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FULL PAPER

Chemoselective alkylation of aminoacetophenones with alcohols by using a palladacycle-phosphine catalyst

Ramesh Mamidala, [a] M. Siva Subramani, [a] Shaikh Samser, [a] Priyabrata Biswal [a] and Krishnan Venkatasubbaiah*[a]

Dedicated to Prof. V. Chandrasekhar on the occasion of his 60th birthday

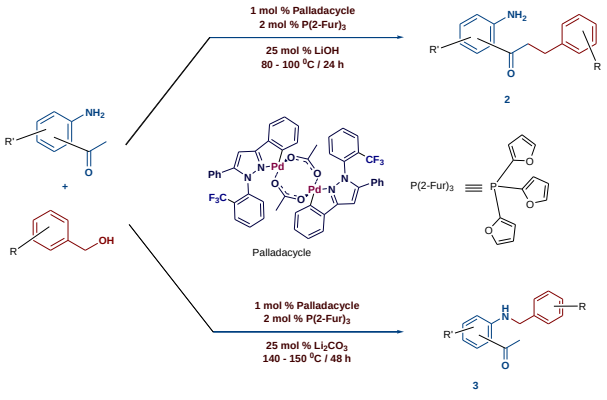
Abstract: The development of efficient and environmentally benign palladacycle-phosphine catalyzed process to enable the formation of chemoselective C-alkylated or N-alkylated aminoacetophenones with alcohols is described. This methodology proved to be tunable by variation of the base and the temperature, which allows for the isolation of structurally diverse C-alkylated and N-alkylated aminoacetophenones. Moreover, this methodology has been applied to the synthesis of biologically and industrially important donepezil.

Introduction

Alkylation of ketones and amines represents a class of important reactions in organic chemistry.[1] Classical methodologies for the alkylation of ketones and amines involves alkyl halides or alkyl sulfonates as alkylating agents.[2] Although most of these methods proved to be efficient in many instances they also produce wastes such as alkyl halides and (or) side-products. The use of hydrogen borrowing or hydrogen auto transfer strategy has been emerged as an environmentally friendly greener approach for the construction of C-C and C-N bonds as this method involves water as the only side product.[3] Over the past decade, several groups have been involved to develop methodologies for the alkylation of ketones[4] and amines[5] using alcohols as benign alkylating agents. Among the precious metal complexes,[6-15] a greater number of progress has been made using Ru[6] and Ir[7] metal complexes. It is interesting to note that Cho *et al* described Ru-based catalyst for the α-alkylation of ketones.[16] Meanwhile Ishi *et al* reported Ir-based catalyst for the same reaction.[17] Feringa and Barta demonstrated the alkylation of amines using alcohols.[18] More recently, Beller and co-workers elegantly utilized the hydrogen borrowing methodology for the synthesis of N-alkylated and C-alkylated products using manganese pincer complex.[14]

Development of efficient and selective transformation of molecules with more than one functional group is an important problem in organic synthesis. A chemoselective reaction offers minimization of the use of protecting or activating groups. Although there are numerous metal catalyzed[6-15] N-alkylation of amines or C-alkylation of ketones using alcohols are reported, chemoselective N-alkylation of amines or C-alkylation of ketones using alcohols is a neglected area. Recently, Li and co-workers reported copper[15d] and iridium[7l] catalyzed regioselective N-alkylation of 2-aminobenzothiazoles or amino-azoles with benzyl alcohols respectively. More recently, the same group reported regioselective N-alkylation of sulfanilamides using alcohols.[7l] 2'-Aminoacetophenones are important class of compounds in the preparation of isatin[19] and indole[20] derivatives. A survey on the literature revealed that there is only one report for the chemoselective alkylation of 2'-aminoacetophenones.[21b]

In 2000, Grigg and co-workers reported pyrazole based palladacycles as catalysts.[21a] The work on pyrazole based palladacycles reported by Grigg and co-workers, inspired us to develop a variety of pyrazole based palladacycles. Recently, we demonstrated pyrazole based palladacycles as catalysts for the C-C and C-N bond forming reactions.[10c,10d,22] As part of our efforts in the development of pyrazole based palladacycles for the activation of alcohols as electrophile, herein we report chemoselective alkylation of aminoacetophenones using palldacycle-phosphine complex (Scheme 1).



Scheme 1. Palladacycle-phosphine catalyzed chemoselective alkylation of aminoacetophenones.

Results and Discussion

Chemoselective C-alkylation

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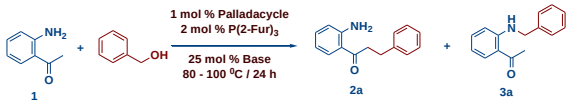
Initially, to explore the alkylation reaction, 2'-aminoacetophenone and benzyl alcohol were chosen as the model substrates using 1 mol% of palldacycle (Scheme 1), 2 mol% of $P(2\text{-Fur})_3$, 25 mol% LiOH under solvent-free condition (Table 1). At 100 °C, use of 1.2 equivalents of benzyl alcohol resulted 18% of the N-alkylated product and 66% of the C-alkylated product (Table 1, entry 1). Surprisingly, when the reaction was carried out using 2 equivalents of benzyl alcohol, the reaction yielded exclusively the C-alkylated product in 95% isolated yield (Table 1, entry 2). Then, we evaluated different bases and temperature. Of the different bases screened, LiOH was found to be promising under solvent-free condition at 80 °C (Table 1, entry 3).

Table 1: Optimization of chemoselective C-alkylation of 2'-aminoacetophenone using benzyl alcohol[a]

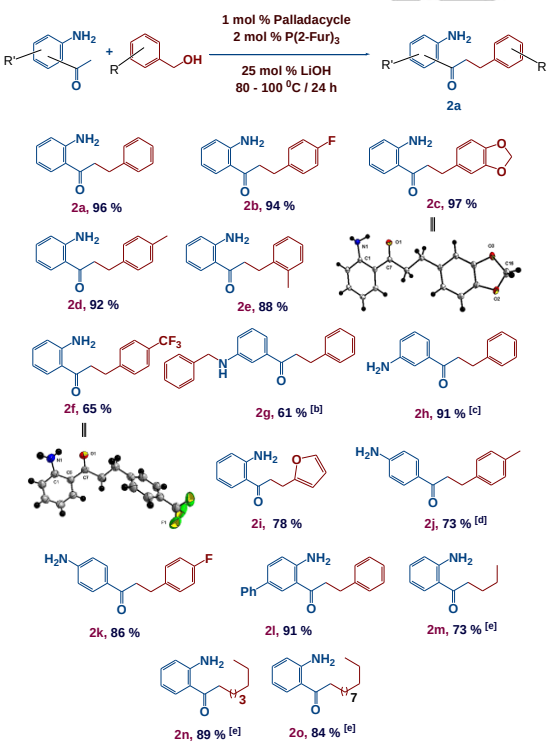


Entry	Base	T (°C)	Yield [b] (%)	
			3a	**2a**
1[c]	LiOH	100	18	66
2	LiOH	100	<5	95
3	LiOH	80	trace	96
4	$CsOH.H_2O$	80	ND	88
5	Li_2CO_3	80	ND	ND
6	Cs_2CO_3	80	ND	ND
7	K_3PO_4	80	ND	ND
8	KOH	80	ND	trace
9	NaOH	80	ND	trace
10	KO^tBu	80	ND	76
11[d]	LiOH	80	ND	ND
12[e]	LiOH	80	ND	ND

[a]Reaction conditions: 2'-Aminoacetophenone 1 mmol, benzyl alcohol 2 mmol, LiOH 0.25 mmol, [b]Isolated yield after column chromatography, [c]Benzyl alcohol 1.2 mmol was used, [d]Palladacycle was not used, [e] Palladacycle and $P(2\text{-Fur})_3$ were not used, ND: Not Detected.

Having established the optimal reaction conditions using the palladacycle-phosphine catalyst, the reaction scope was explored with a range of alcohols and aminoacetophenones. We found that benzyl alcohols bearing electron-donating or electron-withdrawing groups were readily alkylated to the corresponding C-alkylated products (Table 2, compounds **2a-2f**) in 65–97% isolated yields. Furthermore, hetero aromatic furfuryl alcohol was also tolerated under the reaction conditions. (Table 2, compound **2i**). However, reaction of 2'-aminoacetophenone with 4-methoxy benzyl alcohol did not react under the reaction conditions. Challenging aliphatic alcohols such as 1-propanol, 1-hexanol and 1-decanol could be successfully converted to the corresponding C-alkylated products in 73%, 89% and 84% respectively (Table 2, compounds **2m**, **2n**, **2o**).

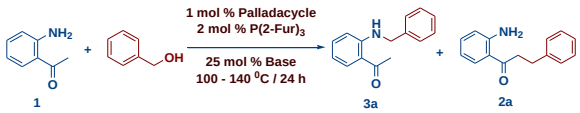
Table 2: Scope of chemoselective C-alkylation of aminoacetophenones using alcohols[a]



[a]Reaction conditions: 2'-Aminoacetophenone 1 mmol, benzyl alcohol 2 mmol, LiOH 0.25 mmol, palladacycle $1x10^{-2}$ mmol, $P(2\text{-Fur})_3$ $2x10^{-2}$ mmol, isolated yield after column chromatography, [b]32% of compound **2h** was also isolated, [c]Reaction was performed at 60 °C, [d]26%dialkylated compound was also isolated, [e]Reactions were performed at 100 °C.

Encouraged by these results, next we explored the scope and limitation of different aminoacetophenones. 3'-Aminoacetophenone which is electronically different from 2'-aminoacetophenone was subjected to the reaction conditions, which resulted 32% of the desired mono C-alkylated product along with 61% of the undesired di-alkylated product (Table 2, compound **2g**). However, decreasing the temperature to 60 °C, resulted exclusively the C-alkylated product in 91% yield (Table 2, compound **2h**). Reaction of 4'-aminoacetophenone with 4-methyl benzyl alcohol or 4-fluoro benzyl alcohol yielded the desired C-alkylated products in 73% and 86% respectively (Table 2, entry **2j** and **2k**). We also observed 26% of the dialkylated product in case of 4'-aminoacetophenone and 4-methyl benzyl alcohol under the reaction conditions mentioned above. 1-(3-Amino-[1,1'-biphenyl]-4-yl)ethanone underwent the C-alkylation comfortably to yield **2l** in 91% yield.

Table 3: Optimization of chemoselective N-alkylation of 2'-aminoacetophenone using benzyl alcohol[a]



Entry	Base	T (°C)	Yield [b] (%)	
			3a	2a
1[c]	LiOH	100	<5	94
2[c]	$CsOH.H_2O$	100	ND	73
3[c]	LiOH	120	ND	98
4[c]	LiOH	130	ND	97
5[c]	$CsOH.H_2O$	130	ND	89
6[c]	Li_2CO_3	130	54	ND
7[d]	Li_2CO_3	130	76	ND
8[d]	Cs_2CO_3	130	ND	ND
9[d]	K_3PO_4	130	ND	ND
10[d]	K_2CO_3	130	ND	ND
11[d]	Li_2CO_3	140	95	ND
12[e]	Li_2CO_3	140	ND	ND
13[f]	Li_2CO_3	140	ND	ND

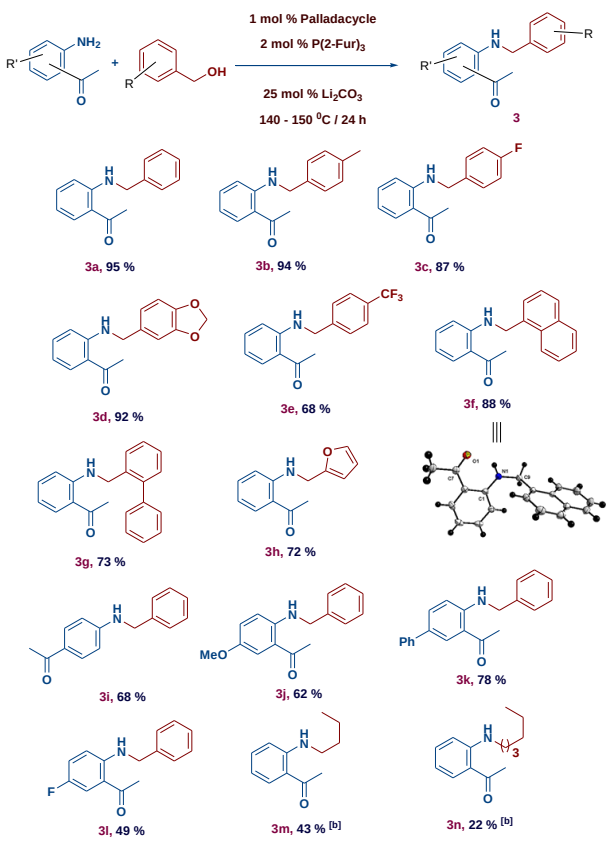
[a]Reaction condition: 2'-Aminoacetophenone 1 mmol, benzyl alcohol 2 mmol, base 0.25 mmol, [b]Isolated yield after column chromatography, [c]Benzyl alcohol 2 mmol was used, [d]Benzyl alcohol 3 mmol was used, [e]Palladacycle was not used, [f]Palladacycle and $P(2\text{-Fur})_3$ were not used ND: Not Detected.

Chemoselective N-alkylation

Next, we turned our attention to investigate the applicability of this method for the chemoselective N-alkylation of aminoacetophenones. Different bases at various temperatures were examined and the results are summarized in Table 3. LiOH and $CsOH.H_2O$ failed to give the desired N-alkylated product even at 130 °C (Table 3, entries 1-5). Among the different bases tested Li_2CO_3 was found to be the only base producing the N-alkylated product at 130 °C with the use of 2 equivalents of benzyl alcohol (Table 3, entry 6). Increasing the amount of benzyl alcohol to 3 equivalents improved the yield of the N-alkylated product to 76% (Table 3, entry 7). As expected, running the reaction at 140 °C increased the yield to 95%. Hence, we selected the reaction of aminoacetophenones (1 mmol), benzyl alcohol (3 mmol), catalyst (1 mol%), Li_2CO_3 (25 mol%) at 140 °C for 24 h as the best reaction condition.

With the optimum reaction conditions, the scope of the palladacycle-phosphine promoted N-alkylation was studied with a range of benzyl alcohols and aminoacetophenones and the results are presented in Table 4. The substitutions on benzyl alcohol and aminoacetophenone with electron-withdrawing groups or electron-donating groups were tolerated. Benzyl alcohols such as 4-methyl benzyl alcohol, 4-fluoro benzyl alcohol, 3,4-methylenedioxy benzyl alcohol, 4-trifluoromethyl benzyl alcohol, 1-naphthyl methanol and 2-biphenyl methanol were converted to the desired products in good to excellent yields (Table 4, compounds **3a-3g**). The reaction with electron withdrawing substituted (F) 2'-aminoacetophenone was slow and gave the respective N-alkylated product in 49% (Table 4, compound **3l**).

Table 4: Scope of chemoselective N-alkylation of aminoacetophenones using alcohols[a]



[a]Reaction conditions: 2'-Aminoacetophenone 1 mmol, benzyl alcohol 3mmol, Li_2CO_3 0.25 mmol, palladacycle 10^{-2} mmol, $P(2\text{-Fur})_3$ 2 x 10^{-2} mmol, isolated yield after column chromatography, [b]Reactions were performed at 150 °C for 48h.

However, electron-donating group substituted (OMe) 2'-aminoacetophenone produced the respective N-alkylated product in 62% yield (Table 4, compound **3j**). Moreover, 2'-aminoacetophenone with phenyl at the 5-position underwent N-alkylation comfortably to yield **3k** in 78%. Furthermore, when N-alkylation was applied to 4-aminoacetophenone, it resulted the desired product **3i** in 68%. Furthermore, hetero aromatic furfuryl alcohol was also tolerated under the reaction conditions (Table 4, compound **3h**). To our delight, the least reactive and challenging aliphatic alcohols such as 1-butanol and 1-hexanol were successfully alkylated to the corresponding products (Table 4, compounds **3m** and **3n**).

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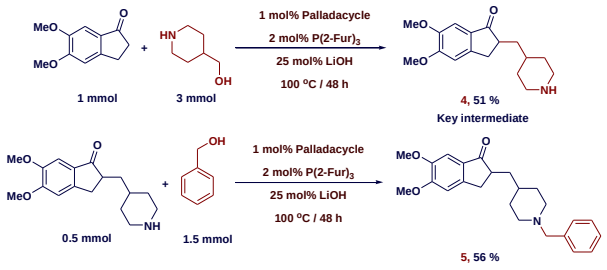
Chemoselective Synthesis of Donepezil

Donepezil is an important biologically active molecule which is used for the treatment of Alzheimer disease. We applied our catalytic protocol for the synthesis of donepenzil that involves chemoselective alkylation followed by N-alkylation. Although, 4-piperidinemethanol is prone to undergo self-coupling or N-alkylation, the reaction of 5,6-dimethoxy indanone with 4-piperidine methanol produced selectively the C-alkylated product (Scheme 2, compound **4**). The subsequent reaction of compound **4** with benzyl alcohol yielded donepezil under the conditions mentioned above. It is worth mentioning that our protocol does not need conventional mutagenic or toxic alkylating agents and represents one of the shortest routes to make this biologically important molecule.



Scheme 2: Chemoselective synthesis of donepezil.

To know the bonding mode of the palladacycle and the ancillary ligand phosphine, we attempted to grow single crystals of palladacycle & tri(2-furyl)phosphine. Although our attempts to crystallize palladacycle-tri(2-furyl)phosphine had been unsuccessful, we were lucky to get crystals of palladacycle-triphenylphosphine (**P-PPh$_3$**) and analyzed using the single crystal X-ray diffraction technique. The molecular structure of compound **P-PPh$_3$** is shown in Figure 1, along with selected bond lengths and bond angles. The Pd-C, Pd-N, Pd-P, and Pd-O bond lengths are comparable to the reported palladacycle complex of similar type.[23] We repeated the reaction of 2'-aminoacetophenone with benzyl alcohol using *in situ* generated palladacycle-triphenylphosphine and isolated palladacycle-triphenylphosphine (**P-PPh$_3$**). The results are summarized in Scheme 3. The results showed that the product yields were slightly higher for the isolated **P-PPh$_3$** over the *in situ* generated complex leading us to conclude that the palladacycle-phosphine complex is the active catalyst (or) pre-catalyst for the N-alkylation and C-alkylation reactions.

Controlled experiments were run with the combination of acetophenone, aniline and benzyl alcohol under the optimized conditions for N-alkylation and C-alkylation (Scheme S1). It is important to note that either N-alkylated (94%) or C-alkylated (84%) compound was observed as the major product, demonstrates that the reaction conditions play a very important role in achieving the chemoselectivity.

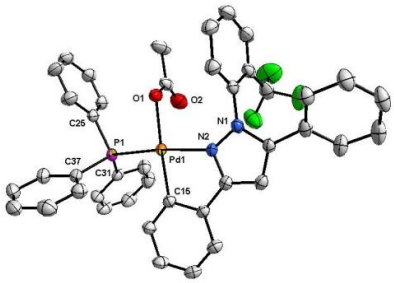
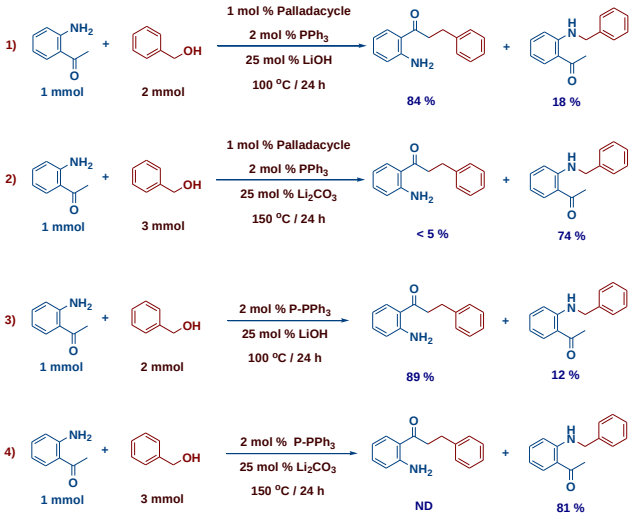
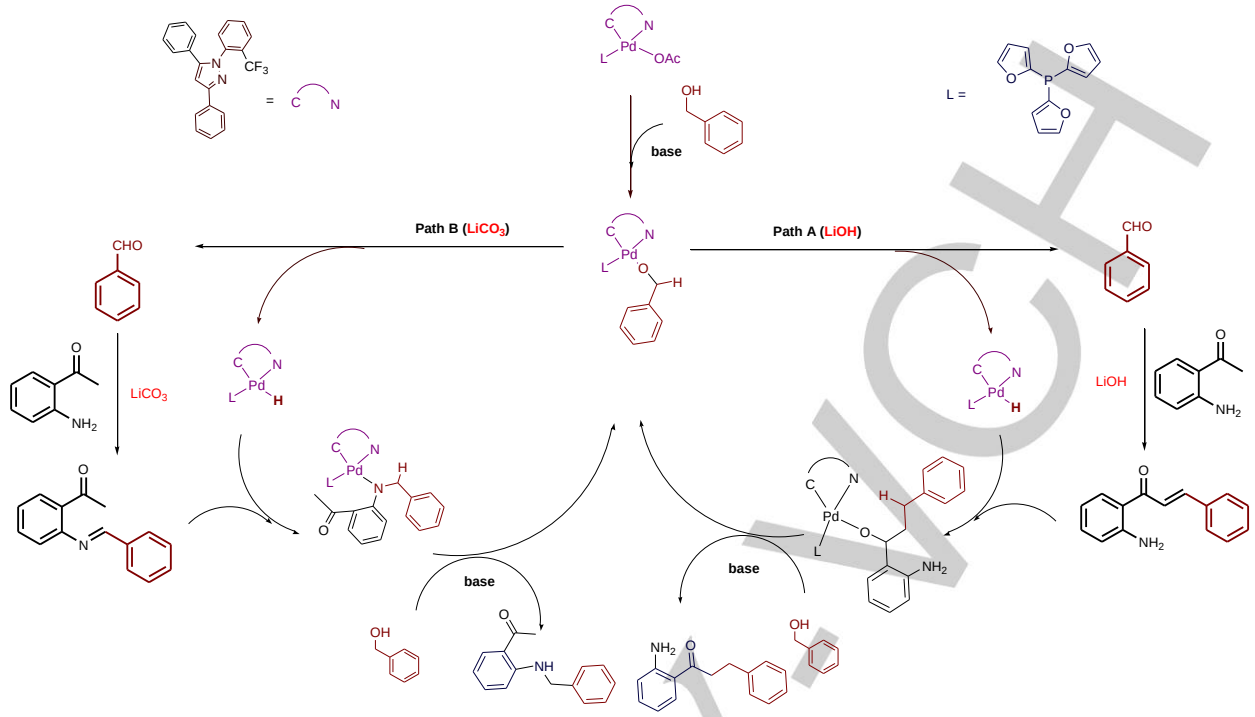


Figure 1. Molecular structure of **P-PPh$_3$** (Thermal ellipsoids at 30% probability); Pd1-P1 2.2397(8), Pd1-O12.099(2), Pd1-N2 2.112(2),Pd1-C15 2.019(3), P1-C25 1.840(3), P1-C37 1.821(4), P1-C31 1.817(4), O1-Pd1-P1 90.59(6), O1-Pd1-N2 95.00(9), N2-Pd1-P1 174.41(7), C15-Pd1-P1 93.33(9), C15-Pd1-O1 176.05(11), C15-Pd1-N2 81.08(11)



Scheme 3. Control experiments with and without isolated **P-PPh$_3$**.

We propose a mechanism (Scheme 4) based on our results in this study and also from the literature studies. As shown in Scheme 4, in the presence of two functional groups, Li_2CO_3 promotes imine condensation where as LiOH promotes aldol condensation. To confirm our hypothesis, we stirred benzaldehyde and 2-aminoacetopheneone in the presence of LiOH and Li_2CO_3 separately. The crude product was analysed using proton NMR (Scheme S2 & S3). Apparently, the formation of imine was observed when Li_2CO_3 was used as a base and aldol condensation product was noticed when LiOH was used as a base.



Scheme 4: Proposed mechanism.

Conclusions

In conclusion, we have established an efficient palladacycle-phosphine catalyzed chemoselective alkylation of aminoacetophenones. Our methodology has the advantage that, just by switching the base and temperature, the reaction changes from C-alkylated product to N-alkylated product. Using this protocol, a wide range of substituted alcohols were successfully alkylated to either the C-alkylated or N-alkylated products in good yields.

Experimental Section

General procedure for C-alkylation of aminoacetophenones:

A Schlenk tube was charged with palldacycle (1 x 10^{-2}mmol), P(2-Fur)$_3$ (2 x 10^{-2}mmol), LiOH (0.25 mmol), aminoacetophenone (1 mmol) and alcohol (2 mmol) under argon atmosphere. The tube was closed with PTFE stopper and the reaction mixture was stirred at 80–100 °C for 24 h. At the end of the reaction, the reaction mixture was cooled to room temperature, diluted with dichloromethane (5 mL), and concentrated under vacuum. The crude was subjected to column chromatography using ethyl acetate and *n*-hexane mixture to afford the α-alkylated product in high purity.

General procedure for N-alkylation of aminoacetophenones:

A Schlenk tube was charged with palladacycle (1 x 10^{-2}mmol or 2 x 10^{-2}mmol), P(2-Fur)$_3$ (2 x 10^{-2}mmol or 4 x 10^{-2}mmol), Li_2CO_3 (0.25 mmol), aminoacetophenone (1 mmol) and alcohol (3 mmol) under argon atmosphere. Then the Schlenk tube was closed with PTFE stopper and the reaction mixture was stirred at 140–150 °C for 24–48 h. At the end of the desired reaction time, the reaction mixture was cooled to room temperature, diluted with dichloromethane (5 mL), and concentrated under vacuum. The crude was subjected to column chromatography using ethyl acetate and *n*-hexane mixture to afford the N-alkylated product in high purity.

Analytical data for the alkylated products:

1-(2-aminophenyl)-3-phenylpropan-1-one (Table 2, compound ***2a****)*[21b]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and benzyl alcohol (0.22g, 2.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.22g, 0.9 mmol, 96%). Mp = 73-74°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.3 Hz, 1H), 7.35–7.22 (m, 6H), 6.65 (t, *J* = 8.4 Hz, 2H), 6.31 (s, 2H), 3.30 (t, *J* = 7.2 Hz, 2H), 3.08 (t, *J* = 7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6, 150.5, 141.6, 134.3, 131.1, 128.6, 128.5, 126.1, 117.9, 117.5, 115.9, 41.0, 30.7 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NO$ ([M+H]): 226.1226, found: 226.1235.

1-(2-aminophenyl)-3-(4-fluorophenyl)propan-1-one (Table 2, compound ***2b****)*[new]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 4-fluorobenzyl alcohol (0.25g, 2.0 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.23g, 0.9 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.1 Hz, 1H),

7.29–7.16 (m, 3H), 6.96 (t, *J* = 8.7 Hz, 2H), 6.62 (m, 2H), 3.23 (t, *J* = 7.6 Hz, 2H), 3.00 (t, *J* = 7.7 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4, 161.5 (d, *J* = 243.7 Hz), 150.4, 137.2 (d, *J* = 3.2 Hz), 134.5, 131.1, 129.9 (d, *J* = 7.8 Hz), 118.0, 117.6, 116.0, 115.3 (d, *J* = 21.1 Hz), 41.1, 29.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -118.37 ppm. HRMS (ESI): calcd. for $C_{15}H_{14}FNO$ ([M+H]): 244.1132, found: 244.1119. IR (KBr): υ (cm^{-1}) = 3475, 3348, 3240, 3038, 2927, 1651, 1614, 1548, 1450, 1157, 830, 753, 652.

1-(2-aminophenyl)-3-(benzo[d][1,3]dioxol-5-yl)propan-1-one (Table 2, compound ***2c****)*[25]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 3,4-methylenedioxybenzyl alcohol (0.30g, 2.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.26g, 0.9 mmol, 97%). Mp = 94–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 6.75–6.61 (m, 5H), 5.92 (s, 2H), 3.23 (t, *J* = 7.9 Hz, 2H), 2.96 (t, *J* = 7.8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6, 150.5, 147.8, 145.9, 135.4, 134.4, 131.1, 121.3, 118.0, 117.5, 116.0, 109.1, 108.4, 100.9, 41.3, 30.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}NO_3$ ([M+H]): 270.1125, found: 270.1111.

1-(2-aminophenyl)-3-(p-tolyl)propan-1-one (Table 2, compound ***2d****)*[new]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 4-methylbenzyl alcohol (0.24g, 2.0 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.22g, 0.9 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.16–7.09 (m, 4H), 6.77–6.66 (m, 2H), 3.26 (t, *J* = 7.6 Hz, 2H), 3.01 (t, *J* = 7.7 Hz, 2H), 2.33 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 138.5, 135.7, 134.4, 131.2, 129.3, 128.4, 118.3, 118.1, 117.0, 116.7, 41.3, 30.3, 21.1 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}NO$ ([M+H]): 240.1383, found: 240.1403. IR (KBr): υ (cm^{-1}) = 3474, 3345, 3132, 3094, 1651, 1584, 1514, 1450, 971, 811, 749.

1-(2-aminophenyl)-3-(o-tolyl)propan-1-one (Table 2, compound ***2e****)*[new]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 2-methylbenzyl alcohol (0.24g, 2.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.21g, 0.8 mmol, 88%). Mp = 57–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.1 Hz, 1H), 7.31–7.26 (m, 1H), 7.20–7.14 (m, 4H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.68 (t, *J* = 7.6 Hz, 1H)., 3.23 (t, *J* = 7.6 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.36 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 149.6, 139.7, 136.2, 134.5, 131.1, 130.5, 128.8, 126.4, 126.3, 118.4, 118.0, 116.6, 39.8, 28.1, 19.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}NO$ ([M+H]): 240.1383, found: 240.1377. IR (KBr): υ (cm^{-1}) = 3452, 3339, 2912, 1641, 1581, 1551, 1198, 1160, 750.

1-(2-aminophenyl)-3-(4-(trifluoromethyl)phenyl)propan-1-one(Table 2, compound ***2f****)*[new]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 4-trifluromethylbenzyl alcohol (0.35g , 2.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.18g, 0.6 mmol 65%).Mp = 95–96 ºC.^{1}H NMR (400 MHz, C_6D_6): δ = 7.30 (d, *J* = 7.7 Hz, 3H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 2H), 6.44 (t, *J* = 7.5 Hz, 1H), 6.13 (d, *J* = 8.1 Hz, 1H), 5.95 (s, 2H), 2.78 (t, *J* = 7.1 Hz, 2H), 2.68 (t, *J* = 6.9 Hz, 2H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.3, 150.9, 146.3, 134.3, 131.2, 129.11, 125.5 (q, *J* = 3.8 Hz), 118.0, 117.4, 115.5, 40.3, 30.2 ppm.HRMS (ESI): calcd. for $C_{16}H_{14}F_3NO$ ([M+H]): 294.1100, found: 294.1123. IR (KBr): υ (cm^{-1}) = 3489, 3352, 1652, 1614, 1589, 1328, 1163, 1100, 1067, 830, 746.

1-(3-(benzylamino)phenyl)-3-phenylpropan-1-one (Table 2, compound ***2g****)*[new]: Prepared from 3'-aminoacetophenone (0.14g, 1.0 mmol) and benzyl alcohol (0.22g, 2.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.19g, 0.6 mmol, 61%). Mp = 83–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.20 (m, 13H), 6.82 (dd, *J* = 8.4, 2.9 Hz, 1H), 4.37 (s, 2H), 3.25 (t, *J* = 7.7 Hz, 2H), 3.06 (t, *J* = 7.5 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.8, 148.3, 141.5, 138.9, 138.0, 129.5, 128.9, 128.6, 128.5, 127.6, 127.5, 126.2, 117.7, 111.9, 48.4, 40.6, 30.4 ppm. HRMS (ESI): calcd. for $C_{22}H_{21}NO$ ([M+H]): 316.1696, found: 316.1714. IR (KBr): υ (cm^{-1}) = 3408, 1667, 1602, 1491, 1341, 1180, 901, 763, 697.

1-(3-aminophenyl)-3-phenylpropan-1-one (Table 2, compound ***2h****)*[new]: Prepared from 3'-aminoacetophenone (0.14g, 1.0 mmol) and benzyl alcohol (0.22g, 2.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.21g, 0.9 mmol, 91%). Mp = 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 8H), 6.90 (dd, *J* = 7.9, 3.1 Hz, 1H), 4.14 (br, 2H), 3.26 (t, *J* = 7.6 Hz, 2H), 3.06 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 146.3, 141.4, 138.0, 129.6, 128.6, 128.5, 126.2, 120.0, 118.9, 114.4, 40.6, 30.3 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NO$ ([M+H]): 226.1226, found: 226.1228. IR (KBr): υ (cm^{-1}) = 3460, 3367, 1679, 1560, 1454, 1316, 1175, 773.

1-(2-aminophenyl)-3-(furan-2-yl)propan-1-one (Table 2, compound ***2i****)*[21b]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 2-furylmethanol (0.20g, 2.0 mmol). After purification by column chromatography, the compound was isolated as a pale yellow solid (0.17g, 0.7 mmol, 78%). Mp = 77–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.6 Hz, 1H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 6.68 (t, *J* = 7.5 Hz, 2H), 6.32–6.31 (m, 1H), 6.07 (d, *J* = 3.1 Hz, 1H), 3.34 (t, *J* = 7.6 Hz, 2H), 3.09 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.9, 155.2, 150.4, 141.2, 134.5, 131.1, 118.0, 117.5, 116.0, 110.4, 105.3, 37.5, 23.0 ppm. HRMS (ESI): calcd. for $C_{13}H_{13}NO_2$ ([M+H]): 216.1019, found: 216.1015.

1-(4-aminophenyl)-3-(p-tolyl)propan-1-one (Table 2, compound ***2j****)*[new]: Prepared from 4'-aminoacetophenone (0.14g, 1.0 mmol) and 4-methylbenzyl alcohol (0.24g, 2.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.17g, 0.7mmol, 73%). Mp = 96–97 ºC.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.7 Hz, 2H), 7.16–7.10 (m, 4H), 6.64 (d, *J* = 8.7 Hz, 2H), 3.19 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.7 Hz, 2H), 2.33 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 151.2, 138.7, 135.6, 130.6, 129.3, 128.4, 127.6, 113.9, 40.1, 30.2, 21.1ppm.HRMS (ESI): calcd. for $C_{16}H_{17}NO$ ([M+H]): 240.1383, found: 240.1401. IR (KBr): υ (cm^{-1}) = 3461, 3360, 3226, 3034, 2919, 1647, 1631, 1590, 1175, 832, 809.

1-(4-aminophenyl)-3-(4-fluorophenyl)propan-1-one (Table 2, compound ***2k****)*[new]: Prepared from 4'-aminoacetophenone (0.14g, 1.0 mmol) and 4-fluorobenzyl alcohol (0.25g, 2.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.21g, 0.8 mmol, 86%). Mp = 94–95 ºC.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.6 Hz, 2H), 7.21–7.17 (m, 2H), 6.96 (t, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 8.3 Hz, 2H), 3.17 (t, *J* = 7.6 Hz, 2H), 3.01 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.5, 161.5 (d, *J* = 243.5 Hz), 151.2, 137.4 (d, *J* = 3.1 Hz), 130.7, 129.9 (d, *J* = 7.8 Hz), 128.6 (d, *J* = 5.5 Hz), 115.3 (d, *J* = 21.1 Hz), 114.0, 39.9, 29.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -118.5 ppm. HRMS (ESI): calcd. for $C_{15}H_{14}FNO$ ([M+H]): 244.1132, found: 244.1121. IR (KBr): υ (cm^{-1}) = 3446, 3344, 3234, 1640, 1593, 1510, 1215, 1175, 978, 826.

1-(4-amino-[1,1'-biphenyl]-3-yl)-3-phenylpropan-1-one (Table 2, compound ***2l****)*[new]: Prepared from 1-(4-amino-[1,1'-biphenyl]-3-yl)ethanone (0.21g, 1.0 mmol) and benzyl alcohol (0.22g, 2.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.27g, 0.9 mmol, 91%). Mp = 122–123 ºC.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 2.1 Hz, 1H), 7.56–7.51 (m, 3H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.36–7.22 (m, 6H), 6.77 (d, *J* = 8.6 Hz, 1H), 3.37 (t, *J* = 7.7 Hz, 2H), 3.10 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.7, 149.6, 141.6, 140.6, 133.3, 129.5, 129.3, 128.9, 128.7, 128.6, 126.7, 126.4, 126.2,

118.2, 118.1, 41.2, 30.7 ppm. HRMS (ESI): calcd. for $C_{21}H_{19}NO$ ([M+H]): 302.1539, found: 302.1536. IR (KBr): υ (cm^{-1}) = 3397, 3304, 3028, 1654, 1621, 1557, 1495, 1198, 980, 830, 797, 757.

1-(2-aminophenyl)pentan-1-one (Table 2, compound ***2m****)*[26]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 1-propanol (0.12g, 2.0 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.13g, 0.7 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.4 Hz, 1H), 7.27–7.23 (m, 1H), 6.67–6.63 (m, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 1.74–1.67 (m, 2H), 1.46–1.37 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.3, 150.3, 134.2, 131.4, 118.2, 117.5, 115.9, 39.2, 27.2, 22.7, 14.1 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}NO$ ([M+H]): 178.1226, found: 178.1245.

1-(2-aminophenyl)octan-1-one (Table 2, compound ***2n****)*[27]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 1-hexanol (0.20g, 2.0 mmol). After purification by column chromatography, the compound was isolated as colourless liquid (0.20g, 0.8 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.1 Hz, 1H), 7.27–7.23 (m, 1H), 6.71–6.65 (m, 2H), 2.91(t, *J* = 7.6 Hz, 2H), 1.73–1.66 (m, 2H), 1.33–1.27 (m, 8H), 0.86 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.4, 149.4, 134.3, 131.4, 118.7, 118.0, 116.6, 39.5, 31.9, 29.6, 29.3, 25.1, 22.8, 14.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{21}NO$ ([M+H]): 220.1696, found: 220.1705.

1-(2-aminophenyl)dodecan-1-one (Table 2, compound ***2o****)*[28]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 1-decanol (0.32g, 2.0 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.23g, 0.8 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 6.67–6.62 (m, 2H), 2.90 (t, *J* = 7.6 Hz, 2H), 1.73–1.65 (m, 2H), 1.32–1.24 (m, 16H), 0.86 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.4, 150.0, 134.2, 131.3, 118.4, 117.8, 116.2, 39.5, 32.0, 29.8, 29.8, 29.7, 29.6, 29.5, 25.1, 22.8, 14.2 ppm. HRMS (ESI): calcd. for $C_{18}H_{29}NO$ ([M+Na]): 298.2141, found: 298.2159.

1-(2-(benzylamino)phenyl)ethanone (Table 4, compound ***3a****)*[21b]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and benzyl alcohol (0.32g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a yellow solid (0.21g, 0.9 mmol, 95%). Mp = 78–79 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.0 Hz, 1H), 7.34–7.26 (m, 6H), 6.78–6.66 (m, 2H), 4.47 (s, 2H), 2.60 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2, 149.9, 135.2, 132.8, 128.8, 127.5, 127.4, 118.8, 115.7, 113.4, 47.7, 28.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NO$ ([M+H]): 226.1226, found: 226.1232.

1-(2-((4-methylbenzyl)amino)phenyl)ethanone (Table 4, compound ***3b****)*[new]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 4-methylbenzyl alcohol (0.37g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.22g, 0.9 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.27-7.14 (m, 4H), 6.72–6.60 (m, 2H), 4.43 (s, 2H), 2.60 (s, 3H), 2.34 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 150.6, 137.0, 135.5, 135.2, 132.8, 129.5, 127.2, 118.2, 114.9, 112.7, 46.9, 28.1, 21.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}NO$ ([M+H]): 240.1383, found: 240.1378. IR (KBr): υ (cm^{-1}) = 3326, 1640, 1516, 1565, 1165, 744.

1-(2-((4-fluorobenzyl)amino)phenyl)ethanone (Table 4, compound ***3c****)*[29]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 4-fluorobenzyl alcohol (0.38g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a yellow solid (0.21g, 0.8 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.2 Hz, 1H), 7.33–7.29 (m, 3H), 7.02 (t, *J* = 8.7 Hz, 2H), 6.64–6.61 (m, 2H), 4.43 (s, 2H), 2.61 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2, 162.1(d, *J* = 245.0 Hz), 150.8, 135.1, 134.5, 132.9, 128.7 (d, *J* = 8.0 Hz), 118.0, 115.6 (d, *J* = 21.4 Hz), 114.7, 112.2, 46.1, 28.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -116.7 ppm. HRMS (ESI): calcd. for $C_{15}H_{14}FNO$ ([M+H]): 244.1132, found: 244.1121.

1-(2-((benzo[d][1,3]dioxol-5-ylmethyl)amino)phenyl)ethanone (Table 4, compound ***3d****)*[new]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 3,4-methylenedioxybenzyl alcohol (0.46g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.25g, 0.9 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.1 Hz, 1H), 7.34–7.28 (m, 1H), 6.82–6.74 (m, 3H), 6.67–6.59 (m, 2H), 5.92 (s, 2H), 4.35 (s, 2H), 2.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 150.8, 148.1, 146.8, 135.1, 132.8, 128.8, 120.3, 118.0, 114.6, 112.3, 108.4, 107.8, 101.1, 46.7, 28.1 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}NO_3$ ([M+H]): 270.1125, found: 270.1113. IR (KBr): υ (cm^{-1}) = 3320, 1688, 1636, 1572, 1446, 1251, 1038, 807, 784, 729, 617.

1-(2-((4-(trifluoromethyl)benzyl)amino)phenyl)ethan-1-one (Table 4, compound ***3e****)*[new]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 4-trifluromethylbenzyl alcohol (0.52g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a yellow solid (0.19g, 0.6mmol, 68%). Mp = 74–75 °C.^{1}H NMR (400 MHz, C_6D_6): δ = 9.63 (s, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 2H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 2H), 6.44 (t, *J* = 7.5 Hz, 1H), 6.30 (d, *J* = 8.5 Hz, 1H), 3.81 (d, *J* = 5.7 Hz, 2H), 2.22 (s, 3H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 200.7, 151.0, 143.5, 135.0, 133.1, 127.3, 125.7 (q, *J* = 3.8 Hz), 118.6, 115.0, 112.3, 46.1, 27.7 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}F_3NO$ ([M+H]): 294.1100, found: 294.1098. IR (KBr): υ (cm^{-1}) = 3315, 1635, 1569, 1516, 1328, 1163, 1129, 1066, 828, 745.

1-(2-((naphthalen-1-ylmethyl)amino)phenyl)ethanone (Table 4, compound ***3f****)*[29]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 1-naphthylmethanol (0.48g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a yellow solid (0.24g, 0.8 mmol, 88%). Mp = 109–110 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.9 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.57–7.47 (m, 3H), 7.43–7.39 (m, 1H), 7.33 (t, *J* = 8.6 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.66 (t, *J* = 7.6 Hz, 1H), 4.91 (s, 2H), 2.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 150.6, 135.2, 134.0, 132.8, 131.4, 129.0, 128.2, 126.5, 125.9, 125.7, 125.2, 123.1, 118.4, 115.1, 112.7, 45.1, 28.1 ppm. HRMS (ESI): calcd. for $C_{19}H_{17}NO$ ([M+H]): 276.1383, found: 276.1380.

1-(2-(([1,1'-biphenyl]-2-ylmethyl)amino)phenyl)ethanone (Table 4, compound ***3g****)*[new]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 2-biphenylmethanol (0.55g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.22g, 0.7 mmol, 73%). Mp = 107–108 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 1H), 7.49–7.23 (m, 10H), 6.59 (t, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 8.5 Hz, 1H), 4.35 (s, 2H), 2.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.0, 150.6, 141.7, 141.0, 135.0, 130.3, 129.2, 128.4, 128.0, 128.0, 127.3, 118.1, 118.0, 114.7, 114.5, 112.5, 112.3, 45.0, 28.1 ppm. HRMS (ESI): calcd. for $C_{21}H_{19}NO$ ([M+H]): 302.1539, found: 302.1545. IR (KBr): υ (cm^{-1}) = 3324, 3023, 2921, 1634, 1573, 1518, 752, 703.

1-(2-((furan-2-ylmethyl)amino)phenyl)ethanone (Table 4, compound ***3h****)*[21b]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 2-furyl methanol (0.29g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a red solid (0.16g, 0.7 mmol, 72%). Mp = 71–72 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.1 Hz, 1H), 7.38–7.34 (m, 2H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.64 (t, *J* = 7.6 Hz, 1H), 6.32 (dd, *J* = 3.1, 1.9 Hz, 1H),6.24 (d, *J* = 3.9 Hz, 1H), 4.43 (s, 2H), 2.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 152.2, 150.6,

142.1, 135.1, 132.8, 118.2, 114.9, 112.1, 110.5, 107.0, 40.3, 28.1 ppm. HRMS (ESI): calcd. for $C_{13}H_{13}NO_2$ ([M+H]): 216.1019, found: 216.1012.

*1-(4-(benzylamino)phenyl)ethanone (Table 4, compound **3i**)*[30]: Prepared from 4'-aminoacetophenone (0.14g, 1.0 mmol) and benzyl alcohol (0.32g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a yellow solid (0.15g, 0.6 mmol, 68%).Mp = 84–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.6 Hz, 2H), 7.36–7.27 (m, 5H), 6.63 (d, *J* = 8.6 Hz, 2H), 4.68 (s, 2H), 2.49 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.9, 151.4, 141.0, 130.9, 128.6, 127.8, 127.6, 127.1, 113.8, 65.3, 26.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NO$ ([M+H]): 226.1226, found: 226.1237.

*1-(2-(benzylamino)-5-methoxyphenyl)ethanone (Table 4, compound **3j**)*[new]: Prepared from 1-(2-amino-5-methoxyphenyl)ethanone (0.17g, 1.0 mmol) and benzyl alcohol (0.32g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.16g, 0.6 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.23 (m, 6H), 7.00 (dd, *J* = 9.2, 3.0 Hz, 1H), 6.64 (d, *J* = 9.2 Hz, 1H), 4.44 (s, 2H), 3.77 (s, 3H), 2.60 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.6, 149.1, 146.1, 139.1, 134.6, 129.9, 128.8, 127.1, 123.4, 116.3, 113.7, 56.3, 47.3, 28.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}NO_2$ ([M+H]): 256.1332, found: 256.1338. IR (KBr): υ (cm^{-1}) = 3336, 1647, 1583, 1553, 1037, 1221, 833.

*1-(4-(benzylamino)-[1,1'-biphenyl]-3-yl)ethanone (Table 4, compound **3k**)*[new]: Prepared from 1-(4-amino-[1,1'-biphenyl]-3-yl)ethanone (0.21g, 1.0 mmol) and benzyl alcohol (0.32g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a yellow solid (0.24g, 0.7 mmol, 78%). Mp = 104–105 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 2.2 Hz, 1H), 7.60–7.53 (m, 3H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.38–7.30 (m, 6H), 6.77 (d, *J* = 8.8 Hz, 1H), 4.53 (d, *J* = 5.6 Hz, 2H), 2.69 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2, 150.3, 140.7, 138.7, 133.9, 131.2, 129.0, 128.8, 127.6, 127.3, 127.1, 126.6, 126.3, 118.2, 112.9, 46.9, 28.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{19}NO$ ([M+H]): 302.1539, found: 302.1504. IR (KBr): υ (cm^{-1}) = 3289, 3059, 3028, 2922, 1631, 1578, 1524, 1492, 1228, 759, 698.

*1-(2-(benzylamino)-5-fluorophenyl)ethanone (Table 4, compound **3l**)*[new]: Prepared from 1-(2-amino-5-fluorophenyl)ethanone (0.15g, 1.0 mmol) and benzyl alcohol (0.32g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.12g, 0.5 mmol, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (dd, *J* = 9.8, 3.0 Hz, 1H), 7.32–7.19 (m, 5H), 6.94–6.89 (m, 1H), 6.40 (dd, *J* = 9.3, 4.5 Hz, 1H), 4.66 (s, 1H), 3.15 (d, *J* = 6.8 Hz, 2H), 2.58 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1, 153.9, 146.8, 140.3 (d, *J* = 504.9 Hz), 129.6, 128.6 (d, *J* = 31.3 Hz), 127.1 (d, *J* = 61.5 Hz), 126.6, 122.7 (d, *J* = 22.9 Hz), 117.3 (d, *J* = 22.1 Hz), 114.6 (d, *J* = 6.9 Hz), 45.4, 28.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -131.11 ppm. HRMS (ESI): calcd. for $C_{15}H_{14}FNO$ ([M+H]): 244.1132, found: 244.1111. IR (KBr): υ (cm^{-1}) = 3293, 3061, 3027, 2921, 1644, 1580, 1518, 1260, 1183, 958, 806, 758, 699.

*1-(2-(butylamino)phenyl)ethanone (Table 4, compound **3m**)*[new]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 1-butanol (0.22g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.08g, 0.4 mmol, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.57 (t, *J* = 7.5 Hz, 1H), 3.20 (t, *J* = 7.0 Hz, 2H), 2.57 (s, 3H), 1.71–1.64 (m, 2H), 1.51–1.42 (m, 2H), 0.98 (d, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.9, 151.3, 135.1, 133.0, 117.5, 113.9, 111.9, 42.5, 31.3, 28.0, 20.5, 14.0 ppm. HRMS (ESI): calcd. for $C_{12}H_{17}NO$ ([M+H]): 192.1383, found: 192.1378. IR (KBr): υ (cm^{-1}) = 3301, 2957, 1633, 1574, 1519, 1163, 952, 741, 620.

*1-(2-(hexylamino)phenyl)ethanone (Table 4, compound **3n**)*[new]: Prepared from 2'-aminoacetophenone (0.14g, 1.0 mmol) and 1-hexanol (0.31g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.05g, 0.2 mmol, 22%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.35 (t, *J* = 7.0 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 6.57 (t, *J* = 7.0 Hz, 1H), 3.22–3.16 (m, 2H), 2.58 (s, 3H), 1.73–1.65 (m, 2H), 1.48–1.27 (m, 6H), 0.91 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 200.8, 151.3, 135.1, 132.9, 117.4, 113.7, 111.8, 42.8, 31.7, 29.2, 28.0, 27.0, 22.7, 14.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{21}NO$ ([M+H]): 220.1696, found: 220.1704. IR (KBr): υ (cm^{-1}) = 3311, 1638, 1575, 1520, 952, 742, 620.

*5,6-dimethoxy-2-(piperidin-4-ylmethyl)-2,3-dihydro-1H-inden-1-one (Scheme 2, compound **4**)*[31]: Prepared from 5,6-dimethoxy indanone (0.19g, 1.0 mmol) and 4-piperidinemethanol (0.35g, 3.0 mmol). After purification by column chromatography, the compound was isolated as a yellow solid (0.15g, 0.5 mmol, 51%). Mp = 97–98 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (s, 1H), 6.85 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.23 (dd, *J* = 17.5, 8.1 Hz, 1H), 3.11–3.06 (m, 2H), 2.74–2.57 (m, 4H), 1.93–1.86 (m, 1H), 1.77–1.61 (m, 2H), 1.34–1.11 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0, 155.6, 149.6, 148.9, 129.5, 107.5, 104.5, 56.3, 56.2, 46.9, 46.8, 45.3, 39.5, 35.0, 34.5, 33.4, 33.1 ppm. HRMS (ESI): calcd. for $C_{17}H_{23}NO_3$ ([M+H]): 290.1751, found: 290.1763.

*2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one (Scheme 2, compound **5**)*[31]: Prepared from 5,6-dimethoxy-2-(piperidin-4-ylmethyl)-2,3-dihydro-1H-inden-1-one (0.14g, 0.5 mmol) and benzylalcohol (0.16g, 1.5 mmol). After purification by column chromatography, the compound was isolated as a yellow semi-liquid (0.11g, 0.5 mmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.31 (m, 4H), 7.27–7.23 (m, 1H), 7.15 (s, 1H), 6.84 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.56 (s, 2H), 3.22 (dd, *J* = 17.6, 8.1 Hz, 1H), 2.96–2.92 (m, 2H), 2.71–2.65 (m, 2H), 2.06–1.99 (m, 2H), 1.93–1.86 (m, 1H), 1.71–1.67 (m, 2H), 1.45–1.25 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.8, 155.6, 149.5, 148.8, 137.6, 129.5, 129.4, 128.3, 127.3, 107.4, 104.5, 63.2, 56.3, 56.2, 45.5, 38.7, 34.3, 33.5, 32.7, 31.6. HRMS (ESI): calcd. for $C_{24}H_{29}NO_3$ ([M+H]): 380.2220, found: 380.2245.

CCDC-1559007-1559009 & 1833945 contains the supplementary crystallographic data of **P-PPh$_3$**, compound **2c**, **2f** & **3f**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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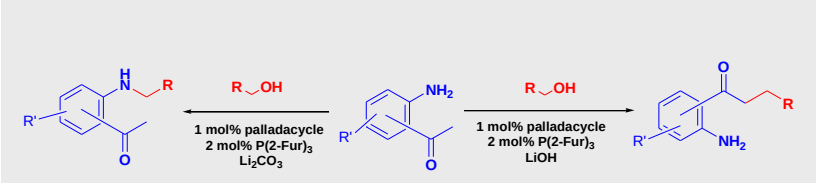

Palladacycle-phosphine catalysed chemoselective alkylation of aminoacetophenones achieved using environmentally friendly hydrogen auto transfer strategy.

*Chemoselective alkylation

Key Topic*

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Chemoselective alkylation of aminoacetophenones with alcohols by using a palladacycle-phosphine catalyst