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Regioselective Arene and Heteroarene Functionalization: N-alkenoxypyridinium Salts as Electrophilic Alkylating Agents for the Synthesis of α-Aryl/α-Heteroaryl Ketones

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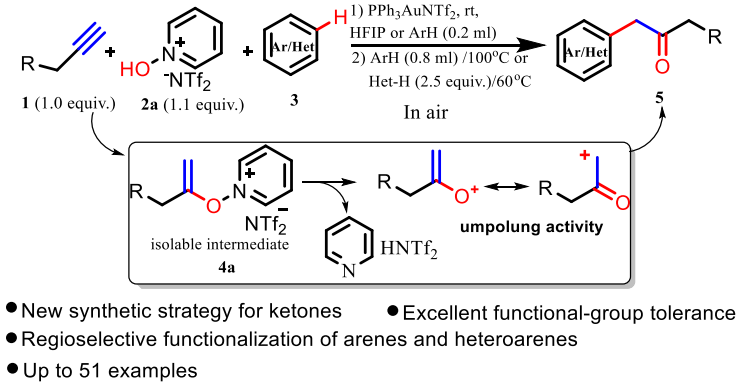
Supporting Information Placeholder



ABSTRACT: A direct regioselective functionalization of arenes and heteroarenes using N-alkenoxypyridinium salts as electrophilic alkylating agents for the synthesis of α-aryl/heteroaryl ketones has been developed. The method generates alkylating agents from alkynes and N-pyridine oxide followed by site-selective electrophilic substitution with a broad range of arenes and heteroarenes including benzene derivates, phenols, ethers, indoles, pyrroles, furans and thiophenes in one pot. KIE measurement and DFT studies reveal that this reaction likely proceeds through a carbon-cation intermediate.

Introduction

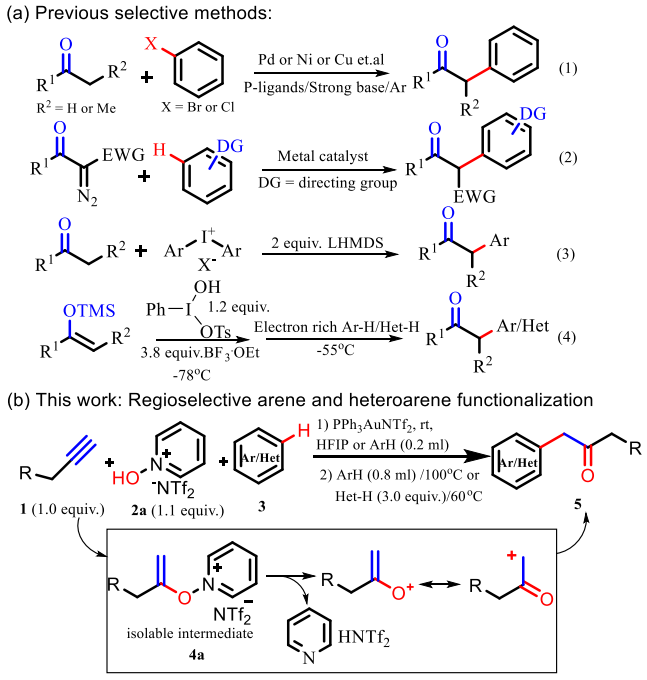
α-Aryl/α-heteroaryl ketones are essential structures in a large proportion of small molecule drugs and bioactive molecules which have important applications on organic synthesis and pharmaceutical chemistry.[1] This has led to the development of numerous elegant methods for the synthesis of α-aryl ketones, including the transition-metal (Pd, Ni or Cu) catalyzed coupling reaction of aryl halides or arenes with ketones, diazo ketones or enol silyl ethers[2-4], the reaction of carbonyl compounds with diaryliodonium salts catalyzed by metal lithium salts,[5-6] and the α-arylation of ketones or ketone enolates[7-9] (Scheme 1, a). However, there are still some shortcomings which have limited the utility of these reactions in some cases. 1) The need for prefunctionalized aryl halide substrates and transition metal catalysts, or reagents; 2) Limited functional-group tolerance is demonstrated; 3) In most cases, the regioselectivity is not good and in order to offer good selectivity, the installing of directing group is needed; 4) The reactions are sensitive to air and water. In addition, some sophisticated starting materials or potentially explosive diazo β-ketones are also prerequisites. Therefore, it is quite urgent to develop a general and efficient method to synthesize α-aryl/heteroaryl ketones with excellent regioselectivity from commercial or readily available starting materials.

Functionalization of C–H bonds has become a dominant research area in the past decade regarded as an approach to efficient synthesis.[10] Direct functionalization of aryl/heteroaryl C-H bonds, such as the Friedel-Crafts reaction, is one of the most powerful methods in terms of synthetic application due to the high prevalence of arene and heteroarene in bioactive compounds. Some progress concerning both Friedel-Crafts acylation reaction[11] and alkylation reactions[12] have been reported in recent years.

Traditionally, Friedel-Crafts alkylation allows the synthesis of alkylated products via the reaction of arene with alkyl halides or alkenes. However, since alkyl substituents activate the arene substrate, polyalkylation always occurs, yielding poor regioselectivity under the harsh reaction conditions. Thus, the generation of electrophiles under mild condition is a promising target. In previous studies on gold-catalyzed reactions of alkynes with pyridine-N-oxides,[13] we found that N-alkenoxypyridinium salts could behave as synthetic equivalents of acylcarbenium ions.[14] We hoped to expand the utility of N-alkenoxypyridinium salts and anticipated that it might be

served as an alkylating agent for intermolecular arene/heteroarene functionalization.

Scheme 1. Previous methods and our work.

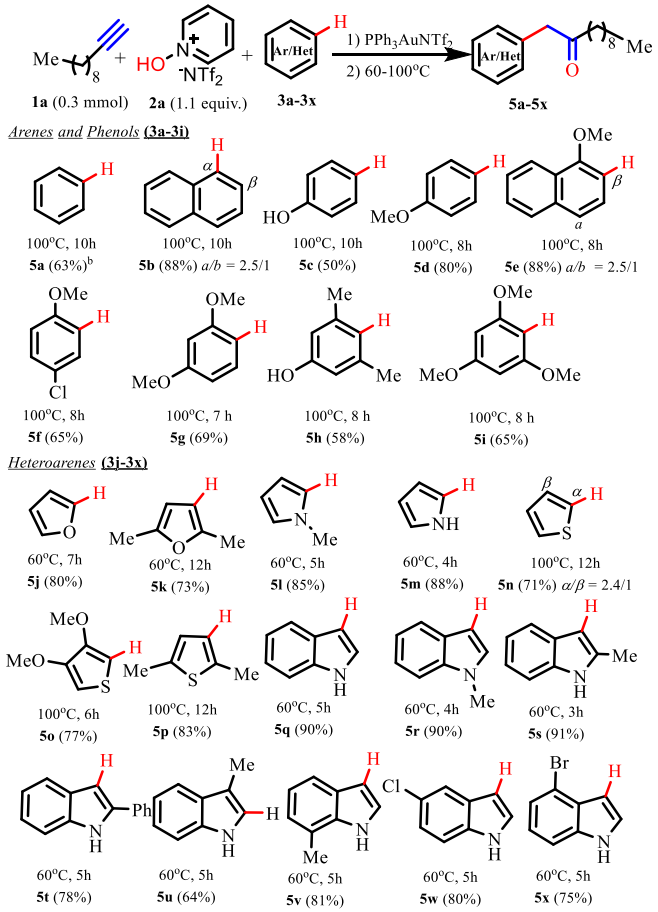


Results and Discussion

We started our investigation by exploring the reaction of alkyne **1a** with N-pyridine oxide **2a** in the presence of PPh_3AuNTf_2 in benzene. After an extensive optimization with various N-alkenoxypyridinium salts, solvents, temperatures and et.al, we found that α-phenyl ketone (**5a**) could be obtained in 63% overall yield (for details, see supporting information). As expected, no diarylation or polyalkylation product was detected by the NMR analysis of the crude reaction mixture. Next we turned to examine the generality of the substrate scope and the results are summarized in **Scheme 2**. To our great delight, wide variety of arenes and heteroarenes are tolerated, delivering the α-aryl ketones in moderate to excellent yields. Naphthalene gave the ortho- and para-isomers (**5b**) as the major products with a 2.5/1.0 selectivity ratio (α/β), due to electronic effects. Potentially reactive functionalities can be incorporated, such as hydroxyl and amino substituents. The active hydroxyl group did not need to be protected prior to this step and was transformed smoothly to the para-product (**5c**) as a single isomer, due to a combination of electronic and steric influence. The same result was also observed with anisole (**5d**). Like naphthalene, 1-methoxynaphthalene provided the ortho- and para-isomers (**5e**) as the main products with a 2.3/1.0 selectivity ratio. Disubstituted or trisubstituted aromatics are also suitable substrates for the reaction and undergo functionalization in moderate to good yields. For example, the selectivity of 4-chloroanisole or 1,3-dimethoxy benzene is governed by electronic effects, affording the ortho para-isomers (**5f-5g**). Substrates with sterically bulky groups did not retard the reaction and gave good yields, such as 1,3,5-trisubstituted phenols or 1,3,5-trimethoxyl benzene, which reacted smoothly, providing the desired products in 58% and 65% yield, respectively (**5h-5i**).

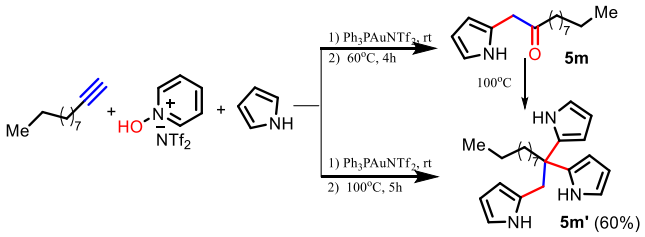
It is well-known that Friedel−Craft alkylation of the parent five-membered heterocycles pyrrole and furan are low yielding due to their tendency to undergo polymerization under acidic reaction conditions as well as their tendency to undergo multiple alkylations.[15] The electrophilicity of the N-alkenoxypyridinium salt intermediate could also be applied to furans and pyrroles to provide the corresponding α-heteroaryl ketones. These substrates underwent electrophilic substitution exclusively at the C-2 position giving the products with 80-88% yields at 60°C (**5j, 5l-5m**). If a substituent group was present on the C-2 position, the reaction would then take place at the C-3 position (**5k**).

Scheme 2. Scopes of arenes and heteroarenes.[a]



[a]Reaction conditions: the reaction was conducted with alkyne **1a** (0.2 mmol), **2a** (1.1 equiv), PPh_3AuNTf_2 (2.5 mol%), HFIP (0.3 ml), rt, 3h and then **3a-3i** (0.8 ml) or **3j-3y** (3.0 equiv.) was added and reacted. The numbers in the brackets are the over-all isolated yields. [b]The reaction was carried out at 1.5 mmol scale and the number in the bracket is the isolated yield.

Scheme 3. The formation of **5m** and **5m'**.

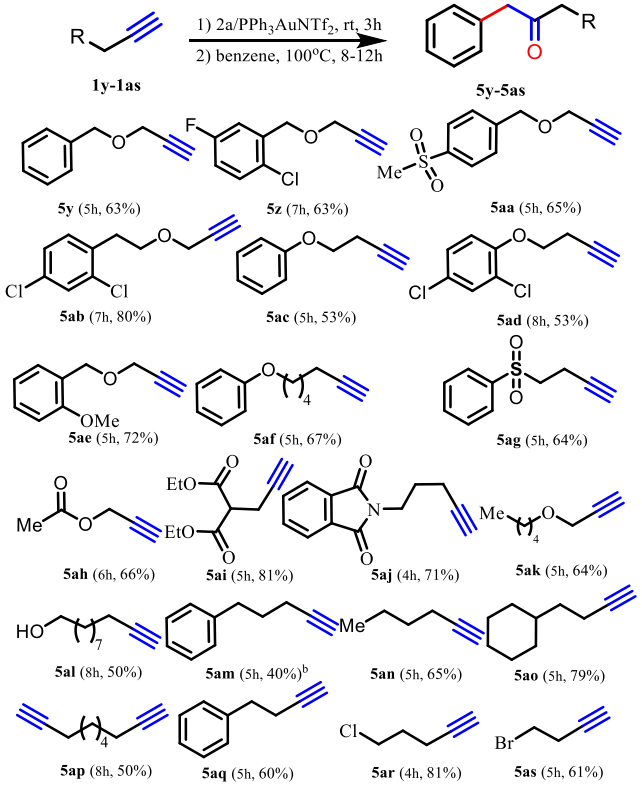


When the reaction temperature was increased to 100°C, pyrrole gave the condensation product **5m'** as the major product indicating that the reaction could be tuned by adjusting the

temperature (**Scheme 3**). Less-activated heterocycles, such as thiophenes can be similarly functionalized at higher temperature (**5n-5p**). Indole gave the product in 90% yield, reacting exclusively at the C-3 position (**5q**). N-Methyl indole gave a similar result (**5r**). Gratifyingly, we found that a variety of N-unsubstituted indoles were suitable substrates and could afford the α-heteroaryl ketones with good to excellent yields as single regio-isomers. Notably, various functional groups including amino, phenyl, chlorine and bromine are compatible with this transformation (**5s-5x**).

Considering benzene is one of the most important raw materials in industry, we subsequently turned to evaluate the scope of the alkylation agents which were generated from alkynes using benzene as a model substrate.

Scheme 4. Scopes of alkynes.[a]

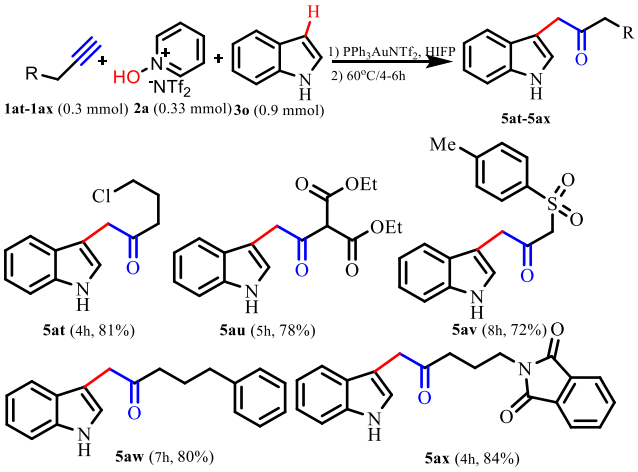


[a]The reaction was conducted with alkyne **1** (0.2 mmol), **2a** (1.1 equiv), PPh_3AuNTf_2 (2.5 mol%), HFIP (0.2 ml) or benzene (0.2 ml), rt, 3h and then benzene (0.6 ml) was added and reacted at 100°C. The numbers in the brackets are the over-all isolated yields. [b]26% cyclized product was observed.

Pleasingly, as revealed in **Scheme 4**, we found a broad range of alkynes possessing phenyl moieties bearing a variety of functional groups such as ether and halides (**5y-5ab** and **5ak**), phenol ethers (**5ac-5af**), sulfonyl (**5ag**), acetate (**5ah-5ai**), amide (**5aj**) and hydroxyl groups (**5al**) are compatible with the transformation and formed alkylating reagents which then underwent a Friedel-Crafts-type intermolecular reaction with benzene in one pot, affording the α-phenyl ketones in moderate to excellent yields. For alkynes containing a benzene ring, no cyclization product was observed except for **5am**. For other aliphatic alkynes, the expected products were also obtained (**5an-5aq**). With 5-chloropent-1-yne or 4-bromo-1-butyne as the substrate, the α-phenyl ketones were obtained in 81% and 61% isolated yield respectively (**5ar-5as**). Under these acidic reaction conditions, the terminal chloride or bromide didn't participate into the Friedel-Crafts alkylation, demonstrating excellent chemio-selectivity.

Indole moieties are found in numerous natural alkaloids and pharmaceutical substances.[16] Therefore, we investigated the scope of the reaction for a range of functionalized alkylation agents with indole. As shown in **Scheme 5**, some functional substituents, such as chlorides, esters, sulfones and amides in the indole are tolerated and afford α-heteroaryl ketones exclusively at the C-3 position in 72-84% yields at 60°C (**5at-5ax**).

Scheme 5. Scope of alkylating agents with indoles.[a]



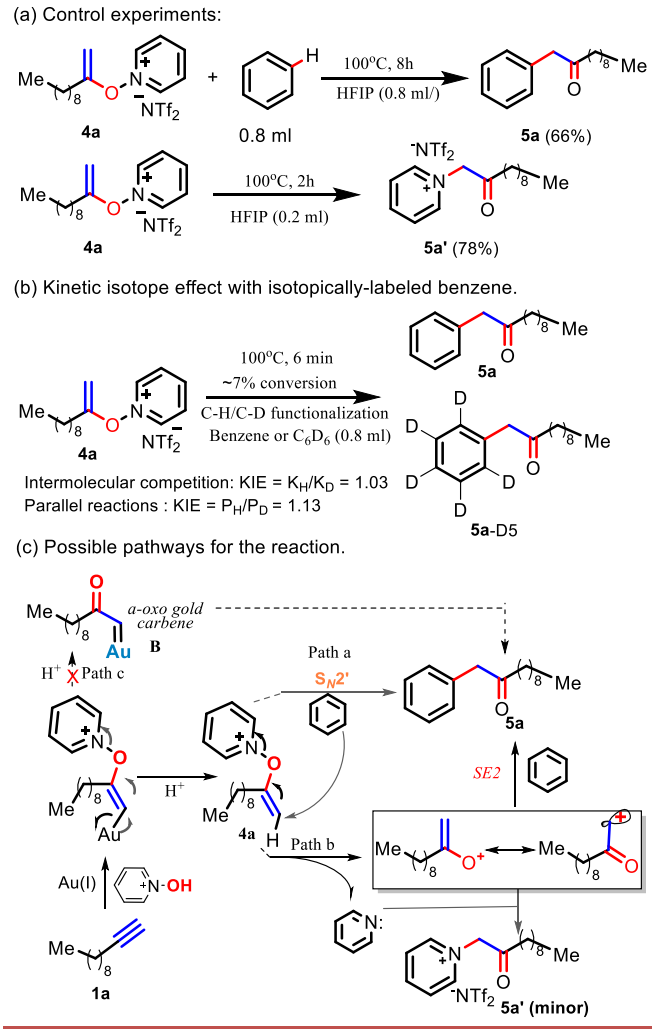
[a]The reaction was conducted with alkyne **1** (0.3 mmol), **2a** (1.1 equiv), PPh_3AuNTf_2 (2.5 mol%), HFIP (0.2 ml), rt, 3h and then **3o** (3.0 equiv.) was added. The numbers in the brackets are the over-all isolated yields.

We next sought to address the mechanism of the reaction. NMR studies of crude products for the second step showed that aside from the major product **5a** and protonated pyridine, there were some other unidentified products. Initially, the pyridine was thought to undergo an electrophilic substitution reaction. We hope to demonstrate this with experimental evidence. In order to simplify the reaction process, **4a** was isolated and used as the reactant for the second step. Then, we ran a simple experiment to determine whether **4a** was stable under thermal conditions. To our surprise, **4a** decomposed completely within 2h and **5a'** was obtained and isolated as the sole product in 78% yield (**Scheme 6**, a). This observation, suggests to some extent that N-O bond cleavage might occur prior to the attack by the arene. After N-O bond cleavage, an electrophilic carbocation species is likely produced. KIE studies for the reaction of **4a** and benzene/D_6H_6 were also performed. KH/KD was measured to be 1.03, while the measured PH/PD was 1.13 (**Scheme 6**, b), indicating the rate-determining step is likely not the cleavage of the Ar-H bond and the reaction of **4a** and benzene should be an electrophilic aromatic substitution. Based on the above evidence, two possible pathways for the reaction are proposed in **Scheme 6**, c. To gain more insight into the mechanism, DFT studies were carried out (**Fig. 1**). To reduce the computational cost, the nonyl group in **4a** was substituted by ethyl group. The results reveal that the calculated barrier height in free energy of pathway a is quite high (43.4 kcal/mol), implying this pathway is kinetically unfavourable.

The N-O bond cleavage step in path b needs to overcome a free energy barrier of 33.5 kcal/mol, whereas the barrier for

the second step is only 14.8 kcal/mol, indicating that the first step is the rate-determining step in path b. It was noted that the barrier of the first step is much lower than 43.4 kcal/mol for pathway a. Therefore, from a kinetic point of view, pathway b should be more facile than pathway a.

Scheme 6. Mechanism studies.



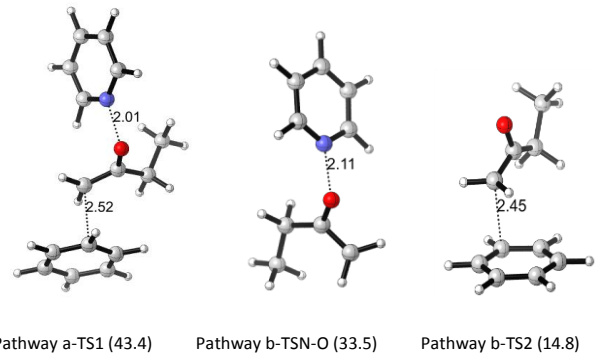


Fig. 1 DFT studies: the optimized structures and the corresponding free energy barrier (in kcal/mol) of the transition states involving in the two pathways.

Conclusion

In summary, we have developed an efficient, convenient, and general approach to α-aryl/α-heteroaryl ketones via intermolecular regioselective arene and heteroarene C–H functionalization. Notably, the reaction proceeds in an intermolecular fashion, without directing groups and the remarkable regioselectivity provides a unique approach to a wide range of structurally diverse α-aryl/α-heteroaryl ketones (up to 51 examples). Furthermore, the mechanism of the reaction has been elucidated through isotopic labeling experiments and DFT studies which reveal that the reaction likely proceeds through a carbon-cation intermediate.

Experimental Section

General Remarks. ^{1}H NMR and ^{13}C NMR spectra were recorded on ECZ-400S (400 MHz) spectrometers using residue solvent peaks as internal standards ($CHCl_3$, ^{1}H: 7.26 ppm; ^{13}C:77.00 ppm). ^{19}F NMR spectra were recorded on JMTC-400/54/SS 400 MHz spectrometer calibrated by trifluoroacetic acid peak (CF_3COOH, ^{19}F: -76.55 ppm). Signal positions were recorded in ppm with the abbreviations s, d, t, q, and m denoting singlet, doublet, triplet, quartet, and multiplet, respectively. All coupling constants *J* were quoted in Hz. Data were reported as follows: chemical shift, multiplicity, coupling constant, and integration. All commercially available reagents were used as received without further purification. Reactions were monitored by thin layer chromatography (TLC) using Silicycle precoated silica gel plates (visualization reagent: $KMnO_4/H_2SO_4$). Flash column chromatography was performed over Silicycle silica gel (300-400 mesh). Infrared spectra were recorded with a PerkinElmer Spectrum Two FT-IR spectrometer and are reported in reciprocal centimeter (cm-1). Mass spectra were recorded with MicroTof-II using electron spray ionization (MeOH as solvent) or Waters GCT Premier time-of-flight mass spectrometer with a field ionization (FI) ion source.

Computational details. All calculations were carried out using the Gaussian 09 program package.[17] The structures were fully optimized by using the M06-2X[18] functional coupled with 6-31G(d,p) basis set. Frequency calculations were performed at the same level of theory to confirm all the stationary points as minima or transition states. Intrinsic reaction coordinate (IRC) [19] analysis were performed to ensure connectivity between the transition structures and the intermediates. For the identified stationary points, we performed additional single-point calculations using a more extended basis set 6-311++G(d,p) with M06-2X functional to obtain more accurate energies. The solvent effects (benzene) were considered by using the SMD[20] solvation model in both geometry optimization and single-point calculations. The energies discussed in the text are Gibbs free energies calculated at 373 K (experimental temperature) unless otherwise stated. To reduce the computational cost, the nonyl group in **4a** was substituted by ethyl group.

Experimental Procedures. General Procedure for the Preparation of Product 5a-5ax. Pyridine N-oxide and Tf_2NH were premixed in a molar ratio of 1.2/1.1, then stored in a vial and used directly for reaction. PPh_3AuNTf_2 (3.7 mg, 0.25 equiv.) was added into a mixture of undec-1-yne (31.4 mg, 0.2 mmol), premixed salt (82.7 mg, 1.1 equiv.), HFIP (0.2 ml) or benzene in a vial at room temperature. The reaction mixture was then stirred at room temperature and the progress of the reaction was monitored by TLC (PE/EA = 10/1, visualization reagent: $KMnO_4/H_2SO_4$). After the reaction was completed (typically 2.5h), the reaction mixture was added with benzene (0.6 ml/0.8 ml)/pyrrole (40.2 mg, 3 equiv.). Then the reaction vial was sealed and heated to 100 °C / 60 °C. The reaction was

monitored by TLC (DCM/MeOH = 50/1, visualization reagent: $KMnO_4$ /H_2SO_4). After the reaction was finished, the mixture was concentrated and the residue was purified by flash chromatography on silica gel (eluent: hexanes/ethyl acetate 10/1) to afford the desired product **5a-5ax**.

*1-phenylundecan-2-one (**5a**)*[21] Colorless oil (236 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 2H), 7.28-7.23 (m, 1H), 7.22-7.15 (m, 2H), 3.67 (s, 2H), 2.42 (t, *J* = 7.3 Hz, 2H), 1.56-1.47 (m, 2H), 1.35-1.11 (m, 12H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 134.4, 129.4, 128.7, 126.9, 50.1, 42.0, 31.8, 29.4, 29.4, 29.2, 29.1, 23.7, 22.7, 14.1; IR (cm^{-1}): 2917, 2849, 1708, 1601,1464, 702; HRMS (ESI) m/z calcd. for $C_{17}H_{25}O$ [M-H]$^-$: 245.1905, found: 245.1906.

1-(naphthalen-2-yl)undecan-2-one (**5b**). Colorless oil (52 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.78 (m, 4H), 7.51 (s, 0.41 H) (minor isomer, Ar-H), 7.50-7.36 (m, 6H), 4.10 (s, 2H) (major isomer), 3.83 (s, 0.83H) (minor isomer), 2.46 (t, *J* = 7.5 Hz, 0.83H) (minor isomer), 2.40 (t, *J* = 7.3 Hz, 2H) (major isomer), 1.69-1.43 (m, 4H), 1.35-1.06 (m, 21H), 0.86 (t, *J* = 6.9 Hz, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1 (major), 208.7 (minor), 133.9 (major), 133.5 (minor), 132.4 (minor), 132.2 (major), 131.9 (minor), 131.2 (major), 128.7 (major), 128.3 (minor), 128.2 (major), 128.0 (minor), 127.9 (major), 127.7 (minor), 127.6 (minor), 127.5 (minor), 126.4 (major), 126.2 (minor), 125.8 (major), 125.7 (minor), 125.5 (major), 123.9 (major), 50.3 (minor), 48.5 (major), 42.1 (minor), 41.5 (major), 31.8 (major), 31.5 (minor), 30.1 (minor), 29.7, 29.3, 29.2(9), 29.2, 29.1, 29.0, 23.7, 22.6, 14.1; IR (cm^{-1}): 2915, 2848, 1712, 1471, 788; HRMS (ESI) m/z calcd. for $C_{22}H_{30}NaO_2$ [M+Na]$^+$: 349.2143, found: 349.2148.

*1-(4-hydroxyphenyl)undecan-2-one (**5c**)*. Colorless oil (26 mg, 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.2 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 5.14 (s, 1H), 3.59 (s, 2H), 2.41 (t, *J* = 7.3 Hz, 2H), 1.59-1.45 (m, 2H), 1.27-1.14 (m, 12H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 154.7, 130.6, 126.3, 115.6, 49.2, 41.9, 31.8, 29.4, 29.3, 29.2, 29.1, 23.8, 22.6, 14.1; IR (cm^{-1}): 2954, 2848, 2921, 1706, 1517, 1455, 1362; HRMS (ESI) m/z calcd. for $C_{17}H_{26}O_2$ [M-H]$^-$: 261.1854, found: 261.1854.

*1-(4-methoxyphenyl)undecan-2-one (**5d**)*. Colorless oil (44 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.19 (m, 1H), 7.16-7.05 (m, 1H), 6.91 (td, *J* = 7.3, 0.9 Hz, 1H), 6.88-6.81 (m, 1H), 3.79 (s, 3H), 3.65 (s, 2H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.54 (t, *J* = 7.3 Hz, 2H), 1.31-1.15 (m, 12H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 131.2, 128.4, 120.6, 110.4, 55.3, 44.7, 41.9, 31.9, 29.5, 29.4, 29.3, 29.2, 23.8, 22.7, 14.1; IR (cm^{-1}): 2920, 1709, 1247, 1066; HRMS (ESI) m/z calcd. for $C_{18}H_{27}O_2$ [M-H]$^-$: 275.2011, found: 275.2010.

*1-(5-methoxynaphthalen-2-yl)undecan-2-one (**5e**)*. Colorless oil (57 mg, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (t, *J* = 8.0 Hz, 3H), 7.75-7.72 (m, 0.7H) (minor isomer), 7.53-7.30 (m, 3.84H), 7.17-7.07 (m, 1H), 4.14 (s, 2H) (major), 4.04 (s, 0.82H) (minor), 3.96 (s, 3H) (major), 3.91 (s, 1.21H) (minor), 2.37 (q, *J* = 6.9 Hz, 2.81H), 1.54-1.48 (m, 2.7H), 1.29-1.16 (m, 19H), 0.94-0.77 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9 (major), 209.6 (minor), 158.2 (minor), 154.8 (major), 133.4 (major), 130.2 (major), 129.9 (minor), 129.3 (minor), 129.1 (major), 129.0 (major), 128.8 (major), 128.5 (major), 127.7, 126.9 (major), 123.5 (major), 123.3 (minor), 123.0, 118.5, 116.4, 113.0, 102.5, 56.4 (major), 55.3 (minor), 49.3 (minor), 41.3 (major), 41.1 (minor), 40.3 (major), 31.8 (major), 31.5 (minor), 30.1, 29.7, 29.4, 29.3, 29.2(8), 29.2, 29.1(8), 29.1, 29.0, 23.8, 23.7, 22.6, 14.1; IR (cm^{-1}): 2922, 2851, 1709, 1455, 806, 745; HRMS (ESI) m/z calcd. for $C_{22}H_{29}O_2$ [M-H]$^-$: 325.2167, found: 325.2164.

*1-(5-chloro-2-methoxyphenyl)undecan-2-one (**5f**)*. Colorless oil (40 mg, 65%); ^{1}H NMR (400 MHz, CDCl3) δ 7.19 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.08 (d, *J* = 2.7 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 3.76 (s, 3H), 3.61 (s, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 1.56-1.48 (m, 2H), 1.34-1.13 (m, 12H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 156.0, 131.0, 128.0, 125.5, 125.3, 111.5, 55.6, 44.3, 42.2, 31.9, 29.4, 29.3(9), 29.3, 29.1, 23.8, 22.7, 14.1; IR (cm^{-1}): 1922, 2851, 1713, 1492, 1464, 1249; HRMS (ESI) m/z calcd. for $C_{18}H_{26}ClO_2$ [M-H]$^-$: 309.1621, found: 309.1626.

*1-(2,4-dimethoxyphenyl)undecan-2-one (**5g**)*. Colorless oil (42 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 5.9 Hz, 1H), 6.47-6.35 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.57 (s, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 1.60-1.46 (m, 2H), 1.40-1.02 (m, 12H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 160.1, 158.2, 131.4, 116.1, 104.1, 98.6, 55.4, 55.3, 44.0, 41.8, 37.7, 31.9, 29.4, 29.3, 29.2, 23.9, 22.7, 14.1; IR (cm-1): 2923, 2852, 1711, 1507, 1464, 1208; HRMS (ESI) m/z calcd. for $C_{19}H_{29}O_3$ [M-H]$^-$: 305.2116, found: 305.2117.

*1-(4-hydroxy-2,6-dimethoxyphenyl)undecan-2-one (**5h**)*. Colorless oil (34 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (s, 2H), 3.64 (s, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 2.15 (s, 6H), 1.68-1.48 (m, 2H), 1.46-0.98 (m, 12H), 0.86 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 154.1, 138.3, 124.3, 115.0, 43.7, 42.0, 31.8, 29.4, 29.4, 29.2(3), 29.2, 23.4, 22.7, 20.5, 14.1; IR (cm^{-1}): 2915, 2849, 1708, 1506, 1264; HRMS (ESI) m/z calcd. for $C_{19}H_{29}O_2$ [M-H]$^-$: 289.2168, found: 289.2171.

*1-(2,4,6-trimethoxyphenyl)undecan-2-one (**5i**)*. Colorless oil (44 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (s, 2H), 3.80 (s, 3H), 3.76 (s, 6H), 3.60 (s, 2H), 2.35 (t, *J* = 7.3 Hz, 2H), 1.56-1.46 (m, 2H), 1.27-1.14 (m, 12H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 160.3, 158.8, 104.7, 90.5, 55.7, 55.3, 41.4, 37.4, 31.9, 29.5, 29.4, 29.3, 29.2, 23.9, 22.7, 14.1; IR (cm^{-1}): 2921, 2851, 1712, 1595, 1500, 1455, 1149; HRMS (ESI) m/z calcd. for $C_{20}H_{31}O_4$ [M-H]$^-$: 335.2222, found: 335.2224.

*1-(furan-2-yl)undecan-2-one (**5j**)*. Colorless oil (38 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 1.4 Hz, 1H), 6.33 (q, *J* = 1.7 Hz, 1H), 6.18 (dd, *J* = 3.2, 0.9 Hz, 1H), 3.68 (s, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 1.54 (t, *J* = 6.4 Hz, 2H), 1.40-1.12 (m, 12H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 148.4, 142.1, 110.6, 108.1, 42.5, 41.9, 31.8, 29.4, 29.3, 29.2, 29.1, 23.6, 22.7, 14.1; IR (cm^{-1}): 2925, 2856, 1735, 1638, 1491, 1132; HRMS (ESI) m/z calcd. For $C_{15}H_{23}O_2$ [M-H]$^-$: 235.1697; found: 235.1697.

*1-(2,5-dimethylfuran-3-yl)undecan-2-one (**5k**)*. Colorless oil (39 mg, 73%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.80 (s, 1H), 3.55 (s, 2H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.10 (s, 3H), 1.91 (s, 3H), 1.65-1.49 (m, 2H), 1.41-1.15 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 155.4, 141.7, 117.6, 108.4, 41.8, 32.0, 29.6, 29.5, 29.4, 29.3, 29.0, 28.2, 28.0, 22.8, 14.2, 10.0; IR (cm^{-1}): 2923, 2853, 1713, 1505, 1405, 798; HRMS (ESI) m/z calcd. For $C_{17}H_{27}O_2$ [M-H]$^-$: 263.2010; found: 263.2005.

*1-(1-methyl-1H-pyrrol-2-yl)undecan-2-one (**5l**)*. Colorless oil (43 mg, 85%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.59 (t, *J* = 2.3 Hz, 1H), 6.08 (t, *J* = 3.2 Hz, 1H), 6.00 (q, *J* = 1.7 Hz, 1H), 3.64 (s, 2H), 3.50 (s, 3H), 2.43 (t, *J* = 7.5 Hz, 2H), 1.53 (t, *J* =

7.1 Hz, 2H), 1.40-1.10 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 125.5, 122.6, 108.7, 107.1, 41.5, 41.4, 33.9, 31.9, 29.4, 29.3(6), 29.2, 29.1, 23.7, 22.7, 14.1; IR (cm^{-1}): 2923, 2853, 1712, 1455, 705; HRMS (ESI) m/z calcd. For $C_{16}H_{26}NO$ $[M-H]^-$: 248.2014; found: 248.2013.

*1-(1H-pyrrol-2-yl)undecan-2-one (**5m**).* Colorless oil (41 mg, 88%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 6.78-6.60 (m, 1H), 6.13 (dd, *J* = 5.9, 2.7 Hz, 1H), 6.03-5.85 (m, 1H), 3.71 (s, 2H), 2.48 (t, *J* = 7.3 Hz, 2H), 1.72-1.41 (m, 2H), 1.36-1.15 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0, 124.0, 117.7, 108.2, 107.2, 42.5, 41.0, 31.8, 29.4, 29.3(5), 29.2, 29.1, 23.7, 22.7, 14.1; IR (cm^{-1}): 3338, 2919, 2851, 1704, 718; HRMS (ESI) m/z calcd. For $C_{15}H_{24}NO$ $[M-H]^-$: 234.1857; found: 234.1854.

*1-(thiophen-3-yl)undecan-2-one (**5n**).* Colorless oil (36 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (q, *J* = 2.6 Hz, 0.48H) (minor), 7.20 (dd, *J* = 5.0, 1.4 Hz, 1H) (major), 7.08 (d, *J* = 1.8 Hz, 0.47H) (minor), 7.00-6.92 (m, 1H) (major), 6.90-6.84 (m, 1H) (major), 3.87 (s, 2H) (major), 3.70 (s, 1H), 2.48 (t, *J* = 7.5 Hz, 2H) (major), 2.43 (t, *J* = 7.3 Hz, 1H) (minor), 1.69-1.46 (m, 3H), 1.25 (d, *J* = 16.5 Hz, 20H), 0.86 (t, *J* = 6.9 Hz, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1 (minor), 207.0 (major), 135.4 (major), 134.0(minor), 128.5 (major), 126.9 (minor), 126.6 (major), 125.8 (minor), 124.9 (major), 122.7 (minor), 44.3, 43.5 (minor), 41.9, 41.7, 31.8, 29.3, 29.3, 29.2, 29.0, 23.7, 22.6, 14.1; IR (cm^{-1}): 2917, 2850, 1709, 1464, 1407, 1247, 799; HRMS (ESI) m/z calcd. for $C_{15}H_{23}OS$ $[M-H]^-$: 251.1469, found: 251.1475.

*1-(3,4-dimethoxythiophen-2-yl)undecan-2-one (**5o**).* Colorless oil (48 mg, 77%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.05 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.70 (s, 2H), 2.46 (t, *J* = 7.3 Hz, 2H), 1.63-1.54 (m, 2H), 1.34-1.16 (m, 12H), 0.86 (t, *J* = 5.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 150.4, 144.5, 118.0, 94.2, 60.6, 57.1, 41.7, 40.3, 31.8, 29.4, 29.3, 29.2, 29.1, 23.7, 22.6, 14.1; IR (cm^{-1}): 2924, 2853, 1713, 1495, 1400, 1044; HRMS (ESI) m/z calcd. for $C_{17}H_{28}O_3SNa$ $[M+Na]^+$: 335.1651; found: 335.1660.

*1-(2,5-dimethylthiophen-3-yl)undecan-2-one (**5p**).* Colorless oil (47 mg, 83%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.80 (s, 1H), 3.55 (s, 2H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.10 (s, 3H), 1.91 (s, 3H), 1.65-1.49 (m, 2H), 1.41-1.15 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 155.4, 141.7, 117.5, 108.3, 41.7, 31.9, 29.5, 29.4, 29.3, 29.2, 28.9, 28.1, 28.0, 22.7, 14.1, 9.9; IR (cm^{-1}): 2923, 2853, 1713, 1505, 1405, 798; HRMS (ESI) m/z calcd. For $C_{17}H_{27}O_2$ $[M-H]^-$: 263.2010; found: 263.2005.

*1-(1H-indol-3-yl)undecan-2-one (**5q**).* Colorless oil (51 mg, 90%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.21 (td, *J* = 7.5, 1.2 Hz, 1H), 7.17-7.10 (m, 2H), 3.81 (s, 2H), 2.47 (t, *J* = 7.5 Hz, 2H), 1.55 (t, *J* = 6.6 Hz, 2H), 1.46-1.03 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 136.1, 127.3, 123.0, 122.2, 119.7, 118.7, 111.1, 108.9, 41.5, 39.8, 31.8, 29.4, 29.3 (6), 29.2, 29.1, 23.8, 22.6, 14.0; IR (cm^{-1}): 3383, 2923, 2853, 1703, 1457, 736; HRMS (ESI) m/z calcd. For $C_{19}H_{26}NO$ $[M-H]^-$: 284.2014; found: 284.2020.

*1-(1-methyl-1H-indol-3-yl)undecan-2-one (**5r**).* Colorless oil (54 mg, 90%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.99 (s, 1H), 3.78 (s, 2H), 3.76 (s, 3H), 2.46 (t, *J* = 7.3 Hz, 2H), 1.54 (t, *J* = 7.1 Hz, 2H), 1.37-1.10 (m, 12H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 136.9, 127.7, 121.7, 119.1, 118.8, 109.2, 107.2, 41.4, 39.7, 32.7, 31.8, 29.4, 29.3(7), 29.2, 29.1, 23.8, 23.7, 22.6, 14.0; IR (cm^{-1}): 2922, 2853, 1708, 1614, 1550, 1455, 740; HRMS (ESI) m/z calcd. for $C_{20}H_{29}NONa$ $[M+Na]^+$: 322.2141; found: 322.2150.

*1-(2-methyl-1H-indol-3-yl)undecan-2-one (**5s**).* Colorless oil (55 mg, 91%);. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.54-7.39 (m, 1H), 7.28 (dd, *J* = 6.7, 1.5 Hz, 1H), 7.19-7.01 (m, 2H), 3.71 (s, 2H), 2.47-2.40 (m, 3H), 2.39 (s, 3H), 1.56-1.45 (m, 2H), 1.42-1.03 (m, 12H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 135.2, 132.5, 128.5, 121.3, 119.6, 117.8, 110.2, 104.9, 41.1, 39.2, 31.8, 29.4, 29.3, 29.2, 29.1, 23.8, 22.6, 14.0, 11.7; IR (cm^{-1}): 3384, 2922, 2853, 1701, 1433, 737; HRMS (ESI) m/z calcd. For $C_{20}H_{28}NO$ $[M-H]^-$: 298.2170; found: 298.2178.

*1-(2-phenyl-1H-indol-3-yl)undecan-2-one (**5t**).* Colorless oil (56 mg, 78%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.58-7.43 (m, 5H), 7.42-7.33 (m, 2H), 7.24-7.18 (m, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 3.90 (s, 2H), 2.42 (t, *J* = 7.3 Hz, 2H), 1.62-1.44 (m, 2H), 1.43-0.97 (m, 12H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 136.0, 135.8, 132.5, 129.0, 129.0, 128.1, 128.0, 122.6, 120,1, 118.9, 110.9, 106.1, 41.6, 39.7, 31.8, 29.4, 29.3(5), 29.2, 29.1, 23.8, 22.6, 14.1; IR (cm^{-1}): 3366, 2923, 2853, 1698, 1457, 738, 697; HRMS (ESI) m/z calcd. For $C_{25}H_{30}NO$ $[M-H]^-$: 360.2327; found: 360.2327.

*1-(3-methyl-1H-indol-2-yl)undecan-2-one (**5u**).* Colorless oil (38 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.22-7.02 (m, 2H), 3.81 (s, 2H), 2.50 (t, *J* = 7.3 Hz, 2H), 2.27 (s, 3H), 1.56 (t, *J* = 7.1 Hz, 2H), 1.35-1.15 (m, 12H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 135.6, 128.6, 127.0, 121.6, 119.1, 118.3, 110.6, 108.6, 42.6, 39.7, 31.8, 29.4, 29.3(7), 29.2, 29.0, 23.5, 22.6, 14.0, 8.5; IR (cm^{-1}): 3351, 2922, 2853, 1703, 14511, 741; HRMS (ESI) m/z calcd. for $C_{20}H_{29}NONa$ $[M+Na]^+$: 322.2141; found: 322.2140.

*1-(7-methyl-1H-indol-3-yl)undecan-2-one (**5v**).* Colorless oil (49 mg, 81%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 2.3 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 6.9 Hz, 1H), 3.79 (s, 2H), 2.51-2.42 (m, 5H), 1.62-1.46 (m, 2H), 1.38-1.06 (m, 12H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 135.7, 126.8, 122.8, 122.7, 120.3, 119.9, 116.4, 109.4, 41.4, 40.0, 31.8, 29.3, 29.2, 29.1, 23.8, 22.6, 16.5, 14.0; IR (cm^{-1}): 3397, 2915, 2850, 1701, 1433, 785; HRMS (ESI) m/z calcd. For $C_{20}H_{28}NO$ $[M-H]^-$: 298.2170; found: 298.2173.

*1-(5-chloro-1H-indol-3-yl)undecan-2-one (**5w**).* Colorless oil (51 mg, 80%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.49 (d, *J* = 1.8 Hz, 1H), 7.25 (s, 1H), 7.14 (dd, *J* = 8.7, 1.8 Hz, 2H), 3.76 (s, 2H), 2.47 (t, *J* = 7.3 Hz, 2H), 1.60-1.50 (m, 2H), 1.35-1.13 (m, 12H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 134.4, 128.4, 125.5, 124.4, 122.6, 118.2, 112.2, 108.7, 41.7, 39.4, 31.8, 29.4, 29.3(6), 29.2, 29.1, 23.8, 22.6, 14.09; IR (cm^{-1}): 3344, 2916, 2850, 1704, 1455, 799; HRMS (ESI) m/z calcd. For $C_{19}H_{25}ClNO$ $[M-H]^-$: 318.1624; found: 318.1626.

*1-(4-bromo-1H-indol-3-yl)undecan-2-one (**5x**).* Colorless oil (55 mg, 75%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.24-7.18 (m, 2H), 7.02 (d, *J* = 2.7 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H), 4.08 (s, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.74-1.49 (m, 2H), 1.49-1.04 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 137.5, 125.3, 124.0, 122.9, 114.0, 110.7, 109.7, 42.2, 40.3, 31.8, 29.4, 29.2, 23.7, 22.6, 14.1; IR (cm^{-1}): 3334, 2952, 2919, 2849, 1706, 1054, 729; HRMS (ESI)

m/z calcd. For $C_{19}H_{25}BrNO$ $[M-H]^-$: 362.1119; found: 362.1110.

*1-(benzyloxy)-3-phenylpropan-2-one (**5y**).* Colorless oil (30 mg, 63%); ^1H NMR (400 MHz $CDCl_3$) δ 7.44-7.25 (m, 8H), 7.23-7.13 (m, 2H), 4.55 (s, 2H), 4.11 (s, 2H), 3.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 137.0, 133.3, 129.4, 128.7, 128.5, 128.0, 127.9, 127.0, 74.3, 73.3, 46.2; IR (cm^{-1}): 2917, 1724, 1495, 1453, 1094, 695; HRMS (ESI) m/z calcd. for $C_{16}H_{15}O_2$ $[M-H]^-$: 239.1067, found: 239.1062.

*1-((2-chloro-5-fluorobenzyl)oxy)-3-phenylpropan-2-one (**5z**).* Colorless oil (37 mg, 63%); ^1H NMR (400 MHz $CDCl_3$) δ 7.39-7.25 (m, 4H), 7.24-7.13 (m, 3H), 6.94 (td, J = 8.3, 3.0 Hz, 1H), 4.60 (s, 2H), 4.22 (s, 2H), 3.80 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 162.7, 160.3, 137.3 (d, J = 6.7 Hz), 133.1, 130.4 (d, J = 7.6 Hz), 129.4, 128.8, 127.2, 115.8 (d, J = 6.7 Hz), 115.6 (d, J = 8.6 Hz), 75.1, 69.9, 46.3; ^{19}F NMR: δ 114.70; IR (cm^{-1}): 2921, 1725, 1472, 1154, 699; HRMS (ESI) m/z calcd. for $C_{16}H_{14}ClFO_2Na$ $[M+Na]^+$: 315.0558, found: 315.0548.

*1-(1-(4-(methylsulfonyl)phenyl)ethoxy)-3-phenylpropan-2-one (**5aa**).* Colorless oil (43 mg, 65%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 7.36-7.26 (m, 3H), 7.22-7.11 (m, 2H), 4.50 (q, J = 6.4 Hz, 1H), 3.98 (d, J = 5.6 Hz, 2H), 3.74 (s, 2H), 3.04 (s, 3H), 1.48 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 149.0, 139.8, 133.1, 129.3, 128.7, 127.8, 127.2, 127.0, 77.8, 46.4, 44.4, 23.7; IR (cm^{-1}): 2985, 1725, 1305, 1047, 699; HRMS (ESI) m/z calcd. for $C_{18}H_{20}O_4SNa$ $[M+Na]^+$: 355.0980; found: 355.0975.

*1-(2,4-dichlorophenethoxy)-3-phenylpropan-2-one (**5ab**).* Colorless oil (52 mg, 80%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 2.3 Hz, 1H), 7.33-7.26 (m, 2H), 7.22 (d, J = 8.7 Hz, 2H), 7.19-7.10 (m, 3H), 4.07 (s, 2H), 3.71 (s, 2H), 3.66 (t, J = 6.9 Hz, 2H), 3.01 (t, J = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 134.6, 133.3, 132.8, 132.0, 129.4, 129.2, 128.7, 127.1, 127.0, 75.0, 70.2, 46.1, 33.3; IR (cm^{-1}): 2933, 1722, 1242, 1104, 699; HRMS (ESI) m/z calcd. For $C_{17}H_{15}Cl_2O_2$ $[M-H]^-$: 321.0448; found: 321.0445.

*4-phenoxy-1-phenylbutan-2-one (**5ac**).* Colorless oil (25 mg, 53%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 2H), 7.30-7.25 (m, 3H), 7.24-7.18 (m, 2H), 6.98-6.90 (m, 1H), 6.89-6.80 (m, 2H), 4.20 (t, J = 6.4 Hz, 2H), 3.77 (s, 2H), 2.91 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 158.4, 133.7, 129.5, 129.4, 128.8, 127.1, 120.9, 114.4, 62.8, 50.7, 41.2; IR (cm^{-1}): 2927, 1702, 1498, 1392, 1245, 1038, 744, 691; HRMS (ESI) m/z calcd. for $C_{16}H_{15}O_2$ $[M-H]^-$: 239.1071, found: 239.1077.

*1-((2,4-dichlorobenzyl)oxy)-3-phenylpropan-2-one (**5ad**).* Colorless oil (33 mg, 53%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.37 (m, 2H), 7.37-7.27 (m, 3H), 7.26-7.19 (m, 3H), 4.61 (s, 2H), 4.21 (s, 2H), 3.80 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 134.1, 133.7, 133.6, 133.5, 133.1, 129.9, 129.4, 129.1, 128.7, 127.2, 74.8, 69.7, 46.3; IR (cm^{-1}): 2922, 1728, 1474, 1057, 1043, 816; HRMS (ESI) m/z calcd. for $C_{16}H_{14}Cl_2O_2Na$ $[M+Na]^+$: 331.0263; found: 331.0259.

1-hydroxy-3-phenylpropan-2-one (***5ae***). Colorless oil (22 mg, 72%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.27 (m, 3H), 7.25-7.18 (m, 2H), 4.30 (s, 2H), 3.73 (s, 2H), 3.02 (t, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 132.6, 129.2, 128.9, 127.4, 67.6, 45.7; IR (cm^{-1}): 3421, 1718, 1403, 1047, 699; HRMS (ESI) m/z calcd. for $C_9H_{10}O_2Na$ $[M+Na]^+$: 173.0573; found: 173.0571.

*7-phenoxy-1-phenylheptan-2-one (**5af**).* Colorless oil (38 mg, 67%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, J = 7.3 Hz, 2H), 7.29-7.22 (m, 3H), 7.19 (d, J = 7.3 Hz, 2H), 6.92 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 3.90 (t, J = 6.4 Hz, 2H), 3.67 (s, 2H), 2.47 (t, J = 7.3 Hz, 2H), 1.81-1.68 (m, 2H), 1.67-1.57 (m, 2H), 1.48-1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 158.9, 134.2, 129.4, 129.3(7), 128.7, 126.9, 120.5, 114.4, 67.4, 50.2, 41.7, 29.0, 25.5, 23.3; IR (cm^{-1}): 2930, 1708, 1602, 1473, 1478, 748, 692; HRMS (ESI) m/z calcd. for $C_{19}H_{21}O_2$ $[M-H]^-$: 281.1541, found: 281.1550.

1-phenyl-4-(phenylsulfonyl)butan-2-one (***5ag***). Colorless oil (37 mg, 64%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.88-7.80 (m, 2H), 7.68-7.62 (m, 1H), 7.58-7.50 (m, 2H), 7.38-7.26 (m, 3H), 7.18-7.09 (m, 2H), 3.70 (s, 2H), 3.34 (t, J = 7.5 Hz, 2H), 2.94 (t, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 138.9, 133.9, 133.1, 129.3, 128.9, 127.9, 127.4, 50.5, 50.0, 34.2; IR (cm^{-1}): 2917, 1718, 1305, 699; HRMS (ESI) m/z calcd. for $C_{16}H_{16}O_3SNa$ $[M+Na]^+$: 311.0712, found: 311.0701.

*2-oxo-3-phenylpropyl acetate (**5ah**).* Colorless oil (25 mg, 66%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 3H), 7.24-7.17 (m, 2H), 4.69 (s, 2H), 3.74 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 170.1, 132.7, 129.3, 128.8, 127.4, 67.4, 46.4, 20.4; IR (cm^{-1}): 2932, 1716, 1498, 699; HRMS (ESI) m/z calcd. for $C_{11}H_{12}O_3Na$ $[M+Na]^+$: 215.0678, found: 215.0679.

*diethyl 2-(2-oxo-3-phenylpropyl)malonate (**5ai**).* Colorless oil (47 mg, 80%); ^1H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 2H), 7.29-7.25 (m, 1H), 7.23-7.16 (m, 2H), 4.16 (qd, J = 7.1, 3.0 Hz, 4H), 3.83 (t, J = 7.1 Hz, 1H), 3.74 (s, 2H), 3.04 (d, J = 7.3 Hz, 2H), 1.23 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 168.7, 133.5, 129.4, 128.7, 127.1, 61.7, 49.8, 47.0, 40.5, 13.9; IR (cm^{-1}): 2957, 1722, 1333, 1177, 700; HRMS (ESI) m/z calcd. for $C_{16}H_{20}O_5$ $[M-H]^-$: 291.1227, found: 291.1224.

*2-(4-oxo-5-phenylpentyl)isoindoline-1,3-dione (**5aj**).* Colorless oil (44 mg, 71%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (q, J = 2.9 Hz, 2H), 7.71 (q, J = 2.9 Hz, 2H), 7.34-7.27 (m, 2H), 7.26-7.20 (m, 1H), 7.20-7.15 (m, 2H), 3.67 (m, 4H), 2.52 (t, J = 7.1 Hz, 2H), 2.02-1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 168.4, 134.1, 133.9, 132.0, 129.4, 128.6, 126.9, 123.2, 50.0, 38.9, 37.1, 22.6; IR (cm^{-1}): 2923, 1770, 1703, 1437, 1394, 699; HRMS (ESI) m/z calcd. for $C_{19}H_{16}NO_3$ $[M-H]^-$: 306.1129, found: 306.1130.

*1-(pentyloxy)-3-phenylpropan-2-one (**5ak**).* Colorless oil (28 mg, 64%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 2H), 7.28-7.25 (m, 1H), 7.24-7.18 (m, 2H), 4.06 (s, 2H), 3.77 (s, 2H), 3.43 (t, J = 6.6 Hz, 2H), 1.68-1.56 (m, 2H), 1.40-1.26 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 133.5, 129.4, 128.6, 127.0, 75.4, 71.9, 46.1, 29.2, 28.1, 22.4, 14.0; IR (cm^{-1}): 2955, 2931, 1723, 1454, 1100, 730, 698; HRMS (ESI) m/z calcd. for $C_{14}H_{20}O_2$ $[M-H]^-$: 219.1379, found: 219.1374.

*11-hydroxy-1-phenylundecan-2-one (**5al**).* Colorless oil (26 mg, 50%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 2H), 7.28-7.22 (m, 1H), 7.22-7.15 (m, 2H), 3.66 (s, 2H), 3.62 (t, J = 6.6 Hz, 2H), 2.42 (t, J = 7.3 Hz, 2H), 1.65-1.45 (m, 2H), 1.35-1.15 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 134.3, 129.3, 128.6, 126.9, 63.0, 50.1, 41.9, 32.7, 29.3, 29.2(9), 29.2, 29.0, 25.6, 23.7; IR (cm^{-1}): 3357, 2923, 2848, 1705, 1074, 699; HRMS (ESI) m/z calcd. for $C_{17}H_{25}O_2$ $[M-H]^-$: 261.1854, found: 261.1848.

*1,5-diphenylpentan-2-one (**5am**).* Colorless oil (19 mg, 40%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.29 (m, 2H), 7.29-

7.22 (m, 3H), 7.21-7.16 (m, 3H), 7.12-7.05 (m, 2H), 3.65 (s, 2H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.46 (t, *J* = 7.3 Hz, 2H), 1.94-1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 141.5, 134.2, 129.3, 128.6, 128.4, 128.3, 126.9, 125.8, 50.1, 41.0, 34.9, 25.1; IR (cm^{-1}): 2928, 1710, 1495, 1463, 697; HRMS (ESI) m/z calcd. for $C_{17}H_{17}O$ $[M-H]^-$: 237.1279, found: 237.1283.

*1-phenylhexan-2-one (**5an**).* Colorless oil (23 mg, 65%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 2H), 7.29-7.23 (m, 1H), 7.23-7.16 (m, 2H), 3.68 (s, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 1.59-1.48 (m, 2H), 1.31-1.21 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 134.3, 129.3, 128.6, 126.9, 50.1, 41.7, 25.8, 22.2, 13.8; IR (cm^{-1}): 2957, 2931, 1710, 1495, 1465, 697; HRMS (ESI) m/z calcd. for $C_{12}H_{16}ONa$ $[M+Na]^+$: 199.1093, found:199.1084.

*4-cyclohexyl-1-phenylbutan-2-one (**5ao**).* Colorless oil (36 mg, 79%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39-7.29 (m, 2H), 7.29-7.23 (m, 1H), 7.22-7.17 (m, 2H), 3.66 (s, 2H), 2.32 (d, *J* = 6.9 Hz, 2H), 1.92-1.76 (m, 1H), 1.69-1.54 (m, 6H), 1.31-1.18 (m, 4H), 0.93-0.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 134.29, 129.4, 128.6, 126.9, 50.7, 49.6, 33.7, 33.1, 29.6, 26.1, 26.0; IR (cm^{-1}): 2957, 2917, 1735, 1193, 852, 755; HRMS (ESI) m/z calcd. for $C_{16}H_{21}O$ $[M-H]^-$: 229.1592, found: 229.1592.

*1,10-diphenyldecane-2,9-dione (**5ap**).* Colorless oil (32 mg, 50%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 4H), 7.27-7.22 (m, 2H), 7.21-7.15 (m, 4H), 3.65 (s, 4H), 2.39 (t, *J* = 7.3 Hz, 4H), 1.54-1.38 (m, 4H), 1.28-1.08 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 134.3, 129.3, 128.6, 126.9, 50.1, 41.7, 28.7, 23.4; IR (cm^{-1}): 2931, 1706, 1498, 1455, 696; HRMS (ESI) m/z calcd. for $C_{22}H_{25}O_2$ $[M-H]^-$: 321.1854, found: 321.1850.

*1,4-diphenylbutan-2-one (**5aq**).* Colorless oil (27 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.22 (m, 5H), 7.20-7.07 (m, 5H), 3.65 (s, 2H), 2.97-2.81 (m, 2H), 2.80-2.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 140.8, 134.0, 129.3, 128.7, 128.4, 128.2, 127.0, 126.0, 50.3, 43.4, 29.7; IR (cm^{-1}): 2929, 1708, 1497, 1364, 700; HRMS (ESI) m/z calcd. for $C_{16}H_{15}O$ $[M-H]^-$: 223.1122, found: 223.1122.

*5-chloro-1-phenylpentan-2-one (**5ar**).* Colorless oil (32 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.31 (m, 2H), 7.30-7.26 (m, 1H), 7.25-7.18 (m, 2H), 3.71 (s, 2H), 3.53 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 6.9 Hz, 2H), 2.19-1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.2, 133.9, 129.3, 128.7, 127.1, 50.2, 44.3, 38.5, 26.2; IR (cm^{-1}): 2921, 2850, 1710, 1495, 1448, 698; HRMS (ESI) m/z calcd. for $C_{11}H_{12}ClO$ $[M-H]^+$: 195.0576, found:195.0576.

*4-bromo-1-phenylbutan-2-one (**5as**).* Colorless oil (28 mg, 61%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (m, 2H), 7.31-7.27 (m, 1H), 7.24-7.17 (m, 2H), 3.72 (s, 2H), 3.52 (t, *J* = 6.9 Hz, 2H), 3.03 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 133.3, 129.4, 128.8, 127.3, 50.4, 44.3, 25.2; IR (cm^{-1}): 2922, 1716, 1495, 1454, 699; HRMS (ESI) m/z calcd. for $C_{10}H_{11}BrONa$ $[M+Na]^+$: 248.9885, found: 248.9886.

*5-chloro-1-(1H-indol-3-yl)pentan-2-one (**5at**).* Colorless oil (38 mg, 81%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.21 (td, *J* = 7.5, 1.1 Hz, 1H), 7.17-7.07 (m, 2H), 3.83 (s, 2H), 3.56-3.46 (m, 2H), 2.67 (t, *J* = 7.1 Hz, 2H), 2.08-1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 136.1, 127.2, 123.1, 122.4, 119.9, 118.6, 111.2, 108.6, 44.4, 40.1, 37.9, 26.4; IR (cm^{-1}): 3350, 1708, 1455, 742; HRMS (ESI) m/z calcd. For $C_{13}H_{13}ClNO$ $[M-H]^-$: 234.0685; found: 234.0679.

*diethyl 2-(3-(1H-indol-3-yl)-2-oxopropyl)malonate (**5au**).* Colorless oil (52 mg, 78%); 1H-NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.20 (td, *J* = 7.5, 1.2 Hz, 1H), 7.17-7.09 (m, 2H), 4.14 (qd, *J* = 7.2, 1.7 Hz, 4H), 3.87 (s, 2H), 3.83 (t, *J* = 3.7 Hz, 1H), 3.08 (d, *J* = 7.3 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 168.9, 136.1, 127.2, 123.2, 122.3, 119.9, 118.6, 111.2, 108.2, 61.6, 47.0, 40.0, 39.7, 13.9; IR (cm^{-1}): 3398, 2933, 1717, 1178, 744; HRMS (ESI) m/z calcd. For $C_{18}H_{20}NO_5$ $[M-H]^-$: 330.1341; found: 330.1339.

*4-(1H-indol-3-yl)-1-tosylbutan-2-one (**5av**).* Colorless oil (49 mg, 72%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.14-7.08 (m, 2H), 3.82 (s, 2H), 3.30 (t, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 144.8, 136.1, 135.9, 129.9, 127.9, 127.0, 123.3, 122.5, 120.0, 118.5, 111.3, 107.7, 50.7, 40.0, 33.7, 21.6; IR (cm^{-1}): 3387, 2923, 1712, 1285,720; HRMS (ESI) m/z calcd. For $C_{19}H_{18}NO_3S$ $[M-H]^-$: 340.1007; found: 340.1006.

*1-(1H-indol-3-yl)-5-phenylpentan-2-one (**5aw**).* Colorless oil (44 mg, 80%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.24-7.18 (m, 3H), 7.18-7.12 (m, 2H), 7.12-7.09 (m, 1H), 7.07 (d, *J* = 7.3 Hz, 2H), 3.78 (s, 2H), 2.57-2.47 (m, 4H), 1.92-1.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 141.6, 136.1, 128.4, 128.2, 127.3, 125.8, 123.0, 122.3, 119.8, 118.7, 111.1, 108.8, 40.5, 39.9, 34.9, 25.2; IR (cm^{-1}): 3289, 2927, 743, 699 ; HRMS (ESI) m/z calcd. For $C_{19}H_{18}NO$ $[M-H]^-$: 276.1388; found: 276.1386.

*2-(5-(1H-indol-3-yl)-4-oxopentyl)isoindoline-1,3-dione (**5ax**).*Colorless oil (58 mg, 84%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.81 (q, *J* = 2.9 Hz, 2H), 7.69 (q, *J* = 2.7 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.21-7.14 (m, 1H), 7.14-7.04 (m, 2H), 3.81 (s, 2H), 3.65 (t, *J* = 6.6 Hz, 2H), 2.54 (t, *J* = 7.3 Hz, 2H), 2.00-1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 168.4, 136.1, 133.8, 132.0, 123.2, 123.1, 122.2, 119.8, 118.7, 111.1, 108.7, 39.8, 38.4, 37.2, 22.7; IR (cm^{-1}): 3383, 2917, 1769, 1698, 1395, 715; HRMS (ESI) m/z calcd. For $C_{21}H_{17}N_2O_3$ $[M-H]^-$: 345.1238; found: 345.1235.

Synthetic procedure and characterization data of compounds 5a'. Pyridine N-oxide and Tf_2NH were premixed in a molar ratio of 1.2/1.1, then stored in a vial and used directly for reaction. PPh_3AuNTf_2 (3.7 mg, 0.25 equiv.) was added into a mixture of undec-1-yne (31.4 mg, 0.2 mmol), premixed salt (82.7 mg, 1.1 equiv.), HFIP (0.2 mL) or benzene in a vial at room temperature. The reaction mixture was then stirred at room temperature and the progress of the reaction was monitored by TLC (PE/EA = 10/1, visualization reagent: $KMnO_4/H_2SO_4$). After the reaction was completed (typically 2.5h), Then the reaction vial was heated to 100 ^oC for 1h. The reaction was monitored by TLC (DCM/MeOH = 20/1. After the reaction was finished, the mixture was concentrated and the residue was purified by flash chromatography on silica gel (eluent: DCM/MeOH = 30/1) to afford the desired product **5a'.**

*1-(2-oxoundecyl)pyridin-1-ium triflimide (**5a'**).* Colorless oil (39 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 5.5 Hz, 2H), 8.54-8.46 (m, 1H), 8.08-7.99 (m, 2H), 5.66 (s, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 1.69-1.60 (m, 2H), 1.43-1.14 (m, 12H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 145.7, 145.6, 121.2, 118.3, 68.2, 40.1, 31.8, 29.3, 29.2, 29.1, 28.9, 22.9, 22.6, 14.0; IR (cm^{-1}): 2925, 2856, 1735, 1638,

1491, 1348, 1132; HRMS (ESI) m/z calcd. for $C_{16}H_{26}NO$ $[M]^+$: 248.2009; found: 248.2009.

Synthetic procedure and characterization data of compounds 5m'. Pyridine N-oxide and Tf_2NH were premixed in a molar ratio of 1.2/1.1, then stored in a vial and used directly for reaction. PPh_3AuNTf_2 (3.7 mg, 0.25 equiv.) was added into a mixture of undec-1-yne (31.4 mg, 0.2 mmol), premixed salt (82.7 mg, 1.1 equiv.), HFIP (0.2 mL) or benzene in a vial at room temperature. The reaction mixture was then stirred at room temperature and the progress of the reaction was monitored by TLC (PE/EA = 10/1, visualization reagent: $KMnO_4/H_2SO_4$). After the reaction was completed (typically 2.5h), the reaction mixture was added with pyrrole (40.2 mg, 3 equiv.). Then the reaction vial was sealed and heated to 90 °C. The reaction was monitored by TLC (DCM/MeOH = 50/1, visualization reagent: $KMnO_4/H_2SO_4$). After the reaction was finished, the mixture was concentrated and the residue was purified by flash chromatography on silica gel (eluent: hexanes/ethyl acetate 10/1) to afford the desired product **5m'**.

*3,3',3''-(undecane-1,2,2-triyl)tris(1H-pyrrole) (**5m'**).* Colorless oil (42 mg, 60%);^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 2H), 7.10 (s, 1H), 6.68-6.55 (m, 2H), 6.51-6.41 (m, 1H), 6.17 (q, J = 2.9 Hz, 2H), 6.15-6.08 (m, 2H), 6.03 (q, J = 2.9 Hz, 1H), 5.91 (t, J = 3.4 Hz, 1H), 3.24 (s, 2H), 1.98-1.72 (m, 2H), 1.35-1.02 (m, 12H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 128.5,117.1, 117.0, 108.1, 107.9, 107.4, 105.7, 43.5, 39.3, 37.4, 31.8, 30.0, 29.5, 29.5, 29.2, 24.2, 22.6, 14.1; IR (cm^{-1}): 3385, 2923, 2853, 1455, 713; HRMS (ESI) m/z calcd. For $C_{23}H_{32}N_3$ $[M-H]^-$: 350.2595; found: 350.2611.

ASSOCIATED CONTENT

*Supporting Information

The Supporting Information is available free of charge on the

ACS Publications website at DOI: xx.xxxx/acs.joc.xxxxxx.

Screening of catalysts and conditions optimization, Determination of rate determining step by kinetic isotopic effect, copies of ^{1}HNMR and ^{13}C NMR spectra for all products were performed (PDF).

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Notes

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