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Mn-Enabled Radical-Based alkyl–alkyl Cross-Coupling Reaction from 4-Alkyl-1,4-dihydropyridines

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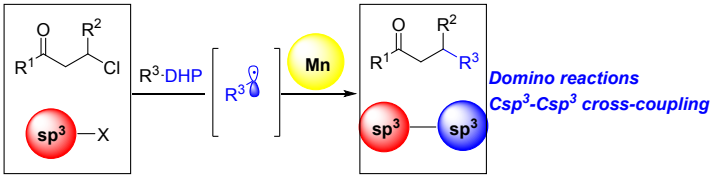


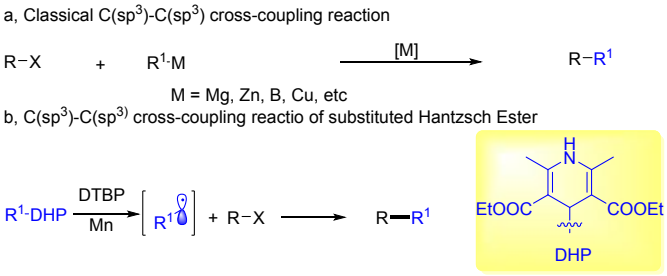
ABSTRACT: Highly efficient alkylation of *β*-chloro ketones and their derivatives were achieved by means of domino dehydrochlorination/Mn-Enabled radical-based alkyl-alkyl cross-coupling reaction. In *situ* generated *a,β*-unsaturated ketone and their analogues were identified as the reaction intermediates. Known bioactive compounds, such as Meperone and Azaperone, could be easily prepared from *β*-chloropropiophenone in two steps.

INTRODUCTION

Transition metal-catalyzed cross-coupling reactions with alkyl halides as electrophiles and organometallics as nucleophiles have been extensively explored in the formation of $C(sp^3)$–$C(sp^3)$ bonds.[1] A wide variety of primary alkyl halides/metals can be used as effective substrates in cross-coupling,[2] but the secondary alkyl halides/metals usually remain as challenging substrates due to the side reaction of *β*-hydride elimination and other undesired reactions.[3] Due to the significance of alkyl-alkyl cross-coupling reactions in constructing key intermediates for medical chemistry and natural product synthesis, the development of novel routes to realize the alkyl-alkyl cross-coupling reaction is highly attractive. Herein, a Mn-induced cross-coupling of *β*-chloropropiophenone with alkyl radical derived from 4-alkyl-1,4-dihydropyridines was reported (Scheme 1). A variety of *β*-chloropropiophenones were well tolerated, leading to the corresponding products in

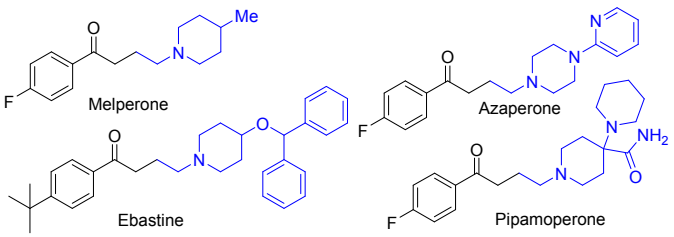
moderate to good yields. The bioactive compounds Meperone and Azaperone could be easily synthesized from *β*-chloropropiophenone in two steps. The preliminary mechanistic study revealed that a domino reaction sequence was involved in this transformation.

Scheme 1. Novel approach to construct C(sp^3)-C(sp^3) bonds.



Alkylphenones are a class of significant compounds, some of which are well-known bioactive compounds, such as Melperone[4], Azaperone[5], Ebastine[6], and Pipamperone (Figure 1). However, to the best of our knowledge, the approach to directly realize cross-coupling of *β*-chloropropiophenone with another secondary alkyl functional group remains relatively unexplored. The major challenge for this alkyl-alkyl cross-coupling reaction is that both coupling partners suffer from side reactions of *β*-hydride elimination[7]. In 2012, the Yu group reported the efficient rhodium(I)-catalyzed arylation of *β*-chloroketones via the domino dehydrochlorination process[8]. 4-Alkyl-1,4-dihydropyridines(Alkyl-DHP)[9], which can be easily prepared from aldehyde in one step, are an important class of free radical precursors. It has been demonstrated that free radicals can be generated via C–C bond cleavage at the 4-position of the dihydro-pyridine ring under thermal or photoredox conditions[10, 29]. Recently, it has been well apply to construct the C(sp^3)–C(sp^3) bonds formation reactions. For example, the direct alkylation of unsaturated olefins[11], heterocycles[12] and imines[13] via the free radical pathway with the 4-Alkyl-1,4-dihydropyridines (Alkyl-DHP) have been well extensively reported.

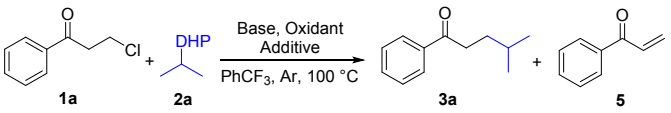
Figure 1. Relevant bioactive alkylphenone compounds.



Thus, the alkyl-alkyl cross-coupling of *β*-chloroketones with an alkyl radical might be achievable via the domino dehydrochlorination process.

RESULTS AND DISCUSSION

Table 1. Optimization of the Mn-induced alkylation of 1a with 2a.[a]



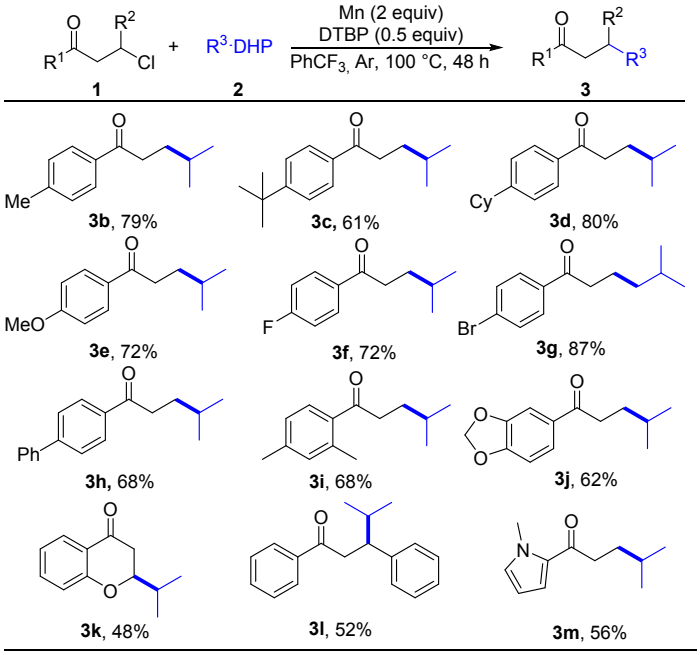
Entry	Base	Additive	Oxidant	Yield	
				3a	**5**
1	K_3PO_4	-	$K_2S_2O_8$	10%	15%
2	K_2CO_3	-	$K_2S_2O_8$	20%	16%
3	$KHCO_3$	-	$K_2S_2O_8$	28%	23%
4	KOAc	-	$K_2S_2O_8$	20%	trace
5	-	-	$K_2S_2O_8$	25%	trace
6	-	-	BPO	trace	trace
7	-	-	*t*-BuOOH	trace	trace
8	-	-	DTBP	32%	trace
9	-	Zn	DTBP	35%	trace
10	-	Cu	DTBP	45%	10%
11	-	In	DTBP	37%	trace
12	-	Mn	DTBP	56%	trace
13[b]	-	Mn	DTBP	65%	trace
14[b,c]	-	Mn	DTBP	82%	trace

[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.15 mmol, 1.5 equiv), Base (2 equiv), Oxidant (2 equiv), Additive (2 equiv), 12 h. [b]0.5 equiv DTBP. [c]Reaction time, 48 h. DTBP = 2-(*tert*-butylperoxy)-2-methylpropane), BPO = Benzoic peroxyanhydride).

With these conditions in mind, we first treated *β*-chloropropiophenone (**1a**) with 4-isopropyl-1,4-dihydropyridine (**2a**) in the presence of $K_2S_2O_8$ and K_3PO_4, in trifluoromethyl benzene at 100 °C for 12 h to investigate whether the alkyl-alkyl cross-coupling could be achieved. The cross-coupling product **3a** was indeed obtained at 10% yield, along with phenylvinylketone (**5**) in 15% yield (Table 1, entry 1). Encouraged by this result, we next screened various bases, such as K_2CO_3, $KHCO_3$, and KOAc, to improve the selectivity of **3a** and **5** (Table 1, entries 2-4). When KOAc was used, a slightly improved yield of **3a** was achieved, along with the side product **5** (entry 4). Interestingly, a better yield of **3a** could be achieved when the reaction was performed without a base (entry 5). A variety of oxidants including DTBP, BPO, and

t-BuOOH, were next investigated to improve the yield of **3a** (entries 6-8). The oxidant DTBP was able to generate the product **3a** in 32% yield, along with recovery of starting material **1a**. To further improve the efficiency of the alky-alkyl cross-coupling reaction, a variety of additives were further explored. The results showed that reducing metals, such as Zn, Cu, In, and Mn, modified the yield and selectivity for this transformation (entries 9-12). When two equivalents of Mn were used, the desired product **3a** was obtained in 56% yield, along with trace amounts of **5**. Additionally, reducing the amount of DTBP to 0.5 equivalents gave an improved yield of **3a** at 65% yield. The yield of **3a** can be improved to 82% when the reaction duration was extended to 48 h(see **ESI**†).

Scheme 2. Substrate scope of *β*-chloropropiophenone.[a]

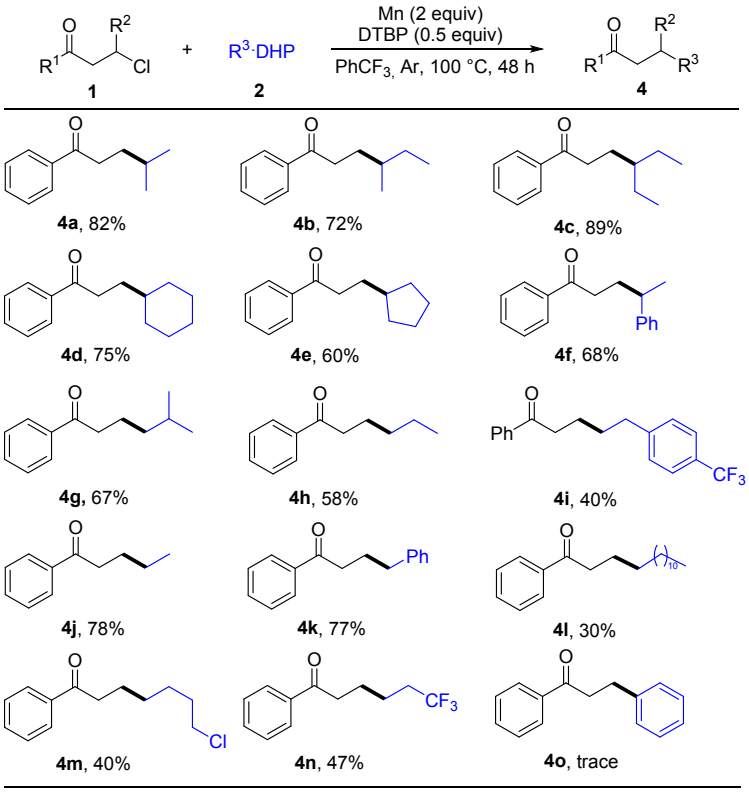


[a]Reaction conditions: **1** (0.1 mmol, 1.0 equiv), **2a** (0.15 mmol, 1.5 equiv), DTBP (0.5 equiv), Mn (2 equiv), $PhCF_3$ (0.25 mL), 100 °C, 48 h, Ar.

With the optimized reaction conditions in hand, we firstly examined the substrate scope of *β*-chloropropiophenone derivatives under standard reaction condition (Scheme 2). Various functional groups, such as Me, *t*-Bu, Cy, MeO, F, and Br, substituted on the phenyl ring were all compatible, leading to the corresponding products (**3b-h**) in 60-90% yields. The disubstituted substrates all performed well, yielding the corresponding products (**3i** and **3j**) in good yields. The secondary *β*-chlorodihydrochalcone was also well tolerated, generating the *β*-isopropylated

dihydrochalcone (**3k**) in moderate yields, along with 17% dehydrochlorided byproducts. The secondary alkyl chloride **1l** performed well, leading to the alkylated product **3l** in 52% yield, along with recovery of the starting material. The *N*-heterocycle substrate **1m** was an effective substrate, affording the alkylated product **3m** in 56% yield, along with 21% of the dehydrochlorided byproduct.

Scheme 3. Substrate scope of Hantzsch esters.[a]



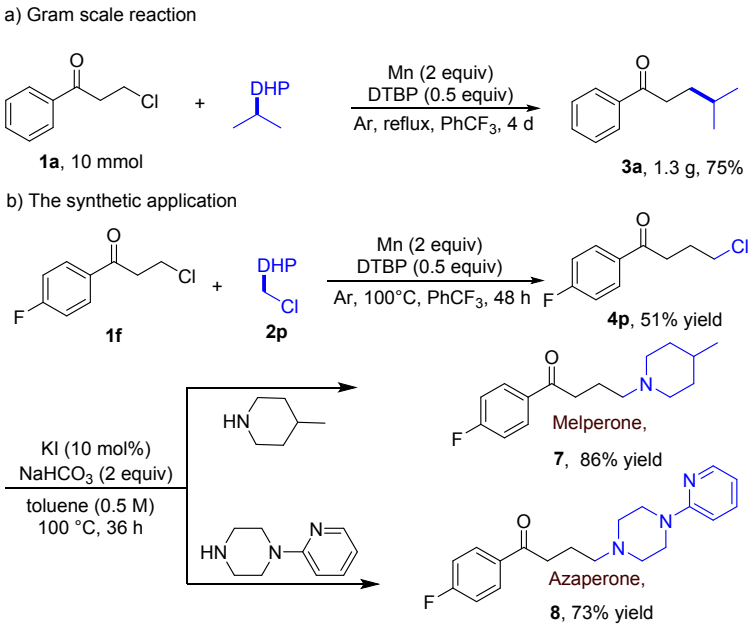
[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2** (0.15 mmol, 1.5 equiv), DTBP (0.5 equiv), Mn (2 equiv), $PhCF_3$ (0.25 mL), 100 °C, 48 h, Ar.

Various 4-alkyl-1,4-dihydropyridines, which were further used as substrates to couple with **1a** under standard reaction conditions, were synthesized. The isobutyl (**4b**), 3-pentyl (**4c**), cyclohexyl (**4d**), cyclopentyl (**4e**), and 1-phenylethyl-1,4-dihydropyridines (**4f**) all performed well, generating the alkylated products in 60-90% yields (Scheme 3). Importantly, the primary radical could be well coupled with **1a**, leading to the alkyl-alkyl coupling products in moderate to good yields (**4g-4k**). The long unbranched carbon chain was compatible in this cross-coupling reaction, but only provided a low yield of the product **4l**. It may be due to the fact that the long carbon chain free alkyl radical is slightly less reactive,

resulting in the byproduct **5** in 35% yield. It is worth noting that there were not any isomerized products formed in these reactions. Particularly, the chloride functional group was well tolerated, yielding the corresponding product **4m** in 40% yield. Trifluoromethyl is a highly important functional group that usually modifies the biochemical activity of a compound. The trifluoropropyl radical can be engaged with **1a**, providing the desired product **4n** in 47% yield, highlighting the synthetic importance of this method. Unfortunately, the phenyl radicals were not tolerated, where only the side product **5** was obtained.

To further demonstrate the synthetic utility of this Mn-enabled radical-based alkyl-alkyl cross-coupling reaction, Gram-scale reactions were further carried out. The scale up reaction proceeded well, leading to the corresponding product **3a** in good yield. Melperone is a well-known drug for the treatment of confusion, anxiety, restlessness (particularly in the elderly)[14] and schizophrenia. Azaperone[15] is capable of eliciting neuroleptic, sedative and antiemetic effects. The key precursor for these two compounds **4p** could be easily prepared in good yield through the cross-coupling of **1f** with **2p**. When the key precursor **2p** was directly treated with the secondary amine, the bioactive compounds, Meperone and Azaperone, were obtained in excellent yields (Scheme 4).[16]

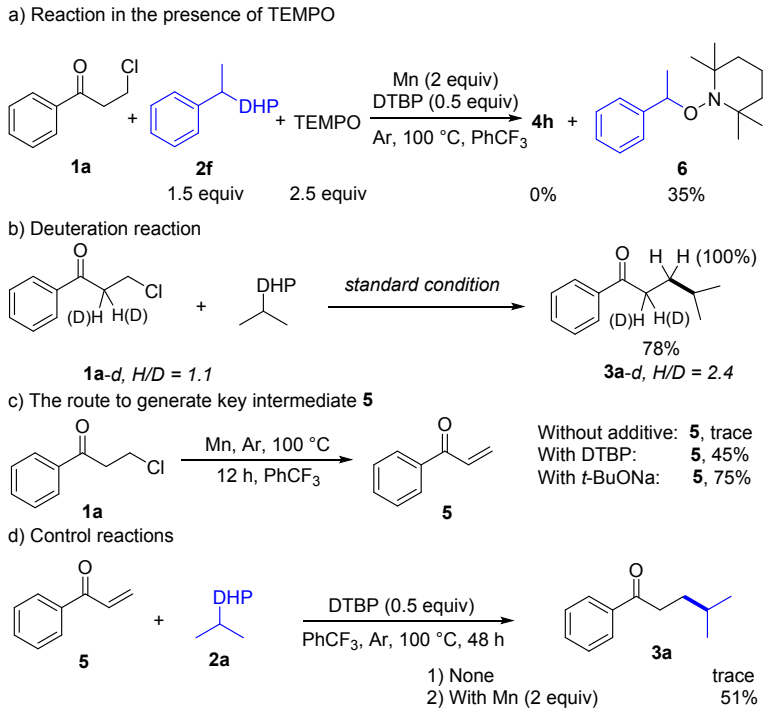
Scheme 4. The Gram scale reaction and synthetic application.



Several parallel reactions were performed to give insight of this reaction pathway

(Scheme 5). First, when the free radical inhibitor TEMPO was added to the reaction, the reaction was completely shut down, along with the recovery of product **6** in 35% yield. This result strongly suggested that the reaction must undergo a radical pathway[17]. Second, deuterated **1a** was prepared and further subjected to the standard reaction conditions[18]. The proportion of deuteration in the alkylated product changed from 48% to 29%, which may indicate that the reaction may have undergone a domino dehydrochlorination process (see **ESI†**).

Scheme 5. Control Experiments

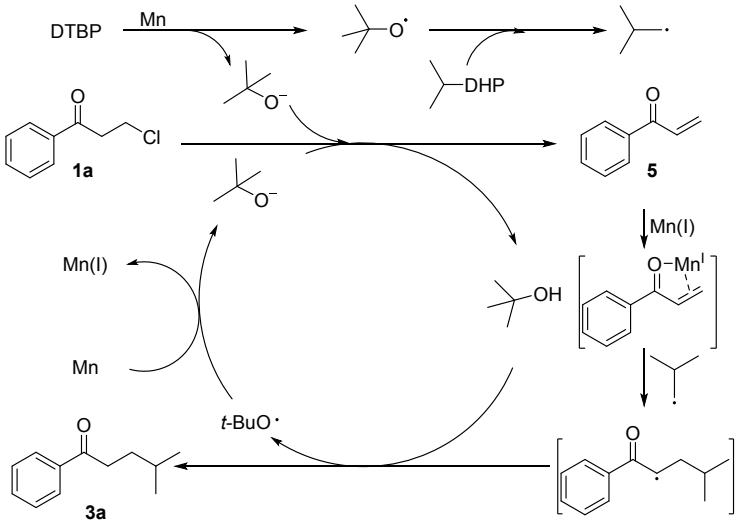


To further support this experimental result, the substrate **1a** was subjected to standard reaction conditions without **2a**, which provided the dehydrochlorided product **5** in 45% yield. When the reaction was carried out without DTBP, only trace amounts of **5** were obtained. It is proposed that the in *situ*-generated *tert*-butanol anion was the key factor to provide intermediate **5**. We subsequently treated **1a** with sodium *tert*-butoxide. As expected, the dehydrochlorided product **5** was observed in 75% yield. These results indicated that the *tert*-butanol anion can result in the key intermediate **5** from **1a**. Finally, when **5** was treated with isopropyl-DHP and DTBP, only trace amounts of **3a** were obtained. Interestingly, the cross-coupling product **3** was obtained in 51% yield when the reactions were carried out under standard reaction conditions. These result may indicate that the in *situ*-generated Mn(I) would

coordinate with the olefin to accelerate the radical addition reaction[19].

Based on these experiment results and previous reports[20], a plausible reaction pathway was proposed in Scheme **6**. First, the reaction undergoes a dehydrochlorination process under assistance of DTBP. The Mn complex coordinates with vinylphenylketone **5** to activate the olefin, which is then followed by radical addition[21] and protonation to release product.

Scheme 6. Plausible Mechanism



In conclusion, we have developed a highly efficient approach to realize the alkyl-alkyl cross-coupling reaction through the direct combination of *β*-chloropropiophenone and 4-alkyl-1,4-dihydropyridines using DTBP as the oxidant and manganese(0) as the effective additive. A variety of *β*-chloropropiophenones were well-tolerated, affording the alkylated products in moderate to good yields. The known bioactive compounds Meperone(**7**) and Azaperone (**8**) could be easily prepared from *β*-chloropropiophenone in two steps. The preliminary mechanistic study indicated that the reaction proceeded through a radical pathway, while the in situ-generated Mn complex coordinated with the olefin to facilitate the radical addition.

EXPERIMENTAL SECTION

General. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Column chromatography purifications were performed using 200–300 mesh silica gel. NMR spectra were recorded on

Varian Inova–400 MHz, Inova–300 MHz, Bruker DRX–400 or Bruker DRX–500 instruments and calibrated using residual solvent peaks as internal reference. Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet. HRMS analysis were carried out using a Bruker micrOTOF–Q instrument or a TOF–MS instrument.

General procedure for the *β*-chloropropiophenone derivatives: [22]

General procedure A: To a solution of aluminium chloride (6.0 mmol, 1.2 equiv) in dry CH_2Cl_2 (5 mL, 1.2 M), 3-chloropropionyl chloride (5.5 mmol, 1.1 equiv) was added dropwise at 0 ^oC, and followed by the addition of substituted benzene(5.0 mmol, 1 equiv) with stirring. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction was quenched by slowly adding crushed ice pieces at 0 ^oC. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic layer was washed with brine (2×5 mL), dried over anhydrous Na_2SO_4 , and evaporated all the volatiles under reduced pressure. The resulting residue was purified by column chromatography (PE/EA = 10/1) on silica gel to give the product. **1b**,[23] **1c**,[24] **1e**,[25] **1i**[26] and **1m**[8] are known compounds.

3-chloro-1-(4-cyclohexylphenyl)propan-1-one (**1d**). White solid, 80%, mp: 46-50 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 3.92 (t, *J* = 6.9 Hz, 2H), 3.43 (t, *J* = 6.9 Hz, 2H), 2.57 (t, *J* = 11.3 Hz, 1H), 1.91 – 1.82 (m, 4H), 1.78 – 1.75 (m, 1H), 1.45 – 1.38 (m, 4H), 1.31 – 1.25 (m, 1H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 196.4, 154.3, 134.3, 128.3, 127.2, 44.7, 41.2, 38.9, 34.1, 26.7, 26.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{19}ClONa$ 273.1022; found 273.1021.

1-([1,1'-biphenyl]-4-yl)-3-chloropropan-1-one (**1h**). White solid, 77%, mp: 105-110 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.64 – 7.62 (m, 2H), 7.50 – 7.46 (m, 1H), 7.43 – 7.40 (m, 2H), 3.96 (t, *J* = 6.8 Hz, 2H), 3.50 (t, *J* = 6.8 Hz, 2H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 196.5, 146.4, 139.8, 135.2, 129.1, 128.8, 128.6, 127.5, 127.4, 41.5, 38.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{13}ClONa$ 267.0553; found 267.0555.

General procedure B: To a mixture of *a, β*-unsaturated ketone (5 mmol, 1 equiv) in CH_2Cl_2 (20 mL, 0.4 M), *t*-BuOCl (5 mmol, 1 equiv) was added and the reaction mixture was stirred at room temperature. On completion (the reaction was monitored by TLC), the mixture was quenched with cold water, extracted with $CHCl_3$, dried over

anhydrous Na_2SO_4, and evaporated all the volatiles under reduced pressure. The resulting residue was purified by column chromatography (PE/EA = 10/1) on silica gel to give the product.

General procedure C:[27] To a mixture of 1-phenylprop-2-en-1-one (264.1 mg, 2 mmol) and DCl (74.0 mg, 2 mmol) in Et_2O (10 mL, 0.2 M) and the reaction mixture was stirred at room temperature. On completion (the reaction was monitored by TLC), the mixture was quenched with cold water, extracted with EA, dried over anhydrous Na_2SO_4, and evaporated all the volatiles under reduced pressure. The resulting residue was purified by column chromatography (PE/EA = 10/1) on silica gel to give the product.

General Procedure for the substituted Hantzsch Ester[28]

General procedure D: Over a solution of ethyl ethyl acetoacetate (20 mmol, 2.0 equiv), ammonium acetate (20 mmol, 2.0 equiv) and the corresponding aldehyde (10 mmol, 1.0 equiv), VB_1 (0.3 mmol, 3 mol %) was added in one portion. The vial was sealed and heated at 80 ^oC oil bath for 0.5-2 h. After complete consumption of the aldehyde, the reaction was cooled to rt and diluted with EtOAc. The solution was poured into a separatory funnel containing brine and extracted three times with EtOAc. After drying (Na_2SO_4), it was filtered and taken to dryness. The residue was purified by chromatography on silica gel. The resulting residue was purified by column chromatography (PE/EA = 20/1 – 8/1) on silica gel to give the product. **2a**[29]**, 2b, 2c, 2j**[30]**, 2d, 2e, 2f**[31]**, 2g, 2h, 2k and 2o**[28] are known compounds.

Diethyl 2,6-dimethyl-4-(4-(trifluoromethyl)phenethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**2i**), Claybank solid, 65%, mp: 116-120 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.38 (m, 2H), 7.35 – 7.31 (m, 2H), 5.60 (br, 1H), 4.24 – 4.10 (m, 4H), 4.07 (t, J = 5.8 Hz, 1H), 2.63 – 2.57 (m, 2H), 2.29 (s, 6H), 1.71 – 1.64 (m, 2H), 1.28 (t, J = 7.1 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.49. ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 168.0, 145.2, 144.2, 131.8, 130.5(q, J_{C-F} = 31.7 Hz), 128.6, 125.0(q, J_{C-F} = 3.8 Hz), 122.4(q, J_{C-F} = 3.8 Hz), 124.5 (q, J_{C-F} = 272.4 Hz), 103.0, 59.9, 38.0, 33.3, 31.4, 19.6, 14.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{26}F_3NO_4^+$ 426.1892; found 426.1890.

Diethyl 4-(4-chlorobutyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**2m**). Yellow solid, 45%, mp: 62-65 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 5.63 (br, 1H), 4.23 – 4.13 (m, 4H), 3.94 – 3.93 (m, 1H), 3.48 (t, J = 6.8 Hz, 2H), 2.28 (s, 6H), 1.76 – 1.68

(m, 2H), 1.33 (dd, J = 6.3, 3.6 Hz, 4H), 1.29 (t, J = 7.1 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.0, 144.9, 103.0, 59.7, 45.2, 35.9, 32.8, 32.6, 22.3, 19.5, 14.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{26}ClNO_4^+$ 344.1629; found 344.1627.

Diethyl 4-undecyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**2l**). Yellow viscous liquid, 36 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (br, 1H), 4.25 – 4.09 (m, 4H), 3.90 (t, J = 5.8 Hz, 1H), 2.26 (s, 6H), 1.30 – 1.18 (m, 26 H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.2, 144.7, 103.3, 59.6, 36.9, 32.9, 31.9, 30.0, 29.8, 29.7, 29.7, 29.6, 29.3, 24.9, 22.7, 19.4, 14.4, 14.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{41}NO_4^+$ 408.3114; found 408.3112.

General Procedure E: To a flask charged with ethyl acetoacetate (2.60 g, 20 mmol) , the aldehyde (10 mmol) and ethanol (20 mL) was added ammonia aqueous solution (4.0 mL, 28%, 60 mmol). The mixture was heated at 70 ^{o}C oil bath for 8 hours. The reaction was allowed to cool to room temperature. The solution was concentrated under reduced pressure. A mixture of water and CH_2Cl_2 were added to the concentrated residue and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 for 3 times. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel. The resulting residue was purified by column chromatography (PE/EA = 20/1 – 8/1) on silica gel to give the product.

Diethyl 4-chloromethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**2p**). Yellow viscous liquid, 28 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (br, 1H), 4.27 – 4.15 (m, 4H), 4.01 (t, J = 5.4 Hz, 1H), 3.46 (d, J = 5.1 Hz, 2H), 2.29 (s, 6H), 1.30 (t, J = 7.1 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.1, 146.0, 100.3, 67.0, 60.1, 36.7, 19.7, 14.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{20}ClNO_4^+$ 302.1159; found 302.1161.

Diethyl 4-((3,3,3-trifluoropropyl))-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**2n**). Yellow viscous liquid, 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (br, 1H), 4.24 – 4.13 (m, 4H), 4.00 (t, J = 5.6 Hz, 1H), 2.31 (s, 6H), 2.03 – 1.96 (m, 2H), 1.61 – 1.54 (m, 2H), 1.30 (t, J = 4.5 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.12; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.7, 145.9, 127.8(q, J_{C-F} = 276.0 Hz) 102.0, 60.0, 32.3, 30.0(q, J_{C-F} = 28.3 Hz)., 28.6(d, J_{C-F} = 1.5 Hz), 19.6, 14.5. HRMS (ESI-TOF) m/z: $[M + H]^+$

Calcd for $C_{16}H_{22}F_3NO_4^+$ 350.1579; found 350.1580.

Experimental Procedure for the Alkyl–Alkyl Cross-Coupling Reaction: A mixture of **1** (0.1 mmol,1 equiv), **2** (0.15 mmol, 1.5 equiv), Mn (10 mg, 0.4 mmol, 2 equiv), DTBP (10 μL, 0.05 mmol, 0.5 equiv) and $PhCF_3$ (0.25 mL, 0.8 M) in a 15 mL glass vial sealed under argon atmosphere was heated at 100 °C oil bath for 48 hours, The reaction mixture cooled to room temperature and concentrated in vacuo. The resulting residue was purified by column chromatography (PE/EA = 200/1 - 20/1) on silica gel to give the product **3** or **4**.

Phenylprop-2-en-1-one (**5**). Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.1 Hz, 2H), 7.60 – 7.58 (m, 1H), 7.51 – 7.47 (m, 2H), 7.16 (dd, *J* = 17.1, 10.6 Hz, 1H), 6.44 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.94 (dd, *J* = 10.6, 1.7 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.0, 137.3, 133.0, 132.4, 130.1, 128.7, 128.6.

4-methyl-1-(p-tolyl)pentan-1-one[32] (**3b**). Yellow oil, 15.1mg, 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 6.7 Hz, 2H), 2.96 – 2.90 (m, 2H), 2.41 (s, 3H), 1.64 – 1.61 (m, 3H), 0.94 (d, *J* = 6.1 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.5, 143.8, 135.0, 129.2, 128.2, 36.6, 33.4, 27.9, 22.5, 21.6.

1-(4-(tert-butyl)phenyl)-4-methylpentan-1-one[33] (**3c**). Yellow oil, 14.1mg, 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 2.98 – 2.91 (m, 2H), 1.67 – 1.59 (m, 3H), 1.34 (s, 9H), 0.94 (d, *J* = 6.2 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.5, 156.5, 134.5, 128.0, 125.5, 36.6, 35.1, 33.4, 31.1, 27.9, 22.5.

1-(4-cyclohexylphenyl)-4-methylpentan-1-one (**3d**). Yellow oil, 20.6mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 2.97 – 2.89 (m, 2H), 2.56 (t, *J* = 11.4 Hz, 1H), 1.86 (t, *J* = 6.1 Hz, 4H), 1.76 – 1.75 (m, 1H), 1.66 – 1.61 (m, 3H), 1.45 – 1.38 (m, 4H), 1.31 – 1.22 (m, 1H), 0.94 (d, *J* = 6.3 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.5, 153.5, 135.0, 128.3, 127.0, 44.7, 36.5, 34.1, 33.4, 27.9, 26.8, 26.1, 22.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{26}O^+$ 259.2062; found 259.2059.

1-(4-methoxyphenyl)-4-methylpentan-1-one (**3e**). Yellow oil, 14.8mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.94 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 2.94 – 2.88 (m, 2H), 1.64 – 1.60 (m, 3H), 0.94 (d, *J* = 6.3 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 199.4, 163.3, 130.3, 130.2, 113.7, 55.5, 36.3, 33.5, 27.9, 22.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{18}O_2Na$ 229.1199; found 229.1183.

1-(4-fluorophenyl)-4-methylpentan-1-one (**3f**). Yellow oil, 18.4 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.98 (dd, *J* = 8.1, 5.8 Hz, 2H), 7.12 (t, *J* = 8.5 Hz, 2H), 2.97 – 2.90 (m, 2H), 1.66 – 1.59 (m, 3H), 0.94 (d, *J* = 5.7 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 198.1, 164.6 (d, *J* = 254.3 Hz), 132.5 (d, *J* = 3.0 Hz), 129.6 (d, *J* = 9.3 Hz), 114.6 (d, *J* = 21.8 Hz), 35.5, 32.1, 26.8, 21.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{15}FONa$ 217.1005; found 217.1005.

1-(4-bromophenyl)-4-methylpentan-1-one (**3g**). Yellow oil, 23.4 mg, 87%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.84 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 2.99 – 2.86 (m, 2H), 1.79 – 1.68 (m, 2H), 1.61 – 1.57 (m, 1H), 1.40 – 1.21 (m, 4H), 0.92 (d, *J* = 6.6 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 199.5, 135.8, 131.9, 129.6, 128.0, 38.8, 38.6, 27.9, 22.5, 22.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{17}BrONa$ 292.1718; found 292.1716.

1-([1,1'-biphenyl]-4-yl)-4-methylpentan-1-one (**3h**). Yellow oil, 17.1mg, 68%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 8.04 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 7.1 Hz, 2H), 7.47 (d, *J* = 7.7 Hz, 2H), 7.42 – 7.38 (m, 1H), 3.03 – 2.96 (m, 2H), 1.70 – 1.64 (m, 3H), 0.97 (d, *J* = 6.3 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 200.5, 145.7, 140.1, 135.9, 129.1, 128.8, 128.3, 127.4, 127.3, 36.8, 33.5, 28.0, 22.6; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{20}ONa$ 275.1412; found 275.1404.

1-(2,4-dimethylphenyl)-4-methylpentan-1-one (**3i**). Yellow oil, 13.9 mg, 68%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.57 (d, *J* = 8.3 Hz, 1H), 7.05 (m, 2H), 2.91 – 2.83 (m, 2H), 2.47 (s, 3H), 2.35 (s, 3H), 1.63 – 1.55 (m, 3H), 0.93 (d, *J* = 6.0 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 204.4, 141.6, 138.4, 135.3, 132.8, 128.8, 126.2, 39.4, 33.5, 27.9, 22.5, 21.4, 21.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{20}ONa$ 227.1412; found 227.1414.

1-(benzo[d][1,3]dioxol-5-yl)-4-methylpentan-1-one (**3j**). Yellow oil, 13.6 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.56 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.44 (d, *J* = 1.6 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.04 (s, 2H), 2.92 – 2.82 (m, 2H), 1.63 – 1.59 (m, 3H), 0.94 (d, *J* = 6.2 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 197.9, 150.5, 147.1, 131.0, 123.2, 106.9, 106.8, 100.8, 35.4, 32.5, 26.9, 21.4; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{16}O_3Na$ 243.0997; found 243.0998.

2-isopropylchroman-4-one (**3k**). Yellow oil, 9.1 mg, 48%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.87 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.01 – 6.97 (m, 2H), 4.22 – 4.16 (m, 1H), 2.75 – 2.62 (m, 2H), 2.08 – 2.03 (m, 1H), 1.08 (d, *J* = 6.8

Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 193.1, 161.9, 135.9, 126.9, 121.1, 117.9, 82.5, 40.1, 32.2, 17.8. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{12}H_{14}O_2Na$ 213.0891; found 213.0887.

4-methyl-1,3-diphenylpentan-1-one (**3l**). Yellow oil, 13.1 mg, 52%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.90 – 7.85 (m, 2H), 7.54 – 7.50 (m, 1H), 7.44 – 7.40 (m, 2H), 7.26 – 7.23 (m, 3H), 7.21 – 7.13 (m, 2H), 3.36 (d, J = 6.7 Hz, 2H), 3.17 (q, J = 7.1 Hz, 1H), 1.97 – 1.92 (m, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 199.6, 143.8, 137.5, 132.9, 128.6, 128.5, 128.2, 128.1, 126.3, 48.0, 42.7, 33.4, 21.1, 20.5. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{18}H_{20}ONa$ 275.1412; found 275.1400.

4-methyl-1-(1-methyl-1H-pyrrol-2-yl)pentan-1-one (**3m**). Yellow oil, 10.0 mg, 56%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 6.95 (dd, J = 4.1, 1.6 Hz, 1H), 6.79 – 6.78 (m, 1H), 6.11 (dd, J = 4.0, 2.5 Hz, 1H), 3.93 (s, 3H), 2.79 – 2.73 (m, 2H), 1.63 – 1.59 (m, 3H), 0.93 (d, J = 6.2 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 192.1, 130.9, 119.0, 107.9, 37.8, 37.3, 34.4, 28.1, 22.6; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{10}H_{16}NO$ 166.1232; found 166.1234.

4-methyl-1-phenylpentan-1-one (**4a**). Yellow oil, 14.2 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.9 (d, J = 7.2 Hz, 2H), 7.56 – 7.53 (m, 1H), 7.47 – 7.43 (m, 2H), 3.01 – 2.93 (m, 2H), 1.65 – 1.62 (m, 3H), 0.95 (d, J = 6.3 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 200.8, 137.1, 132.9, 128.6, 128.1, 36.6, 33.3, 27.9, 22.5; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{12}H_{16}ONa$ 199.1099; found 199.1093.

4-methyl-1-phenylhexan-1-one[34] (**4b**). Yellow oil, 13.6 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.96 (d, J = 7.1 Hz, 2H), 7.57 – 7.53 (m, 1H), 7.48 – 7.44 (m, 2H), 2.99 – 2.94 (m, 2H), 1.83 – 1.72 (m, 1H), 1.58 – 1.50 (m, 1H), 1.48 – 1.33 (m, 2H), 1.23 – 1.16 (m, 1H), 0.93 (d, J = 6.5 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 201.1, 137.2, 133.0, 128.7, 128.2, 36.5, 34.4, 31.1, 29.5, 19.2, 11.5; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{13}H_{18}ONa$ 190.1358; found 190.1355.

4-ethyl-1-phenylhexan-1-one (**4c**). Yellow oil, 18.2 mg, 89%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.96 (m, 2H), 7.57 – 7.53 (m, 1H), 7.48 – 7.44 (m, 2H), 2.97 – 2.91 (m, 2H), 1.72 – 1.67 (m, 2H), 1.37 – 1.32 (m, 5H), 0.88 (t, J = 7.3 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 201.0, 137.1, 132.9, 128.6, 128.1, 40.2, 36.1, 27.3, 25.3, 10.9; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{14}H_{20}ONa$ 227.1412; found 227.1414.

3-cyclohexyl-1-phenylpropan-1-one (**4d**). Yellow oil, 16.1 mg, 75%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.96 (d, *J* = 7.1 Hz, 2H), 7.57 – 7.53 (m, 1H), 7.47 – 7.44 (m, 2H), 3.01 – 2.93 (m, 2H), 1.80 – 1.68 (m, 4H), 1.66 – 1.60 (m, 4H), 1.34 – 1.30 (m, 1H), 1.23 – 1.15 (m, 2H), 1.01 – 0.91 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 201.1, 137.2, 133.0, 128.7, 128.2, 37.6, 36.3, 33.4, 31.9, 26.7, 26.4; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{20}ONa$ 239.1412; found 239.1404.

3-cyclopentyl-1-phenylpropan-1-one (**4e**). Yellow oil, 12.0 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.96 (d, *J* = 8.4, 1.3 Hz, 2H), 7.57 – 7.53 (m, 1H), 7.48 – 7.44 (m, 2H), 3.02 – 2.95 (m, 2H), 1.88 – 1.68 (m, 4H), 1.66 – 1.58 (m, 4H), 1.56 – 1.51 (m, 1H), 1.18 – 1.11 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 200.9, 137.2, 133.0, 128.7, 128.2, 40.0, 38.1, 32.7, 30.8, 25.3; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{18}ONa$ 225.1255; found 225.1242.

1,4-diphenylpentan-1-one (**4f**). Yellow oil, 16.2 mg, 68%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.85 (d, J = 7.1 Hz, 2H), 7.54 – 7.51 (m, 1H), 7.43 – 7.39 (m, 2H), 7.33 – 7.29 (m, 2H), 7.22 – 7.20 (m, 3H), 2.88 – 2.80 (m, 3H), 2.14 – 1.94 (m, 2H), 1.32 (d, J = 6.9 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 200.4, 146.6, 137.0, 132.9, 128.5, 128.0, 127.1, 126.2, 39.5, 36.7, 32.5, 22.6; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{18}ONa$ 261.1255; found 261.1252.

5-methyl-1-phenylhexan-1-one (**4g**). Yellow oil, 14.8 mg, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.96 (d, *J* = 7.7 Hz, 2H), 7.55 (m, 1H), 7.46 (m, 2H), 2.95 (t, *J* = 7.4 Hz, 2H), 1.74 (m, 2H), 1.27 (m, 3H), 0.90 (d, *J* = 6.6 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 200.6, 137.1, 132.9, 128.6, 128.1, 38.9, 38.6, 27.9, 22.5, 22.3; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{18}ONa$ 213.1255; found 213.1253.

1-phenylhexan-1-one (**4h**). Yellow oil, 10.2 mg, 58%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.96 (d, *J* = 7.7 Hz, 2H), 7.57 – 7.53 (m, 1H), 7.48 – 7.44 (m, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 1.76 – 1.71 (m, 2H), 1.38 – 1.35 (m, 4H), 0.91 (d, *J* = 7.0 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 200.8, 137.3, 133.0, 128.7, 128.2, 38.8, 31.7, 24.2, 22.7, 14.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{16}ONa$ 199.1099; found 199.1093.

1-phenyl-5-(4-(trifluoromethyl)phenyl)pentan-1-one (**4i**). Claybank oil, 12.2 mg, 40%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.96 – 7.94 (m, 2H), 7.58 – 7.54 (m, 1H), 7.49 – 7.42 (m, 4H), 7.40 – 7.36 (m, 2H), 3.01 (t, *J* = 7.0 Hz, 2H), 2.77 – 2.68 (m, 2H), 1.86 – 1.68 (m, 4H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.54; ^{13}C {^{1}H} NMR (100 MHz,

$CDCl_3$) (δ, ppm) δ 200.2, 143.2, 137.1, 133.2, 132.0, δ 130.8 (d, J_{C-F} = 31.9 Hz), 128.9, 128.7, δ 128.5 (d, J_{C-F} = 58.8 Hz), δ 124.4 (q, J_{C-F} = 272.0 Hz), δ 124.0 (d, J_{C-F} = 11.4, 3.6 Hz). 38.4, 35.8, 31.0, 24.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{17}F_3ONa$ 329.1129; found 329.1125.

1-phenylpentan-1-one (**4j**). Yellow oil, 12.6 mg, 78%; ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.96 (d, J = 7.6 Hz, 2H), 7.57 – 7.53 (m, 1H), 7.48 – 7.44 (m, 2H), 2.97 (t, J = 7.4 Hz, 2H), 1.78 – 1.66 (m, 2H), 1.47 – 1.36 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 200.5, 137.0, 132.7, 128.4, 127.9, 38.2, 26.3, 22.3, 13.8; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{14}ONa$ 185.0942; found 185.0940.

1,4-diphenylbutan-1-one (**4k**). Yellow oil, 17.2 mg, 77%; ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.98 (d, J = 7.1 Hz, 2H), 7.62 – 7.58 (m, 1H), 7.52 – 7.48 (m, 2H), 7.38 – 7.32 (m, 2H), 7.26 (d, J = 7.2 Hz, 3H), 3.04 (t, J = 7.3 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H), 2.21 – 2.04 (m, 2H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 200.3, 141.8, 137.1, 133.1, 128.7, 128.7, 128.5, 128.2, 126.1, 37.8, 35.3, 25.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{16}ONa$ 247.1099; found 247.1085.

1-phenyltetradecan-1-one (**4l**). Yellow oil, 7.2 mg, 30%; ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.97 – 7.95 (m, 2H), 7.57 – 7.53 (m, 1H), 7.48 – 7.43 (m, 2H), 2.99 – 2.93 (m, 2H), 1.78 – 1.69 (m, 2H), 1.26 (s, 20H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 200.8, 137.2, 133.0, 128.7, 128.2, 38.8, 32.1, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 24.6, 22.8, 14.3; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{32}ONa$ 311.2351; found 311.2348.

7-chloro-1-phenylheptan-1-one (**4m**)[35]. Yellow oil, 9.0 mg, 40%; ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.98 (d, J = 7.1 Hz, 2H), 7.60 – 7.56 (m, 1H), 7.50 – 7.47 (m, 2H), 3.56 (t, J = 6.7 Hz, 2H), 3.00 (t, J = 7.3 Hz, 2H), 1.84 – 1.75 (m, 4H), 1.54 – 1.42 (m, 4H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 200.3, 137.0, 133.0, 128.6, 128.0, 45.1, 38.4, 32.4, 28.6, 26.7, 24.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{17}ClONa$ 224.0968; found 224.0970.

6,6,6-trifluoro-1-phenylhexan-1-one (**4n**). Yellow oil, 10.7 mg, 47%; ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.96 (d, J = 7.4 Hz, 2H), 7.59 – 7.55 (m, 1H), 7.49 – 7.45 (m, 2H), 3.02 (t, J = 7.1 Hz, 2H), 2.18 – 2.11 (m, 2H), 1.89 – 1.78 (m, 2H), 1.71 – 1.61 (m, 2H); ^{19}F NMR (377 MHz, CDCl3) δ -66.33, -66.35, -66.38; ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 198.4, 135.8, 132.1, 127.6, 127.0, 126.1 (q, J_{C-F}=275), 36.9, 32.7 (q, J_{C-F} = 28.5 Hz), 22.1, 20.7 (q, J_{C-F} = 3.0 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$

Calcd for $C_{12}H_{13}F_3ONa$ 253.0816; found 253.0816.

4-chloro-1-(4-fluorophenyl)butan-1-one (**4p**)[36]. Yellow oil, 51%; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 8.02 – 7.96 (m, 2H), 7.15 – 7.09 (m, 2H), 3.68 – 3.65 (m, 2H), 3.14 (t, J = 7.0 Hz, 2H), 2.25 – 2.17 (m, 2H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -105.06; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 197.3, δ 165.8 (d, J_{C-F} = 254.7 Hz)., δ 133.2 (d, J_{C-F} = 3.0 Hz), 130.7 (d, J_{C-F} = 9.4 Hz), 115.7 (d, J_{C-F} = 22.0 Hz), 44.6, 35.2, 26.7.

General Procedure for the synthetic application[4]: The ketone (0.5 mmol) was placed in a vial equipped with a magnetic bar and potassium iodide (10 mol %), sodium bicarbonate (2 equiv), anhydrous toluene (0.5 M), and the corresponding amine (1−2 equiv). The vial was closed and heated in a preheated oil bath at 100 ^{o}C for 36 h under magnetic stirring. The resulting mixture was purified by column chromatography or preparative TLC on silica to obtain the final aminobutyrophenones.

Melperone[14] (**7**). Claybank solid, 86%, mp: 78-82 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.97 (dd, J = 8.5, 5.6 Hz, 2H), 7.11 – 7.07 (m, 2H), 2.95 – 2.92 (m, 2H), 2.83 (d, J = 11.5 Hz, 2H), 2.35 (t, J = 7.3 Hz, 2H), 1.95 – 1.84 (m, 4H), 1.56 (d, J = 13.1 Hz, 2H), 1.36 – 1.25 (m, 1H), 1.19 – 1.09 (m, 2H), 0.87 (d, J = 6.5 Hz, 3H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -105.86; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 198.5, δ 165.6 (d, J = 254.1 Hz), δ 133.6 (d, J_{C-F} = 3.0 Hz), 130.7 (d, J_{C-F} = 9.3 Hz) , 115.51 (d, J_{C-F} = 21.8 Hz), 58.1, 53.9, 36.4, 34.22, 30.8, 21.9.

Azaperone[36] (**8**). Claybank solid, 73%, mp: 87-89 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 8.13 (dd, J = 4.9, 1.2 Hz, 1H), 7.98 – 7.94 (m, 2H), 7.43 – 7.39 (m, 1H), 7.09 – 7.05 (m, 2H), 6.61 – 6.53 (m, 2H), 3.48 – 3.39 (m, 4H), 2.96 (t, J = 7.1 Hz, 2H), 2.55 – 2.46 (m, 4H), 2.41 (t, J = 7.1 Hz, 2H), 1.98 – 1.89 (m, 2H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -105.61; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 198.4, δ 165.6 (d, J_{C-F} = 254.3 Hz)., 159.5, 147.9, 137.4, δ 133.6 (d, J_{C-F} = 2.9 Hz), 130.7 (d, J_{C-F} = 9.1 Hz), 115.58 (d, J_{C-F} = 21.8 Hz), 113.2, 107.0, 57.7, 52., 45.1, 36.1, 21.5.

2,2,6,6-tetramethyl-1-(1-phenylethoxy)piperidine (**6**). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) δ 7.32 – 7.19 (m, 5H), 4.78 (q, J = 6.7 Hz, 1H), 1.48 (d, J = 6.7 Hz, 6H), 1.37 – 1.29 (m, 6H), 1.17 (s, 3H), 1.03 (s, 3H), 0.66 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (δ, ppm) δ 145.9, 128.1, 126.9, 126.7, 83.2, 59.8, 40.5, 34.6, 34.2, 23.7, 20.5, 17.3.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

^{1}H, and ^{13}C NMR spectra for all products (PDF)

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Notes

There are no conflicts of interest

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REFERENCES

(1) For reviews: (a) A. de Meijere, F. Diederich, Eds., Wiley-VCH: New York, **2004**. Denmark, S. E. (p 191). (b) Handbook of Organopalladium Chemistry for Organic Synthesis, E.-i. Negishi, Ed., Wiley Interscience: New York, **2002**.

(2) (a) Jensen, A. E. and Knochel, P. Nickel-Catalyzed Cross-Coupling between Functionalized Primary or Secondary Alkylzinc Halides and Primary Alkyl Halides, *J. Org. Chem.* **2002**, *67(1),* 79-85. (b) Plunkett, S.; Basch, C. H.; Santana, S. O. and Watson, M. P. Harnessing Alkylpyridinium Salts as Electrophiles in Deaminative Alkyl–Alkyl Cross-Couplings, *J. Am. Chem. Soc*. **2019**, *141*, 2257−2262.

(3) (a) Çalimsiz, S. and Organ, M. G. Negishi cross-coupling of secondary alkylzinc halides with aryl/heteroaryl halides using Pd–PEPPSI–Ipent, *Chem. Commun*. **2011**, *47*, 5181–5183. (b) Dupuy, S.; Zhang, K.-F.; Goutierre, A. S. and Baudoin, O.

Terminal‐Selective Functionalization of Alkyl Chains by Regioconvergent Cross‐Coupling, *Angew. Chem. Int. Ed*. **2016**, *55*, 14793–14797. (c) Liu, X.-Q.; Jia, J.-Q. and Rueping, M. Nickel-Catalyzed C–O Bond-Cleaving Alkylation of Esters: Direct Replacement of the Ester Moiety by Functionalized Alkyl Chains, *ACS Catal*. **2017**, *7*, 4491−4496.

(4) Roslin, S. and Odell, L. R. Palladium and visible-light mediated carbonylative Suzuki–Miyaura coupling of unactivated alkyl halides and aryl boronic acids, *Chem*. *Commun*. **2017**, *53*, 6895−6898.

(5) Kolasa, T.; Matulenko, M. A.; Hakeem, A. A.; Patel, M. V.; Mortell, K.; Bhatia, P.; Henry, R.; Nakane, M.; Hsieh, G. C.; Terranova, M. A.; Uchic, M. E.; Miller, L. N.; Chang, R. J.; Donnelly-Roberts, D. L.; Namovic, M. T.; Hollingsworth, P. R.; Martino, B.; Kouhen, O. E.; Marsh, K. C.; Wetter, J. M.; Moreland, R. B.; Brioni, J. D. and Stewart, A. O. 1-Aryl-3-(4-pyridine-2-ylpiperazin-1-yl)propan-1-one Oximes as Potent Dopamine D4 Receptor Agonists for the Treatment of Erectile Dysfunction, *J. Med. Chem*. **2006**, *49(17),* 5093-5109.

(6) El Ouarradi, A.; Isabelle, S. A. and Buisson, D. Biooxidation of methyl group: application to the preparation of alcohol and acid metabolites of terfenadine, ebastine and analogues, *Tetrahedron*, **2008**, *64*, 11738–11744.

(7) Aitken, R. A.; Hodgson, P. K. G.; Morrison, J. J. and Oyewale, A. O. Flash vacuum pyrolysis over magnesium. Part 1. Pyrolysis of benzylic, other aryl/alkyl and aliphatic halides, *J. Chem. Soc. Perkin Trans. 1*, **2002***, 3,* 402–415.

(8) Jiang, Q. B.; Guo, T. G.; Wang, Q. F.; Wu, P. and Yu, Z. K. Rhodium(I)-Catalyzed Arylation of β-Chloro Ketones and Related Derivatives through Domino Dehydrochlorination/Conjugate Addition, *Adv. Synth. Catal.* **2013**, *355(9),* 1874-1880.

(9) (a) Verrier, C.; Alandini, N.; Pezzetta, C.; Moliterno, M.; Buzzetti, L.; Hepburn, H. B.; Vega-Peñaloza, A.; Silvi, M. and Melchiorre, P. Direct Stereoselective Installation of Alkyl Fragments at the β-Carbon of Enals via Excited Iminium Ion Catalysis, *ACS Catal*. **2018**, 8, 1062−1066. (b) Buzzetti, L.; Prieto, A.; Roy, S.-R. and Melchiorre, P. Radical‐Based C−C Bond-Forming Processes Enabled by the Photoexcitation of 4-Alkyl-1,4-dihydropyridines, *Angew. Chem. Int. Ed*. **2017**, *56*, 15039–15043. (c) Song, Z. Y.; Zhang, C. L. and Ye, S. Visible light promoted coupling of alkynyl bromides and Hantzsch esters for the synthesis of internal alkynes, *Org. Biomol. Chem*. **2019**, *17*, 181-185.

(10) (a) Gutiérrez-Bonet, Á.; Tellis, J. C.; Matsui, J. K.; Vara, B. A. and Molander, G. A. 1,4-Dihydropyridines as Alkyl Radical Precursors: Introducing the Aldehyde Feedstock to Nickel/Photoredox Dual Catalysis, *ACS Catal*. **2016**, *6*, 8004−8008. (b) Zhang, H. H. and Yu, S. Y. Radical Alkylation of Imines with 4-Alkyl-1,4-dihydropyridines Enabled by Photoredox/Brønsted Acid Cocatalysis, *J. Org*. *Chem*. **2017**, *82*, 9995−10006.

(11) Wu, Q. Y.; Min, Q. Q.; Ao, G. Z. and Liu, F. Radical alkylation of *para*-quinone methides with 4-substituted Hantzsch esters/nitriles via organic photoredox catalysis, *Org*. *Biomol*. *Chem*. **2018**, *16*, 6391-6394.

(12) Gutiérrez-Bonet, Á.; Remeur, C.; Matsui, J. K.; Molander, G. A. Late-Stage C–H Alkylation of Heterocycles and 1,4-Quinones via Oxidative Homolysis of 1,4-Dihydropyridines, *J. Am*. *Chem*. *Soc*. **2017**, *139*, 12251−12258.

(13) Li, G. X.; Chen, R.; Wu, L.; Fu, Q. Q.; Zhang, X. M. and Tang, Z. Alkyl Transfer from C-C Cleavage, *Angew. Chem. Int. Ed.* **2013***, 52*, 8432–8436.

(14) Mbofana, C. T.; Chong, E.; Lawniczak, J. and Sanford, M. S. Iron-Catalyzed Oxyfunctionalization of Aliphatic Amines at Remote Benzylic C–H Sites, *Org*. *Lett*. **2016**, *18(17),* 4258-4261.

(15) Jaen, J. C.; Caprathe, B. W.; Pugsley, T. A.; Wise, L. D. and Akunne, H. Evaluation of the effects of the enantiomers of reduced haloperidol, azaperol, and related 4-amino-1-arylbutanols on dopamine and .sigma. receptors, *J. Med*. *Chem*. **1993**, *36*, 3929-3936.

(16) Leyva-Pérez, A.; Cabrero-Antonino, J. R.; Rubio-Marqués, P.; Al-Resayes, S. I. and Corma, A. Synthesis of the ortho/meta/para Isomers of Relevant Pharmaceutical Compounds by Coupling a Sonogashira Reaction with a Regioselective Hydration, *ACS Catal*. **2014**, *4*, 722 -731.

(17) Braslau, R.; Tsimelzon, A. and Gewandter, J. Novel Methodology for the Synthesis of N-Alkoxyamines, *Org*. *Lett*. **2004**, *6*(*13)*, 2233-2235.

(18) Mack, D. J.; Batory, L. A. and Njardarson, J. T. Intermolecular Oxonium Ylide Mediated Synthesis of Medium-Sized Oxacycles, *Org*. *Lett*. **2012**, *14* (*1)*, 378-381.

(19) Shen, Z. L.; Goh, K. K. K.; Wong, C. H. A.; Yang, Y. S.; Lai, Y. C.; Cheong, H. L. and Loh, T. P. Direct synthesis of ester-containing indium homoenolate and its application in palladium-catalyzed cross-coupling with aryl halide, *Chem*. *Commun*. **2011**, *47,* 4778–4780. b) Liu, Y. G.; Lin, Q. Z.; Xiao, Z. W.; Zheng, C. G. Guo, Y. Chen, Q.-Y.; Liu, C. Zinc-Mediated Intermolecular Reductive Radical

Fluoroalkylsulfination of Unsaturated Carbon–Carbon Bonds with Fluoroalkyl Bromides and Sulfur Dioxide, *Chem. Eur. J.* **2019**, *25*, 1824 – 1828.

(20) (a) Wang, C. P. and Dong, G. B. Direct β-Alkylation of Ketones and Aldehydes via Pd-Catalyzed Redox Cascade, *J. Am. Chem. Soc*. **2018**, *140*, 19, 6057-6061. (b) Chakraborty, S.; Daw, P.; David, Y. B. and Milstein, D. Manganese-Catalyzed α-Alkylation of Ketones, Esters, and Amides Using Alcohols, *ACS Catal*. **2018**, *8*, 10300-10305.

(21) Lee, G. S. and Hong, S. H. Formal Giese addition of C(sp^3)–H nucleophiles enabled by visible light mediated Ni catalysis of triplet enone diradicals, *Chem. Sci*. **2018**, *9*, 5810–5815.

(22) Salama, T. A. and Elmorsy, S. S. Silicon mediated synthesis and selected transformations of *β*-chloroketones, *Chinese Chemical Letters,* **2011**, *22,* 1171–1174.

(23) Yu, F.; Zhou, J. N.; Zhang, X. C.; Sui, Y. Z.; Wu, F. F.; Xie, L. J.; Chan, A. S. C. and Wu, J. Copper(II) - Catalyzed Hydrosilylation of Ketones Using Chiral Dipyridylphosphane Ligands: Highly Enantioselective Synthesis of Valuable Alcohols, *Chemistry - A European Journal,* **2011**, *17 (50),* 14234-14240.

(24) Jacob, J. L.; Emma, R. C.; Trevor, A. H.; John, M. O.; Christopher, B. K.; A. Michael, M. and Nicholas, E. L. A combined computational and experimental investigation of the oxidative ring-opening of cyclic ethers by oxoammonium cations, *Org. Biomol. Chem.* **2016**,*14,* 3883-3888.

(25) Stephan, H.; Geipel, G.; Bernhard, G.; Comba, P.; Rajaraman, G.; Hahn, U. and Vögtle, F. Synthesis and Binding Properties of Dendritic Oxybathophenanthroline Ligands towards Copper(II), *Eur. J. Inorg. Chem*. **2005**, 4501–4508.

(26) Neudeck, H. K. and Spirane, A. Aromatische Spirane, 20. Mitt.: Darstellung von dimethylsubstituierten 2-Carboxymethyl-indan-1-onen und Benzylchloriden als Synthone für Synthesen von di-bis tetramethylierten 2,2'-Spirobiindandionen, *Monatsh. Chem.* **1996**, *127,* 185– 200.

(27) Singh, P. N. D.; Mandel, S. M.; Sankaranarayanan, J.; Muthukrishnan, S.; Chang, M. X.; Robinson, R. M.; Lahti, P. M.; Ault, B. S. and Gudmundsdóttir, A. D. Selective Formation of Triplet Alkyl Nitrenes from Photolysis of *β*-Azido-Propiophenone and Their Reactivity. *J. Am. Chem. Soc*. **2007**, *129(51)*, 16263-16272.

(28) Xia, J. J. and Wang, G. W. One-Pot Synthesis and Aromatization of 1,4-Dihydropyridines in Refluxing Water, *Synthesis.* **2005**, *14,* 2379–2383.

(29) Li, J. X.; Wu, L.; Lv, G.; Liu, H. X.; Fu, Q. Q.; Zhang X. M. and Tang, Z. Alkyl transfer from C–C cleavage: replacing the nitro group of nitro-olefins, *Chem. Commun*. **2014**, *50,* 6246—6248.

(30) Buzzetti, L.; Prieto, A.; Roy, S. R. and Melchiorre, P. Radical-Based C−C Bond-Forming Processes Enabled by the Photoexcitation of 4-Alkyl-1,4-dihydropyridines, *Angew. Chem. Int. Ed.* **2017**, *56,* 15039–15043.

(31) Chen, W. X.; Liu, Z.; Tian, J. Q.; Li, J.; Ma, J.; Cheng, X. and Li, G. G. Building Congested Ketone: Substituted Hantzsch Ester and Nitrile as Alkylation Reagents in Photoredox Catalysis, *J. Am. Chem. Soc.* **2016**, *138,* 12312−12315.

(32) Deng, W. L.; Ye, C. Q.; Li, Y. J.; Li, D. L. and Bao, H. L. Iron-Catalyzed Oxyalkylation of Terminal Alkynes with Alkyl Iodides, *Org. Lett.* **2019**, *21,* 261-265.

(33) Yin, Z. P.; Zhang, Z.; Zhang, Y. C.; Dixneuf, P. H. and Wu, X. F. Carbonylation of tertiary carbon radicals: synthesis of lactams, *Chem. Commun.* **2019**, *55,* 4655-4658.

(34) Kalutharage, N. and Yi, C. S. Deaminative and Decarboxylative Catalytic Alkylation of Amino Acids with Ketones. *Angew. Chem. Int. Ed*. **2013**, *52*, 13651 –13655.

(35) Huang, F. Q.; Xie, J.; Sun, J. G.; Wang, Y. W.; Dong, X.; L. Qi, W. and Zhang, B. Regioselective Synthesis of Carbonyl-Containing Alkyl Chlorides via Silver-Catalyzed Ring-Opening Chlorination of Cycloalkanols, *Org. Lett.* **2016**, *18(4),* 684-687.

(36) Wang, Y. Y.; Li, X. W.; Ke, Y. B.; Wang, C. F.; Zhang, Y.; Ye, D. Y.; Hu, X.; Zhou, L. and Xia, X. *Molecules*, **2018**, *23(12),* 3215.