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Nickel-Catalyzed Alkylation of Ketone Enolates: Synthesis of Mono-Selective Linear Ketones

Jagadish Das, Mari Vellakkaran, and Debasis Banerjee*

Department of Chemistry, Laboratory of Catalysis and Organic Synthesis, Indian Institute of Technology Roorkee, Roorkee 247667 (India)

ABSTRACT: Herein we have developed a Ni-catalyzed protocol for the synthesis of linear ketones. Aryl, alkyl and hetero-aryl ketones as well as alcohols yielded the mono-selective ketones in up to 90% yield. Catalytic protocol successfully applied in gram scale synthesis. For a practical utility, applications of steroid derivative, oleyl alcohol and naproxen alcohol were employed. Preliminary catalytic investigations involving isolation of a Ni-intermediate and defined Ni-H species as well as a series of deuterium labeling experiments were performed.

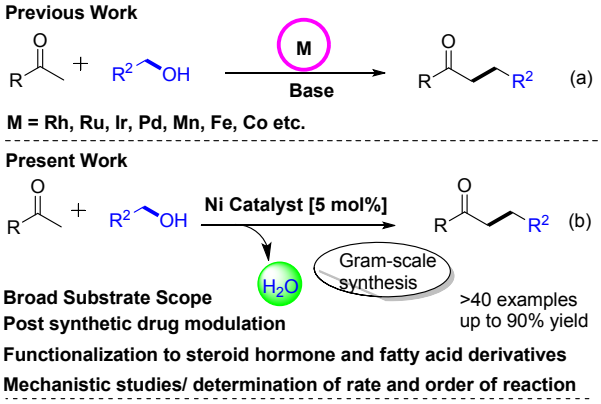
KEYWORDS: Alcohols • Nickel • Borrowing-hydrogen catalysis • α-Alkylation • Earth-abundant metal • Ketones • Mechanistic

INTRODUCTION

Utilization of high natural abundant and inexpensive alcohols and versatility to a broad range of amine and C-nucleophiles enables the synthesis of valuable agrochemicals, pharmaceuticals and bioactive heterocycles involving hydrogen auto-transfer strategy.[1-2] Furthermore, α-alkylation of carbonyl compounds involving ketone enolates using un-activated alcohols represents the most important milestones to forge the new C-C bonds.[3]

Traditionally, hazardous alkyl halides and stoichiometric amount of strong bases are used for such methodologies and equivalent excess of waste are formed. However, the main advantages of HB process is to avoid such stoichiometric salt waste as water is formed as the sole by-product makes this technology more sustainable and atom-economic.[1] Importantly, catalytic upgradation of alcohols to energy efficient biofuels has been developed using Guerbet process. These self-coupling of alcohols could be performed using bifunctional Ir- or Ru-catalysts.[4a-b] In this context, it is noteworthy to mention that, (de)hydrogenative coupling of alcohols for α-alkylation of carbonyl compounds, were generally performed with precious noble-metal catalysts, such as, Ru,[4c-f] Rh,[5] Ir [6] and Pd-complexes (Scheme 1a).[7] In spite of notable progress, potential application of renewable resources along with earth-abundant, inexpensive and non-precious transition metal catalysts for key chemical transformations is a long standing goal and crucial challenge in catalysis.[8] More recently, significant achievements for α-alkylation of carbonyl compounds with alcohols were realized using Fe,[9] Mn,[10] and Co-catalysts.[11] However, use of fancy pincer ligands based on pyridinyl, diethylamine or triazinyl framework is required to achieve higher efficiency.[9-11] Further, application of these highly expensive ligands and their multi-step synthesis often are major concern in comparison to base-metal catalysts.

Scheme 1: Transition-metal catalyzed ketone alkylation



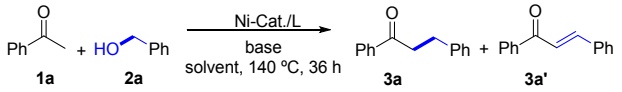
In this direction, nickel has economic benefits and would function as sustainable alternative to palladium.[12] Thus still, there is a need to develop more exciting and challenging methodologies using nickel. However, due to poor leaving ability and strong binding capacity of free hydroxyl group in alcohol, often un-activated alcohols behaves as an inferior substrate class for such nickel-catalyzed transformations.[13a-d] Notably, Yus and co-workers studied the nickel nanoparticle mediated coupling of ketones using primary alcohols.[13e-f] In this direction, herein we demonstrated the homogeneous Ni-catalyzed alkylation of acetophenone derivatives to a range of α-alkylated long chain ketones with a variety of primary alcohol. The catalytic protocol is highly selective to linear α-alkylated ketones following hydrogen-borrowing strategy.[3,14]

RESULTS AND DISCUSSION

Optimization of the catalytic protocol for α-alkylation of carbonyl compounds. As part of our ongoing studies, recently we developed the nickel catalyzed protocols for the synthesis of secondary amines, amides as well as five and six membered heteroarenes.[14a-c] More recently, we established a practical route to bis-substituted branched ketones.[14d] Nevertheless, used of 1 equivalent of *t*-BuOK was crucial to

achieve such goal. At this point, we wondered, whether such Ni-catalyzed system would be beneficial for α-alkylation of methyl ketones or acetophenone derivatives to linear products. Notably, we observed quite poor selectivity to ketone **3a** under the optimized conditions of methylene ketones.[14d] Using 5 mol% $NiBr_2$, 6 mol% 1,10-phenanthroline **L1** and 100 mol% of *t*-BuOK afford the mono-selective ketone **3a** albeit with lower product conversions when toluene was used as solvent in 140 °C (Table 1, entry 17). Notably, application of excess base transformed to reduce alcohol product of **3a** along with higher order ketones.[14d] Therefore, we realized the crucial role of base to achieve higher linear product selectivity. Further, we envisioned that, relatively milder basic conditions might be useful for recent studies (Scheme 1b). For instance, mild basic conditions not only allow higher selectivity to **3a**, it will also prevent *in situ* bis-alkylation to higher order ketones.[14d] However, addition of excess alcohols often displayed reduced alcohol product of **3a.**

Table 1. Discovery of reactions: Mono-alkylation of acetophenone with benzylalcohol.[a,b]



1a 2a 3a 3a'

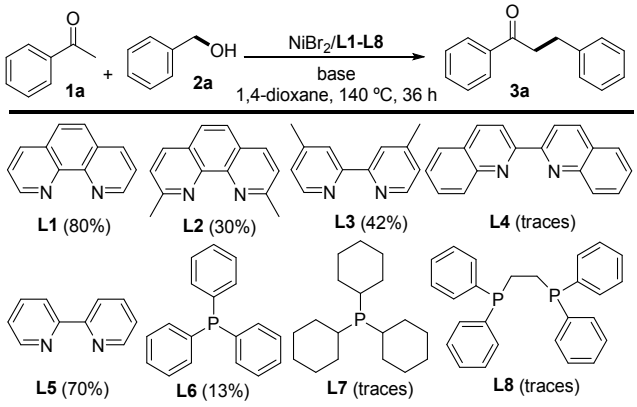
entry	catalyst (mol %)	base (mol %)	GC-MS conv. (%) 3a	3a'
1	$NiBr_2$ (10)	Cs_2CO_3 (10)	80 (76)	7
2	$NiCl_2$ (10)	Cs_2CO_3 (10)	29	2
3	$Ni(acac)_2$ (10)	Cs_2CO_3 (10)	63	9
4	$Ni(cod)_2$ (10)	Cs_2CO_3 (10)	10	0
5	$NiCl_2$.dme (10)	Cs_2CO_3 (10)	22	4
6[c]	**$NiBr_2$ (10)**	**Cs_2CO_3 (10)**	**85 (80)**	10
7[d]	**$NiBr_2$ (5)**	***t*-BuOK (20)**	**94 (82)**	**1**
7[e]	$NiBr_2$ (10)	Cs_2CO_3 (10)	6	0
8[f]	$NiBr_2$ (10)	Cs_2CO_3 (10)	0	0
9[g]	$NiBr_2$ (10)	Cs_2CO_3 (10)	81	5
0[h]	$NiBr_2$ (7.5)	Cs_2CO_3 (10)	63	16
11[i]	$NiBr_2$ (5.0)	Cs_2CO_3 (10)	42	8
12[j]	$NiBr_2$ (2.5)	Cs_2CO_3 (10)	25	3
13	$NiBr_2$(10)	-	0	0
14[k]	$NiBr_2$(10)	Cs_2CO_3 (10)	27	12
15	-	Cs_2CO_3 (10)	6	11
16	-	*t*-BuOK (20)	25	50
17[d]	$NiBr_2$ (5)	*t*-BuOK (100)	20	0

[a]*Reaction conditions:* Acetophenone (0.25 mmol), benzyl alcohol (0.375 mmol), Ni-catalyst. (0.025 mmol), 1,10-phenanthroline (0.05 mmol), Cs_2CO_3 (0.025 mmol), N_2 atmosphere, pre-heated oil bath at 140 °C in 1,4-dioxane for 36 h in a Schlenk tube. Turnover number (TON = 16.4) and turnover frequency (TOF = 0.46 h^{-1}) calculation based on the formation of product **3a** under standard reaction conditions. [b]Conversions were determined using GC-MS considering (starting material + **3a** + **3a'** = 100%) and isolated yield was reported in parenthesis (average yield of two runs). [c]Reaction was performed using benzyl alcohol (0.3125 mmol). [d]Reaction was performed using $NiBr_2$. (0.0125 mmol), 1,10-phenanthroline (0.015mmol), N_2 atmosphere, pre-heated oil bath at 140 °C in toluene for 36 h. [e]130 °C. [f]Reaction was performed at 120 °C. [g]Reaction was performed using **2a** (0.275 mmol). [h]**L1** (15 mol%) was used. [i]**L1** (10 mol%) was used. [j]**L1** (5 mol%) was used. [k]No ligand was used.

Previously we demonstrated the nickel-catalyzed hydrogen borrowing strategy using primary alcohols in combination with various coupling partners.[14] During this present study, our prime focus was to control the undesired side reactions, such as, hydrogenation of carbonyl group as well as base-mediated coupling of ketones (Table 1 and Supporting Information (SI), Table S1-S2).[15] At this point, we realized that, a combination of suitable nickel-catalyst with nitrogen ligand is crucial for such mono-selective transformations.[16]

To achieve this goal, primarily we studied the model reaction of Table 1 using five different nickel pre-catalysts. Gratifyingly, application of 10 mol% $NiBr_2$, 20 mol% 1,10-phenanthroline **L1** and 10 mol% of Cs_2CO_3 afford the desired product **3a** in 76 % isolated yield, when 1,4-dioxane was used as solvent in 140 °C (Table 1, entries 1-5). Under identical catalytic conditions various ligands with electronically different nature were tested and did not improve the product yield further (Table 2).

Table 2. Influence of ligands for alkylation of 1a with 2a.[a,b]



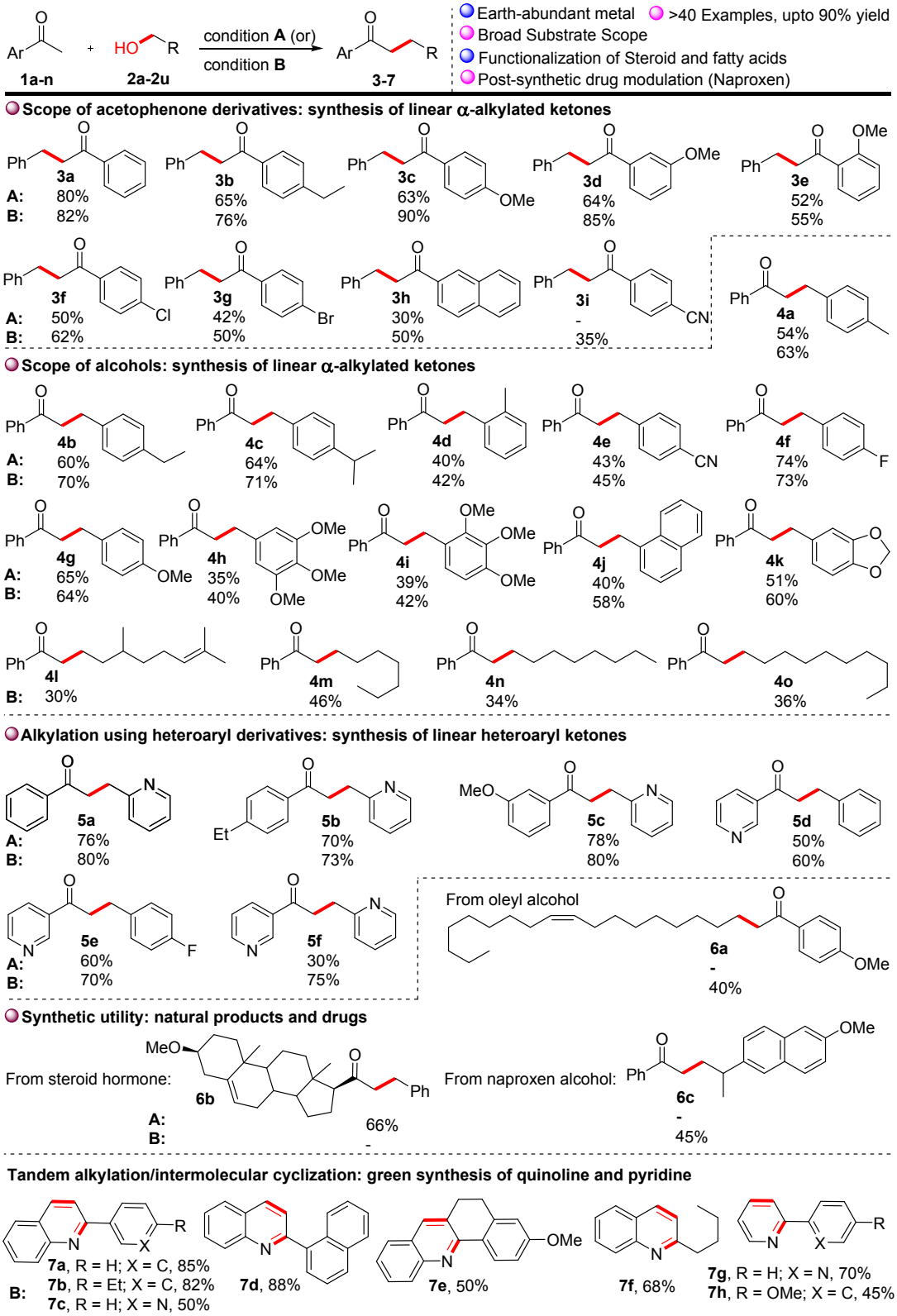
[a]See Table 1 and Supporting Information for detailed of reaction conditions. [b]Conversion was determined by GC-MS.

At this point, application of various polar solvents such as, *n*-propanol, N, N-dimethyl-formamide (DMF), as well as replacement of 1,4-dioxane with toluene and xylene were found inefficient for alkylation of acetophenone (see SI, Table S2). Notably, in absence of solvents only trace amount of enone intermediate was detected along with unidentified side products. Next, influence of different organic and inorganic bases were performed and resulted poor or no product yield (see SI, Table S1). To our delight, we observed a slight increment of product yield, when a lower equivalent of alcohol was used (Table 1, entries 1, 6 and 9). Further reaction using 20 mol% of *t*-BuOK in place of 10 mol% of Cs_2CO_3 with lower catalyst loading resulted 82% isolated yield of **3a** (Table 1, entry 7). As expected, we did not observe any alkylation product in absence of catalyst and base whereas, control experiment in absence of ligand or variable amount of catalyst loading resulted albeit with moderate to poor product yield (Table 1, entries 8-17). Notably, in some cases we observed 2-10% C=O bond reduced product during alkylation process (Table 1).

Mono-selective alkylation of acetophenone with alcohol. A series of ketones with aryl, alkyl and heteroaryl alcohols were tested for selective mono-alkylation (Scheme 2). To our delight, ethyl, methoxy, as well as halide substituents on the aryl ring of acetophenone are well tolerated and resulted α-

alkylated acetophenone in up to 90% yield (**3a-3i**). Importantly, sterically hindered ortho-methoxy acetophenone efficiently converted into 55% yield of **3e**. It is to be note that, under standard conditions 2-naphthyl and 4-cyano substituted acetophenones afford the linear mono-selective ketones **3h-3i** in moderate yields and unreacted acetophenones were recovered (Scheme 2).

Scheme 2: Synthesis of linear α-alkylated ketones



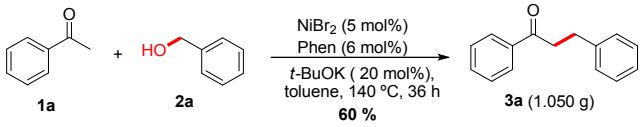
Reaction conditions: For details of conditions A, B, and C, see experimental section.

Notably, the catalytic protocol is highly selective for methyl-ketone derivative and we did not observe any bis-alkylated ketones (Table 1 and SI, Table S1-S2).

α-Alkylation of acetophenone with a range of benzyl and alkyl alcohols. Having witnessed excellent catalytic activity of acetophenone derivatives with benzyl alcohol, next, we studied the reactivity profile of various benzyl alcohols with a series of electronically different acetophenones (Scheme 2, **4a-4k**). Benzyl alcohols bearing electron rich functionalities including 2-methyl substituent at aryl ring, resulted corresponding mono-alkylated products **4a-4d** in 42-71% yield respectively. Advantageously, 4-fluoro and 4-nitrile substituted benzyl alcohols efficiently transformed into the desired products **4e-4f** in up to 74% yield. Notably, when using benzyl alcohols having multiple electron rich substituents, resulted a lower product yield due to strong electronic effect (Scheme 2, **4g-4i**). Gratifyingly, 1-naphthyl methanol as well as benzyl alcohol having oxygen heterocycles selectively converted into linear ketone derivatives **4j-4k**. Further, we employed long chain renewable aliphatic primary alcohols with acetophenone (**4l-4o**, Scheme 2). However, using optimized conditions (Table 1, entry 6), only poor or no product conversions were observed. Therefore, application of *t*-BuOK under standard catalytic conditions resulted in up to 46% isolated yield of **4l-4o** (Table 1, entry 7 and Scheme 2). It is noteworthy to mention that, renewable terpenoid intermediate citronellol efficiently converted to **4l** under standard catalytic conditions. Notably, this is a rare instance of a chemo-selective transformation of an alkyl alcohol having internal double-bond using nickel, often quite challenging under precious-metal catalysis.[4-7]

Alkylation using hetero aromatic ketones and alcohols. Pleasingly, we analyzed the scope of hetero-aryl alcohols for alkylation with methyl ketones. Gratifyingly, 2-pyridinemethanol efficiently alkylated with acetophenone derivatives and resulted in up to 80% yield (Scheme 2, **5a-5c**). Notably, more challenging, 3-acetyl pyridine gave 60% yield of **5d** with benzyl alcohol. Furthermore, 4-fluorophenyl benzyl alcohol and 2-pyridinemethanol afford pharmaceutically active ketones **5e-5f** in 70-75% yield, respectively. It is important to note that, the catalytic protocol is tolerant to the pyridine derivatives, otherwise known to poison the catalytic system.

Scheme 3: Practical utility: gram scale synthesis of 3a.

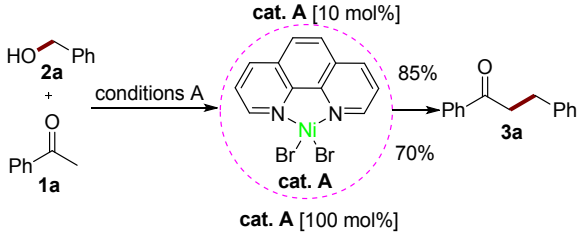


Reaction Conditions (Procedure B): **1a** (1.0 g, 8.33 mmol), **2a** (1.125 g, 10.42 mmol), $NiBr_2$ (91 mg, 5 mol%), phen (90 mg, 6 mol%), *t*-BuOK (187 mg, 7.46 mmol) and toluene (15.0 mL) in a 100 mL pressure tube under nitrogen atmosphere at 140 ºC in oil bath for 36 h.

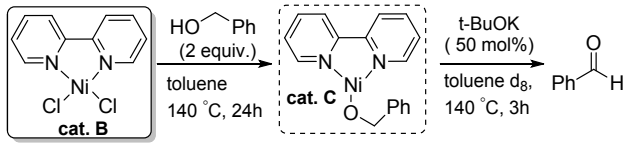
Synthetic applications. Thereafter, we extend our nickel-catalyzed selective alkylation in the synthesis of complex natural products and drug molecules with impressive functional group compatibility (Scheme 2, **6a-6c**). For instance, alcohol derived from sensitive fatty acid, such as, oleic acid, alkylated with 4-methoxy acetophenone to **6a** without significantly affecting the double bond and resulted reasonable product yield. Methyl ketone from steriod hormone efficiently alkylated with benzyl alcohol to **6b**. Again, alkyl alcohol derived from drug, naproxen, transformed to the corresponding α-alkylated product in moderate yield (**6c**). All these examples demonstrate the potential application of the present methodology and could be useful for selective and efficent post-synthetic drug functionalization using nickel catalyst.

Scheme 4: Catalytic and mechanistic studies.

4a: Catalytic and stoichiometric studies using define cat. A



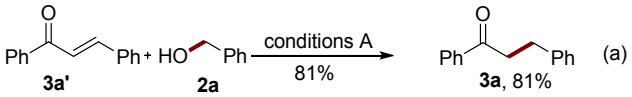
4b: Evidence for intermediate nickel-alkoxy species

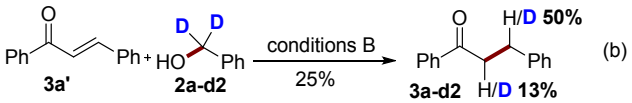


proposed Ni-alkoxy intermediate

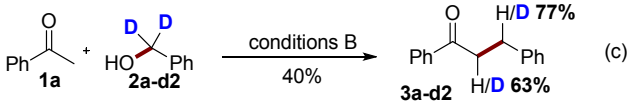
4c:Stoichiometric studies using define Ni-H catalyst

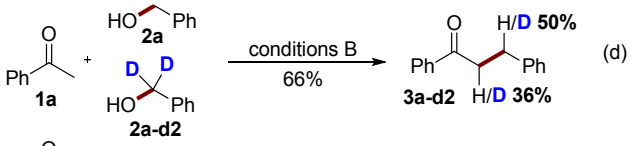
4d: Reduction of enone with alcohols

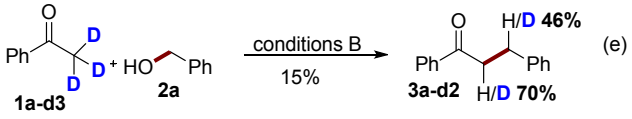


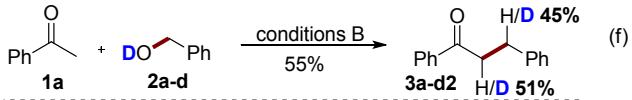


4e: Deuterium incorporation experiments and H/D exchange









Control experiments: **Reaction condition A**: Ketone (0.1 mmol), alcohol (0.125 mmol), $NiBr_2$ (10 mol%), 1,10-phenanthroline (20 mol%), Cs_2CO_3 (50 mol%) and 1,4-dioxane as solvent (2.0 mL) at 140 °C for 48 h. **Reaction condition B**: Ketone (0.1 mmol), alcohol (0.125 mmol),

$NiBr_2$ (10 mol%), 1,10-phenanthroline (20 mol%), and *t*-BuOK (20 mol%) in toluene as solvent (2.0 mL) at 140 °C for 48 h.

Further, we applied our optimized protocol for the synthesis of C-2 substituted quinolines and pyridines using amino alcohols with acetophenone derivatives and resulted in up to 88% yields (Scheme 2, **7a-7h**).

Notably, we observed impressive functional group tolerance for the present catalytic protocol. For instance, halides (Cl, Br, and F), alkyl, alkoxy and di-oxolone functionalities including heteroarenes were used efficiently for alkylation reactions. Importantly, presence of sensitive functionalities such as, nitrile, internal double bond in fatty acid alcohol, citronellol including steroid framework highlights the significance of the developed methodology. Unfortunately, ketones or alcohols bearing nitro, free amines, amides, alkynes and free alcohol functionalities could participate for alkylation process. For a practical utility, the alkylation process was performed using acetophenone **(**1.0 g, 8.33 mmol) with benzyl alcohol and resulted the linear ketone **3a** in 60% product yield (1.050 g, Scheme 3).

Kinetic and mechanistic studies. Having observed excellent catalytic activity for α-alkylation of ketones with primary alcohols, we next focused to study the mechanistic investigation for the course of the reactions. In our earlier studies we observed that,[14] Ni-catalyzed alcohol dehydrogenation is a multi-step process following HB methodology (Scheme 5). Similar to our previous studies, we performed a series of control and mechanistic studies to understand the catalytic behaviour of the Ni-catalyst in case of alkylation of acetophenone derivatives.

Therefore, active nickel pre-catalyst, **cat. A** was prepared,[18] and tested for alkylation as presented in Scheme **4a**. During optimization studies we observed that, base plays a key role to obtain higher product yield (Table 1, entry 13).[14] We anticipated that, base facilitate the process for activation of nickel pre-catalysts *via* dehalogenation of NiX_2 and substitution with alcohol counterpart resulted alkoxy-nickel species. [14d,18] Next, the pre-formed alkoxy-nickel species undergoes β-hydride elimination in presence of a base and aldehyde is formed. Importantly, active nickel-hydride species generate during this process, facilitate enone reduction. Therefore, we synthesized the nickel-alkoxy species of **cat. B**, tested under standard conditions using 50 mol% *t*-BuOK for three hours and as expected, benzaldehyde formation was detected (Scheme 4b and SI Scheme S6). These experiments proof the involvement of the nickel-alkoxy intermediate for alkylation process.[14d]

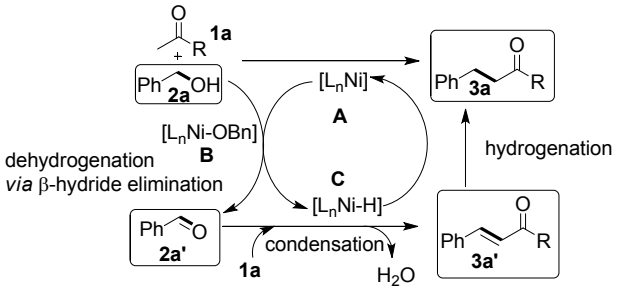
Further to strengthen our hypothesis, we made an attempt to prepare the Ni-H species of **cat. A**., unfortunately, after several attempt at variable temperature we failed to detect any Ni-H species even using an *in situ* NMR studies at -75 °C.[14] Therefore, as observed earlier, we choose highly electron rich phosphine ligand, tri-cyclohexyl phosphine, **L7** and prepared the defined Ni-H complex, $[(Cy)_3]_2PNiBrH$.[17] Further, stoichiometric reaction of $[(Cy)_3]_2PNiBrH$ with enone **3a'** using 20 mol% *t*-BuOK gave 38% yield of **3a** (Scheme 4c). These experimental outcomes strongly support our hypothesis for the involvement of nickel-alkoxy as well as Ni-H species for α-alkylation of methyl ketones using dehydrogenative coupling of alcohols under nickel catalysis as observed in case of methylene ketones.[14d]

Additionally, in similar line of methylene ketones we performed detailed deuterium-labeling experiments for α-alkylation of methyl ketones too (Scheme 4, 4d-4e). When using intermediate **3a '** with benzyl alcohol and **2a-d2**, we observed 13% and 50% incorporation of deuterium in α-, and β-position of **3a-d2** respectively (Scheme 4d). Further reaction using acetophenone with **2a-d2**, resulted equal distribution of deuterium atom in α-, and β-position of **3a-d2** (Scheme 4e, c and Supporting Information Scheme S1). Thereafter a crossover experiments under optimized conditions also resulted **3a-d2** and detected deuterium incorporation at α, and β-position in almost equivalent ratio (Scheme 4e, d and Supporting Information Scheme S2). Next, when **1a-d3** reacted with benzyl alcohol **1a**, a variable D/H exchange-ratio in the product **3a-d2** observed. To our delight, catalytic experiment using **1a-d**, resulted deuterium incorporation at α, and β-position in equal distribution in product **3a-d2** (Scheme 4e, e-f and SI Scheme S4-S5).

We believe that, results obtained using deuterated investigation for alkylation of methyl ketones are in strong agreement for involvement of hydrogen auto-transfer strategy and D/H exchange during the course of the reaction (Scheme 4 and SI Schemes S1-S5).[19a] Notably, alcohol was crucial for generic hydride source, involvement of alkoxy-nickel species as well as *in situ* generated nickel-hydride species was the key for catalytic α-alkylation of methylene ketones.[19] Finally, we also performed kinetic profile for the optimized process and observed first order rate (see Supporting Information, Schemes S7 and S8).

Notably, we observed a similar deuterium studies profile for methyl as well as methylene ketones under nickel-catalysis with the exceptions that; methyl ketones responded under milder conditions in compare to the methylene ketones and displayed the linear products with high selectivity.

Scheme 5: Plausible mechanistic cycle for α-alkylation of methyl ketones.



Based on the above mechanistic studies we herein proposed a plausible mechanism for the nickel catalyzed α-alkylation of methyl ketones (Scheme 5). Initially, nitrogen ligated nickel-complex **A** transformed into the alkoxy-nickel species **B** *via* dehalogenation followed by substitution with benzyl alcohol. Base mediated β-hydride elimination of complex **B**, resulted the formation of transition Ni-H species **C** and benzaldehyde **2a'** is formed. Subsequently, a base catalyzed condensation of benzaldehyde with acetophenone **1a** generates the intermediate enone **3a'**, which, thereafter undergoes hydrogenation by Ni-H species selectively at C=C bond and deliver the product **3a**. Overall, the process is sustainable, atom-economic and water is released as by product. Further detailed mechanistic and kinetic studies regarding α-alkylation

of ketones are presently undergoing in our laboratory and will be disclosed in future communications.

CONCLUSIONS

In summary, we demonstrated an inexpensive and operational simple base-metal catalyzed protocol for selective mon-alkylation of methyl ketones with alcohols using borrowing hydrogen approach. This Ni-catalyzed dehydrogenative coupling of alcohol could be performed in gram scale and extended to a range of aryl, alkyl and hetero-aryl derivatives (>40 examples) in up to 90% yield including green synthesis of N-heterocycles. For a synthetic application, functionalization of steroid hormone, unsaturated fatty acids and post synthetic modification of naproxen drug have shown. Detailed mechanistic studies involving isolation of a Ni-intermediate, defined Ni-H species, intermediate Ni-alkoxy species and determination of rate and order of reaction as well as a series of deuterium labeling experiments were crucial for preliminary mechanistic studies for selective alkylation of methyl ketones. Notably, at this stage, recovery and reuse of the catalytic system for alkylation process were not successful.

EXPERIMENTAL SECTION

General Experimental Details:

All solvents and reagents were used, as received from the suppliers. TLC was performed on Merck Kiesel gel 60, F_{254} plates with the layer thickness of 0.25 mm. Column chromatography was performed on silica gel (100-200 mesh) using a gradient of ethyl acetate and hexane as mobile phase. ^{1}H NMR spectral data were collected at, 400 MHz (JEOL), 500 MHz (Bruker) and ^{13}C NMR were recorded at 100, 125 MHz. ^{1}H NMR spectral data are given as chemical shifts in ppm followed by multiplicity (s- singlet; d- doublet; t- triplet; q- quartet; m- multiplet), number of protons and coupling constants. ^{13}C NMR chemical shifts are expressed in ppm. HRMS (ESI) spectral data were collected using Agilent Q-TOF mass spectrometer. GC-MS were recorded using Agilent GC Mass Spectrometer. All the reactions were performed in a close system using Schlenk tube. All nickel salts were purchased from Sigma Aldrich. Nickel(II) bromide (Assay-98%; CAS Number 13462-88-9; EC Number 236-665-0; Pack Size- No 217891-10G). Potassium *tert*-butoxide (Purity-98%, CAS No: 865-47-4, Catalog No- ASP2012) and Sodium *tert*-butoxide (Purity-97%, CAS No: 865-48-5, Catalog No-ASS2615) were purchased from Avra Synthesis Pvt. Ltd., India.

General procedure for nickel-catalyzed alkylation of acetophenone with benzyl alcohols:

Procedure [A]:

In a 15 mL oven dried Schlenk tube under atmosphere of N_2 acetophenone (0.25 mmol) was taken followed by Cs_2CO_3 (0.025 mmol), 1,10-phenanthroline (20 mol%), $NiBr_2$ (10 mol%) and alcohols (0.3125 mmol) were added. Next, 1,4-dioxane 2.0 mL was added to the whole mixture and was placed in a pre-heated oil bath at 140 °C for 36-48 h in a closed system. After the reported time, reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and concentrated *in vacuo*. The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure product.

Procedure [B]:

In a 15 mL oven dried Schlenk tube under atmosphere of N_2 acetophenone (0.25 mmol) was taken followed by *t*-BuOK (0.050 mmol), 1,10-phenanthroline (6 mol%), $NiBr_2$ (5 mol%) and alcohols (0.3125 mmol) were added. Next, 2.0 mL toluene was added to the whole mixture and was placed in a pre-heated oil bath at 140 °C for 36 h in a closed system. After the reported time, reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and concentrated *in vacuo*. The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure product.

Procedure [C]:

In a 15 mL oven dried Schlenk tube under atmosphere of N_2 acetophenone (0.25 mmol) was taken followed by *t*-BuOK (0.375 mmol), 1,10-phenanthroline (6 mol%), $NiBr_2$ (5 mol%) and alcohols (0.375 mmol) were added. Next, 2.0 mL toluene was added to the whole mixture and was placed in a pre-heated oil bath at 140 °C for 36 h in a closed system. After the reported time, reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and concentrated *in vacuo*. The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure product.

Synthesis of [$NiCl_2$(bpy)] complex (cat. B): A solution of bpy (78 mg, 0.5 mmol) in EtOH (2 mL) was added to a solution of $NiCl_2$•$6H_2O$ (119 mg, 0.5 mmol) in EtOH (2 mL) at room temperature. After stirring for 6 h, a pale green precipitate was formed and filtered off, washed with EtOH (3×3 mL), and dried in *vacuo* to afford **cat. B** as a pale green solid 114 mg (80%) yield. Anal. Calcd for $C_{10}H_8Cl_2N_2Ni$: C, 42.03; H, 2.82; Cl, 24.81; N, 9.80; Found: C, 41.75; H, 2.76; N, 9.61.

Synthesis of (cat. C): cat. B (57 mg, 0.2 mmol) and benzyl alcohol (43.2 mg, 0.4 mmol) in toluene (2 mL) was heated at 140 °C under nitrogen atmosphere in a Schlenk tube, after 24h the precipitate was filtered off, washed with hexane (3×5 mL), and dried *in vacuo* to afford **cat. C** as a pale green solid 50 mg (78%) yield. Then in a Schlenk **cat. C** (40 mg, 0.12 mmol), acetophenone (21.6 mg, 0.18 mmol) and *t*-BuOK (14 mg, 0.12 mmol) in toluene d_8 (0.5mL) under nitrogen atmosphere was heated at 140 °C, after 3h the reaction mixture was cooled to room temperature and the crude reaction mixture was analyzed by GC-MS which confirmed the formation of benzaldehyde (EI, m/z = 106.0).

Gram scale reaction procedure: Gram Scale reaction was performed using acetophenone **1a (**1.0 g, 8.33 mmol), benzyl alcohol **2a** (1.125 g, 10.42 mmol), $NiBr_2$ (91 mg, 5 mol%), phen (90 mg, 6 mol%), *t*-BuOK (187 mg, 1.67 mmol), toluene (15.0 mL) in a 100 mL pressure tube under nitrogen atmosphere at 140 ºC in oil bath for 36 h. The reaction mixture was cooled to room temperature and 15.0 mL of ethyl acetate was added and concentrated in vacuo. The residue was purified by silica-gel column chromatography eluting with 1% ethyl acetate in hexane to afford the pure product **3a** as a white solid (1.050 g, 60% Yield).

1,3-diphenylpropan-1-one (3a)[10]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 80%, 42 mg; B: 82%, 43 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.1 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.32-7.19 (m, 5H), 3.33-3.29 (m, 2H), 3.09 – 3.05 (m, 2H); ^{13}C{1H} NMR

(100 MHz, $CDCl_3$) δ 199.3, 141.4, 136.9, 133.2, 128.7, 128.6, 128.5, 128.1, 126.2, 40.5, 30.2.

1-(4-ethylphenyl)-3-phenylpropan-1-one (3b)[21c]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 65%, 39 mg; B: 76%, 45 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.5 Hz, 2H), 7.32-7.24 (m, 6H), 7.20 (t, J = 7.0 Hz, 1H), 3.28 (t, J = 7.9 Hz, 2H), 3.06 (t, J = 7.6 Hz, 2H), 2.70 (q, J = 7.5 Hz, 2H), 1.25 (t, J = 7.3 Hz, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.0, 150.1, 141.5, 134.7, 128.6, 128.5, 128.4, 128.2, 126.2, 40.7, 30.3, 29.0, 15.3.

1-(4-methoxyphenyl)-3-phenylpropan-1-one (3c)[21c]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. Yield (A: 63%, 38 mg; B: 90%, 54 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.5 Hz, 2H), 7.32-7.20 (m, 5H), 6.92 (d, J = 9.2 Hz, 2H), 3.86 (s, 3H), 3.25 (t, J = 7.9 Hz, 2H), 3.06 (t, J = 7.6 Hz, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 197.9, 163.5, 141.6, 130.4, 130.1, 128.6, 128.5, 126.2, 113.8, 55.6, 40.2, 30.4.

1-(3-methoxyphenyl)-3-phenylpropan-1-one (3d)[21d]: Following the general procedure A and B, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. Yield (A: 64%, 38.5 mg; B: 85%, 51 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.9 Hz, 1H), 7.48 (s, 1H), 7.37-7.19 (m, 6H), 7.11-7.08 (m, 1H), 3.84 (s, 3H), 3.29 (t, J = 7.6 Hz, 2H), 3.06 (t, J = 7.6 Hz, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.1, 159.9, 141.4, 138.3, 129.7, 128.6, 128.5, 126.2, 120.8, 119.7, 112.3, 55.5, 40.7, 30.3.

1-(2-methoxyphenyl)-3-phenylpropan-1-one (3e)[21d]: Following the general procedure A and B, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. Yield (A: 52%, 31 mg; B: 55%, 33 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.7 Hz, 1H), 7.43-7.48 (m, 1H), 7.16-7.31 (m, 5H), 6.95–7.02 (m, 2H), 3.88 (s, 3H), 3.30 (t, J = 8.0 Hz, 2H), 3.02 (t, J = 8.0 Hz, 2H).

1-(4-chlorophenyl)-3-phenylpropan-1-one (3f)[21c]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 50%, 30.5 mg; B: 62%, 38 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 7.30 (t, J = 6.5 Hz, 2H), 7.28 – 7.21 (m, 3H), 3.29 – 3.25 (m, 2H), 3.08 – 3.04 (m, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 198.1, 141.1, 139.6, 135.3, 129.6, 129.0, 128.6, 128.5, 126.3, 40.5, 30.1.

1-(4-bromophenyl)-3-phenylpropan-1-one (3g)[21c]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 42%, 30 mg; B: 50%, 36 mg).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.6 Hz, 2H), 7.33 (dd, J = 9.3, 5.5 Hz, 2H), 7.26 – 7.17 (m, 3H), 3.31 – 3.27 (m, 2H), 3.11 – 3.06 (m, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.3, 141.4, 133.1, 132.0, 129.6, 128.7, 128.6, 128.5, 126.2, 40.5, 30.2.

1-(naphthalen-2-yl)-3-phenylpropan-1-one (3h)[21c]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 30%, 19.5 mg; B: 50%, 32.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.06 (dd, J = 8.6, 1.7 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.93 – 7.90 (m, 2H), 7.64 – 7.61 (m, 1H), 7.59 – 7.56 (m, 1H), 7.37 – 7.32 (m, 4H), 7.25 (dd, J = 9.0, 4.3 Hz, 1H), 3.49 – 3.46 (m, 2H), 3.18 – 3.15 (m, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.1, 141.4, 135.6, 134.2, 132.5, 129.7, 129.6, 128.6, 128.5, 127.8, 126.8, 126.2, 123.9, 40.4, 30.4.

4-(3-phenylpropanoyl)benzonitrile (3i)[22b]**:** Following the general procedure B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield 35%, 20.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 8.6 Hz, 2H), 7.31-7.28 (m, 2H), 7.23-7.21 (m, 3H), 3.30 (t, J = 7.6 Hz, 2H), 3.07 (t, J = 7.6 Hz, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 197.9, 140.9, 138.6, 132.6, 128.7, 128.5, 128.4, 126.4, 117.9, 116.5, 40.8, 29.9.

1-phenyl-3-(*p*-tolyl)propan-1-one (4a)[20a]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 54%, 30 mg; B: 63%, 35 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 2H), 7.54 (t, J = 8.0 Hz, 1H), 7.44 (t, J = 6.8 Hz, 2H), 7.20 – 7.09 (m, 4H), 3.29 – 3.25 (m, 2H), 3.04 – 3.00 (m, 2H), 2.31 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.4, 138.3, 136.9, 135.7, 133.1, 129.3, 128.7, 128.4, 128.1, 40.7, 29.8, 21.1.

3-(4-ethylphenyl)-1-phenylpropan-1-one (4b)[20b]: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 60%, 36 mg; B: 70%, 41.5 mg).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.1 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.19-7.12 (m, 4H), 3.29 (t, J = 7.8 Hz, 2H), 3.04 (t, J = 7.8 Hz, 2H), 2.62 (q, J = 7.6 Hz, 2H), 1.23 (t, J = 7.6 Hz, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.5, 142.2, 138.5, 136.9, 133.1, 129.8, 128.7, 128.5, 128.1, 40.7, 29.8, 28.5, 15.7.

3-(4-isopropylphenyl)-1-phenylpropan-1-one (4c)[20c]: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 64%, 40 mg; B: 71%, 45 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.3 Hz, 2H), 7.55 (t, J = 6.7 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.15-7.20 (m, 4H), 3.30 (t, J = 7.6 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H), 2.90-2.85 (m, 1H), 1.24 (d, J = 6.7 Hz, 6H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ199.5, 146.8, 138.7, 136.9, 133.1, 128.7, 128.4, 128.1, 126.6, 40.6, 33.8, 29.8, 24.1.

1-phenyl-3-(o-tolyl)propan-1-one (4d)[11]: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 40%, 22.5 mg; B: 42%, 23.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.6 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.23-7.12 (m, 4H), 3.25 (t, J = 7.9 Hz, 2H), 3.05 (t, J = 7.9 Hz, 2H), 2.35 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.5, 139.5, 136.9, 136.1, 133.2, 130.4, 128.7, 128.6, 128.1, 126.4, 126.3, 39.2, 27.6, 19.4.

4-(3-oxo-3-phenylpropyl)benzonitrile (4e)[22a]: Following the general procedure A and B, the title compound was isolated as a colorless solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. Yield (A: 43%, 25 mg; B: 45%, 26.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.3 Hz, 2H), 7.57 (t, J = 6.7 Hz, 3H), 7.46 (t, J = 7.7 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 3.33 (t, J = 7.3 Hz, 2H), 3.14 (t, J = 7.4 Hz, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 198.3, 147.1, 136.6, 133.4, 132.4, 129.4, 128.8, 128.1, 119.1, 110.2, 39.5, 30.1.

3-(4-fluorophenyl)-1-phenylpropan-1-one (4f)[20d]: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 74%, 42 mg; B: 73%, 41.5 mg).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.94 (m, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.22-7.19 (m, 2H), 6.99-6.95 (m, 2H), 3.28 (t, J = 7.6 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.1,161.5 (d, $J_{C\text{-}F}$= 243 Hz), 136.9, 136.8, 133.2, 129.9 (d, $J_{C\text{-}F}$= 9 Hz), 128.7, 128.1, 115.3(d, $J_{C\text{-}F}$= 19 Hz), 40.5, 29.3.

3-(4-methoxyphenyl)-1-phenylpropan-1-one (4g)[20c]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. Yield (A: 65%, 39 mg; B: 64%, 38.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H), 3.28 (t, J = 7.6 Hz, 2H), 3.02 (t, J = 7.6 Hz, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.5, 158.1, 137.0, 133.4, 133.1, 129.4, 128.7, 128.1, 114.0, 55.3, 40.8, 29.4.

1-phenyl-3-(3,4,5-trimethoxyphenyl)propan-1-one (4h)[21b]: Following the general procedure A and B, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 15% ethyl acetate in hexane. Yield (A: 35%, 34 mg; B: 40%, 30 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 8.7, 1.3 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 8.0 Hz, 2H), 6.47 (s, 2H), 3.84 (s, 6H), 3.82 (s, 3H), 3.32 – 3.28 (m, 2H), 3.04 – 3.00 (m, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.4, 153.3, 137.2, 136.9, 133.2, 128.7, 128.1, 105.4, 60.9, 56.2, 40.7, 30.7.

1-phenyl-3-(2,3,4-trimethoxyphenyl)propan-1-one (4i): Following the general procedure A and B, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 15% ethyl acetate in hexane. Yield (A: 39%, 29 mg; B: 42%, 31.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.3 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 6.89 (d, J = 8.5 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.25 (t, J = 7.9 Hz, 2H), 2.98 (t, J = 7.6 Hz, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.9, 152.5, 152.0, 142.4, 136.9, 133.1, 128.6, 128.2, 127.2, 124.1, 107.3, 60.9, 60.8, 56.1, 39.9, 25.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{21}O_4$ 301.1434; Found 301.1437.

3-(naphthalen-1-yl)-1-phenylpropan-1-one (4j)[21c]: Following the general procedure A and B, the title compound was isolated as a colorless solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 40%, 26 mg; B: 58%, 38 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 7.2 Hz, 2H), 7.91 (d, J = 7.3 Hz, 1H), 7.79 – 7.77 (m, 1H), 7.60 – 7.50 (m, 2H), 7.49 – 7.44 (m, 4H), 7.32 (dd, J = 11.6, 7.9 Hz, 1H), 3.59 – 3.56 (m, 2H), 3.48 – 3.45 (m, 2H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 199.3, 137.4, 136.9, 133.9, 133.1, 131.7, 128.9, 128.6, 128.1, 127.0, 126.2, 126.1, 125.7, 125.6, 123.5, 39.8, 27.2.

3-(benzo[d][1,3]dioxol-5-yl)-1-phenylpropan-1-one (4k)[21a]: Following the general procedure A and B, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 4% ethyl acetate in hexane. Yield (A: 51%, 32 mg; B: 60%, 38 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.3 Hz, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 6.66-6.60 (m, 3H), 5.84 (s, 2H), 3.18 (t, J = 7.6 Hz, 2H), 2.91 (t, J = 7.6 Hz, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.3, 147.7, 145.9, 136.9, 135.2, 133.2, 128.7, 128.1, 121.3, 109.0, 108.4, 100.9, 40.7, 29.9.

5,9-dimethyl-1-phenyldec-8-en-1-one (4l)[23a]: Following the general procedure C, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 2% ethyl acetate in hexane. Yield (30%, 19.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 8.3, 1.0 Hz, 2H), 7.59 – 7.54 (m, 1H), 7.46 (t, J = 7.6 Hz, 2H), 5.09 (td, J = 5.6, 4.2 Hz, 1H), 2.95 (t, J = 7.4 Hz, 2H), 1.99 – 1.94 (m, 2H), 1.77 (dddd, J = 10.6, 8.6, 6.0, 3.3 Hz, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.46 – 1.42 (m, 1H), 1.38 – 1.32 (m, 2H), 1.20 – 1.14 (m, 2H), 0.90 (d, J = 6.3 Hz, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 200.7, 137.2, 132.9, 131.2, 128.6, 128.1, 124.9, 39.0, 37.1, 36.7, 32.4, 25.8, 25.6, 21.9, 19.6, 17.7.

1-phenylnonan-1-one (4m)[22c]: Following the general procedure C, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 46%, 25 mg). ^{1}H NMR (400 MHz) δ 7.96 (d, J = 7.8 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.2 Hz, 2H), 2.96 (t, J = 7.4 Hz, 2H), 1.77 – 1.70 (m, 2H), 1.35-1.25 (d, J = 8.1 Hz, 10H), 0.88 (t, J = 7.4 Hz, 3H); GC-MS (EI) m/z = 218.1.

1-phenyldecan-1-one (4n)[20c]: Following the general procedure C, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 34%, 20 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.4 Hz, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.9 Hz, 2H), 2.95 (t, J = 7.4 Hz, 2H), 1.76-1.71 (m, 2H), 1.33-1.22 (m, 9H), 0.88- 0.85 (m, 6H); GC-MS (EI) m/z = 232.2.

1-phenyldodecan-1-one (4o)[22d]: Following the general procedure C, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 36%, 23.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 7.1 Hz, 2H), 7.58 (t, J = 6.1 Hz, 1H), 7.49 (t, J = 7.9 Hz, 2H), 2.99 (t, J = 7.4 Hz, 2H), 1.79 – 1.73 (m, 2H), 1.42-1.21 (m, 16H), 0.88 (t, J = 7.1 Hz, 3H); GC-MS (EI) m/z = 260.2.

1-phenyl-3-(pyridin-2-yl)propan-1-one (5a)[23b]: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 10% ethyl acetate in hexane. Yield (A: 76%, 40 mg; B: 80%, 42 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.6 Hz, 1H), 7.99 (d, J = 7.1 Hz, 2H), 7.62 – 7.52 (m, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.26 (d, J = 7.9 Hz, 1H), 7.12 – 7.09 (m, 1H), 3.51 (t, J = 7.2 Hz, 2H), 3.24 (t, J = 7.3 Hz, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.4, 160.8, 149.4, 136.9, 136.4, 133.1, 128.6, 128.1, 123.5, 121.3, 37.9, 32.2.

1-(4-ethylphenyl)-3-(pyridin-2-yl)propan-1-one (5b): Following the general procedure A and B, the title compound

was isolated as a yellow oil using silica-gel column chromatography eluting with 10% ethyl acetate in hexane. Yield (A: 70%, 42 mg; B: 73%, 43.5 mg). ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.49 (dd, J = 4.8, 0.6 Hz, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.56 (ddd, J = 7.7, 1.8, 0.9 Hz, 1H), 7.25 – 7.22 (m, 3H), 7.08 (dd, J = 7.0, 5.4 Hz, 1H), 3.46 (t, J = 7.3 Hz, 2H), 3.21 (t, J = 7.3 Hz, 2H), 2.67 (q, J = 7.6 Hz, 2H), 1.23 (t, J = 7.6 Hz, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.0, 160.9, 150.0, 149.3, 136.4, 134.7, 128.4, 128.1, 123.4, 121.3, 37.8, 32.2, 28.9, 15.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{18}NO$ 240.1383; Found 240.1387.

1-(3-methoxyphenyl)-3-(pyridin-2-yl)propan-1-one (5c): Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 15% ethyl acetate in hexane. Yield (A: 78%, 47 mg; B: 80%, 48 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.7 Hz, 1H), 7.61 – 7.57 (m, 2H), 7.52 – 7.51 (m, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.12 – 7.08 (m, 2H), 3.84 (s, 3H), 3.50 (t, J = 7.2 Hz, 2H), 3.23 (t, J = 7.2 Hz, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.2, 160.8, 159.9, 149.3, 138.3, 136.4, 129.6, 123.4, 121.3, 120.9, 119.7, 112.3, 55.5, 37.9, 32.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{16}NO_2$ 242.1176; Found 242.1186.

3-phenyl-1-(pyridin-3-yl)propan-1-one (5d)[23c]: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 10% ethyl acetate in hexane. Yield (A: 50%, 26.5 mg; B: 60%, 31.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.77 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.32 – 7.27 (m, 2H), 7.21 (ddd, J = 7.1, 4.8, 2.9 Hz, 2H), 3.33 – 3.28 (m, 2H), 3.08 (t, J = 7.6 Hz, 2H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 198.1, 153.5, 149.6, 140.8, 135.3, 128.6, 128.4, 126.3, 123.7, 115.0, 40.7, 29.8.

3-(4-fluorophenyl)-1-(pyridin-3-yl)propan-1-one (5e): Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 10% ethyl acetate in hexane. Yield (A: 60%, 34 mg; B: 70%, 40 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (d, J = 1.5 Hz, 1H), 8.78 (dd, J = 4.8, 1.6 Hz, 1H), 8.23 – 8.21 (m, 1H), 7.43 – 7.40 (m, 1H), 7.21 (dd, J = 8.5, 5.5 Hz, 2H), 6.98 (t, J = 8.7 Hz, 2H), 3.30 (t, J = 7.4 Hz, 2H), 3.07 (t, J = 7.5 Hz, 2H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 197.8, 161.5 (d, $J_{C\text{-}F}$= 240 Hz), 153.6, 149.6, 136.4, 135.3, 132.0, 129.9(d, $J_{C\text{-}F}$= 7.5 Hz), 123.7, 115.4(d, $J_{C\text{-}F}$= 21.3 Hz), 40.7, 28.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{13}FNO$ 230.0976; Found 230.0983.

3-(pyridin-2-yl)-1-(pyridin-3-yl)propan-1-one (5f): Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 25% ethyl acetate in hexane. Yield (A: 30%, 16 mg; B: 75%, 40 mg).^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, J = 2.1 Hz, 1H), 8.75 (dd, J = 4.8, 1.7 Hz, 1H), 8.49 (d, J = 4.6 Hz, 1H), 8.24 (ddd, J= 7.9, 3.8, 1.8 Hz, 1H), 7.59 (td, J = 7.7, 1.8 Hz, 1H), 7.39 (dd, J = 8.2, 4.8 Hz, 1H), 7.25 (d, J = 3.2 Hz, 1H), 7.10 (dd, J = 7.5, 4.9 Hz, 1H), 3.52 (t, J = 7.1 Hz, 2H), 3.25 (t, J = 7.1 Hz, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 198.4, 160.2, 153.5, 149.8, 149.3, 136.5, 135.4, 132.3, 123.6, 123.4, 121.4, 37.9, 31.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{13}N_2O$ 213.1022; Found 213.1029.

(Z)-1-(4-methoxyphenyl)icos-11-en-1-one (6a): Following the general procedure C, the title product was obtained as a yellow oil using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield: 40%, 40 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.91 (m, 2H), 6.95 – 6.90 (m, 2H), 5.33 (t, J = 4.8 Hz, 2H), 3.86 (s, 3H), 2.89 (t, J = 8.0 Hz, 2H), 2.02 – 1.97 (m, 4H), 1.72 – 1.67 (m, 2H), 1.27 – 1.25 (m, 24H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 199.3, 163.4, 130.4, 130.3, 130.00, 129.9, 113.7, 55.5, 38.4, 31.9, 29.85, 29.84, 29.60, 29.59, 29.57, 29.52, 29.40, 29.37, 27.3, 24.7, 22.8, 14.2. Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07; Found: C, 80.65; H, 10.76.

1-(3-methoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15, 16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-3-phenylpropan-1-one (6b): Following the general procedure A (50 mol% of $Cs_2CO_3$was used), the title product was obtained as a yellow oil using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield: 66%, 69 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, J = 10.2, 4.6 Hz, 2H), 7.19 – 7.14 (m, 3H), 5.35 – 5.31 (m, 1H), 3.34 (s, 3H), 3.04 (tt, J = 11.2, 4.4 Hz, 1H), 2.88 (t, J = 7.6 Hz, 2H), 2.74 – 2.63 (m, 2H), 2.47 (t, J = 8.9 Hz, 1H), 2.41 – 2.35 (m, 1H), 2.22 – 2.11 (m, 2H), 1.97 – 1.82 (m, 4H), 1.63 – 1.37 (m, 8H), 1.30 – 1.15 (m, 3H), 0.98 – 0.95 (m, 4H), 0.56 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 210.6, 141.6, 140.9, 128.5, 126.1, 121.4, 121.3, 80.4, 63.2, 60.7, 57.1, 55.7, 50.7, 50.1, 49.6, 47.3, 46.1, 44.4, 39.1, 38.7, 37.0, 31.9, 29.9, 28.1, 24.6, 23.0, 21.1, 19.4, 13.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{41}O_2$ 421.3101; Found 421.3108.

4-(6-methoxynaphthalen-2-yl)-1-(4-methoxyphenyl)pentan-1-one (6c): Following the general procedure C, the title product was obtained as a colorless solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane.(Yield: 45%, 36 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 4H), 7.57 – 7.51 (m, 2H), 7.31 (dd, J = 8.3, 1.2 Hz, 1H), 7.15 – 7.11(m, 3H), 3.91 (s, 6H), 2.81 – 2.75 (m, 2H), 2.11 (dd, J = 8.0, 0.9 Hz, 2H), 1.86-1.84 (m, 1H), 1.33-1.29 (m, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 198.9, 157.2, 139.5, 135.4, 132.9, 129.6, 128.9, 127.6, 126.8, 125.5, 124.9, 123.7, 122.4, 118.7, 112.2, 105.8, 55.4, 28.9, 21.9, 15.7, 14.5. Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94; Found: C, 78.92; H, 6.27.

2-phenylquinoline (7a)[14c]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 85%, 43.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.07 (m, 4H), 7.78 (d, J = 8.6 Hz, 1H), 7.74 – 7.72 (m, 1H), 7.64 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.46 – 7.41 (m, 3H), 7.40 – 7.36 (m, 1H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 157.5, 148.4, 139.8, 136.9, 129.8, 129.4, 128.9, 127.7, 127.6, 127.3, 126.4, 119.1, 119.0.

2-(4-Ethylphenyl)quinoline (7b)[14c]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product was obtained as a colorless solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 82%, 48 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (t, J = 8.0 Hz, 2H), 8.09 (d, J = 6.8 Hz, 2H), 7.85 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.71 (t, J = 7.7 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.36 (d, J = 7.8 Hz, 2H), 2.73 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 157.5, 148.4, 145.8, 137.3, 136.7, 129.8, 129.7, 128.5, 127.6, 127.5, 127.2, 126.2, 119.0, 28.8, 15.7.

2-(Pyridin-3-yl)quinoline (7c)[14c]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product

was obtained as a colorless solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield: 50%, 26 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, J = 1.6 Hz, 1H), 8.69 (dd, J = 4.8, 1.5 Hz, 1H), 8.53 – 8.48 (m, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.86 (dd, J = 12.8, 8.4 Hz, 2H), 7.75 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.55 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.45 (dd, J = 7.3, 4.8 Hz, 1H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 154.7, 150.3, 148.9, 148.5, 137.3, 135.2, 135.1, 130.1, 129.8, 127.7, 127.5, 126.9, 123.8, 118.6.

2-(Naphthalen-2-yl)quinoline (7d)[24a]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product was obtained as a colorless solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 88%, 56 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.41 (dd, J = 8.6, 1.7 Hz, 1H), 8.27 (dd, J = 12.5, 8.6 Hz, 2H), 8.05 (dd, J = 15.8, 8.2 Hz, 3H), 7.93 (dd, J = 5.9, 3.4 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.79 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.57 (dd, J = 6.4, 2.9 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 157.2, 148.4, 136.9, 136.9, 133.9, 133.5, 129.8, 128.9, 128.6, 128.5, 127.8, 127.5, 127.3, 127.1, 126.8, 126.4, 119.2, 115.0.

2-methoxy-5,6-dihydrobenzo[c]acridine (7e)[14c]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product was obtained as a colorless solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield: 50%, 32.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.11 (m, 2H), 7.90 (s, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.64 (dd, J = 8.2, 7.1 Hz, 1H), 7.47 (dd, J = 8.0, 7.0 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 6.94 (dd, J = 8.3, 2.8 Hz, 1H), 3.96 (s, 3H), 3.12 – 3.06 (m, 2H), 2.96 – 2.90 (m, 2H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 159.2, 153.4, 147.6, 135.8, 133.8, 131.9, 130.8, 129.5, 129.1, 128.7, 128.0, 127.0, 126.2, 117.0, 109.7, 55.7, 29.2, 27.6.

2-propylquinoline (7f)[24]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product was obtained as a pale yellow oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 68%, 29 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (t, J = 7.5 Hz, 2H), 7.76 (dd, J = 8.1, 1.1 Hz, 1H), 7.67 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.47 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 7.31 – 7.24 (m, 1H), 2.97 – 2.91 (m, 2H), 1.88 – 1.80 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H).
7.8 Hz, 2H), 1.32 – 1.29 (m, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 157.6, 145.3, 136.9, 128.3, 126.9, 125.9, 121.8, 120.3, 115.0, 28.7, 15.5.

2,2'-Bipyridine (7g)[14c]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product was obtained as a colorless solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield: 70%, 27 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 4.0 Hz, 2H), 8.41 (t, J = 6.5 Hz, 2H), 7.83 (td, J = 7.8, 1.8 Hz, 2H), 7.32 (ddd, J = 7.3, 4.7, 1.0 Hz, 2H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 156.2, 149.3, 136.9, 123.7, 121.1.

2-(4-Methoxyphenyl)pyridine (7h)[14c]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product was obtained as a colorless oil using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield: 45%, 21 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 4.1 Hz, 1H), 8.00 – 7.95 (m, 2H), 7.73 (ddd, J = 20.6, 13.4, 4.9 Hz, 1H), 7.20 (ddd, J = 7.2, 4.8, 1.2 Hz, 1H), 7.03 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 8.9 Hz, 1H), 3.89 (s, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 160.5, 157.1, 149.5, 136.7, 132.0, 128.2, 121.4, 119.9, 114.1, 55.4.

AUTHOR INFORMATION

Corresponding Author

* E-mail: dbane.fcy@iitr.ac.in

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.xxxxxxxx.

^{1}H NMR, ^{13}C NMR spectra, kinetic studies (PDF)

Notes

The authors declare no competing financial interest.

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Graphical Abstract