xH_2O$	dioxane	n.d.
17	$Pd(TFA)_2$	–	$Cu(TFA)_2{\cdot}xH_2O$	dioxane	66
18	$ZnCl_2$[g]	Bphen	$Cu(TFA)_2{\cdot}xH_2O$	dioxane	n.d.
19	$AlCl_3$[g]	Bphen	$Cu(TFA)_2{\cdot}xH_2O$	dioxane	n.d.
20[h]	$Pd(TFA)_2$	Bphen	$Cu(TFA)_2{\cdot}xH_2O$	dioxane	57
21[i]	$Pd(TFA)_2$	Bphen	$Cu(TFA)_2{\cdot}xH_2O$	dioxane	49
22[j]	$Pd(TFA)_2$	Bphen	$Cu(TFA)_2{\cdot}xH_2O$	dioxane	51
23[k]	$Pd(TFA)_2$	Bphen	$Cu(TFA)_2{\cdot}xH_2O$	dioxane	46

[a]Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (1.2 mmol), **2a** (1.0 mmol), [Pd] (10 mol %), **L** (20 mol %), [O] (0.5 equiv), O_2 (1 atm), solvent (3 mL), 100 °C, 20 h. [b]Yield based on **2a**. [c]Phen = 1,10-phenanthroline. [d]Bpy = 2,2′-Bpyridyl. [e]DPEPhos = Bis[(2-diphenylphosphinophenyl)] ether. [f]Bphen = 4,7-dimethyl-1,10-phenanthroline. [g]Lewis acid (1 equiv). [h]Adding 0.5 equiv of $ZnCl_2$. [i]Adding 0.5 equiv of $AlCl_3$. [j]Adding 0.5 equiv of $FeCl_3$. [k]Adding 0.5 equiv of TFA.

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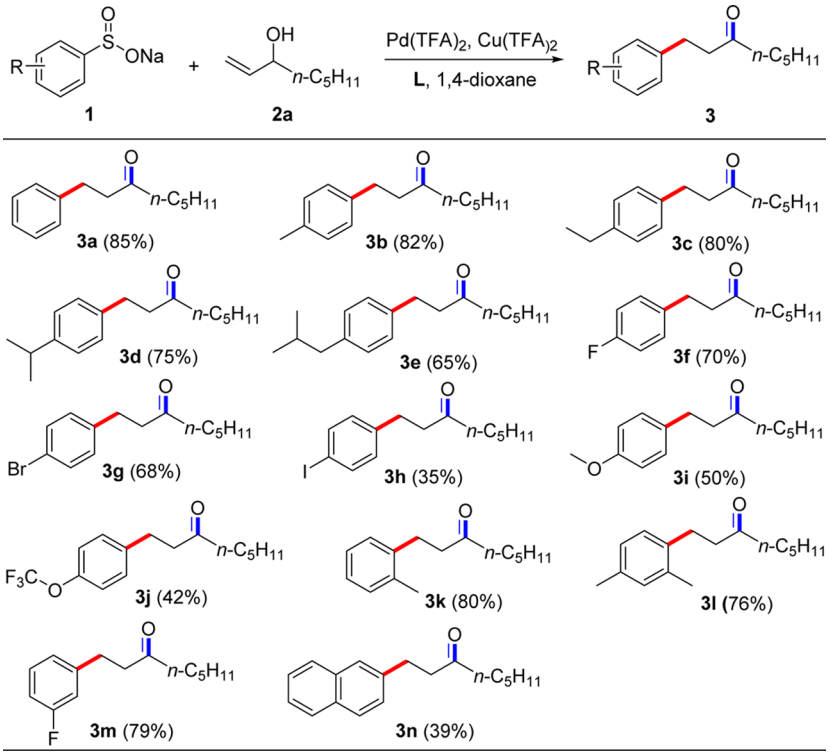
Table 2. Scope of Sodium Arylsulfinates[a,b]



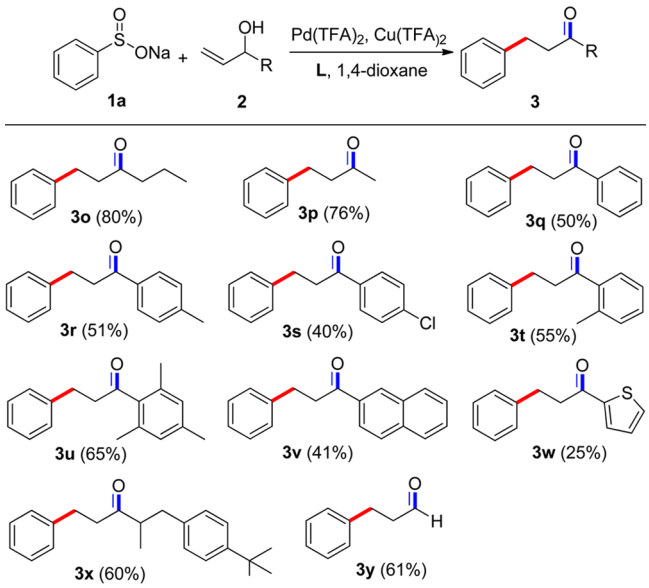
[a]Reaction conditions: **1** (1.2 mmol), **2a** (1.0 mmol), $Pd(TFA)_2$ (10 mol %), **L** (4,7-dimethyl-1,10-phen) (20 mol %), $Cu(TFA)_2{\cdot}xH_2O$ (0.5 mmol), dioxane (3 mL), 100 °C, 20 h. [b]Yield based on **2a**.

proved to be optimal (85%). Additionally, control experiments were explored that the transformation failed to afford the desired product **3a** without palladium catalyst (Table 1, entry 16). The importance of ligand control was realized through the reduced productivity in the absence of the Bmphen ligand using the optimized conditions (Table 1, entry 17). And no desired product was detected in the presence of Lewis acids ($ZnCl_2$, $AlCl_3$) (Table 1, entries 18−19). Besides, the reduced yields were detected by adding 0.5 equiv of LAs (Table 1, entries 20−23).

Having established the optimal reaction conditions (Table 1, entry 12), we next explored the reactivities of different sodium aryl sulfinates. A series of *para*-substituted sodium aryl sulfinates were found to be suitable substrates, and the corresponding products were formed in good to excellent yields (Table 2, **3a−e**). Importantly, sodium aryl sulfinates substituted with halogens, such as F, Br, I, were transformed to the desired *β*-aryl ketones in 35−70% yields (Table 2, **3f−h**). Compared to the −F, −Br substituted sodium aryl sulfonates, the higher activity of C−I bond was found to be less compatible with the formation of a Heck-type product as the side product. The presence of both strongly electron-donating methoxy group and electron-withdrawing functional groups was also tolerated (Table 2, **3i, j**). This oxidative Pd (II)-catalyzed oxidative Heck-type protocol was also applied to *ortho*- and *meta*-substituted sodium aryl sulfinates substrates. The desired products were efficiently obtained in good yields (Table 2, **3k−m**). Sodium naphthalene-2-sulfinate (**1n**) was compatible with the transformation and afforded the corresponding product in moderate yield (Table 2, **3n**). However, the heteroarylsulfinates, such as furan and thiophene, failed to finish the corresponding *β*-heteroarene ketone products.

To further demonstrate the generality of this protocol, we explored the scope of allylic alcohols for *β*-aryl ketone and aldehyde synthesis (Table 3). Good yields of products were obtained from the alkyl substituents at the allylic position (Table 3, **3o, p**). The phenyl substituted allyl alcohols with electron-donating groups in the 2-, 4-, and 6-positions and

Table 3. Scope of Allyl Alcohols[a,b]



[a]Reaction conditions: **1** (1.2 mmol), **2a** (1.0 mmol), $Pd(TFA)_2$ (10 mol %), **L** (4,7-dimethyl-1,10-phen) (20 mol %), $Cu(TFA)_2{\cdot}xH_2O$ (0.5 mmol), dioxane (3 mL), 100 °C, 20 h. [b]Yield based on **2a**.

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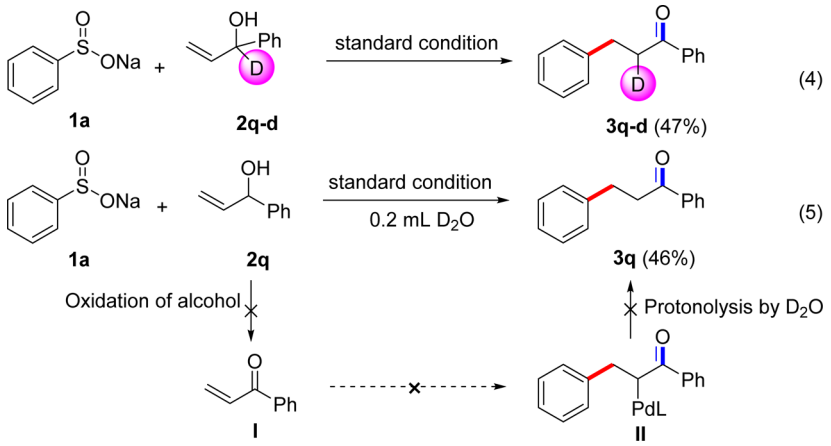
Scheme 2. Mechanistic Studies

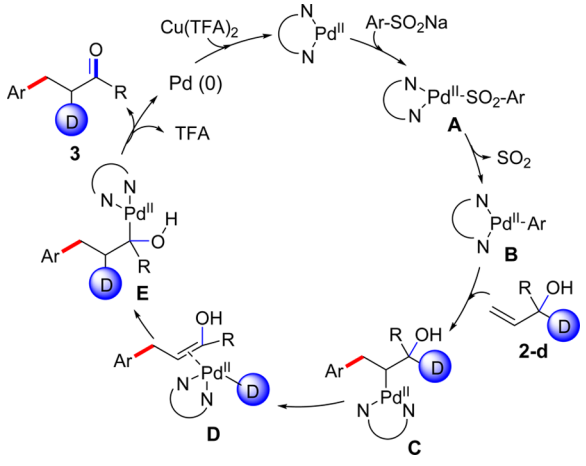


halide functional group were tolerated in this transformation (Table 3, **3q–v**). To our delight, the oxidative Heck-type reaction of heteroarenes, such as thiophene, afforded the corresponding product (Table 3, **3w**). In addition, the substrate of 5-(4-(*tert*-butyl) phenyl)-4-methylpent-1-en-3-ol (**2x**) obtained from the natural product of Lily aldehyde could give a 60% yield of product (Table 3, **3x**). The simple allyl alcohol with a primary hydroxyl group also worked well to finish the C–C bond transformation (Table 3, **3y**).

To gain further insight into this process, the deuterium-labeled (**2q–d**) experiments were further performed. Sodium benzenesulfinate (**1a**) was reacted with [D]-1-phenylprop-2-en-1-ol under the standard reaction conditions (Scheme 2, eq 4). It was found that 47% of the deuterium of **2q** was incorporated into **3q–d** with α-[D]-β-aryl ketone product exclusively. The isotopically unmodified product (**3q–d**) could not be detected when 0.2 mL deuterated water was added to the standard protocol (Scheme 2, eq 5), which indicated that a [1, 2-H] shift should be involved in this process.

On the basis of the above results and previous reports,[7a,8] we propose that the current reaction proceeds through a Pd (II)-catalyzed oxidative Heck-type reaction between arenes and allylic alcohols through selective β–H elimination (Scheme 3). The arylpalladium complex **B** is first generated from the intermediate **A** by coordination of the aromatic sulfinic sodium salt to palladium(II) with the extrusion of SO_2. Subsequently, the allylic alcohol is inserted to the arylpalladium complex to afford the σ-allkylpalladium complex **C**. The selective β-H elimination of **D** occurred as well as the spontaneous insertion into the enol to afford the σ-allkylpalladium complex **E** with the transfer of deuterium to the α-carbon. Elimination of **E** from the α-OH groups affords the desired product **3**. However, an anion-mediated reductive elimination cannot be overlooked for this transformation. Finally, palladium(II) active species are oxidized by $Cu(TFA)_2{\cdot}xH_2O$, thereby initiating the new catalytic cycle.

Scheme 3. Proposed Mechanism



In summary, we have presented a practical Pd-catalyzed oxidative coupling reaction of allylic alcohols to construct β-aryl ketones and aldehydes using the commercially readily sodium sulfinites as aryl reagents. This work occurs with excellent regioselectivity by the selective β-hydride elimination. Such a new and straightforward protocol, which utilizes cheap aryl reagents, provides a practical and efficient approach to synthesize various β-aryl ketones and aldehydes. It would extend the potential applications of β-aryl-containing ketones and aldehydes in pharmaceutical and synthetic chemistry.

EXPERIMENTAL SECTION

General Information. Melting points were measured with a melting point instrument and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a 400/600 MHz NMR spectrometer. The chemical shifts are referenced to signals at 7.24 and 77.0 ppm, respectively, and $CDCl_3$ is solvent with TMS as the internal standard. IR spectra were obtained either as potassium bromide pellets or as liquid films between two potassium bromide pellets with a spectrometer. GC-MS was obtained using electron ionization. HRMS was obtained with a LCMS-IT-TOF mass spectrometer. TLC was performed by using commercially prepared 100–400 mesh silica gel plates, and visualization was effected at 254 nm. Starting materials were prepared according to previously reported methods [1-phenylprop-2-en-1-ol,[21] 1-*p*-tolylprop-2-en-1-ol,[21] 1-(naphthalen-2-yl)-prop-2-en-1-ol,[21] 1-(4-chlorophenyl)prop-2-en-1-ol,[21] 1- mesitylprop-2-en-1-ol,[22] 1-(*o*-tolyl)prop-2-en-1-ol,[23] 1-(thiophen-2-yl)prop-2-en-1-ol.[24] Oct-1-en-3-ol, hex-1-en-3-ol, but-3-en-2-ol, and prop-2-en-1-ol were commercially available. Except for **2x**, all the starting allylic alcohols are already known in the literature. 5-(4-(*tert*-Butyl)phenyl)-4-methylpent-1-en-3-ol (**2x**) was prepared as following the literature procedure.[23] Vinylmagnesium bromide (1 equiv, 1 M in THF) was added slowly to a stirred solution of freshly distilled 3-(4-(*tert*-butyl)phenyl)-2-methylpropanal (1 equiv) in dry THF (0.2 M) maintaining an internal temperature below 5 °C. After 15 min, the reaction was allowed to warm to room temperature and stirred for an additional 1–3 h. The reaction was quenched by addition of saturated NH_4Cl solution and extracted with Et_2O. The combined organic

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extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvent removed in vacuum to give the crude product.

General Procedure for Reactions of Allylic Alcohols with Aryl Sodium Sulfinites. In a sealed test tube, a mixture of sodium sulfinate **1** (1.2 mmol), allylic alcohol **2** (1 mmol), $Pd(TFA)_2$ (33.2 mg, 0.1 mmol), $Cu(TFA)_2{\cdot}xH_2O$ (145 mg, 0.5 mmol), and 3 mL of dioxane was vigorously stirred together at 100 °C for 20 h. After completion of the reaction, the mixture was extracted with ethyl acetate (3 × 10 mL). The combined ethyl acetate layer was then dried over sodium sulfate and concentrated in vacuum. And the resulting crude product was purified by silica gel chromatography using a mixture of EtOAc-*n*-hexane (1:100) as eluent to afford the desired product.

*5-(4-(tert-Butyl)phenyl)-4-methylpent-1-en-3-ol (**2x**).* (580.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 7.4 Hz, 2H), 7.10 (d, J = 7.4 Hz, 2H), 5.91 (tt, J = 8.2 Hz, J = 16.2 Hz, 1H), 5.27−5.15 (m, 2H), 4.00 (dd, J = 14.9 Hz, J = 20.7 Hz, 1H), 2.83 (dd, J = 4.5 Hz, J = 13.4 Hz, 1H), 2.40−2.30 (m, 1H), 1.93 (dt, J = 6.3 Hz, J = 12.8 Hz, 1H), 1.68 (s, 1H), 1.30 (s, 9H), 0.85 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 148.6, 139.0, 137.7, 128.9, 128.8, 125.1, 116.2, 75.5, 40.7, 38.2, 34.4, 31.5, 15.0. HRMS (ESI) m/z: calcd for $C_{16}H_{24}NaO$ [M + Na]$^+$, 255.1719; found, 255.1717.

*1-Phenyloctan-3-one (**3a**).* Yield: 85% (173.4 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 2H), 7.22 (d, J = 7.3 Hz, 3H), 2.93 (t, J = 7.6 Hz, 2H), 2.76 (t, J = 7.6 Hz, 2H), 2.41 (t, J = 7.4 Hz, 2H), 1.64−1.56 (m, 2H), 1.38−1.24 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 210.3, 141.2, 128.5, 128.3, 126.1, 44.2, 43.0, 31.4, 29.8, 23.5, 22.4, 13.9 ppm; ν_{max}(KBr)/cm^{-1} 2955, 1713, 1604, 1458, 11127, 1031, 670. HRMS (ESI) m/z: calcd for $C_{14}H_{20}NaO$ [M + Na]$^+$, 227.1406; found, 227.1410.

*1-(p-Tolyl)octan-3-one (**3b**).* Yield: 82% (178.8 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09−7.05 (m, 4H), 2.85 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 2.30 (s, 3H), 1.59−1.51 (m, 2H), 1.32−1.19 (m, 4H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 210.5, 138.1, 135.53 129.2, 128.20, 44.4, 43.0, 31.4, 29.4, 23.5, 22.5, 21.09, 13.9 ppm; ν_{max}(KBr)/cm^{-1} 2929, 2865, 1713, 1459, 1411, 1372, 1242, 1075, 807, 530. HRMS (ESI) m/z: calcd for $C_{15}H_{22}NaO$ [M + Na]$^+$, 241.1563; found, 241.1564.

*1-(4-Ethylphenyl)octan-3-one (**3c**).* Yield: 80% (185.6 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11−7.07 (m, 4H), 2.85 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 2.60 (q, J = 7.6 Hz, 2H), 2.35 (t, J = 7.4 Hz, 2H), 1.59−1.51 (m, 2H), 1.31−1.19 (m, 7H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 210.4, 142.0, 138.4, 128.3, 128.0, 44.4, 43.0, 31.4, 29.5, 28.5, 23.5, 22.5, 15.7, 13.9 ppm; ν_{max}(KBr)/cm^{-1} 2926, 2928, 1714, 1515, 1460, 1371, 1124, 1077, 825, 549; HRMS (ESI) m/z: calcd for $C_{16}H_{24}NaO$ [M + Na]$^+$, 255.1719; found, 255.1723.

*1-(4-Isopropylphenyl)octan-3-one (**3d**).* Yield: 75% (184.5 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (q, J = 7.8 Hz, 4H), 2.86 (dd, J = 7.5 Hz, J = 15.1 Hz, 3H), 2.70 (t, J = 7.5 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 1.59−1.53 (m, 2H), 1.2830−1.21 (m, 10H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 210.5, 146.6, 138.5, 128.3, 126.5, 44.3, 43.0, 33.7, 31.4, 29.4, 24.1, 23.5, 22.5, 13.9 ppm; ν_{max}(KBr)/cm^{-1} 2966, 2928, 2867, 1714, 1514, 1462, 1124, 1043, 882, 567; HRMS (ESI) m/z: calcd for $C_{17}H_{26}NaO$ [M + Na]$^+$, 269.1876; found, 269.1881.

*1-(4-Isobutylphenyl)octan-3-one (**3e**).* Yield: 65% (169.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 7.8 Hz, 2H), 7.11 (d, J = 7.7 Hz, 2H), 2.86 (t, J = 7.6 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.37 (t, J = 7.4 Hz, 2H), 1.59−1.52 (m, 2H), 1.30−1.20 (m, 13H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 210.6, 148.9, 138.1, 128.0, 125.4, 44.3, 43.0, 34.4, 31.4, 29.3, 23.5, 22.5, 13.9 ppm; ν_{max}(KBr)/cm^{-1} 2964, 2928, 2862, 1715, 1465, 1411, 1365, 1266, 1020, 829, 739, 566; HRMS (ESI) m/z: calcd for $C_{18}H_{28}NaO$ [M + Na]$^+$, 283.2032; found, 283.2036.

*1-(4-Fluorophenyl)octan-3-one (**3f**).* Yield: 70% (155.4 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 2.85 (t, J = 7.6 Hz, 2H), 2.70 (t, J = 7.6 Hz, 2H), 2.37 (t, J = 7.6 Hz, 2H), 1.59−1.52 (m, 2H), 1.32−1.20 (m, 4H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 210.1, 162.6, 160.1, 136.8 (d, J = 3.3 Hz), 129.7 (d, J = 7.7 Hz), 115.3, 115.1, 44.2, 43.0, 31.4, 28.9, 23.5, 22.4, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.37 ppm; ν_{max}(KBr)/cm^{-1} 2960, 2930, 2863, 1714, 1511, 1223, 1016, 882, 605; HRMS (ESI) m/z: calcd for $C_{14}H_{19}FNaO$ [M + Na]$^+$, 245.1312; found, 245.1310.

*1-(4-Bromophenyl)octan-3-one (**3g**).* Yield: 68% (191.8 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 2.85 (t, J = 7.4 Hz, 2H), 2.70 (t, J = 7.4 Hz, 2H), 2.37 (t, J = 7.4 Hz, 2H), 1.59−1.52 (m, 2H), 1.32−1.20 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 209.9, 140.9, 137.5, 130.5, 91.1, 43.9, 43.0, 31.4, 29.2, 23.5, 22.4, 13.9 ppm; ν_{max}(KBr)/cm^{-1} 2959, 2928, 2860, 1714, 1489, 1407, 1072, 1011, 882, 808, 568; HRMS (ESI) m/z: calcd for $C_{14}H_{19}BrNaO$ [M + Na]$^+$, 305.0511; found, 305.0507.

*1-(4-Iodophenyl)octan-3-one (**3h**).* Yield: 35% (115.5 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 7.8 Hz, 2H), 2.83 (t, J = 7.3 Hz, 2H), 2.69 (t, J = 7.4 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 1.61−1.54 (m, 2H), 1.34−1.21 (m, 4H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 209.9, 140.9, 137.5, 130.5, 91.1, 43.9, 43.0, 31.4, 29.2, 23.5, 22.4 ppm; ν_{max}(KBr)/cm^{-1} 2925, 1712, 1460, 1218, 711; HRMS (ESI) m/z: calcd for $C_{14}H_{19}INaO$ [M + Na]$^+$, 353.0373; found, 353.0366.

*1-(4-Methoxyphenyl)octan-3-one (**3i**).* Yield: 50% (117.0 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 7.9 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 3.77 (s, 3H), 2.83 (t, J = 7.4 Hz, 2H), 2.68 (t, J = 7.4 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 1.58−1.51 (m, 2H), 1.31−1.19 (m, 4H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 210.6, 158.0, 133.2, 129.2, 113.9, 55.2, 44.5, 43.1, 31.4, 29.0, 23.5, 22.4, 13.9 ppm; ν_{max}(KBr)/cm^{-1} 2955, 2931, 2859, 1713, 1612, 1513, 1246, 1126, 1038, 882, 589; HRMS (ESI) m/z: calcd for $C_{15}H_{22}NaO_2$ [M + Na]$^+$, 257.1512; found, 257.1523.

*1-(4-(Trifluoromethoxy)phenyl)octan-3-one (**3j**).* Yield: 42% (121.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.18 (m, 4H), 2.94 (t, J = 7.5 Hz, 2H), 2.70 (t, J = 7.6 Hz, 2H), 2.38 (t, J = 7.4 Hz, 2H), 1.60−1.53 (m, 2H), 130−1.24 (m, 4H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 209.9, 147.6, 133.6, 131.0, 127.6, 126.8, 120.58 (q, J = 248 Hz),120.4, 42.9, 42.5, 31.4, 24.2, 23.5, 22.4, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.97 ppm; ν_{max} (KBr)/cm^{-1} 2961, 2929, 2857, 1717, 1494, 1485, 1257, 1218, 1162, 575; HRMS (ESI) m/z: calcd for $C_{15}H_{19}F_3NaO_2$ [M + Na]$^+$, 311.1229; found, 311.1232.

*1-(o-Tolyl)octan-3-one (**3k**).* Yield: 80% (174.4 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10−7.06 (m, 4H), 2.89−2.82 (m, 2H), 2.68 (q, J = 7.9 Hz, 2H), 2.39−2.33 (m, 2H), 2.30 (s, 3H), 1.60−1.53 (m, 2H), 1.31−1.22 (m, 4H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 210.6, 148.9, 138.1, 128.0, 125.4, 44.3, 43.0, 34.4, 31.4, 29.3, 23.5, 22.5, 13.9 ppm; ν_{max} (KBr)/cm^{-1} 2959, 2928, 2858, 1714, 1460, 1125, 1041, 1016, 882, 747; HRMS (ESI) m/z: calcd for $C_{15}H_{22}NaO$ [M + Na]$^+$, 241.1563; found, 241.1567.

*1-(2,4-Dimethylphenyl)octan-3-one (**3l**).* Yield: 76% (176.3 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 7.4 Hz, 1H), 6.91 (d, J = 7.9 Hz, 2H), 2.83 (t, J = 7.7 Hz, 2H), 2.65 (t, J = 8.0 Hz, 2H), 2.38 (t, J = 7.4 Hz, 2H), 2.26 (d, J = 8.6 Hz, 6H), 1.61−1.54 (m, 2H), 1.33−1.23 (m, 4H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 210.5, 139.1, 135.5, 132.7, 130.2, 129.5, 126.9, 43.1, 43.0, 31.5, 27.2, 23.6, 22.5, 20.9, 18.8, 13.9 ppm; ν_{max}(KBr)/cm^{-1} 2959, 2927, 2862, 1714, 1503, 1460, 1373, 1075, 809; HRMS (ESI) m/z: calcd for $C_{16}H_{24}NaO$ [M + Na]$^+$, 255.1719; found, 255.1724.

*1-(3-Fluorophenyl)octan-3-one (**3m**).* Yield: 79% (175.4 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (q, J = 7.1 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.86 (t, J = 9.6 Hz, 2H), 2.89 (t, J = 7.2 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.37 (t, J = 7.2 Hz, 2H), 1.59−1.52 (m, 2H), 1.33−1.19 (m, 4H), 0.87 (t, J = 6.4 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 209.8, 164.1, 161.7, 143.8 (d, J = 7.3 Hz), 129.9 (d, J = 8.3 Hz), 124.00 (d, J = 2.7 Hz), 115.3, 115.1, 113.0, 112.8, 43.7, 43.0, 31.4, 29.4, 29.4, 23.5, 22.4, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.54 ppm; ν_{max} (KBr)/cm^{-1} 2960, 2931, 2863, 1714, 1589, 1190,

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1121, 883, 569; HRMS (ESI) m/z: calcd for $C_{14}H_{19}FNaO$ $[M + Na]^+$, 245.1312; found, 245.1311.

*1-(Naphthalen-2-yl)octan-3-one (**3n**).* Yield: 39% (99.1 mg); colorless solid, mp 35−37 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (t, J = 10.0 Hz, 3H), 7.57 (s, 1H), 7.43−7.36 (m, 2H), 7.27 (d, J = 8.4 Hz, 1H), 3.01 (t, J = 7.5 Hz, 2H), 2.73 (t, J = 7.6 Hz, 2H), 2.31 (t, J = 7.4 Hz, 2H), 1.56−1.49 (m, 2H), 1.28−1.15 (m, 4H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 210.2, 138.8, 133.7, 132.2, 128.1, 127.7, 127.5, 127.2, 126.5, 126.1, 125.4, 44.1, 43.1, 31.5, 30.0, 23.6, 22.5, 14.0 ppm; ν_{max} (KBr)/cm^{-1} 2958, 2928, 2862, 1713, 1633, 1124, 1017, 745, 606, 568; HRMS (ESI) m/z: calcd for $C_{18}H_{22}NaO$ $[M + Na]^+$, 277.1563; found, 277.1563.

*1-Phenylhexan-3-one (**3o**).* Yield: 80% (140.8 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.16 (m, 5H), 2.89 (t, J = 7.6 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.36 (t, J = 7.3 Hz, 2H), 1.63−1.54 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 210.2, 141.2, 128.5, 128.3, 126.1, 45.0, 44.3, 29.8, 17.3, 13.8 ppm; ν_{max}(KBr)/cm^{-1} 2963, 1712, 1454, 1124, 1033, 882, 746, 699; HRMS (ESI) m/z: calcd for $C_{12}H_{16}NaO$ $[M + Na]^+$, 199.1093; found, 199.1094.

*4-Phenylbutan-2-one (**3p**).* Yield: 76% (112.5 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, J = 7.4 Hz, 2H), 7.21 (d, J = 7.6 Hz, 3H), 2.92 (t, J = 7.6 Hz, 2H), 2.76 (t, J = 7.6 Hz, 2H), 2.14 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 207.7, 141.1, 128.5, 128.3, 126.1, 45.1, 30.0, 29.8 ppm; ν_{max}(KBr)/cm^{-1} 3062, 3028, 2925, 1717, 1603, 1496, 1453, 1409, 1358, 1162; HRMS (ESI) m/z: calcd for $C_{10}H_{12}NaO$ $[M + Na]^+$, 171.0780; found, 171.0780.

*1,3-Diphenylpropan-1-one (**3q**).* Yield: 50% (105.0 mg); yellow solid, mp 62−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.5 Hz, 2H), 7.46 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.4 Hz, 2H), 7.23−7.10 (m, 5H), 3.21 (t, J = 7.6 Hz, 2H), 2.98 (t, J = 7.6 Hz, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 199.2, 141.3, 136.9, 133.1, 128.6, 128.6, 128.5, 128.1, 126.2, 40.5, 30.12 ppm; ν_{max}(KBr)/cm^{-1} 3059, 1685, 1594, 1447, 1207, 976, 746, 694; HRMS (ESI) m/z: calcd for $C_{15}H_{14}NaO$ $[M + Na]^+$, 233.0937; found, 233.0933.

*3-Phenyl-1-(p-tolyl)propan-1-one (**3r**).* Yield: 51% (114.2 mg); colorless solid, mp 62−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.8 Hz, 2H), 7.29−7.21 (m, 7H), 3.24 (t, J = 7.5 Hz, 2H), 3.04 (t, J = 7.5 Hz, 2H), 2.37 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 198.9, 143.9, 141.5, 134.5, 129.3, 128.6, 128.5, 128.2, 126.1, 40.4, 30.3, 21.7 ppm; ν_{max}(KBr)/cm^{-1} 3060, 1677, 1606, 1450, 1291, 974, 700; HRMS (ESI) m/z: calcd for $C_{16}H_{16}NaO$ $[M + Na]^+$, 247.1093; found, 247.1099.

*1-(4-Chlorophenyl)-3-phenylpropan-1-one (**3s**).* Yield: 40% (97.6 mg); yellow solid, mp 69−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 7.3 Hz, 2H), 7.21 (dd, J = 7.5 Hz, J = 16.9 Hz, 3H), 3.25 (t, J = 7.6 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 198.0, 141.1, 139.5, 135.2, 129.5, 128.9, 128.6, 128.4, 126.2, 40.4, 30.1 ppm; ν_{max}(KBr)/cm^{-1} 3028, 2960, 1667, 1590, 1452, 1290, 1013, 978, 883; HRMS (ESI) m/z: calcd for $C_{15}H_{13}ClNaO$ $[M + Na]^+$, 267.0547; found, 267.0545.

*3-Phenyl-1-(o-tolyl)propan-1-one (**3t**).* Yield: 55% (123.2 mg); yellow oil; 1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.6 Hz, 1H), 7.33−7.17 (m, 8H), 3.19 (t, J = 7.3 Hz, 2H), 3.02 (t, J = 7.0 Hz, 2H), 2.45 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 203.4, 141.3, 138.2, 138.0, 132.0, 131.3, 128.6, 128.5, 128.5, 126.2, 125.7, 43.3, 30.4, 21.3 ppm; ν_{max}(KBr)/cm^{-1} 3466, 3374, 3026, 2966, 2855, 16846, 1453, 1066, 751, 699, 566; HRMS (ESI) m/z: calcd for $C_{16}H_{16}NaO$ $[M + Na]^+$, 247.1093; found, 247.1098.

*1-Mesityl-3-phenylpropan-1-one (**3u**).* Yield: 65% (163.8 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.16 (m, 5H), 6.80 (s, 2H), 3.06−2.99 (m, 4H), 2.26 (s, 3H), 2.11 (s, 6H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 209.7, 141.0, 139.5, 138.4, 132.6, 128.5, 128.5, 126.2, 46.4, 29.5, 21.1, 19.1 ppm; ν_{max}(KBr)/cm^{-1} 3028, 2922, 1696, 1451, 1229, 1037, 922, 745, 700; HRMS (ESI) m/z: calcd for $C_{18}H_{20}NaO$ $[M + Na]^+$, 275.1406; found, 275.1413.

*1-(Naphthalen-2-yl)-3-phenylpropan-1-one (**3v**).* Yield: 41% (106.6 mg); yellow solid, mp 92−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.77−7.72 (m, 2H), 7.71 (d, J = 7.2 Hz, 1H), 7.42 (td, J = 7.0 Hz, J = 14.7 Hz, 2H), 7.20−7.13 (m, 5H), 3.28 (t, J = 7.5 Hz, 2H), 3.04 (t, J = 7.5 Hz, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 202.4, 140.1, 134.9, 132.9, 131.5, 129.1, 127.9, 127.5, 127.4, 127.3, 126.8, 126.3, 126.0, 125.4, 125.1, 125.0, 124.7, 124.6, 123.3, 122.8, 42.7, 40.6, 29.5, 26.9 ppm; ν_{max}(KBr)/cm^{-1} 2930, 1680, 1024, 1027, 882, 588; HRMS (ESI) m/z: calcd for $C_{19}H_{16}NaO$ $[M + Na]^+$, 283.1093; found, 283.1098.

*3-Phenyl-1-(thiophen-2-yl)propan-1-one (**3w**).* Yield: 25% (54.0 mg); brown solid, mp 45−46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.54 (d, J = 4.8 Hz, 1H), 7.24−7.11 (m, 5H), 7.03 (s, 1H), 3.15 (t, J = 7.6 Hz, 2H), 2.99 (t, J = 7.6 Hz, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 192.2, 144.2, 141.0, 133.6, 131.8, 128.6, 128.4, 128.1, 126.2, 41.2, 30.4 ppm; ν_{max}(KBr)/cm^{-1} 3444, 3374, 3026, 2925, 2853, 1664, 1414, 1264, 1065, 950; HRMS (ESI) m/z: calcd for $C_{13}H_{12}NaOS$ $[M + Na]^+$, 239.0501; found, 239.0503.

*1-(4-(tert-Butyl)phenyl)-2-methyl-5-phenylpentan-3-one (**3x**).* Yield: 60% (184.8 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.22 (m, 4H), 7.18−7.15 (m, 1H), 7.09 (d, J = 7.4 Hz, 2H), 7.04 (d, J = 7.6 Hz, 2H), 2.89 (dd, J = 7.2 Hz, J = 13.2 Hz, 1H), 2.80−2.70 (m, 4H), 2.56−2.49 (m, 2H), 1.30 (s, 9H),1.05 (d, J = 6.7 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 213.4, 149.1, 141.3, 136.6, 128.6, 128.4, 128.3, 126.0, 125.3, 48.3, 43.8, 38.8, 34.4, 31.4, 29.6, 16.4 ppm; ν_{max}(KBr)/cm^{-1} 2963, 1711, 1123, 1038, 882, 744, 568; HRMS (ESI) m/z: calcd for $C_{22}H_{28}NaO$ $[M + Na]^+$, 331.2032; found, 331.2036.

*3-Phenylpropanal (**3y**).* Yield: 61% (81.7 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.28 (t, J = 7.0 Hz, 2H), 7.19 (t, J = 7.5 Hz, 3H), 2.95 (t, J = 7.3 Hz, 2H), 2.76 (t, J = 7.3 Hz, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 201.6, 140.4, 128.6, 128.3, 126.33, 45.3, 28.2 ppm; ν_{max}(KBr)/cm^{-1} 3028, 2924, 1716, 1410, 1260, 950, 695; HRMS (ESI) m/z: calcd for $C_9H_{10}NaO$ $[M + Na]^+$, 157.0624; found, 157.0622.

*1-Phenylprop-2-en-1-d-1-ol (**2q−d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5H), 6.05 (dd, J = 10.4 Hz, J = 17.0 Hz, 1H), 5.35 (d, J = 17.1 Hz, 1H), 5.19 (d, J = 10.1 Hz, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ142.6, 140.2, 128.6, 127.8, 126.3, 115.2 ppm.

*1,3-Diphenylpropan-1-one-2-d (**3q−d**).* Yield: 47% (99.2 mg); yellow solid, mp 66−67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.3 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.3 Hz, 2H), 7.31−7.20 (m, 5H), 3.31−3.25 (m, 1H), 3.06 (d, J = 7.4 Hz, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 199.3, 141.3, 136.9, 133.1, 128.6, 128.6, 128.4, 128.1, 126.2, 40.5, 40.3, 40.1, 39.9, 30.1, 29.7 ppm. HRMS (ESI) m/z: calcd for $C_{15}H_{13}DNaO$ $[M + Na]^+$, 234.1000; found, 234.1001.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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^{1}H and ^{13}C NMR spectra for all compounds prepared (PDF)

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Notes

The authors declare no competing financial interest.

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