JOC The Journal of Organic Chemistry

Article

Regiospecific Benzoylation of Electron-Deficient N-Heterocycles with Methylbenzenes via a Minisci Type Reaction

Wajid Ali, Ahalya Behera, Srimanta Guin, and Bhisma K. Patel

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b00501 • Publication Date (Web): 04 May 2015

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Regiospecific Benzoylation of Electron-Deficient *N*-Heterocycles with Methylbenzenes via a Minisci Type Reaction

Wajid Ali, Ahalya Behera, Srimanta Guin, Bhisma K. Patel*

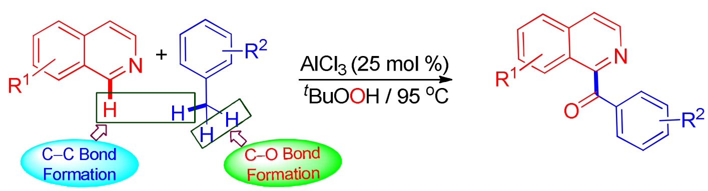
Department of Chemistry

Indian Institute of Technology Guwahati, Guwahati-781039, India

Fax: (+91)361-26909762.

E-mail: patel@iitg.ernet.in

RECEIVED DATE (will be automatically inserted after manuscript is accepted).



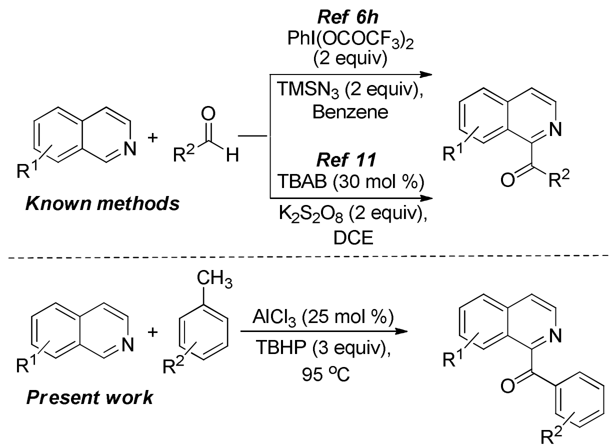
ABSTRACT: A regioslective cross-dehydrogenative coupling between electron-deficient *N*–heterocycles (isoquinoline, quinolines and quinoxalines) and methylbenzenes leading to regiospecific C–aroylation has been accomplished using $AlCl_3$ as the catalyst in the presence of oxidant TBHP. This protocol is a practical alternative to classical Minisci reaction.

INTRODUCTION

In organic chemistry one of the most important and fundamental challenge is to build C–C bonds in a rapid and efficient manner.[1] Of significant interests are methods that provide access to molecule in step and atom economic fashion from readily available precursors. In past few decades, the construction of C–C bonds through C–H bonds activation is a rapidly expanding field of research as it provides atom economical and shorter route for the synthesis of organic compounds and offers substantial benefits.[2] In this context, cross-dehydrogenative coupling between two different C–H bonds represent an useful alternative approach towards C–C bond formations between organic components through the functionalization of all types (sp, sp^2, sp^3) of C–H bonds.[1a,d,e,3] Mild reactivity and poor site selective are the two important challenges that need to be addressed in CDC protocols. Hence, the developments of new and efficient CDC reactions in which such challenges can be overcome are of great significance in synthetic organic chemistry.

Nitrogenous heterocycles are widely distributed in nature and present in large proportion in commercial drugs.[4] These heterocycles have also enormous applications in both chemistry and biology.[5] Heterocyclic moieties bearing acyl group have been found in drugs which are important in pharmacological studies.[4] Till date a number of methods have been developed for the synthesis of electron-deficient heterocycles, but their functionalization using cross-dehydrogenative coupling is far less visited. In contrast to electron-rich heterocycles,[6a-g] acylation of electron-deficient heterocycles are much more challenging and only few reports are available.[6h-j] Among these, Minisci reaction is the most commonly used approach,[4a,6i,7-10] which involves the addition of an *in situ* generated nucleophilic acyl radical from aldehyde to an electron-deficient heterocycle. Although it represents a straightforward stratergy but suffers from certain drawbacks such as harsh reaction conditions, poor site selectivity, limited substrate scope and the use of transition metal salts up to stoichiometric amounts.[7a] To overcome these aspects, Antonchick[6h] and Prabhu[11] groups independently reported metal free analogues of Minisci reaction under ambient conditions (Scheme 1, known methods).

Scheme 1. Reported and designed route for the direct acylation



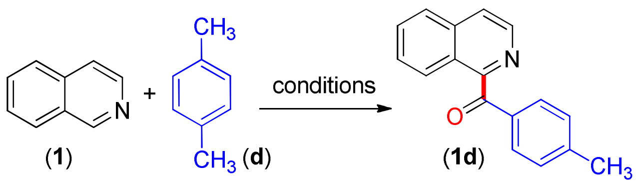
Recently our group has developed a number of CDC protocols for the construction of C–C and C–O bonds using alkylbenzenes as the surrogates of $ArCH_2O$–,[12a] ArCO–,[12b,c,d] $ArCH_2$–[12e] and ArCOO–[12e,f] under oxidative conditions. In continuation to our interest in utilizing alkylbenzenes as different surrogates via metal and metal free C–H functionalization strategies, we envisaged that can an acyl radical (generated *in situ* from methylarenes under oxidative conditions) be utilized for the direct acylation of *N*-heterocycles. Antonchick *et al*[6h] in their report demonstrated that the *in situ* generated CF_3COOH from $PhI(OCOCF_3)_2$ protonates the *N*-atom of heterocycle thereby making α–C to nitrogen more electrophilic in nature. This facilitates the attack of the nucleophilic acyl radical on to the α–C. Intrigued by the key mechanistic features; we anticipated that the direct use of CF_3COOH could generate a similar protonated intermediate. On the other hand employing TBHP as the oxidant is expected to afford the other coupling counterpart the acyl radical from methylarenes.[12b,c,d]

RESULTS AND DISCUSSION

To give a practical shape to this coupling concept, a reaction between isoquinoline (**1**) and *p*-xylene (**d**) were initiated in the presence of CF_3COOH and TBHP at 110 ^oC. As hypothesized, the reaction provided C1-aroylated product (**1d**) but in a mere yield of 26% (Table 1, entry 1). In a quest to improve the yield, both weak (CH_3COOH) and strong (CF_3SO_3H) organic acids were used in lieu of CF_3COOH; however poorer yields were obtained in both these cases (Table 1, entries 2 and 3). Even a threefold excess of CF_3COOH had no substantial effect on the product yield (Table 1, entry 4). These observations suggest that neither the strength of acid nor their concentrations are the determining factors for better conversion. Thus we attempted the reaction in the presence of Lewis acids instead of protic acids.

Gratifyingly, the use of Lewis acid $AlCl_3$ afforded the acylated product in an improved yield of 58% (Table 1, entry 5). Encouraged by this result, other Lewis acids such as $FeCl_3$ (42%), $ZnCl_2$ (< 8%), $TiCl_4$ (40%), $SnCl_2$ (48%) and $Cu(OTf)_2$ (38%) were tested but all were found to be inferior to $AlCl_3$ (58%) (Table 1, entries 5−10). Interestingly, when the quantity of $AlCl_3$ was reduced to half (50 mol %) and quarter (25 mol %) the yield virtually remained unaltered (Table 1, entries 11 and 12). However, the yield dropped marginally when $AlCl_3$ loading was decreased to 20 mol % (Table 1, entry 13). A 9% increase in the yield was observed (Table 1, entry 14) upon performing the reaction at a lower temperature of 95 ^oC. The better yield (65%) obtained at lower temperature (95 ^oC) compared to the lower yield (56%) at higher temperature (110 ^oC) may be related to some of the thermodynamic parameters in the reaction as the acylated product formed is stable at high temperature. Maintaining the temperature at 95 ^oC and performing the reaction under N_2 atmosphere resulted in 6% further enhancement in the yield (Table 1, entry 15). No major improvements in the product yield was noticed with an increased amount of oxidant (3.5 equiv), while the use of 2 equiv was not sufficient for this transformation (Table 1, entries 16 and 17). Aq TBHP was found to be less effective compared to that of a decane solution of TBHP (Table 1, entry 18). Control experiment in the absence of Lewis acid $AlCl_3$ afforded acylated product in < 15% suggesting the essential requirement of $AlCl_3$ to bring about the desired transformation (Table 1, entry 19). To check whether $AlCl_3$ has definite role or the acid (HCl) generated in the reaction medium is activating the *N*-atom a reaction was carried out in the presence of 1 equiv. of HCl. The formation of product in a modest yield of 33% ascertains the distinct role of $AlCl_3$ in this transformation. From these screening studies, the optimal condition established was the use of $AlCl_3$ (25 mol %) and TBHP (5−6 M in decane) (3 equiv) at 95 ^{o}C under N_2 atmosphere (Table 1, entry 15).

Table 1. Screening of Reaction Conditions[a]



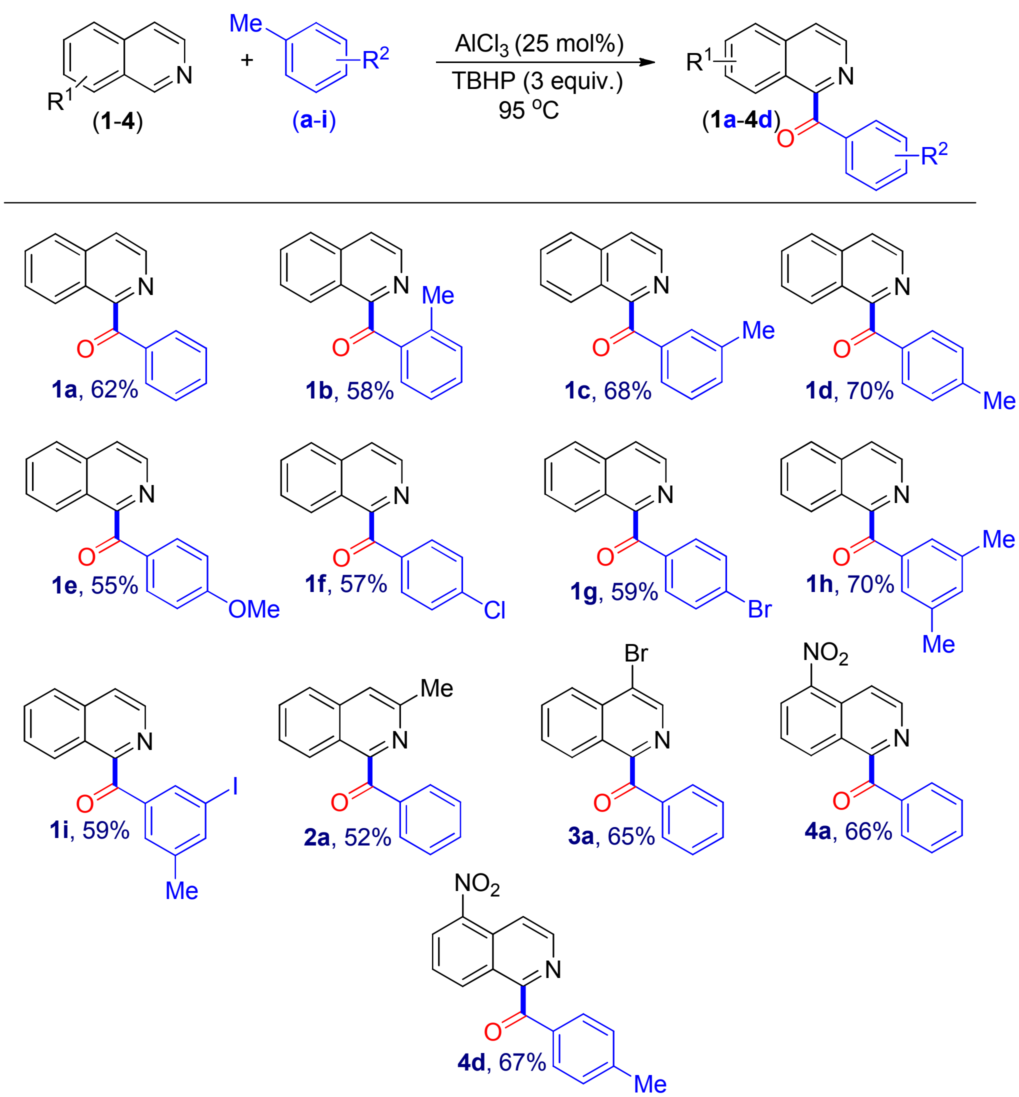
entry	catalyst (mol %)	oxidant (equiv)	temp (^{o}C)	yield [b] (%)
1	CF_3COOH (100)	TBHP (3)	110	26
2	CH_3COOH (100)	TBHP (3)	110	09
3	CF_3SO_3H (100)	TBHP (3)	110	13
4	CF_3COOH (300)	TBHP (3)	110	15
5	$AlCl_3$ (100)	TBHP (3)	110	58
6	$FeCl_3$ (100)	TBHP (3)	110	42
7	$ZnCl_2$ (100)	TBHP (3)	110	<8
8	$TiCl_4$ (100)	TBHP (3)	110	40

9	$SnCl_2$ (100)	TBHP (3)	110	48
10	$Cu(OTf)_2$ (100)	TBHP (3)	110	38
11	$AlCl_3$ (50)	TBHP (3)	110	57
12	$AlCl_3$ (25)	TBHP (3)	110	56
13	$AlCl_3$ (20)	TBHP (3)	110	51
14	$AlCl_3$ (25)	TBHP (3)	95	65
15[c]	**$AlCl_3$ (25)**	**TBHP (3)**	**95**	**71**
16[c]	$AlCl_3$ (25)	TBHP (3.5)	95	72
17[c]	$AlCl_3$ (25)	TBHP (2)	95	51
18[c]	$AlCl_3$ (25)	aq.TBHP(3)	95	47
19[c]	-	TBHP (3)	95	<15

[a]Reaction condition: **1** (0.25 mmol), **d** (1.25 mmol), time 18 h. [b]Isolated pure product. [c]Under N_2 atmoshphere.

With this optimized conditions in hand we examined the scope of this cross-dehydrogenative couplings by reacting isoquinoline (**1**) with a set of alkylbenzenes (**a–i**) possessing both electron-donating as well as electron-withdrawing substituents (Scheme 2). Under the present conditions, isoquinoline was smoothly acylated with various alkylbenzenes to afford the corresponding coupled products (**1a–1i**) in moderate to good yields as shown in Scheme 2. Substituents present in the phenyl ring of alkylbenzenes play a role in controlling the product yields as evident from their yields and the reaction times (Scheme 2). Methylbenzenes bearing additional -Me group(s) irrespective of their position like *o*–Me (**b**), *m*–Me (**c**) and *p*–Me (**d**) provided good yields of their corresponding coupled products (**1b–1d**) with the retention of other -Me group(s); an observation consistent with our previous reports.[12a-f] However, a slightly lower yield was obtained for *ortho* substituted alkylbenzene, *o*–xylene (**b**) compared to *m*– and *p*– analogues (**1c** and **1d**) could be due to steric reason imparted by the *ortho*-substituent. Where a strongly electron-donating −OMe (**e**) group is expected to give higher yield of the acylated product (**1e**, Scheme 2) but the actual result was contrary to the expected. This may be due to the coordination of the methoxy group of alkylbenzene (**e**) with the Lewis acid ($AlCl_3$) thereby making it less available for its catalytic activity. In order to expand the scope of this coupling reaction isoquinoline substituted with various groups like 3−Me (**2**), 4−Br (**3**) and 5−NO_2 (**4**) were reacted with alkylbenzenes (**a** and **d**) (Scheme 2). As can be seen from Scheme 2, all these isoquinolines underwent efficient coupling with alkylbenzenes (**a** and **d**) under the present reaction conditions to afford products (**2a**), (**3a**), (**4a**), and (**4d**) in good to moderate yields (Scheme 2).

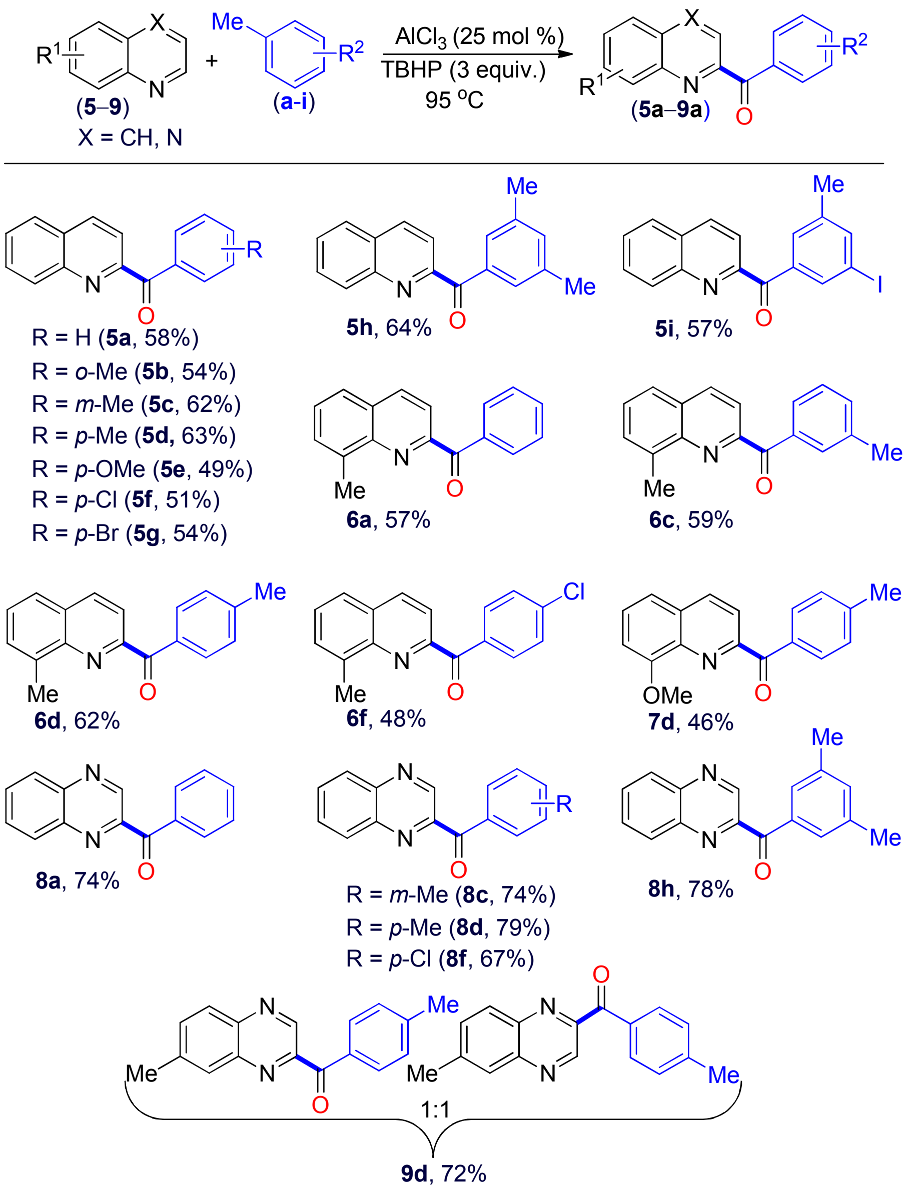
Scheme 2. Substrate Scope for C1 Acylation of Isoquinolines[a,b]



[a]Reaction conditions: isoquinoline (0.5 mmol), alkylbenzenes (2.5 mmol), $AlCl_3$ (0.125 mmol), TBHP in decane (5–6 M) (3 equiv), 95 °C, time 18–24 h. [b]Yields of the pure product reported.

The next focus of this strategy was to acylate other electron-deficient heterocyclic compounds such as quinolines and quinoxalines (Scheme 3). Quinoline underwent cross-dehydrogenative coupling with different alkylbenzenes (**a–i**) to give exclusive C2 monoacylated products (**5a–5i**, Scheme 3). It is to be noted that in case of quinolines the acylation took place regioselectively at its C2 position only with no traces of other regioisomers. However, in earlier reports by Antonchick[6h] and Prabhu[11] a mixture of both mono- (at C2 position) and di- (at C2 and C4 positions) acylated products were formed in various proportions. No C4 aroylation product was observed even when the C2 position was blocked with a methyl or a *tert*-butyl groups suggesting the strong regioselective nature of the present transformation (Scheme 4). It is well known that under an acidic condition (protic acid) because of the *N*-protonation in quinoline both C-2 and C-4 positions are susceptible towards nucleophilic radical addition. Due to pronounced –I effect of adjacent protonated *N*-atom there is higher preference at the C-2 position. However, coordination of weak Lewis acid ($AlCl_3$) with nitrogen of quinoline is just sufficient to activate the C-2 position and not the C-4 thereby giving only one regioisomer. The reactivity of different alkylbenzenes with quinoline is similar to that observed for their reaction with isoquinoline, but the overall yields of coupled products were marginally lower (Scheme 3). Other substituted quinolines like 8–methylquinoline (**6**) and 8-methoxyquinoline (**7**) reacted with alkylbenzenes (**a**, **c**, **d** and **f**) to provide their respective acylated products (**6a**, **6c**, **6d**, **6f** and **7d**) in moderate yields as shown in Scheme 3. Heterocycles bearimg two *N*-atoms like quinoxaline (**8**) were also mono functionalized in good yields (**8a–8h**, Scheme 3). Similarly, electron-deficient heterocycle, 7–methylquinoxaline (**9**) when coupled with *p*-xylene (**d**) under the optimized reaction conditions resulted in an inseparable mixture of two regioisomeric acylated products (**9d**, Scheme 3).

Scheme 3. Scope of *N*-Heterocyles[a,b]

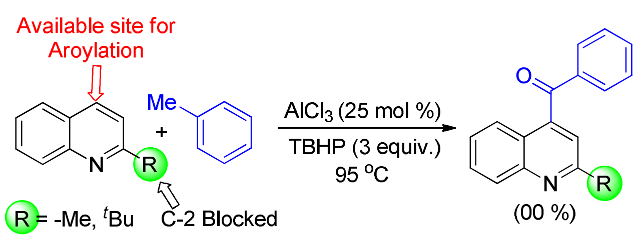


[a]Reaction conditions: **5-9** (0.5 mmol), alkylbenzenes (2.5 mmol), $AlCl_3$ (0.125 mmol), TBHP in decane (5–6 M) (3 equiv), 95 °C, time 18–24 h. [b]Yields of the pure product reported.

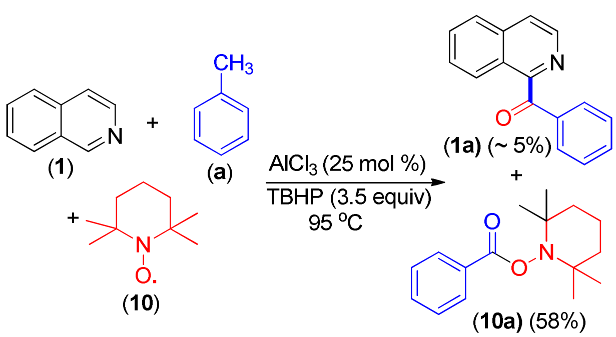
Next the mechanism of the direct acylation was investigated. Substantial quenching of product formation in the presence of radical inhibitor (TEMPO) was observed (Scheme 5).

Along with the formation of a trace (~ 4%) of coupled product, a TEMPO ester (58%) was also isolated under the reaction conditions. This provides an evidence for the formation of an acyl radical in the medium, thus supporting a radical pathway. The observed kinetic isotope effect (k_H/k_D~1) (see SI for calculation) during an intermolecular competing reaction of toluene and d_8-toluene with isoquinoline implies sp^3 C–H bond cleavage not to be the rate determining step in this process (Scheme 6). Based on these observations and literature precedences, a plausible mechanism is proposed in Scheme 7.

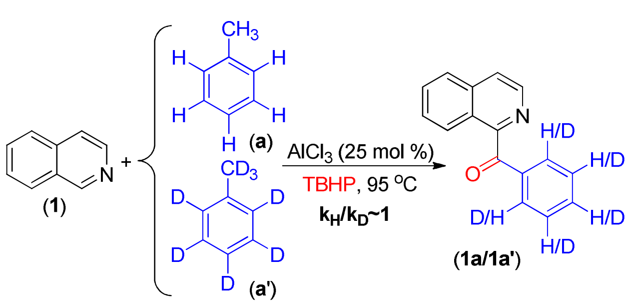
Scheme 4. Demonstration of Regioselectivity in Quinoline



Scheme 5. Trapping of Acyl Intermediate with TEMPO

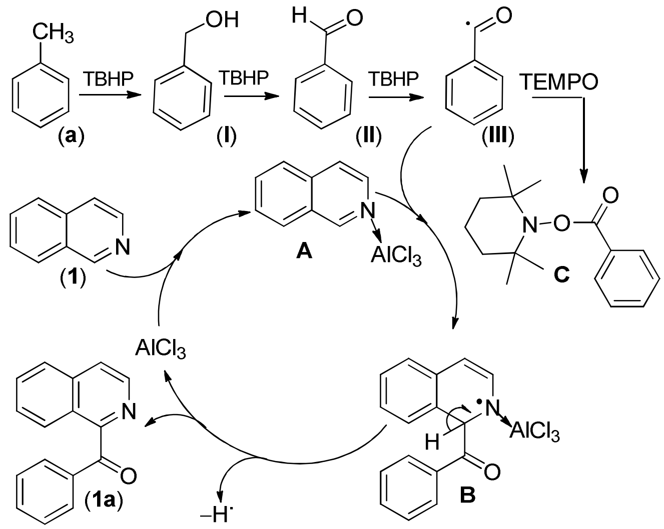


Scheme 6. Kinetic Isotope Study



In the presence of TBHP, alkylbenzene (**a**) is oxidized sequentially to benzyl alcohol (**I**), benzaldehyde (**II**) which subsequently generates acyl radical (**III**) via the cleavage of aldehydic C–H bond. On the other hand $AlCl_3$ co-ordinates with the *N*-atom of heterocycle (**1**) to form intermediate (**A**), making the heterocyclic ring further electron-deficient. An acyl radical (**III**) formed in the medium is nucleophilic in nature which attacks at the more electrophilic C1 position of heterocycle to form corresponding radical intermediate (**B**). Re-aromatization of intermediate (**B**) provides the desired acylated product (**1a**) (Scheme 7). When the reaction was performed either with benzyl alcohol or with benzaldehyde instead of toluene under otherwise identical conditions the yields of product (**1a**) obtained was 84% and 90% respectively, thereby supporting the intermediacy of benzylalcohol and aldehyde in this reaction. The selective acylation could be explained in term of nucleophilic character of acyl radical (**III**) generated, which attacks at the more electrophilic position of co-ordinated heterocycle (**A**). A similar mechanism is expected for other *N*-heterocycles.

Scheme 7. Proposed Reaction Mechanism



CONCLUSION

In conclusion, we have developed an efficient, mild and cost effective method for the regiospecific acylation of electron-deficient *N*–heterocycles using methylbenzenes. In this transformation Lewis acid $AlCl_3$ is used as catalyst and TBHP as oxidant. This reaction tolerates wide range of functional groups and proceeds efficiently for the acylation of *N*–heterocycles. The reaction serves as complement to classical Minisci reaction.

EXPERIMENTAL SECTION

General information:

All the compounds were commercial grade and were used without further purification. Organic extract were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduce pressure. Silica gel (60–120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for proton NMR (400 and 600 MHz) $CDCl_3$ solvent as internal standard for ^{13}C NMR (100 and 150 MHz). HRMS spectra were recorded using ESI mode (Q-TOF type Mass Analyzer). IR spectra were recorded in KBr or neat.

General Procedure for the Synthesis of Isoquinolin-1-yl(*p*-tolyl)methanone (1d). Isoquinoline (0.5 mmol, 64.5 mg), $AlCl_3$ (0.125 mmol, 16.6 mg), *p*-xylene (2.5 mmol, 265 mg) and 5−6 M decane TBHP (1.5 mmol, 300 μL) were added sequentially into an oven dried 25 mL round bottom flask. Then the resultant mixture was heated at 95 °C for 18 h under an atmosphere of N_2 sealed with a rubber septum. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature and admixed with ethyl acetate (30 mL). The organic layer was washed sequentially with a saturated solution of sodium bicarbonate (2 x 5 mL) and water (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude product so obtained was then purified by column chromatography using EtOAc and hexane (0.4:9.6) to give aroylated product **1d** (88 mg, 71%).

Trapping of Radical Intermediates with Radical Scavenger TEMPO. Isoquinoline (0.5 mmol, 64.5 mg), $AlCl_3$ (0.125 mmol, 16.6 mg), toluene (2.5 mmol, 230 mg) and 5−6 M decane TBHP (1.5 mmol, 300 μL) and TEMPO (1.5 mmol, 234 mg) were added sequentially into an oven dried 25 mL round bottom flask. Then the resultant mixture was heated at 95 °C for 18 h. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature and admixed with ethyl acetate (30 mL). The organic layer was washed sequentially with a saturated solution of sodium bicarbonate (2 x 5 mL) and water (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude products so obtained were then purified by column chromatography using EtOAc and hexane as the eluents. TEMPO ester adduct 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**10a**) was isolated in 58% yield along with a trace of (**1a**).

Kinetic Isotope Effect Studies. To a mixture of isoquinoline (**1**) (0.5 mmol, 64.5 mg) and $AlCl_3$ (0.125 mmol, 16.6 mg) was added an equimolar quantity of toluene (**a**) (1.25 mmol, 115 mg), and d_8-toluene (**a'**) (1.25 mmol, 125 mg). To this resultant heterogeneous mixture was then added 5–6 M decane TBHP (300 μL, 1.5 mmol) and the resultant mixture was heated in a pre heated oil bath at 95 ^{o}C for 18 h. The reaction mixture was admixed with water (10 mL) and the product was extracted with ethyl acetate (50 mL). The organic phase was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude product so obtained was purified over a column of silica gel and eluted with hexane/ethyl acetate 9.4:0.4 to give the expected product in 42% yield (**1a** and **1a'**). The ratio of the deuterated (**1a'**) and non deuterated (**1a**) aroylated product was calculated on the basis of the integration ratio of the aromatic proton peak at 7.48 (originating from toluene) and –aromatic proton at 8.60 (originated from *N*-heterocycle) by adopting the procedure of (Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 9902).

Isoquinoline-1-yl(phenyl)methanone (1a).[6h] Orange gummy; yield 72 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 (t, 2H, *J* = 7.6 Hz), 7.59–7.64 (m, 2H), 7.74 (t, 1H, *J* = 7.6 Hz), 7.81 (d, 1H, *J* = 6.0Hz), 7.91–7.96 (m, 3H), 8.22 (d, 1H, *J* = 8.8 Hz), 8.60 (d, 1H, *J* = 5.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 122.8, 126.4, 126.6, 127.3, 128.5, 128.7, 130.9, 133.8, 136.8, 136.9, 141.4, 156.6, 194.9; IR (KBr): 3056, 2926, 2851, 1671, 1581, 1248, 1154, 1020 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{11}NO$ (MH^+) 234.0913; found 234.0919.

Isoquinolin-1-yl(*o*-tolyl)methanone (1b).[6h] Brown gummy; yield 72 mg, 58%; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.53 (s, 3H), 7.21 (t, 1H, *J* = 7.8 Hz), 7.32 (d, 1H, *J* = 7.8 Hz), 7.40 (d, 1H, *J* = 7.8 Hz), 7.43 (t, 1H, *J* = 8.4 Hz), 7.67 (t, 1H, *J* = 6.6 Hz), 7.76 (t, 1H, *J* = 7.8 Hz), 7.79 (d, 1H, *J* = 6.0 Hz), 7.92 (d, 1H, *J* = 7.8 Hz), 8.62 (d, 1H, *J* = 8.4 Hz), 8.86 (d, 1H, *J* = 5.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.5, 123.1, 125.7, 126.5, 126.6, 127.3, 128.8, 130.9, 131.99, 132.0, 132.3, 137.0, 137.6, 139.9, 141.6, 157.2, 198.0; IR (KBr): 3057, 2926, 2855, 1669, 1576, 1243, 1156, 1041 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO$ (MH^+) 248.1070; found 248.1074.

Isoquinolin-1-yl(*m*-tolyl)methanone (1c).[6h] Orange gummy; yield 84 mg, 68%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H), 7.33 (t, 1H, *J* = 7.6 Hz), 7.40 (d, 1H, *J* = 7.6 Hz), 7.59 (t, 1H, *J* = 6.8 Hz), 7.71 (d, 2H, *J* = 9.6 Hz), 7.74 (d, 1H, *J* = 7.6 Hz), 7.78 (d, 1H, *J* = 5.6 Hz), 7.90 (d, 1H, *J* = 8.0 Hz), 8.49 (d, 1H, *J* = 8.4 Hz), 8.58 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 122.7, 126.4, 126.5, 127.3, 128.3, 128.4, 128.6, 130.9, 131.2, 134.7, 136.8, 138.5, 141.4, 156.9, 195.2; IR (KBr): 3055, 2924, 2854, 1668, 1584, 1279, 1175, 1049 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO$ (MH^+) 248.1070; found 248.1076.

Isoquinolin-1-yl(*p*-tolyl)methanone (1d).[6h,11] Orange gummy; yield 86 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 7.27 (d, 2H, *J* = 8.0 Hz), 7.60 (t, 1H, *J* = 7.6 Hz), 7.73 (t, 1H, *J* = 6.8 Hz), 7.79 (d, 1H, *J* = 5.2 Hz), 7.85 (d, 2H, *J* = 8.4 Hz), 7.91 (d, 1H, *J* = 8.0 Hz), 8.91 (d, 1H, *J* = 8.4 Hz), 8.59 (d, 1H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.0, 122.6, 126.4, 126.6, 127.3, 128.4, 129.4, 130.9, 131.1, 134.3, 136.9, 141.4, 144.9, 157.0, 194.7; IR (KBr): 3054, 2923, 1665, 1604, 1249, 1152, 1018 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO$ (MH^+) 248.1070; found 248.1073.

Isoquinolin-1-yl(4-methoxyphenyl)methanone (1e).[6h,11] Brown gummy; yield 72 mg, 55%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 3.84 (s, 3H), 6.92 (d, 2H, *J* = 9.0 Hz), 7.57 (t, 1H, *J* = 7.8 Hz), 7.70 (t, 1H, *J* = 7.8 Hz), 7.76 (d, 1H, *J* = 5.4 Hz), 7.88 (d, 1H, *J* = 8.4 Hz), 7.91 (d, 2H, *J* = 8.4 Hz), 8.14 (d, 1H, *J* = 9.0 Hz), 8.56 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.7, 114.0, 122.4, 126.5, 127.2, 128.3, 129.8, 130.0, 130.9, 133.3, 136.9, 141.4, 157.3, 164.3, 193.6; IR (KBr): 3055, 2932, 2840, 1661, 1596, 1422, 1254, 1171, 1074 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO_2$ (MH^+) 264.1019; found 264.1017.

(4-Chlorophenyl)(isoquinolin-1-yl)methanone (1f).[13b] Brown solid; yield 76 mg, 57%; M. P. 73–75 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.43 (d, 2H, *J* = 8.4 Hz), 7.62 (t, 1H, *J* = 8.0 Hz), 7.74 (t, 1H, *J* = 8.0 Hz), 7.80 (d, 1H, *J* = 5.2 Hz), 7.89–7.92 (m, 3H), 8.23 (d, 1H, *J* = 8.4 Hz), 8.58 (d, 1H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 123.2, 126.3, 126.7, 127.4, 128.7, 129.0, 131.0, 132.4, 135.3, 137.0, 140.4, 141.3, 155.9, 193.6; IR (KBr): 3054, 2926, 2854, 1664, 1584, 1249, 1090 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}ClNO$ (MH^+) 268.0524; found 268.0528.

(4-Bromophenyl)(isoquinolin-1-yl)methanone (1g).[11] Brown solid; yield 91 mg, 59%; M. P. 70–72 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60–7.66 (m, 3H), 7.75 (t, 1H, *J* = 8.0 Hz), 7.82–7.85 (m, 3H), 7.93 (d, 1H, *J* = 8.4 Hz), 8.26 (d, 1H, *J* = 8.8 Hz), 8.59 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 123.2, 126.3, 126.7, 127.4, 128.7, 129.2, 131.0, 132.0, 132.4, 135.7, 137.0, 141.3, 155.8, 193.8; IR (KBr): 3053, 2925, 2854, 1662, 1580, 1393, 1247, 1070 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}BrNO$ (MH^+) 312.0019; found 312.0024.

(3,5-Dimethylphenyl)(isoquinolin-1-yl)methanone (1h).[6h] Yellow gummy; yield 92 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.33 (s, 6H), 7.24 (s, 1H), 7.54 (s, 2H), 7.60 (t, 1H, *J* = 8.4

Hz), 7.73 (t, 1H, *J* = 6.8 Hz), 7.79 (d, 1H, *J* = 5.6 Hz), 7.91 (d, 1H, *J* = 8.4 Hz), 8.17 (d, 1H, *J* = 8.4 Hz), 8.59 (d, 1H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 122.6, 126.4, 126.5, 127.2, 128.4, 128.6, 130.8, 135.7, 136.8, 136.9, 138.3, 141.3, 157.1, 195.5; IR (KBr): 3054, 2919, 2859, 1668, 1601, 1453, 1299, 1144, 1085 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}NO$ (MH^+) 262.1226; found 262.1233.

(3-Iodo-5-methylphenyl)(isoquinolin-1-yl)methanone (1i). Brown gummy; yield 111 mg, 59%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H), 7.65 (t, 1H, *J* = 8.0 Hz), 7.70 (s, 1H), 7.74–7.78 (m, 2H), 7.84 (d, 1H, *J* = 5.6 Hz), 7.94 (d, 1H, *J* = 8.0 Hz), 8.06 (s, 1H), 8.23 (d, 1H, *J* = 8.4), 8.60 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 94.3, 123.2, 126.3, 126.7, 128.8, 130.8, 131.0, 135.3, 136.8, 138.7, 140.6, 14.6, 141.4, 143.1, 155.8, 193.6; IR (KBr): 2923, 2853, 1667, 1562, 1429, 1277, 1146, 1018 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{12}INO$ (MH^+) 374.0036; found 374.0036.

(3-Methylisoquinolin-1-yl)(phenyl)methanone (2a). Brown solid; yield 64 mg, 52%; M. P. 95–97 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.71 (s, 3H), 7.38–7.49 (m, 3H), 7.57–7.60 (m, 2H), 7.65 (t, 1H, *J* = 9.6 Hz), 7.79 (d, 1H, *J* = 7.8 Hz), 7.95 (d, 2H, *J* = 6.6 Hz), 8.05 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 24.3, 120.6, 124.6, 126.1, 126.4, 126.7, 127.3, 128.6, 130.7, 131.0, 133.9, 136.6, 137.5, 150.4, 195.1; IR (KBr): 3059, 2924, 2855, 1670, 1589, 1447, 1239, 1027 cm^{-1}; HRMS (ESI): calcd. for C_{17}H13NO (MH^+) 248.1070; found 248.1072.

(4-Bromoisoquinolin-1-yl)(phenyl)methanone (3a). Red solid; yield 101 mg, 65%; M. P. 129–130 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.48 (t, 2H, *J* = 7.8 Hz), 7.62 (t, 1H, *J* = 7.2 Hz), 7.69 (t, 1H, *J* = 7.8 Hz), 7.87 (t, 1H, *J* = 8.4 Hz), 7.94 (d, 2H, *J* = 7.8 Hz), 8.23 (d, 1H, *J* = 9.0 Hz), 8.29 (d, 1H, *J* = 9.0 Hz), 8.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.0, 126.7, 126.9, 127.8, 128.7, 129.4, 130.9, 132.2, 134.1, 135.7, 136.6, 143.1, 155.9, 194.2; IR

(KBr): 3056, 2961, 2855, 1659, 1523, 1268, 1158, 1018 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}BrNO$ (MH^+) 312.0019; found 312.0025.

(5-Nitroisoquinolin-1-yl)(phenyl)methanone (4a). White solid; yield 92 mg, 66%; M. P. 106–108 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.49 (t, 2H, *J* = 7.8 Hz), 7.64 (t, 1H, *J* = 7.2 Hz), 7.72 (t, 1H, *J* = 7.8 Hz), 7.93 (d, 2H, *J* = 7.8 Hz) 8.55 (t, 2H, *J* = 7.2 Hz), 8.62 (d, 1H, *J* = 6.0 Hz), 8.82 (d, 1H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 117.8, 126.89, 126.92, 128.7, 128.8, 129.3, 131.0, 133.4, 134.4, 136.2, 144.6, 145.5, 157.3, 193.9; IR (KBr): 3066, 2922, 2844, 1661, 1526, 1353, 1276, 1161, 1069 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}N_2O_3$ (MH^+) 279.0764; found 279.0770.

(5-Nitroisoquinolin-1-yl)(*p*-tolyl)methanone (4d). Brown solid; yield 98 mg, 67%; M. P. 107–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 7.30 (d, 2H, *J* = 8.4 Hz), 7.72 (t, 1H, *J* = 8.4 Hz), 7.83 (d, 2H, *J* = 8.0 Hz), 7.50–8.57 (m, 2H), 8.62 (d, 1H, *J* = 6.4 Hz), 8.81 (t, 1H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.0, 117.6, 119.5, 126.8, 126.9, 128.7, 129.3, 129.6, 131.1, 133.5, 133.8, 134.0, 144.7, 157.7, 193.6; IR (KBr): 3063, 2924, 2853, 1669, 1448, 1246, 1215, 1180, 1024 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{12}N_2O_3$ (MH^+) 293.0921; found 293.0922.

Phenyl(quinolin-2-yl)methanone (5a).[13a] Red solid; yield 68 mg, 58%; M. P. 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.50 (t, 2H, *J* = 7.6 Hz), 7.59–7.66 (m, 2H), 7.77 (t, 1H, *J* = 7.2 Hz), 7.89 (d, 1H, *J* = 8.4 Hz), 8.09 (d, 1H, *J* = 8.4 Hz), 8.17–8.22 (m, 3H), 8.33 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 121.0, 127.8, 128.4, 128.6, 129.1, 130.3, 130.8, 131.6, 133.3, 136.4, 137.3, 147.0, 154.9, 194.0; IR (KBr): 3054, 2925, 2853, 1661, 1450, 1317, 1168, 1019 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{11}NO$ (MH^+) 234.0913; found 234.0915.

Quinolin-2-yl(*o*-tolyl)methanone (5b). Yellow solid; yield 67 mg, 54%; M. P. 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 7.28 (t, 1H, *J* = 7.6 Hz), 7.33 (d, 1H, *J* = 7.6 Hz), 7.45 (t, 1H, *J* = 7.2 Hz), 7.60 (d, 1H, *J* = 8.0 Hz,), 7.65 (t, 1H, *J* = 7.2 Hz), 7.75 (t, 1H, *J* = 8.0 Hz), 7.90 (d, 1H, *J* = 8.0 Hz), 8.14 (t, 2H, *J* = 8.4 Hz), 8.34 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.0, 120.5, 125.2, 127.8, 128.8, 129.2, 130.2, 131.0, 131.3, 131.4, 137.3, 137.4, 138.8, 147.3, 155.0, 197.7; IR (KBr): 3055, 2923, 2853, 1660, 1561, 1454, 1313, 1260, 1092 cm^{-1}; HRMS (ESI): calcd.for $C_{17}H_{13}NO$ (MH^+) 248.1070; found 248.1079.

Quinolin-2-yl(*m*-tolyl)methanone (5c). White solid; yield 77 mg, 62%; M. P. 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 7.38 (d, 1H, *J* = 8.0 Hz), 7.43 (t, 1H, *J* = 7.2 Hz), 7.66 (t, 1H, *J* = 7.2 Hz), 7.79 (t, 1H, *J* = 7.2 Hz), 7.91 (d, 1H, *J* = 8.0 Hz), 8.00 (d, 2H, *J* = 6.8 Hz), 8.08 (d, 1H, *J* = 8.4 Hz), 8.21 (d, 1H, *J* = 8.4 Hz), 8.34 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.6, 121.0, 127.8, 128.2, 128.5, 129.0, 129.1, 130.3, 130.8, 131.9,134.1, 136.3, 137.2, 138.1, 146.9, 155.1, 194.4; IR (KBr): 3052, 2924, 2856, 1660, 1596, 1458, 1313, 1139, 1139, 1013 cm^{-1}; HRMS (ESI): calcd.for $C_{17}H_{13}NO$ (MH^+) 248.1070; found 248.1067.

Quinolin-2-yl(*p*-tolyl)methanone (5d).[11] Brown solid; yield 78 mg, 63%; M. P. 62–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 7.30 (d, 2H, *J* = 8.0 Hz), 7.64 (t, 1H, *J* = 6.8Hz), 7.76 (t, 1H, *J* = 7.6 Hz), 7.88 (d, 1H, *J* = 8.0 Hz), 8.06 (d, 1H, *J* = 8.4 Hz), 8.13 (d, 2H, *J* = 8.0 Hz), 8.18 (d,1H, *J* = 8.4 Hz), 8.32 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 22.0, 121.0, 127.9, 128.5, 129.07, 129.13, 130.3, 130.7, 131.8, 133.8, 137.2, 144.2, 147.0, 155.3, 193.7; IR (KBr): 3066, 2922, 2852, 1659, 1456, 1317, 1161, 1112 cm^{-1}; HRMS (ESI): calcd.for $C_{17}H_{13}NO$ (MH^+) 248.1070; found 248.1077.

(4-Methoxyphenyl)(quinolin-2-yl)methanone (5e).[13b] White solid; yield 65 mg, 49%; M. P. 65–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.87 (s, 3H), 6.99 (d, 2H, J = 7.2 Hz), 7.65 (t, 1H, J = 7.6 Hz), 7.78 (t, 1H, J = 7.2 Hz), 7.90 (d, 1H, J = 7.6 Hz), 8.06 (d, 1H, J = 8.4 Hz), 8.20 (d, 1H, J = 8.0 Hz), 8.28 (d, 2H, J = 6.8 Hz), 8.33 (d, 1H, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.7, 113.8, 121.1, 127.9, 128.4, 129.0, 129.2, 130.2, 130.7, 134.1, 137.2, 146.9, 155.6, 163.9, 192.4; IR (KBr): 3059, 2927, 2848, 1652, 1507, 1319, 1256, 1157, 1025 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO_2$ (MH^+) 264.1019; found 264.1025.

(4-Chlorophenyl)(quinolin-2-yl)methanone (5f).[13b] Brown solid; yield 68 mg, 51%; M. P. 105–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 (d, 2H, J = 8.4 Hz), 7.65 (t, 1H, J = 8.4 Hz), 7.78 (t, 1H, J = 6.8 Hz), 7.89 (d, 1H, J = 7.6 Hz), 8.11 (d, 1H, J = 8.8 Hz), 8.17 (d, 1H, J = 8.4 Hz), 8.22 (d, 2H, J = 8.8 Hz), 8.34 (d, 1H, J = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 120.9, 127.9, 128.7, 128.8, 129.2, 130.4, 130.7, 133.1, 134.8, 137.5, 139.8, 146.9, 154.5, 192.6; IR (KBr): 2926, 2854, 1663, 1590, 1459, 1316, 1209, 1170, 1089 HRMS (ESI): calcd. for $C_{16}H_{10}ClNO$ (MH^+) 268.0524; found 268.0521.

(4-Bromophenyl)(quinolin-2-yl)methanone (5g). Brown solid; yield 84 mg, 54%; M. P. 111–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.65 (t, 3H, J = 9.6 Hz), 7.78 (t, 1H, J = 9.2 Hz), 7.89 (d, 1H, J = 7.6 Hz), 8.10–8.17 (m, 4H), 8.33 (d, 1H, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 120.9, 127.9, 128.5, 128.8, 129.2, 130.4, 130.7, 131.6, 133.2, 135.2, 137.4, 146.9, 154.4, 192.7; IR (KBr): 3048, 2956, 2926, 1664, 1586, 1458, 1316, 1167, 1068 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}BrNO$ (MH^+) 312.0019; found 312.0026.

(3,5-Dimethylphenyl)(quinolin-2-yl)methanone (5h). Red solid; yield 84 mg, 64%; M. P. 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.37 (s, 6H), 7.24 (s, 1H), 7.64 (t, 1H, J = 8.0 Hz), 7.75–7.79 (m, 3H), 7.89 (d, 1H, J = 8.0 Hz), 8.03 (d, 1H, J = 8.8 Hz), 8.19 (d, 1H, J = 8.4 Hz), 8.32 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.5, 121.0, 127.8, 128.5, 129.1, 129.3, 130.2, 130.8, 135.1, 136.4, 137.2, 138.0, 147.0, 155.4, 194.7; IR (KBr): 3060, 2923, 2855, 1662, 1598, 1461, 1325, 1143, 1035 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}NO$ (MH^+) 262.1226; found 262.1229.

(3-Iodo-5-methylphenyl)(quinolin-2-yl)methanone (5i). Brown solid; yield 106 mg, 57%; M. P. 121–123 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.37 (s, 3H), 7.66 (t, 1H, *J* = 7.2 Hz), 7.76–7.80 (m, 2H), 7.89 (d, 1H, *J* = 8.0 Hz), 7.95 (s, 1H), 8.08 (d, 1H, *J* = 8.8 Hz), 8.19 (d, 1H, *J* = 8.0 Hz), 8.33 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.2, 93.9, 120.9, 127.9, 128.8, 129.2, 130.4, 130.8, 131.4, 137.4, 137.6, 138.1, 140.2, 142.5, 147.0, 154.3, 192.6; IR (KBr): 2924, 2853, 1664, 1563, 1311, 1143, 1016 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{12}INO$ (MH^+) 374.0036; found 374.0041.

(8-Methylquinolin-2-yl)(phenyl)methanone (6a).[13c] White solid; yield 70 mg, 57%; M. P. 63–64 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.78 (s, 3H), 7.50–7.57 (m, 3H), 7.63 (t, 2H, *J* = 7.2 Hz), 7.74 (d, 1H, *J* = 8.0 Hz), 8.19 (d, 1H, *J* = 8.8 Hz), 8.31 (d, 1H, *J* = 8.4 Hz), 8.36 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 18.1, 120.6, 125.7, 128.1, 128.6, 129.2, 130.3, 131.9, 132.9, 136.8, 137.4, 139.1, 146.1, 153.3, 193.7; IR (KBr): 3056, 2953, 2922, 1660, 1594, 1445, 1322, 1286, 1159, 1070 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO$ (MH^+) 248.1070; found 248.1078.

(8-Methylquinolin-2-yl)(*m*-tolyl)methanone (6c). Yellow liquid; yield 77 mg, 59%; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 2.77 (s, 3H), 7.38 (t, 1H, *J* = 7.8 Hz), 7.42 (d, 1H, *J* = 7.8 Hz), 7.52 (t, 1H, *J* = 7.8 Hz), 7.62 (d, 1H, *J* = 6.6 Hz), 7.71 (d, 1H, *J* = 8.4 Hz), 8.15 (t, 2H, *J* = 8.4 Hz), 8.20 (s, 1H), 8.28 (d, 1H, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 18.1, 21.6, 120.6, 125.7, 127.9, 128.5, 129.15, 129.17, 130.2, 132.4, 133.7, 136.7, 137.3, 137.7, 139.0, 146.0, 153.4, 193.7; IR (KBr): 3043, 2955, 2923, 1659, 1584, 1465, 1374, 1287, 1141, 1079 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}NO$ (MH^+) 262.1226; found 262.1228.

(8-Methylquinolin-2-yl)(*p*-tolyl)methanone (6d). Yellow liquid; yield 81 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.47 (s, 3H), 2.80 (s, 3H), 7.32 (d, 2H, *J* = 8.0 Hz), 7.54 (t, 1H, *J* = 8.0 Hz), 7.63 (d, 1H, *J* = 7.2 Hz), 7.73 (d, 1H, *J* = 8.0 Hz), 8.16 (d, 1H, *J* = 8.4 Hz), 8.28–8.31 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 18.2, 22.0, 120.7, 125.7, 128.4, 128.9, 129.2, 130.2, 132.1, 134.2, 137.4, 139.0, 143.8, 146.1, 153.7, 193.2; IR (KBr): 3093, 2922, 1653, 1463, 1319, 1250, 1156, 1020 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}NO$ (MH^+) 262.1226; found 262.1219.

(4-Chlorophenyl)(8-methylquinolin-2-yl)methanone (6f). Yellow solid; yield 67 mg, 48%; M. P. 79–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.78 (s, 3H), 7.50 (d, 2H, *J* = 8.8 Hz), 7.56 (t, 1H, *J* = 7.6 Hz), 7.65 (t, 1H, *J* = 7.6 Hz), 7.74 (d, 1H, *J* = 8.4 Hz), 8.19 (d, 1H, *J* = 8.4 Hz), 8.32 (d, 1H, *J* = 8.0 Hz), 8.35 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 18.2, 120.6, 125.8, 128.4, 128.8, 129.3, 130.4, 133.4, 135.2, 137.6, 139.0, 139.4, 146.0, 152.9, 192.3; IR (KBr): 2962, 2923, 2855, 1638, 1459, 1311, 1089 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{12}ClNO$ (MH^+) 282.0680; found 282.0685.

(8-Methoxyquinolin-2-yl)(*p*-tolyl)methanone (7d). Red liquid; yield 64 mg, 46%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 4.05 (s, 3H), 7.10 (d, 1H, *J* = 7.2 Hz), 7.30 (d, 2H, *J* = 8.4 Hz), 7.44 (d, 1H, *J* = 7.2 Hz), 7.56 (t, 1H, *J* = 8.4 Hz), 8.09 (d, 1H, *J* = 8.8 Hz), 8.24–8.29 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.9, 56.4, 108.6, 119.5, 121.6, 127.2, 128.9, 130.2, 132.1, 133.8, 137.0, 138.9, 144.0, 153.9, 156.5, 193.0; IR (KBr): 3066, 2928, 2838, 1655, 1606, 1465, 1325, 1260, 1131, 1040 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}NO_2$ (MH^+) 278.1176; found 278.1172.

Phenyl(quinoxalin-2-yl)methanone (8a).[13a] Black solid; yield 86 mg, 74%; M. P. 100–102 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.52 (t, 2H, *J* = 7.8 Hz), 7.64 (t, 1H, *J* = 7.8 Hz), 7.84 (t, 1H, *J* = 6.6 Hz), 7.88 (t, 1H, *J* = 8.4 Hz), 8.19 (m, 2H), 8.22 (d, 2H, *J* = 7.8 Hz), 9.47 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 128.6, 129.6, 130.6, 130.9, 131.0, 131.5, 132.2, 132.4, 133.8, 143.3, 143.4, 145.5, 192.5; IR (KBr): 3062, 2925, 2853, 1659, 1597, 1322, 1234, 1127, 1014 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{10}N_2O$ (MH^+) 235.0866; found 235.0869.

Quinoxalin-2-yl(*m*-tolyl)methanone (8c). Brown gummy; yield 92 mg, 74%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 7.43 (t, 1H, *J* = 8.0 Hz), 7.48 (d, 1H, *J* = 7.2 Hz), 7.85−7.93 (m, 2H), 8.00 (s, 2H), 8.22 (d, 2H, *J* = 8.8 Hz), 9.47 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.6, 128.5, 128.9, 129.6, 130.7, 130.9, 131.7, 132.2, 134.7, 135.8, 138.5, 140.7, 143.3, 145.5, 149.1, 192.9; IR (KBr): 2924, 2854, 1658, 1489, 1317, 1151, 1017 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{12}N_2O$ (MH^+) 249.1022; found 249.1028.

Quinoxalin-2-yl(*p*-tolyl)methanone (8d).[6h,11,13a] Red solid; yield 98 mg, 79%; M. P. 97–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 7.30 (d, 2H, *J* = 7.6 Hz), 7.78−7.87 (m, 2H), 8.11 (d, 2H, *J* = 8.4 Hz), 8.16 (d, 2H, *J* = 8.4 Hz), 9.42 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 22.0, 129.3, 129.5, 130.5, 130.9, 131.5, 132.0, 133.1, 140.6, 143.2, 144.8, 145.5, 149.1, 192.0; IR (KBr): 3053, 2922, 2851, 1657, 1601, 1324, 1229, 1157, 1121 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{12}N_2O$ (MH^+) 249.1022; found 249.1019.

(4-Chlorophenyl)(quinoxalin-2-yl)methanone (8f).[13d] Brown solid; yield 90 mg, 67%; M. P. 85–87 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.50 (d, 2H, *J* = 8.4 Hz), 7.83−7.88 (m, 1H), 7.90 (t, 1H, *J* = 8.4 Hz), 8.17–8.23 (m, 4H), 9.49 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 129.0, 129.7, 130.7, 130.9, 131.2, 132.5, 132.9, 134.1, 140.5, 143.3, 145.5, 148.4, 191.2; IR

(KBr): 2926, 2855, 1663, 1460, 1313, 1164, 1087 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_9ClN_2O$ (MH^+) 269.0476; found 269.0480.

(3,5-Dimethylphenyl)(quinoxalin-2-yl)methanone (8h). Red solid; yield 102 mg, 78%; M. P. 151–152 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2,40 (s, 6H), 7.30 (s, 1H), 7.78 (s, 2H), 7.86–7.91 (m, 2H), 8.20–8.22 (m, 2H), 9.43 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.5, 129.1, 129.6, 130.7, 131.0, 132.1, 135.7, 135.8, 138.3, 140.8, 143.3, 145.4, 149.4, 193.2; IR (KBr): 3063, 2920, 2859, 1659, 1601, 1327, 1214, 1149, 1031 cm^{-1} HRMS (ESI): calcd. for $C_{17}H_{14}N_2O$ (MH^+) 263.1179; found 263.1184.

(6-Methylquinoxalin-2-yl)(*p*-tolyl)methanone and (7-Methylquinoxalin-2-yl)(*p*-tolyl)methanone (9d). Red semisolid; yield 95 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 2.62 (s, 3H), 7.31 (d, 2H, J = 8.0 Hz), 7.65–7.71 (m, 1H), 7.94 (s, 1H), 8.06 (d, 1H, J = 8.4 Hz), 8.11 (d, 2H, J = 8.0 Hz), 9.39 (d, 1H, J = 15.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 22.0, 22.3, 22.9, 128.4, 129.1, 129.3, 129.4, 130.2, 131.6, 133.31, 133.34, 134.5, 139.2, 140.8, 141.7, 141.9, 143.2, 143.4, 144.7, 144.75, 144.8, 145.6, 148.4, 149.2, 192.25, 192.31; IR (KBr): 2953, 2924, 2854, 1656, 1497, 1322, 1276, 1167, 1017 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{14}N_2O$ (MH^+) 263.1179; found 263.1174.

2,2,6,6-Tetramethylpiperidin-1-yl benzoate (10a).[12f] Yellow gummy; yield 76 mg, 58%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.16 (s, 6H), 1.31 (s, 6H), 1.48–1.52 (broad singlet, 1H), 1.61–1.64 (broad singlet, 2H), 1.71 (m, 3H), 7.50 (t, 2H, J = 7.6 Hz), 7.61 (t, 1H, J = 6.8 Hz), 8.11 (d, 2H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.1, 21.0, 32.1, 39.2, 60.5, 128.6, 129.7, 133.0, 166.5; IR (KBr): 2974, 2934, 1749, 1540, 1378, 1255, 1176, 1081, cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{23}NO_2$ (MH^+) 262.1802; found 262.1806.

AUTHOR INFORMATION

Corresponding Author

*E mail: patel@iitg.ernet.in.

ACKNOWLEDGMENT

B. K. P acknowledges the support of this research by the Department of Science and Technology (DST) (SB/S1/OC-53/2013), New Delhi, and the Council of Scientific and Industrial Research (CSIR) (02(0096)/12/EMR-II). WA and SG thank CSIR for fellowship.

Supporting Information Available

Kinetic isotope effect experiment and spectral data for all compounds. This material is available free of charge *via* the Internet at http://pubs.acs.org.

REFERENCES

(1) For recent reviews on C–H activation, see: (a) Bras, J. L.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (b) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (d) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (e) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (f) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (g) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (h) Mousseau, J. J.; Charette, A. B. *Acc. Chem. Res.* **2013**, *46*, 412. (i) Lin, B.; Dixneuf, P. H. *Chem. Soc. Rev.* **2013**, *42*, 5744.

(2) Arndtsen, B.; Bergman, R.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res*. **1995**, *28*, 154.

(3) For recent reviews on C–H activation, see (a) Beccalli, S.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.*, **2007**, *107*, 5318. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem.Int. Ed.*, **2009**, ***48***, 9792. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q.

Angew. Chem. Int. Ed., **2009**, *48*, 5094. (d) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (e) Lautens, M.; Thansandote, P. *Chem. Eur. J.*, **2009**, *15*, 5874. (f) Kitamura, T. *Eur. J. Org. Chem.* **2009**, 1111. (g) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu ,J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (h) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (i) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, *16*, 2654. (j) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (k) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (l) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212. (m) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (n) Yeung, C. S.; Dong, V. M. *Chem. Rev*. **2011**, *111*, 1215. (o) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev*. **2011**, *111*, 1780. (p) Yoo, W. J.; Li, C. -J. *Top. Curr. Chem*. **2010**, *292*, 281.

(4) (a) Duncton, M. A. *J. Med. Chem. Commun*. **2011**, *2*, 1135. (b) Al-Khalil, S.; Schiff, P. L. *J. Nat. Prod*. **1985**, *48*, 989. (c) Baser, K. H. C. *J. Nat. Prod*. **1982**, *45*, 704. (d) Slavík, J.; Slavíková, L. *Collect. Czech. Chem.Commun*. **1996**, *61*, 1047.

(5) (a) Bentley, K.W. *Nat. Prod. Rep*. **2006**, *23*, 444. (b) Bentley, K.W. *Nat. Prod. Rep*. **2005**, *22*, 249. (c) Bentley, K.W. *Nat. Prod. Rep*. **2004**, *21*, 395. (d) Bentley, K.W. *Nat. Prod. Rep*. **2003**, *20*, 342.

(6) (a) Wertz, S.; Leifert, D.; Studer, A. *Org. Lett*. **2013**, *15*, 928. (b) Tang, B.-X.; Song, R.-J.; Wu, C.-Y.; Liu, Y.; Zhou, M.-B.; Wei, W.-T.; Deng, G.-B.; Yin, D.-L.; Li, J.-H. *J. Am. Chem*. *Soc.* **2010**, *132*, 8900. (c) Chan, C.-W.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett*. **2010**, *12*, 3926. (d) Baslé, O.; Bidange, J.; Shuai, Q.; Li, C.-J. *Adv. Synth.Catal*. **2010**, *352*, 1145. (e) Wang, P.; Rao, H.; Hua, R.; Li, C.-J. *Org. Lett*. **2012**, *14*, 902. (f) Rao, H.; Ma, X.; Liu, Q.; Li, Z.; Cao, S.; Li, C.-J. *Adv.Synth. Catal*. **2013**, *355*, 2191. (g) Shi, Z.; Glorius, F.

Chem. Sci. **2013**, *4*, 829. (h) Matcha, K.; Antonchick, A. P. *Angew. Chem. Int. Ed*. **2013**, *52*, 2082. (i) Pruet, J. M.; Robertus, J. D.; Anslyn, E. V. *Tetrahedron Lett*. **2010**, *51*, 2539. (j) Caronna, T.; Galli, R.; Malatesta, V.; Minisci, F. *J. Chem. Soc. C* **1971**, 1747.

(7) For reviews on Minisci reaction, see: (a) Punta, C.; Minisci, F. *Trends Heterocycl. Chem*. **2008**, *13*, 1. (b) Minisci, F.; Fontana, F.; Vismara, E. *J. Heterocycl. Chem*. **1990**, *27*, 79. (c) Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res*. **1983**, *16*, 27. (d) Minisci, F. *Synthesis* **1973**, 1.

(8) (a) Duncton, M. A. J.; Estiarte, M. A.; Johnson, R. J.; Cox, M.; Mahony, D. J. R. O.; Edwards, W. T.; Kelly, M. G. *J. Org. Chem*. **2009**, *74*, 6354. (b) Minisci, F.; Recupero, F.; Cecchetto, A.; Punta, C.; Gambarotti, C.; Fontana, F.; Pedulli, G. F. *J. Heterocycl. Chem*. **2003**, *40*, 325. (c) Phillips, O. A.; Murthy, K. S. K.; Fiakpui, C. Y.; Knaus, E. E. *Can. J. Chem*. **1999**, *77*, 216. (d) Murthy, K. S. K.; Knaus, E. E.; *Drug Dev. Res*. **1999**, *46*, 155. (e) Desaubry, L.; Bourguignon, J.-J. *Tetrahedron Lett*. **1995**, *36*, 7875. (f) Baur, R.; Sugimoto, T.; Pfleiderer, W.; *Helv. Chim. Acta.* **1988**, *71*, 531. (g) Pfleiderer, W. *Tetrahedron Lett*. **1984**, *25*, 1031. (h) Baur, R.; Sugimoto, T.; Pfleiderer, W. *Chem. Lett*. **1984**, *13*, 1025. (i) Correia, C. A.; Yang, L.; Li, C.-J. *Org. Lett*. **2011**, *13*, 4581.

(9) For an excellent review on the applications of acyl radicals, see: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev*. **1999**, *99*, 1991.

(10) (a) Ischay, M. A.; Yoon, T. P. *Eur. J. Org. Chem*. **2012**, 3359. (b) Recupero, F.; Punta, C. *Chem. Rev*. **2007**, *107*, 3800. (c) Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev*. **2007**, *36*, 1803. (d) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377. (e) Togo, H.; Katohgi, M. *Synlett* **2001**, 565. (f) Renaud, P.; Sibi, M. P. *Radicals in Organic Synthesis*, Wiley-VCH, Weinheim,**2001**.

(11) Siddaraju, Y.; Lamani, M.; Prabhu, K. R. *J. Org. Chem*. **2014**, *79*, 3856.

(12) (a) Rout, S. K.; Guin, S.; Ghara, K. K.; Banerjee, A.; Patel, B. K. *Org. Lett*. **2012**, *14*, 3982. (b) Guin, S.; Rout, S. K.; Banerjee, A.; Nandi, S.; Patel, B. K. *Org. Lett*. **2012**, *14*, 5294. (c) Rout, S. K.; Guin, S.; Banerjee, A.; Khatun, N.; Gogoi, A.; Patel, B. K. *Org. Lett*. **2013**, *15*, 4106. (d) Ali, W.; Guin, S.; Rout, S. K.; Gogoi, A.; Patel, B. K. *Adv. Synth. Catal*. **2014**, *356*, 3099. (e) Majji, G.; Guin, S.; Gogoi, A.; Rout, S. K.; Patel, B. K. *Chem. Commun*. **2013**, *49*, 3031. (f) Rout, S. K.; Guin, S.; Ali, W.; Gogoi, A.; Patel, B. K. *Org. Lett*. **2014**, *16*, 3086.

(13) (a) Yin, Z.; Zhang, Z.; Kadow, J. F.; Meanwell, N. A.; Wang, T. *J. Org. Chem.* **2004**, *69*, 1364. (b) Reux, B.; Nevalainen, T.; Raitio, K. H.; Koskinen, A. M. P. *Bioorganic & Medicinal Chemistry* **2009**, *17*, 4441. (c) Mao, Z.; Qu, H.; Zhao, Y.; Lin, X. *Chem. Commun.* **2012**, *48*, 9927. (d) Suzuki, Y.; Iwamoto, K.-ichi; Oishi, E.; Higashino, T.; Miyashita, A. *Heterocycles* **1998**, *49*, 405.