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Note

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Palladacycle-phosphine catalyzed methylation of amines and ketones using methanol

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KEYWORDS: N-methylation of amines, C-methylation of ketones, palladacycle, hydrogen borrowing

ABSTRACT: Methylation of amines and ketones with palladacycle precatalyst has been performed using methanol as an environmentally benign reagent. Various ketones and amines undergo methylation reaction to yield monomethylated amines or ketones in moderate to good isolated yields. Moreover, this protocol was tested for the chemoselective methylation of 4-aminobenzenesulfonamide. The scope of the reaction was further extended to the deuteromethylation of ketones.

Environmentally benign hydrogen borrowing (HB) using inexpensive substrates such as alcohols has emerged as a powerful tool over the last few decades to make C-C and C-N bonds.[1] In particular, use of methanol as an agent has emanated as an active area of research. Conventionally, toxic and/or hazardous agents such as iodomethane, diazomethane, dimethyl sulfate and dimethyl carbonate used for the formation of methylated products.[2] An added disadvantage of these reagents is the formation of stoichiometric amount of waste apart from the selectivity of the desired product. Hence, much attention has been paid on methanol, since it serves as a cheap, abundant and renewable C-1 source to make C─C and C─N bonds.[3] Although, methanol is the simplest alcohol, relatively high energy is required to activate or dehydrogenate over other alcohols such as ethanol and higher *n*-alkyl alcohols.[4a-c] Moreover, methanol has also proved to be useful for the production of formaldehyde which can be further used to from different useful products.[4d-g]

Pioneering studies by Grigg and co-workers[5] to use alcohols as alkylating reagents motivated many researchers to develop transition metal based efficient catalysts for the alkylation of amines and ketones using hydrogen borrowing strategy.[1] Numerous transition metal based catalysts were reported for the alkylation of amines and ketones using long chain *n*-alkyl alcohols.[1] However, as mentioned *vide supra* it was found to be difficult to apply the hydrogen borrowing strategy for methanol. Recently, the utility of this approach (HB) using methanol as a C1 source has attracted much attention.[6-8] For example Donohoe and co-workers demonstrated a Rh-phosphine complex for C-methylation of ketones under mild reaction conditions.[6a] Yasushi Obora and co-workers reported an Ir-phosphine catalyst for the methylation of ketones using methanol.[7a] Later, Feng Li and co-workers explored the catalytic activity of C_5Me_5-Ir complex for methylation of ketones.[7b] Andersson and co-workers reported an N-heterocyclic carbene based Ir complex for C-methylation of ketones.[7d] Recently, Dafa Chen and co-workers demonstrated an Ir-complex bearing a 2-hydroxpyridylmethylene fragment for C-methylation of ketones and amines under milder reaction conditions.[7f] More recently Sortais group and El-Sepelgy and Rueping groups described manganese based catalysts for C-methylation and C-trideuteromethylation respectively.[9] Although, palladium based catalysts were examined for dehydrogenation of alcohols,[10] N-alkylation of amines[11] and C-alkylation of ketones,[12] to our surprise there is only one report for C-methylation of ketones using methanol as a methylating agent,[13] however, to the best of our knowledge there are no reports for N-methylation of amines using methanol as a reagent. Here we describe, a new palladium based catalytic system for C-methylation as well as N-methylation of ketones and amines respectively using methanol as a methylating agent.

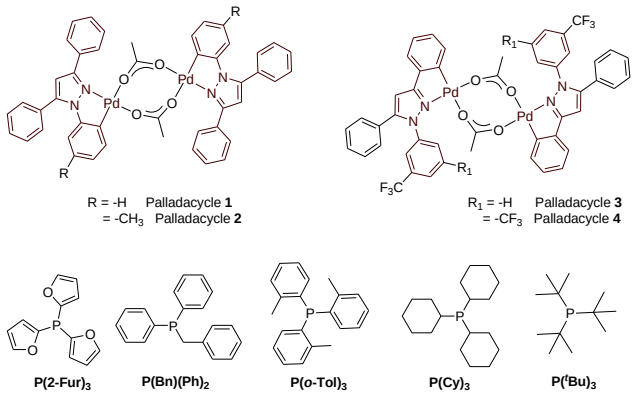


Figure 1. Palladacycles and phosphines used in this study.

We recently explored pyrazole based palladacycles as catalysts or pre-catalysts for N-alkylation of amines,[11c] C-alkylation of ketones[12b] using hydrogen borrowing strategy as well as Suzuki and Heck coupling reactions.[14] Motivated by these results we continued our efforts to develop an efficient palladacycle-based catalytic system to methylate amines and ketones using methanol as a C-1 source. Our initial investigation concentrated on testing various pre-catalysts for the reaction of propiophenone using 2 mol% of palladacycle (or) pre-catalyst, 4 mol% of

tri(2-furyl)phosphine and 30 mol% of LiOH in 1 mL methanol at 100 °C for 48h (Table 1). Use of palladacycle **1** and **2** (Figure 1) under the reaction conditions mentioned above, no product formation was observed. However, when we performed the reaction using palladacycle-**3**, the desired C-methylated product was obtained in 12% isolated yield, showing that palladacycle-**3** (Figure 1) is active under the reaction conditions. With the aim of improving the efficiency of the catalyst we designed palladacycle-**4** and examined the reaction. Interestingly, palladacycle-**4** showed superior activity with 76 % isolated yield of the desired product (table 1, entry 4).

Table 1: Optimization of C-methylation of ketones using propiophenone and methanol[a]

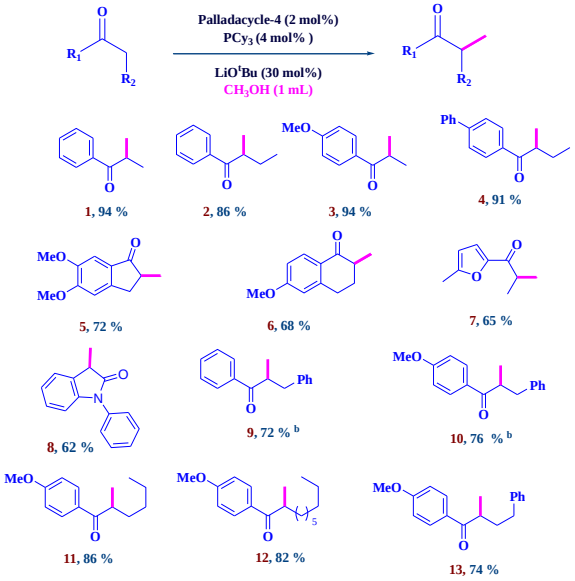
S.No.	Palladacycle	Phosphine	Base	T (°C)	Yield (%)[b]
1	**1**	P(2-Fur)$_3$	LiOH	100	ND
2	**2**	P(2-Fur)$_3$	LiOH	100	ND
3	**3**	P(2-Fur)$_3$	LiOH	100	12
4	**4**	P(2-Fur)$_3$	LiOH	100	76
5	**4**	P(2-Fur)$_3$	LiO^{t}Bu	100	82
6	**4**	P(2-Fur)$_3$	CsOH.H$_2$O	100	ND
7	**4**	P(2-Fur)$_3$	Cs_2CO_3	100	ND
8	4	P(2-Fur)$_3$	KO^{t}Bu	100	41
9	**4**	P(2-Tol)$_3$	LiO^{t}Bu	100	trace
10	**4**	P(Bn)(Ph)$_2$	LiO^{t}Bu	100	trace
11	**4**	P(^{t}Bu)$_3$	LiO^{t}Bu	100	72
12	**4**	P(Cy)$_3$	LiO^{t}Bu	100	86
13	**4**	P(Cy)$_3$	LiO^{t}Bu	110	91
14	**4**	P(Cy)$_3$	LiO^{t}Bu	120	94
15	-	P(Cy)$_3$	LiO^{t}Bu	120	ND[c]
16	**4**	P(Cy)$_3$	-	120	ND[d]
17	**4**	P(Cy)$_3$	LiO^{t}Bu	120	86[e]
18	-	P(Cy)$_3$	LiO^{t}Bu	120	7[f]
19	-	P(Cy)$_3$	LiO^{t}Bu	120	11[g]
20	-	P(Cy)$_3$	LiO^{t}Bu	120	14[h]

[a]Reaction conditions: propiophenone 1 mmol, base $3x10^{-1}$ mmol, precatalyst $2x10^{-2}$ mmol, phosphine $4x10^{-2}$ mmol, [b]All yields are isolated yields. [c]Reactions were performed without palladacycle-**4**. [d]Reactions were performed without LiO^{t}Bu. [e]$2x10^{-1}$mmol LiO^{t}Bu was used. [f]Reaction was performed using $4x10^{-2}$ mmol of Pd(OAc)$_2$. [g]Reaction was performed using $4x10^{-2}$ mmol of $PdCl_2(MeCN)_2$. [h]Reaction was performed using $2x10^{-2}$ mmol of $Pd_2(dba)_3$.

We were delighted to observe an increased yield of 82% using LiO^{t}Bu instead of LiOH as a base (table 1, entry 5). The methylated product was not observed when we used CsOH.H$_2$O and Cs_2CO_3 as a base. However, use of KO^{t}Bu as a base yielded the desired product in 41% (table 1, entry 8). LiOH and LiO^{t}Bu were found to be suitable over other bases studied in our laboratory (entries 6–8).[15]

Next, our investigation focused on identifying an appropriate monodentate phosphine with the aim of improving the yield of the C-methylated product. P(2-Tol)$_3$ and P(Bn)(Ph)$_2$ failed to give the desired product (table 1, entries 9 and 10). The yield of the C-methylated product improved to 72% with P^{t}Bu$_3$ as a ligand. Use of P(Cy)$_3$ as a ligand resulted a maximum yield of the desired product (86%). The donor strength as well as steric effect of the phosphine could be a factor for the enhancement in catalytic performance under the reaction conditions. Increasing the temperature to 120 °C resulted in 94% yield of the C-methylated product (table 1, entry 14). Moreover, the reaction did not proceed in the absence of palladacycle-**4** and (or) LiO^{t}Bu (table 1, entries 15 and 16), indicating the requirement of both palladacycle-**4** and LiO^{t}Bu for the C-methylation of propiophenone. It is noteworthy to mention that palladium salts such as Pd(OAc)$_2$, $PdCl_2(MeCN)_2$, (or) $Pd_2(dba)_3$ resulted lower yields of the desired product (7%, 11%, and 14% respectively; Table 1, entries 18-20) under the optimized conditions.

Table 2: Substrate scope for methylation of ketones[a]

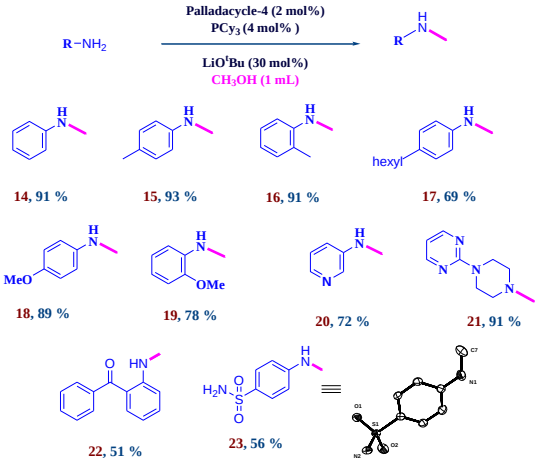


[a]Reaction conditions: ketone 1 mmol, base $3x10^{-1}$ mmol, precatalyst $2x10^{-2}$ mmol, phosphine $4x10^{-2}$ mmol at 120 °C for 48 h. All yields are isolated yields. [b]Reactions were performed using 3 mol% palladacycle-**4**, 6 mol% PCy$_3$, base $5x10^{-1}$ mmol at 130 °C for 48 h.

In order to explore the substrate scope and limitations of this method under the optimized reaction conditions, we examined different arylketones. Good to excellent isolated yields of the C-methylated ketone products **1**, **2**, **3** and **4** were observed from propiophenone, butyrophenone, 4'-methoxy propiophenone and 4'-phenylbutyrophenone (Table 2) respectively. Cyclic ketones such as 5,6-dimethoxy indanone and 6-methoxy tetralone were smoothly methylated to yield the corresponding products (Table 2, compounds **5** and **6**). Notably, our catalytic system tolerated heteroaryl ketones such as 2-methyl-5-propionyl furan and N-phenyl oxindole to yield the corresponding C-methylated products in 65% and 62% respectively (Table 2, compound **7** and **8**). To show the proficiency of our catalytic system 1,3-diphenylpropan-1-one, 1-(4-methoxyphenyl)-3-phenylpropan-1-one, 1-(4- methoxyphenyl)hexan-1-one, 1-(4-methoxyphenyl)decan-1-one, and 1-(4-methoxyphenyl)-4-phenylbutan-1-one were examined under the reaction conditions, and the corresponding C-methylated compounds **9**-**13** were obtained in 72-

86% isolated yields. However, our catalytic system did not produce the desired products when we used 4'-bromo propiophenone and 4'-chloro propiophenone under the reaction conditions. However, when we used 4'-fluoro propiophenone under the reaction conditions, we observed 4'-methoxy propiophenone (methoxylated product) formation by nucleophilic aromatic substitution of C─F bond.

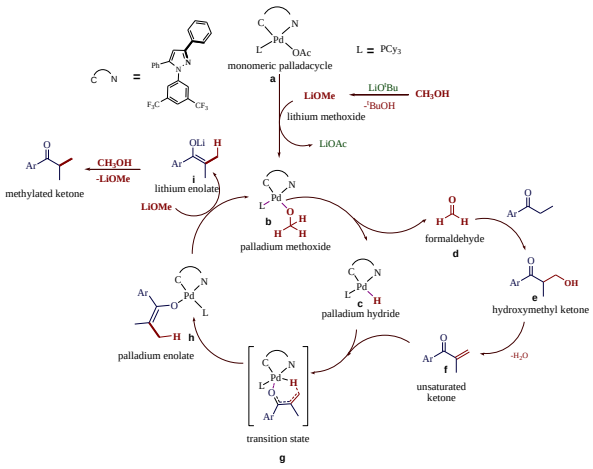
Table 3: Substrate scope for methylation of amines[a]



[a]Reaction conditions: amine 1 mmol, base $3x10^{-1}$ mmol, precatalyst $2x10^{-2}$ mmol, phosphine $4x10^{-2}$ mmol at 120 °C for 48 h. All yields are isolated yields.

Motivated by the results obtained for C-methylation of aryl ketones with methanol, we next concentrated on N-methylation of amines using methanol as the alkylating agent. N-methylated amines are important structural scaffolds, and frequently observed in fine chemicals, pharmaceuticals and natural products.[16] Significantly, they also play a crucial role in biological processes, gene regulation, protein function and RNA processing.[17] Traditionally, toxic and/or hazardous methyl halides or sulfates have been used as the methylating agents to synthesize N-methylated compounds.[18,2c] N-methylation of amines using methanol as a reagent has received much attention owing to its atom economy and limited waste. Despite of this importance, till date very few studies were performed for N-methylation of amines using methanol as a reagent.[3a,6c,6e,7e,8] To the best of our knowledge, there are no reports on palladium-catalyzed N-methylation of amines by methanol. In order to examine the efficiency of the palladacycle-**4** and phosphine system, we performed N-methylation of aniline under the reaction condition mentioned above. To our delight, selective mono N-methylation of aniline proceeded smoothly and furnished the desired product in 91% isolated yield (Table 3, compound **14**). Encouraged by these results, we further explored the scope of the methodology using different amines under the reaction conditions. Anilines with substitution at different position yielded the N-methylated products in good to excellent isolated yields (**14**-**19**: 69%–93%) with good selectivity. 4-Methyl aniline and 4-methoxy aniline gave isolated yields of 93% and 89% respectively (Table 3, compounds **15** and **18**), whereas sterically hindered 2-methyl aniline and 2-methoxy aniline gave yield of 91% and 78% respectively (Table 3, compounds **16** and **19**). Heteroaryl amines such as 3-aminopyridine and 2-(piperazin-1-yl)pyrimidine were well tolerated (Table 3, compounds **20** and **21**). Notably, only mono methylated products were observed in most of the cases of aromatic primary amines. In addition, N-methylation of 2-aminophenyl(phenyl)methanone provided the corresponding N-methylated product (Table 3, compound **22**) in 51 % isolated yield. However, 4-(trifluoromethyl)aniline did not yield the desired product under our experimental conditions.[19] Selective transformation of molecules with more than one functional group *ie* chemoselectivity is an important problem in organic synthesis and less explored using reactions that follow hydrogen borrowing strategy.[20] We tested 4-aminobenzenesulfonamide with two functional groups for its chemoselectivity. The reaction of 4-aminobenzenesulfonamide yielded the N-methylation at the primary amine nitrogen in 56 % (compound **23**).

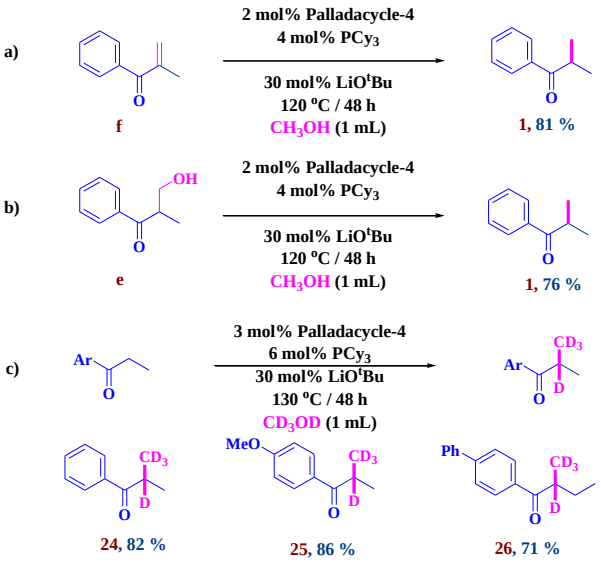
Scheme 1: Proposed reaction mechanism.



A plausible mechanism starting from the phosphine ligated monomeric palladacycle is proposed in scheme 1, for the C-methylation of propiophenone. Palladacycle-**4** could readily form monomeric palladacycle in the presence of PCy_3. The catalytic cycle could be initiated by LiOMe in the presence of monomeric palladacycle to generate palladium methoxide (**b**). Complex **b**, liberates formaldehyde and palladium hydride (**c**) on β-hydride abstraction. The transient formaldehyde condenses with propiophenone to generate unsaturated ketone. The resultant unsaturated ketone gets reduced by the palladium hydride in the presence of methanol to yield the product. Control experiments were performed using the intermediates **e** and **f** as starting materials (Scheme 2) to validate the proposed mechanism. Under the optimized conditions, proposed intermediates **e** and **f** were converted to the desired product **1**. From these experiments we came to know that compounds **e** and **f** could be the intermediates in C-methylation of ketones. Under the optimized reaction conditions, propiophenone selectively converted to C-deuteromethylated product in 82 % isolated yield (compound **24**) using CD_3OD as a solvent and reagent. Then, we extended the deuteromethylation to two more substrates which resulted compounds **25** and **26** in 86 % and 71 % isolated yield respectively (Scheme 2). Deuteromethylation experiments further supports that proton at the α-carbon is coming from the methanol in course of the reaction. The importance of isotope-labelled C-methylated products were highlighted by Rueping and coworkers in a recent study.[9c] We propose a mechanism for the N-methylation of amines using methanol as a reagent similar to that proposed for the C-alkylation of ketones using methanol (Scheme S1).

In conclusion, we have identified homogeneous palladacycle phosphine based catalyst or precatalyst for the selective N-methylation of amines and C-methylation of ketones using methanol as a greener and more sustainable methylating agent, following the catalytic hydrogen borrowing strategy. The catalytic system is widely applicable for different ketones and amines to yield the corresponding methylated products. Importantly, the palladacycle-phosphine precatalyst has given chemoselective monomethylated product of sulfanilamide, under the reaction conditions. Finally our catalytic system also tolerated methanol-d_4 as a deuteromethylation source for ketones under the reaction conditions.

Scheme 2: Possible intermediates involved in C-methylation of propiophenone and Trideuteromethylation of ketones



EXPERIMENTAL SECTION:

General: All reagents and solvents were obtained from commercial sources. Solvents were purified according to standard procedures. 1,3,5-triphenyl pyrazole,[14] 3,5-diphenyl-1-(*m*-tolyl)-1H-pyrazole, [21a] palladacycle-**1**,[14] were synthesized following literature reported methods. All 400 (or) 700 MHz ^{1}H, 100 (or) 176 MHz ^{13}C spectra were recorded on a spectrometer operating at 400 (or) 700 MHz. All ^{1}H and ^{13}C NMR spectra were referenced internally to solvent signals. ^{19}F NMR spectra were externally referenced to α,α,α-trifluorotoluene in $CDCl_3$ (δ = -63.73 ppm). IR spectra were recorded with Perkin Elmer instrument. High-resolution mass spectra (HRMS) were recorded with using the microTOF-QII mass spectrometer. Single-crystal X-ray diffraction data were collected at 296 K using, Mo-Kα radiation (0.71073 Å) or Cu-Kα radiation (1.54184 Å). Crystallographic data for palladacycle-**4**, and compound **23** and details of X-ray diffraction experiments and crystal structure refinements are given in Table S1. The structures were solved and refined with SHELX suite of programs or Olex. All non-hydrogen atoms were refined with anisotropic displacement coefficients. The H atoms were placed at calculated positions and were refined as riding atoms. (CCDC deposition no. 1906689-1906690).

General procedure for synthesis of 1,3,5-triaryl pyrazole derivatives. 1,3-Diphenylpropane-1,3-dione (10.0 mmol) and corresponding arylhydrazine (10.0 mmol) were taken in a 100 mL round bottom flask. Subsequently, 10 mL of methanol and 10 mL of acetic acid were added to the flask and the reaction mixture was refluxed for 12 h. To the reaction mixture, saturated sodium carbonate solution was added and the compound was extracted using dichloromethane. The solvent was removed under vacuum and the residue was purified by column chromatography (*n*-hexane–ethyl acetate as an eluent).

***3, 5-diphenyl-1-(m-tolyl)-1H-pyrazole*[21a]:** Prepared from 1,3-diphenylpropane-1,3-dione (2.24 g, 10.00 mmol) and *m*-tolylphenyl hydrazine hydrochloride (1.59 g, 10.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 98:2), the compound was isolated as a white solid (2.45 g, 7.9 mmol, 79%). Mp = 75-76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.94 (d, *J* = 7.5, 2H), 7.44 (t, *J* = 7.5, 2H), 7.33 (d, *J* = 9.9, 7H), 7.20 (t, *J* = 7.7, 1H), 7.12 (d, *J* = 7.4, 1H), 7.07 (d, *J* = 7.7, 1H), 6.83 (s, 1H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 144.5, 139.2, 130.8, 128.8, 128.7, 128.6, 128.5, 128.4, 128.1, 126.1, 126.0, 122.6, 105.2, 21.4 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2$ 311.1543; found: 311.1561. IR (cm^{-1}): 3047 (s), 1489 (s), 1460 (s), 1363 (m), 799 (m), 766 (s), 695 (s), 501 (m).

***3,5-Diphenyl-1-(3-(trifluoromethyl) phenyl)-1H-pyrazole*[21b]:** Prepared from 1,3-diphenylpropane-1,3-dione (2.42 g, 10.0 mmol) and (3-(trifluoromethyl)phenyl) hydrazine (1.76g, 10.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 98:2), the compound was isolated as a white solid (3.21 g, 8.8 mmol, 88%). Mp = 40-41 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.3, 2H), 7.73 (s, 1H), 7.53 (dd, *J* = 16.7, 6.8, 2H), 7.46 (t, *J* = 7.2, 3H), 7.38 (s, 4H), 7.33 – 7.26 (m, 2H), 6.85 (s, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 152.7, 144.7, 140.6, 132.8, 132.6, 131.6 (q, *J* = 33 Hz), 130.2, 129.5, 128.9, 128.8, 128.4, 128.1, 127.3, 126.0, 123.8 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272 Hz), 122.0 (q, *J* = 4 Hz), 106.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ= -62.82 ppm. IR (KBr): ν (cm^{-1}) = 3069 (m), 2811 (m), 1596 (m), 1459 (m), 1365 (s), 1326 (s), 1169 (m), 1125 (s), 1066 (m), 809 (s), 694 (s). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}F_3N_2$ 365.1260; found: 365.1256.

***1-(3,5-bis(trifluoromethyl)phenyl)-3,5-diphenyl-1H-pyrazole*[new]:** Prepared from 1,3-diphenylpropane-1,3-dione (2.42 g, 10.0 mmol) and 3,5-bis((trifluoromethyl)phenyl) hydrazine (2.44 g, 10.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 98:2), the compound was isolated as a white solid (3.93 g, 9.1 mmol, 91%). Mp = 88-89 °C. ^{1}H NMR (400 MHz, $CDCl_3$):) δ = 7.94 (d, *J* = 7.5, 2H), 7.84 (s, 2H), 7.75 (s, 1H), 7.43 (tt, *J* = 14.6, 7.3, 6H), 7.34 – 7.27 (m, 2H), 6.87 (s, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 153.4, 145.0, 141.2, 132.4, 132.3 (q, *J* = 34 Hz), 129.9, 129.4, 129.1, 129.0, 128.9, 128.8, 127.3, 126.1, 124.4 (q, *J* = 3.3 Hz), 122.9 (q, *J* = 271 Hz), 120.3 (q, *J* = 3.6 Hz), 120.2, 107.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ -63.18 ppm. IR (cm^{-1}): 3075 (m), 2936 (m), 1480 (m), 1384 (s), 1279 (s), 1187 (m), 1135 (s), 892 (m), 764 (m), 698 (m). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{15}F_6N_2$ 433.1134; found: 433.1142.

***General procedure for the synthesis of palladacycles*.** Palladium acetate (5.00 mmol) and corresponding 1,3,5-arylpyrazole (5.00 mmol) were suspended in glacial acetic acid (15 mL) and the mixture was heated in an oil bath (100 °C, 2 h). The reaction mixture was filtered through celite to remove palladium black

and the resultant solution was concentrated. The residue was re-dissolved in dichloromethane, layered with *n*-hexane and stored at 5 °C for 24 h and filtered through celite (1cm height) silicagel (100-200 mesh, 1cm height) to remove palladium black traces, and repeated the same three times. The solution was concentrated and recrystallized from a mixture of dichloromethane and *n*-hexane.

***Palladacycle-2^{new}*:** Prepared from palladium acetate (1.00 g, 4.4 mmol) and 3, 5-diphenyl-1-(*m*-tolyl)-1H-pyrazole (1.37 g, 4.4 mmol). Yield: 1.34 g (64%). Mp = 188-189 °C (decompose). 1H NMR (400 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 7.5, 4H), 7.56 (t, *J* = 7.4, 2H), 7.42 (dt, *J* = 13.3, 6.8, 10H), 7.15 (s, 4H), 6.81 (d, *J* = 7.8, 2H), 6.60 (d, *J* = 7.7, 2H), 6.13 (s, 2H), 5.92 (s, 2H), 1.92 (s, 6H), 1.25 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ= 181.2, 154.2, 143.1, 141.9, 133.0, 132.8, 130.5, 129.9, 129.7, 129.6, 128.9, 128.7, 128.1, 124.8, 113.6, 110.0, 23.0, 21.2 ppm. Elemental analysis calcd (%) for $C_{48}H_{40}N_4O_4Pd_2.(C_7H_8)_{0.3}$: C 61.57, H 4.37, N 5.73; found: C 61.71, H 4.13, N 5.93. IR (cm^{-1}): 3057 (m), 1572 (s), 1469 (m), 1412 (s), 1373 (m), 802 (m), 763 (s), 699 (s).

Palladacycle-3^{new}: Prepared from palladium acetate (1.00 g, 4.4 mmol) and 3,5-diphenyl-1-(3-(trifluoromethyl) phenyl)-1H-pyrazole (1.60 g, 4.4 mmol). Yield: 1.97 g (85%). Mp = 220-221 °C (decompose). ^1H NMR (400 MHz, $CDCl_3$): ^1H NMR (400 MHz, $CDCl_3$) δ = 7.53 (dt, *J* = 15.2, 7.5, 6H), 7.36 – 7.30 (m, 2H), 7.26 (t, *J* = 7.6, 4H), 7.20 (d, *J* = 7.3, 2H), 7.14 (s, 2H), 7.06 (t, *J* = 7.2, 2H), 6.88 (d, *J* = 7.9, 4H), 6.83 (t, *J* = 7.4, 2H), 6.76 (d, *J* = 7.6, 2H), 6.34 (s, 2H), 1.33 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 180.1, 160.1, 146.2, 145.5, 137.3, 136.4, 131.9, 131.7, 130.3 (q, *J* = 34 Hz), 129.4, 129.3, 129.1, 128.8, 128.5, 125.8, 125.2 (q, *J* = 3.4 Hz), 124.9, 124.3, 124.1, 124.1 (q, *J* = 4 Hz), 123.5 (q, *J* = 273 Hz), 122.2, 102.4, 23.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.79 ppm. Elemental analysis calcd (%) for $C_{48}H_{34}F_6N_4O_4Pd_2$: C 54.41, H 3.24, N 5.30; found: C 54.69, H 3.02, N 5.52. IR (cm-1) = 3061 (m), 2914 (m), 1593 (m), 1576 (s), 1420 (s), 1380 (m), 1327 (s), 1176 (m), 1123 (s), 1070 (m), 804 (m), 758 (s), 697(s).

***Palladacycle-4^{new}*:** Prepared from palladium acetate (1.00 g, 4.4 mmol) and 1-(3,5-bis(trifluoromethyl)phenyl)-3,5-diphenyl-1H-pyrazole (1.90 g, 4.4 mmol). Yield: 2.44 g (91%). Mp = 227-229 °C (decompose). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.78 (s, 2H), 7.34 (m, 12H), 7.08 (t, *J* = 7.3 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 6H), 6.68 (d, *J* = 7.6 Hz, 2H), 6.47 (s, 2H), 1.35 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 180.1, 160.7, 146.1, 146.0, 137.1, 136.7, 131.8, 131.5 (q, *J* = 34 Hz), 129.8, 129.1, 128.7, 128.1, 127.9 (q, *J* = 3.8 Hz), 126.2, 124.5, 122.8(q, *J* = 273 Hz), 122.6, 122.1 (q, *J* = 3.5 Hz), 103.0, 23.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.83 ppm. Elemental analysis calcd (%) for $C_{50}H_{32}F_{12}N_4O_4Pd_2$: C 50.31, H 2.70, N 4.69; found: C 50.69, H 2.40, N 5.02. IR (cm^{-1}) = 3060 (m), 1575 (s), 1418 (s), 1394 (s), 1280 (s), 1184 (s), 1139 (s), 899 (m), 760 (m), 700 (m).

General procedure for α-methylation of ketones and amines using methanol. An oven dried Schlenk tube was charged with palladacycle (2 x 10^{-2} mmol to 3 x 10^{-2} mmol), $P(Cy)_3$ (4 x 10^{-2} mmol to 6 x 10^{-2} mmol). Under inert atmosphere LiO^tBu (0.30 mmol), ketone or amine (1.0 mmol), methanol (0.5 to 1 ml) were added to the reaction mixture and the system was purged with nitrogen gas for 10 minutes. Then the Schlenk tube was closed with PTFE stopper and the reaction mixture was stirred at 110 - 130 °C for 48 h. The reaction mixture was cooled to room temperature, diluted and washed with dichloromethane (3 x 5 mL), and concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using n-hexane and ethyl acetate mixtures to afford the α-methylated product in high purity.

Analytical data for methylated compounds

***2-methyl-1-phenylpropan-1-one (Table 2, entry 1)*[8]:** Prepared from propiophenone (0.13 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 98:2), the compound was isolated as a colourless liquid (0.15 g, 0.94 mmol, 94%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 3.56 (h, *J* = 8.0 Hz, 1H), 1.22 (d, *J* = 8.0 Hz, 6H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 204.6, 136.3, 132.9, 128.7, 128.4, 35.5, 19.3 ppm.

***2-methyl-1-phenylbutan-1-one (Table 2, entry 2)*[8]:** Prepared from butyrophenone (0.15 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as a colourless liquid (0.14 g, 0.86 mmol, 86%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, *J*=7.4, 2H), 7.54 (t, *J*=7.3, 1H), 7.46 (t, *J*=7.5, 2H), 3.40 (h, *J* = 6.7, 1H), 1.89 – 1.77 (m, 1H), 1.55 – 1.42 (m, 1H), 1.19 (d, *J* = 6.9, 3H), 0.91 (t, *J* = 7.4, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 204.5, 136.8, 132.8, 128.6, 128.3, 42.1, 26.7, 16.8, 11.8 ppm. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{14}ONa$ 185.0937; found: 185.0932.

***1-(4-methoxyphenyl)-2-methylpropan-1-one (Table 2, entry 3)*[6c]:** Prepared from 4-methoxypropiophenone (0.16 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 98:2), the compound was isolated as a colourless liquid (0.17 g, 0.94 mmol, 94%). ^1H NMR (400 MHz, DMSO-d6) δ = 7.94 (d, *J* = 8.7, 2H), 7.03 (d, *J* = 8.7, 2H), 3.83 (s, 3H), 3.58 (dq, *J* = 13.1, 6.6, 2H), 1.08 (d, *J* = 6.8, 7H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 202.1, 162.9, 130.4, 128.4, 113.9, 55.4, 34.0, 19.1 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{15}O_2$ 179.1067; found: 179.1064.

***1-([1,1'-biphenyl]-4-yl)-2-methylbutan-1-one (Table 2, entry 4)^{new}*:** Prepared from 4-butyrobiphenyl (0.22 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as a colourless liquid (0.22 g, 0.91 mmol, 91%). ^1H NMR (700 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 7.1 Hz, 2H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 3.45 (h, *J* = 6.8 Hz, 1H), 1.90–1.86 (m, 1H), 1.57–1.51 (m, 1H), 1.24 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 204.1, 145.6, 140.0, 135.6, 129.0, 129.0, 128.3, 127.4, 127.3, 42.3, 26.8, 16.9, 11.9 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}O$ 239.1430; found: 239.1421.

***5,6-dimethoxy-2-methyl-2,3-dihydro-1H-inden-1-one (Table 2, entry 5)*[21c]:** Prepared from 5,6-dimethoxyindanone (0.19 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as a yellow colour solid (0.15 g, 0.72 mmol, 72%). Mp = 131–132 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (s, 1H), 6.86 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.30 (dd, *J* = 16.7, 7.3 Hz, 1H), 2.72–2.60 (m, 2H), 1.29 (d, *J* = 7.4 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 208.4, 155.6, 149.6, 148.8, 129.2, 107.5, 104.6,

56.34, 56.2, 42.3, 34.9, 16.8 ppm. HRMS (ESI-TOF) m/z: [M + Na] $^+$ Calcd for $C_{12}H_{14}O_3Na$ 229.0835; found: 229.0835.

***6-methoxy-2-methyl-3,4-dihydronaphthalen-1(2H)-one (Table 2, entry 6)*[21d]:** Prepared from 6-methoxy-1-tetralone (0.18 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as a colourless liquid (0.13 g, 0.68 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.7 Hz, 1H), 6.78 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 3.82 (s, 3H), 2.97–2.90 (m, 2H), 2.55–2.46 (m, 1H), 2.18–2.11 (m, 1H), 1.87–1.77 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 197.4, 163.7, 147.1, 129.8, 126.5, 113.2, 112.8, 55.5, 39.0, 30.3, 29.8, 23.5 ppm. HRMS (ESI-TOF) m/z: [M + H] $^+$ Calcd for $C_{12}H_{15}O_2$ 191.1067; found: 191.1069.

***2-methyl-1-(5-methylfuran-2-yl)propan-1-one (Table 2, entry 7)*[6a]:** Prepared from 1-(5-methylfuran-2-yl)propan-1-one (0.14 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as a colourless liquid (0.099 g, 0.65 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 3.4 Hz, 1H), 6.14 (d, *J* = 3 Hz, 1H), 3.30–3.23 (m, 1H), 2.38 (s, 3H), 1.18 (d, *J* = 6.9 Hz, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 193.3, 157.8, 150.9, 119.4, 108.9, 36.0, 19.2, 14.2 ppm.

***3-methyl-1-phenylindolin-2-one (Table 2, entry 8)*[6c]:** Prepared from 1-phenyloxindole (0.21 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as a colourless liquid (0.14 g, 0.62 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (t, *J* = 8 Hz, 2H), 7.45-7.41 (m, 3H), 7.33 (d, *J* = 8 Hz, 1H), 7.23 (t, *J* = 8 Hz, 1H), 7.12 (t, *J* = 8 Hz, 1H), 6.84 (d, *J* = 8 Hz, 1H), 3.64 (q, *J* = 8 Hz, 1H), 1.62 (d, *J* = 8 Hz, 3H) ppm. ^{13}C{^{1}H} (100 MHz, $CDCl_3$): δ ppm: 178.0, 143.9, 134.6, 130.4, 129.6, 127.9, 127.7, 123.8, 122.8, 109.3, 40.7, 15.7 ppm. HRMS (ESI-TOF) m/z: [M + Na] $^+$ Calcd for $C_{15}H_{13}NONa$ 246.0889; found: 246.0880.

***2-methyl-1,3-diphenylpropan-1-one (Table 2, entry 9)*[6a]:** Prepared from 1,3-diphenylpropan-1-one (0.21 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as a colourless liquid (0.16 g, 0.72 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (d, *J* = 7.9, 2H), 7.55 (t, *J* = 7.3, 1H), 7.45 (t, *J* = 7.7, 2H), 7.30 – 7.23 (m, 2H), 7.19 (dd, *J* = 12.6, 6.9, 3H), 3.76 (h, *J* = 6.8, 1H), 3.18 (dd, *J* = 13.7, 6.3, 1H), 2.70 (dd, *J* = 13.7, 7.8, 1H), 1.21 (d, *J* = 6.8, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 203.9, 140.1, 136.6, 133.0, 129.2, 128.7, 128.4, 126.3, 42.9, 39.5, 17.5 ppm. HRMS (ESI-TOF) m/z: [M + H] $^+$ Calcd for $C_{16}H_{17}O$ 225.1274; found: 225.1282.

***1-(4-methoxyphenyl)-2-methyl-3-phenylpropan-1-one (Table 2, entry 10)*[6a]:** Prepared from 1-(4-methoxyphenyl)-3-phenylpropan-1-one (0.24 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 98:2), the compound was isolated as a colourless liquid (0.19 g, 0.76 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.9 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.23 –7.15 (m, 3H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 3.74–3.65 (m, 1H), 3.16 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.69 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 202.4, 163.5, 140.2, 130.7, 129.5, 129.20, 128.5, 126.2, 113.9, 55.6, 42.4, 39.6, 17.7 ppm. HRMS (ESI-TOF) m/z: [M + H] $^+$ Calcd for $C_{17}H_{19}O_2$ 255.1380; found: 255.1376.

***1-(4-methoxyphenyl)-2-methylhexan-1-one (Table 2, entry 11)*[7c]:** Prepared from 1-(4-methoxyphenyl)hexan-1-one (0.21 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as a colourless liquid (0.19 g, 0.86 mmol, 86%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.41 (h, *J* = 6.8 Hz, 1H), 1.82–1.73 (m, 1H), 1.46–1.38 (m, 1H), 1.34–1.22 (m, 4H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 203.3, 163.4, 130.6, 129.9, 113.9, 55.6, 40.2, 33.8, 29.8, 23.0, 17.5, 14.1 ppm. HRMS (ESI-TOF) m/z: [M + H] $^+$ Calcd for $C_{14}H_{21}O_2$ 221.1536; found: 221.1536.

***1-(4-methoxyphenyl)-2-methyldecan-1-one (Table 2, entry 12)*[new]:** Prepared from 1-(4-methoxyphenyl)decan-1-one (0.26 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as a colourless liquid (0.23 g, 0.82 mmol, 82%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.2 Hz, 2H), 6.90 (d, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 3.40–3.36 (m, 1H), 1.77–1.73 (m, 1H), 1.40–1.21 (m, 13H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 203.1, 163.3, 130.5, 129.8, 113.8, 55.4, 40.2, 34.0, 31.9, 29.8, 29.5, 29.3, 27.5, 22.7, 17.5, 14.1 ppm. HRMS (ESI-TOF) m/z: [M + H] $^+$ Calcd for $C_{18}H_{29}O_2$ 277.2162, found: 277.2164.

***1-(4-methoxyphenyl)-2-methyl-4-phenylbutan-1-one (Table 2, entry 13)*[new]:** Prepared from 1-(4-methoxyphenyl)-4-phenylbutan-1-one (0.26 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as pale yellow liquid (0.20 g, 0.74 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, *J* = 8.8, 2H), 7.31 (t, *J* = 7.3, 2H), 7.21 (dd, *J* = 16.9, 7.5, 3H), 6.95 (d, *J* = 8.9, 2H), 3.89 (s, 3H), 3.47 (h, *J* = 6.7, 1H), 2.69 – 2.64 (m, 2H), 2.21 (dq, *J* = 15.3, 7.1, 1H), 1.85 – 1.71 (m, 1H), 1.26 (d, *J* = 6.9, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 202.7, 163.4, 141.9, 130.6, 129.5, 128.5, 128.4, 125.9, 113.8, 55.5, 39.3, 35.4, 33.5, 17.5 ppm. HRMS (ESI-TOF) m/z: [M + H] $^+$ Calcd for $C_{18}H_{21}O_2$ 269.1536, found: 269.1547.

***N*-methylaniline (Table 3, entry 14)*[6c]:** Prepared from aniline (0.093 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 98:2), the compound was isolated as a colourless liquid (0.097 g, 0.91 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, *J* = 7.8 Hz, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 2H), 3.72 (s, 1H), 2.90 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 149.5, 129.3, 117.4, 112.5, 30.8 ppm.

***N*,4-dimethylaniline (Table 3, entry 15)*[11b]:** Prepared from *p*-toluidine (0.11 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 96:4), the compound was isolated as a pale yellow liquid (0.11 g, 0.93 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 8.2 Hz, 2H), 2.82 (s, 3H), 2.26 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.3, 129.8, 126.6, 112.8, 31.2, 20.5 ppm.

***N*,2-dimethylaniline (Table 3, entry 16)*[6c]:** Prepared from *o*-toluidine (0.11 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 96:6), the compound was isolated as a pale yellow liquid (0.11 g, 0.91 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 3.59

(s, 1H), 2.93 (s, 3H), 2.17 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.4, 130.0, 127.3, 122.0, 117.0, 109.2, 30.9, 17.5 ppm.

***4-hexyl-N-methylaniline (Table 3, entry 17)[new]*:** Prepared from 4-hexylaniline (0.18 g, 1 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as pale yellow liquid (0.13 g, 0.69 mmol, 69%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.03 (d, *J* = 8.3, 2H), 6.60 (d, *J* = 8.2, 2H), 3.41 (s, 1H), 2.84 (s, 3H), 2.57 – 2.46 (m, 2H), 1.58 (p, *J* = 7.6, 2H), 1.37 – 1.30 (m, 7H), 0.90 (t, *J* = 6.7, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 147.1, 132.2, 129.2, 112.8, 35.2, 32.0, 31.9, 31.3, 29.14, 22.8, 14.2 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{22}N$ 192.1747; found: 192.1741.

***4-methoxy-N-methylaniline (Table 3, entry 18)[6c]*:** Prepared from *p*-anisidine (0.12 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as a pale yellow liquid (0.12 g, 0.89 mmol, 89%). ^1H NMR (400 MHz, $CDCl_3$): δ 6.82 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 3.77 (s, 3H), 3.36 (s, 1H), 2.81 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.1, 143.8, 115.0, 113.7, 55.9, 31.7 ppm.

***2-methoxy-N-methylaniline (Table 3, entry 19)[21e]*:** Prepared from *o*-anisidine (0.12 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as a pale yellow liquid (0.11 g, 0.78 mmol, 78%). ^1H NMR (400 MHz, $CDCl_3$): δ 6.95 (d, *J* = 6.5 Hz, 1H), 6.80 (s, 1H), 6.73 (s, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 4.19 (s, 1H), 3.88 (s, 3H), 2.91 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.0, 139.4, 121.4, 116.5, 109.5, 109.4, 55.5, 30.5 ppm.

***N-methylpyridin-3-amine (Table 3, entry 20)[6c]*:** Prepared from pyridin-3-amine (0.094 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 90:10), the compound was isolated as pale yellow liquid (0.0778 g, 0.72 mmol, 72%). ^1H NMR (700 MHz, $CDCl_3$) δ = 8.04 (s, 1H), 7.91 (d, *J* = 4.5, 1H), 7.12 (dd, *J* = 8.3, 4.8, 1H), 6.91 (d, *J* = 8.3, 1H), 2.84 (s, 3H), 2.07 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 174.6, 145.7, 136.9, 134.4, 124.2, 118.9, 30.2 ppm.

***2-(4-methylpiperazin-1-yl)pyrimidine (Table 3, entry 21)[new]*:** Prepared from 2-(piperazin-1-yl)pyrimidine (0.16 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as a pale yellow liquid (0.16 g, 0.91 mmol, 91%). ^1H NMR (700 MHz, $CDCl_3$): δ 8.28 (d, *J* = 4.7 Hz, 2H), 6.46 (t, *J* = 4.7 Hz, 1H), 3.83 (s, 4H), 2.46 (d, *J* = 5.1 Hz, 4H), 2.32 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 161.8, 157.8, 110.0, 55.0, 46.2, 43.6 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{15}N_4$ 179.1291; found: 179.1294.

2-(methylamino)phenyl)(phenyl)methanone *(Table 3, entry 22)[21f]*: Prepared from (2-aminophenyl)(phenyl)methanone (0.197 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 95:5), the compound was isolated as a yellow liquid (0.11 g, 0.51 mmol, 51%). ^1H NMR (700 MHz, $CDCl_3$) δ = 7.60 (d, *J* = 7.1, 2H), 7.53 – 7.47 (m, 2H), 7.47 – 7.40 (m, 3H), 6.80 (d, *J* = 8.5, 1H), 6.57 (t, *J* = 7.5, 1H), 2.98 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ = 199.4, 140.6, 135.6, 135.2, 130.9, 129.1, 128.2, 114.21, 111.6, 29.9 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}NO$ 212.1070; found: 212.1074.

4-(methylamino)benzenesulfonamide *(Table 3, entry 23)[new]*: Prepared from 4-aminobenzenesulfonamide (0.17 g, 1.00 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 90:10), the compound was isolated as a pale yellow solid (0.10 g, 0.56 mmol, 56%). ^1H NMR (400 MHz, DMSO-d_6) δ = 7.52 (d, *J* = 8.7, 2H), 6.90 (s, 2H), 6.57 (d, *J* = 8.7, 2H), 6.37 (s, 1H), 2.71 (d, *J* = 4.9, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 152.3, 129.8, 127.3, 110.3, 29.3 ppm. HRMS (ESI-TOF) m/z: $[M + K]^+$ Calcd for $C_7H_{10}N_2O_2SK$ 225.0095; found: 225.0091.

***1-(4-methoxyphenyl)-2-methylpropan-1-one-2,3,3,3-d4 (scheme 2, entry 24)[9c]*:** Prepared from propiophenone (67 mg, 0.50 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 98:2), the compound was isolated as a pale yellow liquid (62.5 mg, 0.41 mmol, 82%). ^1H NMR (700 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 7.6, 2H), 7.58 (t, *J* = 7.4, 1H), 7.49 (t, *J* = 7.7, 2H), 1.25 (d, *J* = 8.7, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 199.6, 163.3, 130.2, 113.7, 55.4, 31.3–30.4 (m), 8.3 ppm.

***1-(4-methoxyphenyl)-2-methylpropan-1-one-2,3,3,3-d4 (scheme 2, entry 25)[new]*:** Prepared from 4-methoxypropiophenone (82 mg, 0.50 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 98:2), the compound was isolated as a pale yellow liquid (79 mg, 0.43 mmol, 86%). ^1H NMR (700 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 1.15 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 199.6, 163.3, 130.2, 113.7, 55.4, 31.3–30.4 (m), 8.3 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{11}D_4O_2$ 183.1318; found: 183.1322.

***1-([1,1'-biphenyl]-4-yl)-2-(methyl-d3)butan-1-one-2-d (scheme 2, entry 26)[new]*:** Prepared from 4-butyrobiphenyl (0.11 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc : 98:2), the compound was isolated as white solid (0.12 g, 0.36 mmol, 71%). Mp = 86–87 °C. ^1H NMR (700 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.1 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 1.80–1.77 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 200.4, 145.7, 140.1, 136.0, 129.1, 128.8, 128.3, 127.4, 127.4, 40.8–39.1 (m), 29.9, 18.0, 14.0 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}D_4O$ 243.1681; found: 243.1679.

ASSOCIATED CONTENT

Supporting Information. Supporting information is available free of charge via the Internet at http://pubs.acs.org. NMR spectra for all compounds, crystal data, molecular structure of plladacycle-**4** and compound **23**.

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Notes

The authors declare no competing financial interest.

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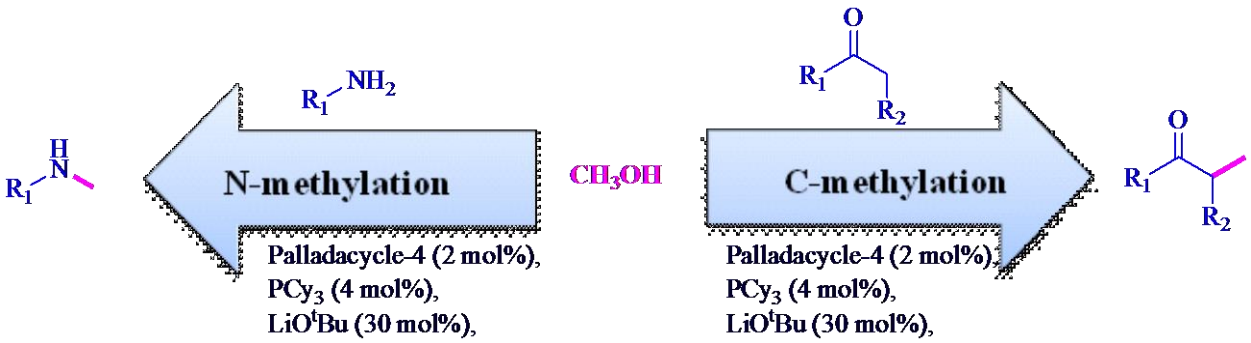

Table of Contents artwork