Chapter 3: NHC-Catalyzed Benzylic sp\(^3\) C–H Bond Activation of Alkylarenes and N-Benzylamines for the Synthesis of 3H-Quinazolin-4-ones – Experimental and Theoretical Study

Graphical Abstract

3.1. Introduction

3.1.1. C–H Bond Oxidation

Oxidation of C–H bond to its corresponding carbonyl compound enables generation of large number of synthetically important molecules. It is an essential organic process, which introduces oxygen atom into the organic moiety. This strategy offers direct access to complex building blocks from readily available simple compounds. In general, traditional methodologies often requires activation of C–H bonds through the pre-installation of functional groups. In many strategies harsh reaction conditions were used that can lead to the competitive formation of byproducts. To overcome these problems, over past few decades, the direct functionalization of C–H bonds has come to limelight, which avoids the pre-functionalization of starting material and became an important research area in the organic synthesis.

3.1.2. Benzylic sp$^3$ C–H Bond Oxidation

Direct activation of C–H bonds is limited due to less electronegativity difference between carbon and hydrogen i.e. inert nature. Benzylic sp$^3$ C–H bond activation is one such process that offers important intermediates such as aldehydes, ketones which are useful in construction large molecules. Traditional method involves the usage of stoichiometric amount of metal oxidants such potassium permanganate or potassium dichromate under harsh reaction conditions.

Due to the stringent environmental policies, these methods were replaced by catalytic oxidation, where a transition metal was employed as a catalyst in the presence of stoichiometric terminal oxidants, most commonly, tert-butyl hydroperoxide (TBHP) and other oxidants like KBrO$_3$, N-hydroxyphthalimide (NHPI), H$_2$O$_2$ and Oxone. In similar lines, there were few reports on application of oxygen, an
environmental friendly and green oxidant, as terminal oxidant in presence of precious metals like Pt, Rh etc.\(^9\) However most of the above procedures have limitations such as usage of toxic metals, low yields of the desired product and limited substrate scope.

### 3.1.3. Metal-Catalyzed Benzylic sp\(^3\) C–H Bond Oxidation

In 1980’s Gif reagents were used as hydrocarbon-oxidizing reagents where an oxidant in combination with Fe/Cu were extensively used for oxidation of C–H bonds. Different branches of the family of Gif reagents in chronological order are summarized in Table 3.1.\(^{10}\)

<table>
<thead>
<tr>
<th>Table 3.1. Gif oxygenation systems in chronological order of development</th>
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<tr>
<td><strong>System</strong></td>
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<tr>
<td>Gif(^I)</td>
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<td>Gif(^III)</td>
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<tr>
<td>GoAgg(^IV)(^h)</td>
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<tr>
<td>GoAgg(^V)(^h)</td>
</tr>
</tbody>
</table>

\(^a\) Although no compound is added, the zero-valent metal partially dissolves in solution. \(^b\) Usually [Fe\(_3\)(OAc)\(_6\)(py)\(_3\)]\(0.5\)py. \(^c\) At room temperature, unless otherwise noted. \(^d\) Addition of H\(_2\)O is optional. \(^e\) Under inert gas (Ar, N\(_2\)). \(^f\) Usually FeCl\(_3\)/6H\(_2\)O. \(^g\) Under inert gas or O\(_2\). \(^h\) Later expelled from the Gif family. \(^i\) Usually Fe(NO\(_3\))\(_3\)/9H\(_2\)O.
In recent years, numerous reports have appeared in the literature on transition metal-catalyzed oxidative C–H bond functionalization for the formation of carbon–carbon and carbon–heteroatom bonds from unactivated C–H bonds.\textsuperscript{11} Some reports on photo-catalyzed,\textsuperscript{12} metal-free\textsuperscript{13} benzylic sp\textsuperscript{3} C–H bond oxidation were also reported.

### 3.1.4. Organocatalyzed Benzylic sp\textsuperscript{3} C–H Bond Oxidation

In 2005, Xu and co-workers established a metal-free organocatalytic system involving anthraquinones and NHPI for the oxidation of benzylic C–H bonds (Scheme 3.1). Using this strategy various substituted fluorenes 3.1 were converted to fluorenones 3.2 up to 85% yield at 80 °C.\textsuperscript{14a}

![Scheme 3.1. NHPI-catalyzed benzylic oxidation of alkylarenes](image)

In 2015, Wang and co-workers established an organocatalytic TEMPO-mediated aerobic oxidation of benzylic sp\textsuperscript{3} C–H bonds of cyclic ethers 3.3 and alkylarenes 3.5 (Scheme 3.2). This reported methodology employs metal-free and recyclable TEMPO derived sulphonic acid salt catalyst along with mineral acids (HCl and NaNO\textsubscript{2}) as the catalytic system. This methodology enabled the synthesis of wide range of synthetically and biologically important isochromanones 3.4 and xanthenes 3.6 from readily available substrates.\textsuperscript{14b}
These methods were well studied and extensively used, but the main disadvantages of these methods are the requirement of ligands, use of additives, use of base and reagents in stoichiometric amount, limited substrate scope and/or the poor product selectivity etc. Moreover, the reaction conditions are generally harsh and the use of excess amount of base and oxidant leads to large amount of waste. So there is scope for devising an ideal strategy to overcome these drawbacks employing cheaper reagents to get desirable product yield. To overcome the problems associated with these benzylic oxidations, a modified approach, involving the use of organocatalyst was found to be effective to carry out this transformation. In this aspect, the use of N-heterocyclic carbenes (NHC) as organocatalyst for the aforementioned transformation can be envisioned as an alternative for the existing strategies and till date, NHC-catalyzed benzylic oxidation was not reported in the literature.
3.2. Results and Discussion

3.2.1. Oxidative Benzylic sp\(^3\) C–H Bonds of Alkylarenes via NHC-Catalysis

In Chapter 2, NHC-catalyzed oxidative amidation of aldehydes with amines was demonstrated. During this process, when dibenzylamine 2.50p was used as the amine variant for amidation of aldehyde 2.49a, the desired amide 2.51p was obtained as the major product along with N-benzylbenzamide 2.51p'. The formation of 2.51p' as a side product can be attributed to the benzylic C–H oxidation of 2.50p shown in Scheme 3.3.

![Scheme 3.3. Oxidative amidation of dibenzylamine via NHC-catalysis](image)

Inspired by this result, the benzylic sp\(^3\) C–H bond oxidation of alkylarenes was attempted. In this Chapter, NHC-catalyzed benzylic sp\(^3\) C–H bond oxidation of alkylarenes and N-benzylamines under metal-free conditions using TBHP as the oxidant to give the corresponding carbonyl derivatives was demonstrated (Scheme 3.4). Finally, the application of this protocol was extended for the synthesis of 3H-quinazolin-4-ones, a class of bioactive heterocyclic compound.

![Scheme 3.4. NHC-catalyzed benzylic sp\(^3\) C–H bond oxidation of alkylarenes](image)
3.2.2. Optimization Condition for Oxidation of Benzylic sp$^3$ C–H Bonds of Alkylarenes

To know the best condition for benzylic C–H bond oxidation, several conditions were varied by taking diphenylmethane 3.7a as the model substrate. To start with, 10 mol% of NHC pre-catalysts, 10 mol% of base, 3.0 mmol of oxidant in solvent (2 mL) at 80 °C was used. To know the best catalyst, different commercially available NHCs were employed. Variation of different NHCs A to G as precatalyst and Et$_3$N as base in the presence of TBHP in water as oxidant in CH$_3$CN at 80 °C was performed and it was observed that precatalyst D gave better results than the other precatalysts with 95% yield. (Scheme 3.5). The corresponding carbonyl compound benzophenone 3.8a was obtained which was purified via column chromatography and isolated yield for each condition were reported.

a Diphenylmethane (1.0 mmol), NHC precatalyst (10 mol%), Et$_3$N (10 mol%), TBHP (3.0 mmol) in CH$_3$CN (2 mL), 80 °C, 15 h, Isolated yields.

Scheme 3.5. Various N-heterocyclic carbenes used in the benzylic sp$^3$ C–H bonds oxidation$^a$
Table 3.2. Optimization conditions for NHC-catalyzed benzylic oxidation of alkylarenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Oxidant</th>
<th>Solvent</th>
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<td>TBHP</td>
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<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>&lt;5&lt;sup&lt;l&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Diphenylmethane 3.7a (1.0 mmol), NHC precatalyst D (10 mol%), base (10 mol%), oxidant (3.0 mmol), solvent (2 mL), 80 °C, 15 h. <sup>b</sup> Isolated yield. <sup>c</sup> Oxidant: TBHP in decane. <sup>d</sup> BQ: Benzoquinone. <sup>e</sup> AQ: Anthraquinone. <sup>f</sup> Reaction at rt. <sup>g</sup> Reaction at 60 °C. <sup>h</sup> Reaction at 70 °C. <sup>i</sup> 1.0 mmol of oxidant used. <sup>j</sup> 2.0 mmol of oxidant used. <sup>k</sup> NHC precatalyst (5 mol%) and Et<sub>3</sub>N (5 mol%) for 24 h. <sup>l</sup> Reaction carried out in absence of NHC precatalyst with Et<sub>3</sub>N (10 mol%) and TBHP (3.0 mmol) for 24 h.

With optimized NHC precatalyst in hand, other reaction conditions were varied and results were shown in Table 3.2. Screening of different oxidants indicated that TBHP was the oxidant of choice and the yield was better with aq.TBHP than TBHP in
decane (entries 1-10). In order to choose the best base for this transformation, various bases were explored and it was observed that inorganic bases like K$_2$CO$_3$, Cs$_2$CO$_3$ and t-BuOK decreased the product yield (entries 11-13). Diethyl azodicarboxylate (DEAD) also did not improve the product yield (entry 14). Different solvents were tested and among them, CH$_3$CN gave the best yield (entries 1, 15-20). When the reaction was performed at room temperature, the desired ketone was not detected (entry 21). A gradual increase in the temperature increases the product yield and the yield was optimal at 80 °C and further increase in temperature did not improve the product yield (entries 22, 23 and 1). The yield decreased dramatically when the amount of oxidant was decreased from 3.0 to 1.0 mmol (entries 1, 24 and 25). There was significant decrease in the product yield when the amount of NHC precatalyst used was decreased to 5 mol% even when the reaction was prolonged for 24 h (entry 26). The desired product was not obtained, when the reaction was carried out in absence of NHC and with 10 mol% of Et$_3$N and 3.0 mmol of TBHP (entry 27). This reaction proves that the aforementioned reaction is not simply a base-catalyzed reaction, but proceeds in presence of NHC as organocatalyst. Thus the optimized condition was fixed as: NHC precatalyst D (10 mol%), Et$_3$N (10 mol%) as base, aq.TBHP as oxidant (3.0 mmol) in CH$_3$CN at 80 °C for 15 h. The formed product benzophenone 3.37a was spectroscopically analyzed and compared with the literature details.

3.2.3. NHC-Catalyzed Benzylic sp$^3$ C–H Bond Oxidation: Scope and Limitations of Alkylarenes

With the optimized results in hand, the scope of the benzylic sp$^3$ C–H bond activation is tested for structurally diverse alkylarenes 3.7 and the results are summarized in Scheme 3.6. The reaction proceeded smoothly to generate the corresponding carbonyl compounds in good to excellent yields. Ethylbenzene and
1,2,3,4-tetrahydronaphthalene gave the expected products, acetophenone and 3,4-dihyronaphthalen-1(2H)-one respectively in good yields albeit longer reaction time (24 h) and excess of oxidant (5 mmol) (entries 3.8b and 3.8c). When 3.0 mmol of oxidant was used, the yield of the products 3.8b and 3.8c were low even when the reaction was prolonged for 24 h (69% and 67% respectively). Similarly, the reaction was sluggish and required 5 mmol of oxidant in case of indan and the desired product indanone was obtained in low yield of 48%, whereas the yield was considerably low (34%) with 3.0 mmol of oxidant (entry 3.8d). In case of 9,10-dihydroanthracene, instead of formation of carbonyl compound, complete aromatization of the ring due to oxidative dehydrogenation was observed, leading to the formation of anthracene in good yield (entry 3.8e). 9H-Xanthene yielded the required 9H-xanthen-9-one in excellent yield of 95% (entry 3.8f). The yields were good when oxygen is present in the ring adjacent to benzylic position, as witnessed in the case of isochroman and 1,3-dihydroisobenzofuran (entries 3.8g and 3.8h). Similarly, 1,2,3,4-tetrahydroisoquinoline, a cyclic secondary amine, gave the desired carbonyl product in good yield (entry 3.8i), whereas the similar trend was not observed with 1,2,3,4-tetrahydroquinoline. In this case, it was observed that the substrate underwent oxidative dehydrogenation leading to the formation of quinoline instead of 2,3-dihydroquinolin-4(1H)-one and the reaction was found to be slow inspite of using excess of oxidant (entry 3.8j). In case of fluorene derivatives, the reactivity depends on the nature of the substituent present (entries 3.8k-m). Fluorene gave the required fluorenone in excellent yield of 91%, whereas when bromine or amino groups are present on the aromatic ring, the yields were comparatively low. In case of 9H-fluoren-2-amine, it underwent chemoselective oxidation at the benzylic position and the corresponding amine oxidized product 2-nitro-9H-fluorene was not observed.
3.7a–m  

\[
\begin{align*}
\text{Ar} & \quad \text{R} \quad \text{D (10 mol%), Et₃N (10 mol%) TBHP (3.0 mmol), CH₃CN, 80 °C} \\
\text{3.7a–m} & \\
13 \text{ Examples} \\
\text{Yield = 34-95%}
\end{align*}
\]

\[\begin{align*}
\text{3.8a, 95%} & \\
\text{3.8b, 69%} & (84%)^b \\
\text{3.8c, 67%} & (82%)^c \\
\text{3.8d, 34%} & (48%)^c \\
\text{3.8e, 89%} & \\
\text{3.8f, 95%} & \\
\text{3.8g, 87%} & \\
\text{3.8h, 81%} & \\
\text{3.8i, 75%} & \\
\text{3.8j, 52%} & (67%)^c \\
\text{3.8k, 91%} & \\
\text{3.8l, 79%} & \\
\text{3.8m, 73%} & 
\end{align*}\]

\text{Scheme 3.6. N-heterocyclic carbene-catalyzed benzylic oxidation of alkylarenes}

3.2.4. NHC-Catalyzed Oxidative Benzylic sp³ C–H Bonds Adjacent to Heteroatom

Oxidation of benzylic sp³ C–H bond adjacent to nitrogen has been extensively explored as the method is essential for the synthesis of natural products as well as pharmaceuticals possessing heteroatoms. The higher reactivity of benzylic C–H bond adjacent to heteroatom like nitrogen and oxygen prompted us to widen the scope of this benzylic sp³ C–H bond activation to acyclic secondary amines \textit{viz.} N-substituted benzylamines (Scheme 3.7).
The required \(N\)-benzylamines 3.9 were synthesized from aryl aldehydes 3.11 and aryl or alkyl amines 3.12 via reductive amination. Various \(N\)-benzylamines were synthesized with good to excellent yield shown in Scheme 3.8.

Various \(N\)-benzylamines 3.9 were converted into corresponding benzamides 3.10 under the optimized reaction condition (Scheme 3.9). Initially, various \(N\)-benzyylanilines were made to undergo the aforementioned reaction. The corresponding \(N\)-benzoylaniline was obtained in moderate to good yields irrespective of the nature of the substituents present in benzyl part (3.10a-3.10d). The reaction gave moderate yield.
when \(N\)-benzyl-4-chloroaniline was used as the substrate (3.10e). When the reaction was performed with heteroaromatic \(N\)-(thiophen-2-ylmethyl)aniline, the required product \(N\)-phenylthiophene-2-carboxamide (3.10f) was obtained in 76% yield. When dibenzylamine was taken, the corresponding \(N\)-benzylbenzamide was obtained in 68% (3.10g). In similar lines, \(N\)-butylbenzamide and \(N\)-cyclohexylbenzamide were achieved in good yields from their respective amines \textit{viz.} \(N\)-benzylbutan-1-amine and \(N\)-benzylcyclohexylamine (3.10h and 3.10i).

\[
\begin{array}{c}
\text{Ar}^+\text{N}^+\text{R}^+ \xrightarrow{D (10 \text{ mol}%), \text{Et}_3\text{N} (10 \text{ mol}%)}, \text{TBHP (3.0 mmol), CH}_3\text{CN, }80^\circ\text{C, 15 h, Yields refers to isolated yields.}}
\end{array}
\]

\textbf{Scheme 3.9.} NH₃-catalyzed benzylic oxidation of \(N\)-benzylamines

3.2.5. Synthesis of 3\textit{H}-Quinazolin-4-ones \textit{via} NHC-Catalysis

3\textit{H}-Quinazolin-4-ones show broad range of biological and pharmaceutical activities including anti-hypertensive,\textsuperscript{16a, b} antidiabetic,\textsuperscript{16c} antibacterial,\textsuperscript{16d} anticonvulsant,\textsuperscript{16e} antitumor,\textsuperscript{16f, g} central nervous system (CNS) depressants,\textsuperscript{16h, i} diuretic
activity$^{16j}$ and calcium receptor antagonist.$^{16k}$ Selected examples of bioactive quinazolin-4ones are shown in Figure 3.1.

![Figure 3.1. Selected bioactive compounds bearing quinazolinone moiety](image)

Traditionally, $3H$-quinazolin-4-ones were prepared by coupling 2-aminobenzoic acid or its derivatives with acylchloride or carboxylic acid anhydride followed by further treatment with amine.$^{17}$ Recently, other synthetic routes have developed for the synthesis of $3H$-quinazolin-4-ones.$^{18}$ However, these methods have several drawbacks, in terms of substrate scope, yields and the reaction conditions. Thus, an extension of our NHC-catalyzed benzylic oxidation procedure for the synthesis of $3H$-quinazolin-4-ones could be an elegant and useful synthetic strategy.

![Scheme 3.10. Synthetic route for the preparation of $3H$-quinazolin-4-ones](image)
The synthetic strategy for the preparation of 3\(H\)-quinazolin-4-ones is synthesized as described in Scheme 3.10. The primary coupling partner 2-((alkylamino)methyl)aniline 3.20 was synthesized from 2-nitrobenzaldehyde 3.17 via reductive amination with amines 3.18 to yield compound 3.19.\(^{15a}\) Further reduction of 3.19 with Pd/C and NaBH\(_4\) yielded 3.20a-e (Scheme 3.11).\(^{15b}\)

![Scheme 3.11. Synthesis of 2-((alkylamino)methyl)anilines 3.20a-e](image)

Treatment of compound 3.20 with arylaldehydes 3.21 in ethanol at ambient temperature afforded the required precursors 3.22 in good yields. The optimized reaction conditions for the benzylic oxidation was then employed for the synthesis of 3\(H\)-quinazolin-4-ones 3.23 starting from compounds 3.22 and the results are shown in Scheme 3.12. A variety of 3-alkyl-1,2,3,4-tetrahydroquinazolines 3.22 was converted into the corresponding 2,3-disubstituted-3\(H\)-quinazolin-4-ones 3.23. Irrespective of the nature of the substituents on the 2-aryl moiety the reaction proceeded well to furnish the products 3.23a-e in good yields. But when there is phenyl derivatives on 3\(^{rd}\) position of the ring, the reaction failed to give corresponding carbonyl derivatives (3.23f-3.23h).
The reaction also tolerated phenethyl amine and variation of different aryl aldehydes with phenethyl amine gave the products 3.23i-3.23l in good yields. Importantly, the developed protocol was employed for the synthesis of a potent calcium receptor antagonist NPS 53574 3.23l.16k

Scheme 3.12. Synthesis of 3H-quinazolin-4-ones via NHC-catalyzed oxidation

3.2.6. Density Functional Theory (DFT) Study

To get an insight on the role of NHC as catalyst in the oxidation of diphenylmethane using TBHP as oxidant, a DFT calculation using M06-2X/6-31g (d,p) level of theory was carried out. In the control experiments, the facile conversion of diphenylmethane to the intermediate diphenylmethanol only in the presence of NHC catalyst was observed. Hence only the first step of catalytic reaction was considered for
the DFT studies. The optimized structure of the reactants, intermediates, and products without geometrical constraints were shown in Figure 3.2.

![Figure 3.2. Optimized geometries of all the stationary points involved in the NHC-catalyzed oxidation of diphenylmethane](image)

To understand the role of NHC for the reaction, the strategy of Tang et al. was followed, where they used the Global reactivity index.\(^{19}\) In similar lines, the chemical hardness, global electrophilicity and nucleophilicity for the NHC (Cat), diphenylmethane (Sub), intermediate (I1), oxidant (Oxd) and the transition state (TS1) formed during the course of the reaction were computed. The calculated results for the nucleophilic index were shown in Table 3.3. Nucleophilic index of the Sub before and after the attack of Cat has increased remarkably. The NBO analysis shows that charge on the carbene carbon of Cat slightly increased after attacking the Sub (0.133e to
0.153e) possibly the reason for the H atom transfer from Sub to Cat. There is lowering of HOMO-LUMO energy gap from 8.51 to 6.18 eV as Sub forms I1, which was substantiated by the increase in reactivity of the I1 as compared to the Cat and Sub.

Table 3.3. Energy of HOMO (E_H, in a.u.), energy of LUMO (E_L, in a.u.), Electronic chemical potential μ (a.u.), chemical hardness η (a.u.), global electrophilicity ω (eV) and global nucleophilicity indices (eV)

<table>
<thead>
<tr>
<th></th>
<th>(E_H) (a.u)</th>
<th>(E_L) (a.u)</th>
<th>(μ) (a.u)</th>
<th>(η) (a.u)</th>
<th>(ω) (eV)</th>
<th>N (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub</td>
<td>-0.281</td>
<td>0.031</td>
<td>-0.125</td>
<td>0.313</td>
<td>0.67</td>
<td>2.95</td>
</tr>
<tr>
<td>Cat</td>
<td>-0.270</td>
<td>0.028</td>
<td>-0.121</td>
<td>0.299</td>
<td>0.66</td>
<td>3.24</td>
</tr>
<tr>
<td>TS1</td>
<td>-0.189</td>
<td>0.023</td>
<td>-0.083</td>
<td>0.212</td>
<td>0.44</td>
<td>5.44</td>
</tr>
<tr>
<td>I1</td>
<td>-0.203</td>
<td>0.026</td>
<td>-0.089</td>
<td>0.229</td>
<td>0.46</td>
<td>5.06</td>
</tr>
<tr>
<td>Oxd</td>
<td>-0.306</td>
<td>0.107</td>
<td>-0.100</td>
<td>0.413</td>
<td>0.33</td>
<td>2.26</td>
</tr>
</tbody>
</table>

To understand the reason for titled reaction to occur at high temperature, the potential energy surface was computed, which is shown in Figure 3.3. The formation of TS1 has an activation barrier of 56.65 kcal mol\(^{-1}\) which may be due to the formation of three membered ring between hydrogen, benzylic carbon and carbene carbon. The 1,2-shift of H atom from benzylic carbon to carbene carbon gives I1 with an energy release of about 46.09 kcal mol\(^{-1}\). The second step involves a simultaneous reaction in which TBHP (Oxd) abstracts H atom from carbene carbon of I1, and transfer of hydroxyl group to benzylic carbon of the Sub. This leads to the regeneration of NHC from I1 yielding diphenylmethanol 2 and t-butylalcohol TBA via TS2. The computed energy barrier for the above step was 4.74 kcal mol\(^{-1}\), much lower than the first step. Thus in this reaction, the formation of I1 can be the rate determining step as shown in Figure 3.3. The reaction did not proceed at room temperature possibly due to high free energy barrier for the formation of Intermediate.
The natural bond orbital (NBO) charge values on the C−H bond for various species involved in the reactions are summarized in Table 3.4. The negative charge on the benzylic carbon of Sub decreases from -0.494 to -0.354 e, which readily facilitates the attack of hydroxyl group of TBHP oxidant, resulting in the lowering of energy barrier as illustrated in Figure 3.3.

Table 3.4. Values of NBO charges (e) on atoms C_{carbene}, C_{ben} H_{1} and H of Sub, Cat, TS1 and TS2

<table>
<thead>
<tr>
<th></th>
<th>C−H_{1}</th>
<th>C−H_{2}</th>
<th>C_{carb}</th>
<th>C_{ben}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub</td>
<td>0.260</td>
<td>0.260</td>
<td>-</td>
<td>-0.494</td>
</tr>
<tr>
<td>Cat</td>
<td>-</td>
<td>-</td>
<td>0.133</td>
<td>-</td>
</tr>
<tr>
<td>TS1</td>
<td>0.281</td>
<td>0.271</td>
<td>0.153</td>
<td>-0.354</td>
</tr>
<tr>
<td>TS2</td>
<td>0.225</td>
<td>0.493</td>
<td>0.135</td>
<td>0.0890</td>
</tr>
</tbody>
</table>
To confirm that the reaction occurs through **TS1**, Atom in molecule (AIM) analysis on the transition state structures was carried out. Topology analysis of electron density is a main component of Bader’s AIM theory.\textsuperscript{20} In Figure 3.4, the topological diagram for **TS1** is provided with the bond critical points along the bond paths. Correspondingly, the electron densities ($\rho_{bcp}$), Lagrangian kinetic energies ($G_b$), potential energy densities $V_b$, energy densities ($H_b$), and Laplacian of electron densities ($\nabla^2 \rho$) at the bond critical points (BCPs) along the bond paths are summarized in Table 3.5.

![Figure 3.4. Bond critical points (BCPs, colored red) along the bond paths (colored white) for topological analysis of **TS1**](image)

The additional stabilization to favor the transition state **TS1** happens through a network of noncovalent interactions (NCI) such as CH---$\pi$ (methyl C–H bond interaction with aromatic $\pi$ cloud), lp---$\pi$ (lone pair of nitrogen atom with aromatic $\pi$ cloud) and $\pi$---$\pi$ between the phenyl rings of catalyst and the substrate. These
interactions lead to a conformation which facilitates the Hydrogen transfer in TS1. By taking into account of various electron density distributions and NCI, it was concluded that the catalyst can improve the efficiency of substrate reactivity by the formation of I1 through TS1.

**Table 3.5. Summary of Types of Interaction, \( \rho_{\text{bcp}} \), \( G_b \), \( V_b \), \( H_b \), and \( \nabla^2 \rho \) at the Bond Critical Points (BCPs) along the Bond Paths in TS1**

<table>
<thead>
<tr>
<th>BCP index</th>
<th>Type of interaction</th>
<th>( \rho_{\text{bcp}} \times 10^{-1} )</th>
<th>( \nabla^2 \rho \times 10^{-1} )</th>
<th>( G_b \times 10^2 )</th>
<th>( V_b \times 10^2 )</th>
<th>( H_b \times 10^{-3} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>π…. Π</td>
<td>0.0093</td>
<td>-0.0071</td>
<td>0.0059</td>
<td>0.0047</td>
<td>-0.0011</td>
</tr>
<tr>
<td>2</td>
<td>CH…. π</td>
<td>0.0066</td>
<td>-0.0057</td>
<td>0.0045</td>
<td>0.0034</td>
<td>-0.0011</td>
</tr>
<tr>
<td>3</td>
<td>CH…. π</td>
<td>0.0105</td>
<td>-0.0089</td>
<td>0.0073</td>
<td>0.0058</td>
<td>-0.0015</td>
</tr>
<tr>
<td>4</td>
<td>CH…. π</td>
<td>0.0059</td>
<td>-0.0042</td>
<td>0.0034</td>
<td>0.0026</td>
<td>-0.0008</td>
</tr>
<tr>
<td>5</td>
<td>CH…. π</td>
<td>0.0110</td>
<td>-0.0087</td>
<td>0.0075</td>
<td>0.0062</td>
<td>-0.0012</td>
</tr>
<tr>
<td>6</td>
<td>lp…. π</td>
<td>0.2737</td>
<td>0.2013</td>
<td>0.1480</td>
<td>0.3494</td>
<td>0.4974</td>
</tr>
<tr>
<td>7</td>
<td>lp…. π</td>
<td>0.2750</td>
<td>0.1909</td>
<td>0.1933</td>
<td>0.3842</td>
<td>0.5775</td>
</tr>
</tbody>
</table>

### 3.2.7. Control Experiments to Arrive at Plausible Mechanism

In order to arrive at plausible reaction mechanism, several control reactions were performed as shown in Scheme 3.13. The reaction of diphenylmethane in the absence of NHC precatalyst D and in presence of oxidant (Oxd) gave 7% of the desired product (eq. 1). Similarly, in absence of oxidant, only 4% of carbonyl product was observed (eq. 2). These blank reactions emphasize the role of both NHC and oxidant for this benzylic C–H activation. When diphenylmethanol (R2) was subjected to benzylic oxidation with aq.TBHP in absence of NHC, quantitative formation of benzophenone was observed (eq. 3). When the reaction was interrupted, intermediate alcohol (R2) can be isolated and analyzed.
Scheme 3.13. Control experiments for benzylic sp$^3$ C–H bond oxidation

3.2.8. Plausible Mechanism for NHC-Catalyzed Oxidation of Benzylic sp$^3$ C–H Bonds

Based on the aforementioned theoretical studies and the control experiments, the plausible mechanism was proposed as shown in Scheme 3.14. The initial step is the generation of free carbene \textbf{Cat} from imidazolium salt precursor \textbf{D} by treating with base. NHC activates the benzylic position of the alkylarene to generate intermediate \textbf{I1} through the transition state \textbf{TS1}. The intermediate \textbf{I1} further reacts with TBHP (Oxd) to generate secondary alcohol \textbf{R2}, which was isolated and confirmed by $^1$H-NMR. \textbf{R2} on oxidation with TBHP generates the desired product along with the regeneration of free carbene, thus making this reaction catalytic.
3.3. Conclusions

In conclusion, a novel method for benzylic sp³ C–H bond activation of alkylarenes and N-benzylamines was developed under metal-free conditions by oxidative NHC catalysis. The reaction was tolerant to various alkylarenes and N-benzylamines to furnish the corresponding carbonyl compounds in good to excellent yields. This oxidative strategy was extended to the synthesis of an important bioactive 3H-quinazolin-4-ones, including NPS 53574, a potent calcium receptor antagonist. The theoretical studies shows that benzylic C–H bond activation takes place through
nucleophilic attack of carbene on the benzylic carbon of the substrate with hydrogen transfer.

3.4. Experimental Section

3.4.1. General Information

For general information see Section 2.41 of Chapter 2.

3.4.2. General Procedure for Benzylic Oxidation of Alkylarenes (3.8a-m)

A mixture of NHC (0.1 mmol) and base (0.1 mmol) in CH$_3$CN (2 mL) was stirred at 25 °C for 30 min. To this solution, alkylarene 3.7 (1.0 mmol) followed by 70% aq.TBHP (3.0 mmol) was added and stirring was continued at 80 °C for 24 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was evacuated in vacuum, washed with water and extracted with ethyl acetate. The resultant extract was washed with brine solution and dried over anhydrous Na$_2$SO$_4$. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography using hexane/ethyl acetate mixture.

3.4.3. Characterization Data for the Products (3.8a-m)

**Benzophenone (3.8a):**$^{13d}$

Appearance: Colorless solid.

Isolated yield: 95% (172 mg).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.72 (dd, $J = 5.1, 3.3$ Hz, 2H), 7.54-7.47 (m, 1H), 7.43-7.36 (m, 2H).
$^{13}$C NMR (75 MHz, CDCl$_3$): δ 196.8, 137.6, 132.4, 130.1, 128.3.

**Acetophenone (3.8b):**$^{13}$d

- Appearance: Colorless liquid.
- Isolated yield: 84% (101 mg).

$^1$H NMR (300 MHz, CDCl$_3$): δ 8.01-7.94 (m, 2H), 7.61-7.54 (m, 1H), 7.47 (m, 2H), 2.62 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 198.0, 137.0, 133.1, 128.5, 128.2, 26.5.

**3,4-Dihyronaphthalen-1(2H)-one (3.8c):**$^{13}$d

- Appearance: Colorless oil.
- Isolated yield: 82% (119 mg).

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.96 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.40 (m, 1H), 7.28-7.13 (m, 2H), 2.90 (t, $J =$ 6.0 Hz, 2H), 2.59 (t, $J =$6.0 Hz, 2H), 2.13-1.99 (m, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 198.3, 144.5, 133.4, 132.5, 128.8, 127.0, 126.5, 39.1, 29.6, 23.2.

**2,3-Dihydro-1H-inden-1-one (3.8d):**$^{13}$d

- Appearance: Colorless liquid.
- Isolated yield: 48% (57 mg).

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.69 (d, $J =$ 7.8 Hz, 1H), 7.52 (m, 1H), 7.44-7.36 (m, 1H), 7.33-7.26 (m, 1H), 3.08 (d, $J =$ 6.0 Hz, 2H), 2.67-2.54 (m, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 207.1, 155.2, 137.2, 134.6, 127.3, 126.7, 123.7, 36.2, 25.8.

**Anthracene (3.8e):**$^{21}$

- Appearance: Colorless solid.
- Isolated yield: 89% (158 mg).
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.43 (s, 1H), 8.00 (dd, $J = 6.3, 3.3$ Hz, 2H), 7.46 (dd, $J = 6.6, 3.3$ Hz, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 131.7, 128.2, 126.2, 125.4.

$4H$-Xanthenc-9(9$H$)-one (3.8f):$^{13d}$

\[
\text{Appearance: Colorless solid.}
\]

\[
\text{Isolated yield: 95% (188 mg).}
\]

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.38-8.31 (dd, $J = 9.0$ Hz, 3.0 Hz, 1H), 7.72 (m, 1H), 7.53-7.46 (m, 1H), 7.43-7.33 (m, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 177.2, 156.1, 134.8, 126.7, 123.9, 121.8, 118.0.

Isocroman-1-one (3.8g):$^{13d}$

\[
\text{Appearance: Colorless solid.}
\]

\[
\text{Isolated yield: 87% (128 mg).}
\]

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.09 (d, $J = 7.8$ Hz, 1H), 7.55 (t, $J = 7.2$ Hz, 1H), 7.40 (t, $J = 7.5$ Hz, 1H), 7.27 (d, $J = 7.5$ Hz, 1H), 4.54 (t, $J = 6.0$ Hz, 2H), 3.07 (t, $J = 6.0$ Hz, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 165.2, 139.6, 133.7, 130.2, 127.6, 127.3, 125.2, 67.4, 27.7.

Isobenzofuran-1(3$H$)-one (3.8h):$^{13d}$

\[
\text{Appearance: Colorless liquid.}
\]

\[
\text{Isolated yield: 81% (108 mg).}
\]

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.93 (d, $J = 7.5$ Hz, 1H), 7.75-7.66 (m, 1H), 7.54 (dd, $J = 12.0, 7.5$ Hz, 2H), 5.34 (s, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 171.2, 146.6, 134.1, 129.0, 125.5, 122.2, 69.7.
3,4-Dihydroisoquinolin-1(2H)-one (3.8i):\textsuperscript{22}

\[ \text{Appearance: Light yellow oil.} \]
\[ \text{Isolated yield: 75\% (110 mg).} \]
\[ ^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta 8.34 (s, 1H), 7.39-7.32 (m, 1H), 7.31-7.24 (m, 2H), 7.16 (d, } J = 7.5 \text{ Hz, 1H), 3.82-3.70 (td, } J = 9.0 \text{ Hz, 3.0 Hz, 2H), 2.80-2.71 (d, } J = 6.0 \text{ Hz, 2H).} \]
\[ ^13\text{C NMR (75 MHz, CDCl}_3\text{): } \delta 160.4, 136.3, 131.1, 128.5, 127.4, 127.3, 127.1, 47.3, 25.0. \]

Quinoline (3.8j):\textsuperscript{13d}

\[ \text{Appearance: Light yellow oil.} \]
\[ \text{Isolated yield = 67\% (86 mg).} \]
\[ ^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta 8.92 (dd, } J = 4.2, 1.8 \text{ Hz, 1H), 8.22-8.06 (m, 2H), 7.83 (dd, } J = 8.1, 1.2 \text{ Hz, 1H), 7.73 (m, 1H), 7.55 (m, 1H), 7.41 (dd, } J = 8.4, 4.2 \text{ Hz, 1H).} \]
\[ ^13\text{C NMR (75 MHz, CDCl}_3\text{): } \delta 150.3, 148.1, 136.2, 129.5, 129.3, 128.3, 127.8, 126.6, 121.1. \]

9H-Fluoren-9-one (3.8k):\textsuperscript{13d}

\[ \text{Appearance: Light yellow crystalline solid.} \]
\[ \text{Isolated yield: 91\% (163 mg).} \]
\[ ^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta 7.66 (d, } J = 7.5 \text{ Hz, 2H), 7.49 (dd, } J = 6.9, 0.9 \text{ Hz, 4H), 7.40-7.20 (m, 2H).} \]
\[ ^13\text{C NMR (75 MHz, CDCl}_3\text{): } \delta 193.9, 144.4, 134.7, 134.1, 129.1, 124.3, 120.3. \]

2-Bromo-9H-fluoren-9-one (3.8l):\textsuperscript{13d}

\[ \text{Appearance: Yellow crystalline solid.} \]
\[ \text{Isolated yield: 79\% (204 mg).} \]
\( ^1 \)H NMR (300 MHz, CDCl\(_3\)): \( \delta 7.69 \) (s, 1H), 7.56 (dd, \( J = 15.3, 7.5 \) Hz, 2H), 7.44 (d, \( J = 3.9 \) Hz, 2H), 7.32 (d, \( J = 7.8 \) Hz, 1H), 7.28-7.21 (m, 1H).

\( ^{13} \)C NMR (75 MHz, CDCl\(_3\)): \( \delta 192.4, 143.7, 143.0, 137.1, 135.8, 135.0, 133.7, 129.4, 127.6, 124.6, 122.9, 121.7, 120.4. \)

**2-Amino-9H-fluoren-9-one (3.8m)**:\(^{23}\)

\[
\text{Appearance: Yellow coloured oil.}
\]

\[
\text{Isolated yield: 73\% (136 mg).}
\]

\( ^1 \)H NMR (300 MHz, CDCl\(_3\)): \( \delta 7.49 \) (d, \( J = 7.2 \) Hz, 1H), 7.43-7.23 (m, 2H), 7.20 (d, \( J = 6.9 \) Hz, 1H), 7.16-7.00 (td, \( J = 7.2 \) Hz, 1.2 Hz, 1H), 6.89 (d, \( J = 2.4 \) Hz, 1H), 6.65 (dd, \( J = 7.8, 2.4 \) Hz, 1H), 3.82 (s, 2H).

\( ^{13} \)C NMR (75 MHz, CDCl\(_3\)): \( \delta 194.4, 147.6, 145.6, 135.9, 134.8, 134.6, 134.0, 127.2, 124.2, 121.4, 119.6, 119.1, 111.0. \)

### 3.4.4. General Procedure for the Preparation of N-Benzylamines (3.9 a-i)\(^ {16} \)

\[
\begin{array}{c}
\text{O} \\
\text{Ar} \\
3.11a-i
\end{array}
+ 
\begin{array}{c}
\text{R-NH}_2 \\
3.12a-i
\end{array}
\xrightarrow{\text{NaBH}_4 (1.5 \text{ mmol)}}
\begin{array}{c}
\text{Ar} \\
\text{N}
\end{array}_{\text{R}}
\begin{array}{c}
3.9a-i
\end{array}
\quad \text{Yield = 82-95%}
\]

A solution of aldehyde 3.11 (1.0 mmol) and amine 3.12 (1.0 mmol) in CH\(_3\)OH (1 mL) was stirred for 4 h. Formation of imine was monitored by TLC and the reaction mixture was cooled in ice-cold condition followed by the addition of NaBH\(_4\) in portion wise. The reaction was further stirred for 12 h at room temperature and the formation of amine was observed using TLC. The reaction mixture was concentrated and the residue was washed with water and extracted with ethyl acetate. The resulting extract was washed with brine solution, dried over Na\(_2\)SO\(_4\) and concentrated under vacuum to yield the crude product, which was purified by column chromatography.
3.4.5. General Procedure for the Preparation of Benzamides (3.10a-i)

A mixture of NHC (0.1 mmol) and base (0.1 mmol) in CH$_3$CN (2 mL) was stirred at 25 °C for 30 min. To this solution, benzylamine 3.9 (1.0 mmol) followed by 70% aq.TBHP (3.0 mmol) was added and stirring was continued at 80 °C for 15 h. Progress of the reaction was monitored by TLC and after the completion of the reaction, the solvent was evacuated under pressure, washed with water and extracted with ethyl acetate. The extract was then washed with brine solution and dried over anhydrous Na$_2$SO$_4$. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography using hexane/ethyl acetate mixture.

3.4.6. Characterization Data for the Products (3.10a-i)

**N-Phenylbenzamide (3.10a):**

- Appearance: Colorless solid.
- Isolated yield: 73% (143 mg).

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.80 (d, J = 7.2 Hz, 3H), 7.58 (d, J = 8.1 Hz, 2H), 7.52-7.45 (m, 1H), 7.41 (t, J = 7.2 Hz, 2H), 7.30 (t, J = 7.8 Hz, 2H), 7.09 (t, J = 7.2 Hz, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 165.8, 137.9, 135.0, 131.9, 129.1, 128.8, 127.0, 124.6, 120.21.
4-Methyl-N-phenylbenzamide (3.10b):\(^4\)

Appearance: Colorless solid.

Isolated yield: 70\% (147 mg).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.76 (s, 1H), 7.72-7.67 (m, 2H), 7.60-7.53 (m, 2H), 7.33-7.26 (m, 2H), 7.23-7.19 (m, 2H), 7.11-7.04 (m, 1H), 2.35 (s, 3H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 165.7, 142.4, 138.0, 132.1, 129.5, 129.1, 127.0, 124.4, 120.2, 21.5.

4-Chloro-N-phenylbenzamide (3.10c):\(^4\)

Appearance: Colorless solid.

Isolated yield: 82\% (189 mg).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.75 (d, \(J = 8.4\) Hz, 2H), 7.56 (d, \(J = 7.8\) Hz, 2H), 7.40 (d, \(J = 8.4\) Hz, 2H), 7.31 (t, \(J = 7.8\) Hz, 2H), 7.10 (t, \(J = 7.2\) Hz, 1H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 164.7, 142.4, 138.2, 137.0, 133.2, 128.9, 128.2, 128.0, 123.7, 120.3.

4-Methoxy-N-phenylbenzamide (3.10d):\(^4\)

Appearance: Colorless solid.

Isolated yield: 77\% (174 mg).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.84 (dt, \(J = 5.1, 3.0\) Hz, 2H), 7.80 (s, 1H), 7.72-7.58 (m, 2H), 7.37 (dd, \(J = 10.8, 5.1\) Hz, 2H), 7.14 (t, \(J = 7.5\) Hz, 1H), 7.05-6.94 (m, 2H), 3.87 (s, 3H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 165.3, 162.5, 138.1, 129.1, 128.9, 127.1, 124.4, 120.2, 114.0, 55.5.
N-(4-Chlorophenyl)benzamide (3.10e):²⁴

Appearance: Colorless solid.
Isolated yield: 69% (159 mg).

\[
^1H \text{ NMR (300 MHz, CDCl}_3\): } \delta 8.08-7.98 (m, 1H), 7.81-7.77 (m, 2H), 7.56-7.51 (m, 2H), 7.50-7.40 (m, 3H), 7.30-7.23 (m, 2H).
\]

\[
^{13}C \text{ NMR (75 MHz, CDCl}_3\): } \delta 165.7, 136.5, 134.6, 132.1, 129.1, 128.9, 128.5, 127.0, 121.4.
\]

N-Phenylthiophene-2-carboxamide (3.10f):²⁵

Appearance: Colorless solid.
Isolated yield: 76% (154 mg).

\[
^1H \text{ NMR (300 MHz, CDCl}_3\): } \delta 7.76 (s, 1H), 7.58-7.51 (m, 3H), 7.46 (dd, J = 5.1, 1.2 Hz, 1H), 7.32-7.24 (m, 2H), 7.11-7.01 (m, 2H).
\]

\[
^{13}C \text{ NMR (75 MHz, CDCl}_3\): } \delta 160.0, 139.3, 137.6, 130.8, 129.1, 128.5, 127.8, 124.6, 120.3.
\]

N-Benzylbenzamide (3.10g):²⁶

Appearance: Colorless crystalline solid.
Isolated yield: 68% (143 mg).

\[
^1H \text{ NMR (300 MHz, CDCl}_3\): } \delta 7.79 (m, 2H), 7.54-7.24 (m, 8H), 6.43 (s, 1H), 4.65 (d, J = 12.0 Hz, 2H).
\]

\[
^{13}C \text{ NMR (75 MHz, CDCl}_3\): } \delta 167.5, 138.3, 134.4, 131.5, 128.8, 128.6, 127.9, 127.6, 127.0, 44.1.
\]

N-Butylbenzamide (3.10h):²⁶

Appearance: Colorless oil.
Isolated yield: 78% (138 mg).
\( ^1 \text{H NMR} \ (300 \text{ MHz}, \text{CDCl}_3) : \delta 7.81-7.73 \text{ (m, 2H)}, \ 7.51-7.41 \text{ (m, 3H)}, \ 6.16 \text{ (s, 1H)}, \ 3.46 \text{ (dd, } J = 12.9, 7.2 \text{ Hz, 2H)}, \ 1.61 \text{ (dt, } J = 14.7, 7.2 \text{ Hz, 2H)}, \ 1.41 \text{ (dt, } J = 14.1, 7.2 \text{ Hz, 2H)}, \ 0.96 \text{ (t, } J = 7.2 \text{ Hz, 3H}). \)

\( ^{13} \text{C NMR} \ (75 \text{ MHz, CDCl}_3) : \delta 167.7, \ 134.8, \ 131.3, \ 128.8, \ 126.9, \ 39.8, \ 31.7, \ 20.7, \ 13.8. \)

**N-Cyclohexylbenzamide (3.10i):**

![N-Cyclohexylbenzamide](image)

Appearance: Colorless oil.

Isolated yield: 73% (148 mg).

\( ^1 \text{H NMR} \ (300 \text{ MHz, CDCl}_3) : \delta 7.75 \text{ (d, } J = 7.2 \text{ Hz, 2H)}, \ 7.53-7.38 \text{ (m, 3H)}, \ 6.01 \text{ (s, 1H)}, \ 3.99 \text{ (dd, } J = 11.1, 7.2 \text{ Hz, 1H)}, \ 2.04 \text{ (d, } J = 9.0 \text{ Hz, 2H)}, \ 1.80-1.64 \text{ (m, 4H)}, \ 1.43 \text{ (d, } J = 12.3 \text{ Hz, 2H)}, \ 1.30-1.17 \text{ (m, 3H)}. \)

\( ^{13} \text{C NMR} \ (75 \text{ MHz, CDCl}_3) : \delta 166.8, \ 135.0, \ 131.2, \ 128.4, \ 127.0, \ 48.8, \ 33.1, \ 25.5, \ 25.0. \)

**3.4.7. General Procedure for the Synthesis of 2-((alkylamino)methyl)aniline 3.20**

![General Procedure Diagram](image)

To a solution of 2-nitrobenzaldehyde 3.17 (1.0 mmol) in CH\(_3\)OH (1 mL), alkylamine 3.18 (1.0 mmol) was added and stirred at room temperature for 2 h. After the imine formation was observed using TLC, the reaction mixture was cooled to ice cold condition and NaBH\(_4\) was added in portion wise. After completion of the reaction, as monitored by TLC, the reaction mixture was concentrated and the crude reaction mixture was washed with water and extracted with ethyl acetate. The resultant extract was washed with brine solution, dried over Na\(_2\)SO\(_4\) and concentrated under reduced
pressure to yield 3.19. The catalytic hydrogenation was achieved by dissolving 3.19 in 
CH₃OH (3 mL) and Pd/C (10 mol %) was added in portion-wise in ice-cold condition 
followed by NaBH₄. The reaction was stirred for 2 h and completion of reaction was 
monitored by TLC for the formation of 3.20. After completion of the reaction, the 
catalyst was removed by filtration and the filtrate was evaporated under reduced 
pressure. The crude mixture was washed with water and then extracted with ethyl 
acetate and the resulting extract was washed with brine solution, dried over Na₂SO₄ and 
concentrated under vacuum. The crude mixture was purified by column 
chromatography to yield the desired product 3.20 using hexane/ethyl acetate mixture.

3.4.8. Characterization Data for the Products (3.20a-e)

2-((Butylamino)methyl)aniline (3.20a):¹³d

\[
\begin{align*}
\text{Appearance: Colorless oil.} \\
\text{Isolated yield: 86\% (153 mg).}
\end{align*}
\]

¹H NMR (300 MHz, CDCl₃): δ 7.14-7.04 (m, 2H), 6.74-6.65 (m, 2H), 4.70 (s, 3H), 3.87 (s, 2H), 2.66 (t, J = 9.0 Hz, 2H), 1.57-1.47 (m, 2H), 1.38-1.25 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 146.6, 130.9, 129.2, 120.9, 118.2, 116.4, 50.7, 47.7, 30.4, 20.2, 13.8.

N-(2-Aminobenzyl)aniline (3.20b):¹³d

\[
\begin{align*}
\text{Appearance: Colorless solid.} \\
\text{Isolated yield: 82\% (162 mg).}
\end{align*}
\]

¹H NMR (300 MHz, CDCl₃): δ 7.72-7.67 (m, 2H), 7.60-7.53 (m, 3H), 7.09-7.01 (m, 2H), 6.98-6.62 (m, 2H), 4.59 (s, 2H), 3.00 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 160.7, 151.13, 142.4, 138.0, 133.9, 133.6, 130.4, 129.5, 122.5, 120.6, 68.1.
2-((Phenethylamino)methyl)aniline (3.20c):\textsuperscript{13d}

\begin{center}
\textbf{Appearance: Colourless oil.}
\end{center}

Isolated yield: 89\% (201 mg).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.35-7.23 (m, 4H), 7.22-7.01 (m, 3H), 6.67 (t, \(J = 6.0\) Hz, 2H), 3.89 (s, 2H), 3.82 (m, 2H), 3.78 (t, \(J = 9.3\) Hz, 2H), 3.32 (s, 3H).

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ 146.8, 140.0, 130.0, 129.3, 128.4, 128.2, 127.1, 123.7, 117.8, 115.8, 53.2, 52.2, 50.9.

\textsc{N-}(2-Aminobenzyl)-2-ethylaniline (3.20d):\textsuperscript{13d}

\begin{center}
\textbf{Appearance: Colorless oil.}
\end{center}

Isolated yield: 81\% (183 mg).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.18-7.11 (m, 2H), 7.05-6.94 (m, 2H), 6.77-6.58 (s, 2H), 6.48-6.22 (m, 2H), 4.58 (s, 2H), 3.21 (s, 3H), 2.97 (q, \(J = 7.2\) Hz, 2H), 2.02 (t, \(J = 9.0\) Hz, 3H).

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ 163.3, 160.5, 138.1, 133.5, 129.1, 128.9, 127.1, 124.4, 120.2, 114.0, 63.4, 55.5, 38.1.

\textsc{N-}(2-Aminobenzyl)-2-chloroaniline (3.20e):\textsuperscript{13d}

\begin{center}
\textbf{Appearance: White solid.}
\end{center}

Isolated yield: 85\% (197 mg).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.22-7.16 (m, 2H), 7.10-6.92 (m, 2H), 6.79-6.54 (s, 2H), 6.46-6.23 (m, 2H), 4.48 (s, 2H), 3.11 (s, 3H).

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ 162.7, 148.7, 136.5, 134.6, 132.1, 129.1, 128.9, 128.5, 127.0, 121.4, 68.1.
3.4.9. General Procedure for the Synthesis of 3-Alkyl-1,2,3,4-tetrahydroquinazolines (3.22 a-l)

![Reaction Scheme]

To a solution of 2-((alkylamino)methyl)aniline 3.20 in EtOH (2 mL), 1.0 mmol of aldehyde 3.21 was added and stirred at rt for 6 h. Formation of cyclized product 3.22 was observed by TLC. The reaction mixture was evaporated under reduced pressure to remove solvent and taken for the next step without further purification.

3.4.10. General Procedure for the Synthesis of 3H-Quinazolin-4 ones (3.23a-l)

![Reaction Scheme]

A mixture of NHC D (0.1 mmol) and Et₃N (0.1 mmol) in 2 mL of CH₃CN was stirred at 25 °C for 30 min. To this reaction mixture, 3-alkyl-1,2,3,4-tetrahydroquinazolines 3.22 was added followed by aq.TBHP (3.0 mmol) and stirred at 80 °C for 12 h. After completion of the reaction, as monitored by TLC, reaction mixture was concentrated and the crude mixture was washed with water and extracted with ethylacetate. The extract was washed with brine solution, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography using hexane/ethyl acetate mixture. All the 3H-quinazolin-4 ones 3.23 given below are synthesized using the general procedure.
3.4.11. Spectroscopic Data for the Products (3.23a-l)

3-Butyl-2-phenylquinazolin-4(3H)-one (3.23a):\(^{13d}\)

\[
\begin{align*}
\text{Appearance: Colorless crystalline solid.} \\
\text{Isolated yield: 69\% (191 mg).} \\
\text{\(^1\)H NMR (300 MHz, CDCl\textsubscript{3}):} \delta 8.26 \text{ (d, } J = 7.8 \text{ Hz, 1H),} \\
7.72-7.63 \text{ (m, 2H), 7.48-7.40 (m, 6H), 3.95-3.86 (m, 2H), 1.57-1.45 (m, 2H), 1.09 (dt, } J = 14.7, 7.5 \text{ Hz, 2H), 0.68 (t, } J = 7.2 \text{ Hz, 3H).} \\
\text{\(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}):} \delta 162.1, 156.2, 147.1, 135.6, 134.2, 129.8, 128.7, 127.8, \\
127.4, 126.9, 126.7, 45.7, 30.7, 19.9, 13.4.
\end{align*}
\]

3-Butyl-2-(p-tolyl)quinazolin-4(3H)-one (3.23b):\(^{27}\)

\[
\begin{align*}
\text{Appearance: Colorless crystalline solid.} \\
\text{Isolated yield: 75\% (219 mg).} \\
\text{\(^1\)H NMR (300 MHz, CDCl\textsubscript{3}):} \delta 8.13-8.04 \text{ (m, 1H), 7.56-} \\
7.44 \text{ (m, 2H), 7.27 (m, 1H), 7.19 (d, } J = 8.1 \text{ Hz, 2H), 7.09 (d, } J = 7.8 \text{ Hz, 2H), 3.81-} \\
3.71 \text{ (m, 2H), 2.22 (s, 3H), 1.41-1.31 \text{ (m, 2H), 0.96 (dq, } J = 14.7, 7.5 \text{ Hz, 2H), 0.55 (t, } J = 7.2 \text{ Hz, 3H).} \\
\text{\(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}):} \delta 162.3, 156.5, 147.3, 139.9, 134.2, 132.8, 129.4, 127.7, \\
127.4, 126.8, 126.7, 120.9, 45.8, 30.8, 21.4, 19.9, 13.5.
\end{align*}
\]

3-Butyl-2-(4-methoxyphenyl)quinazolin-4(3H)-one (3.23c):\(^{13d}\)

\[
\begin{align*}
\text{Appearance: Colorless crystalline solid.} \\
\text{Isolated yield: 76\% (234 mg).} \\
\text{\(^1\)H NMR (300 MHz, CDCl\textsubscript{3}):} \delta 8.34-8.25 \text{ (m, 1H), 7.77-} \\
7.66 \text{ (m, 2H), 7.49 (m, 3H), 7.05-6.95 \text{ (m, 2H), 4.07-3.95 \text{ (m, 2H), 3.88 (s, 3H), 1.59} } \\
(tt, J = 7.8, 6.6 \text{ Hz, 2H), 1.26-1.11 \text{ (m, 2H), 0.79 (t, } J = 7.2 \text{ Hz, 3H).} \\
\end{align*}
\]
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 162.3, 160.6, 156.2, 147.2, 134.2, 129.4, 128.0, 127.3, 126.8, 126.7, 120.8, 114.1, 55.4, 45.8, 30.7, 19.9, 13.5.

3-Butyl-2-(4-chlorophenyl)quinazolin-4(3H)-one (3.23d):$^{27}$

Appearance: Colorless crystalline solid.

Isolated yield: 81% (252 mg).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.29-8.22 (m, 1H), 7.73-7.61 (m, 2H), 7.49-7.38 (m, 5H), 3.94-3.85 (m, 2H), 1.50 (m, 2H), 1.20-1.08 (m, 2H), 0.72 (t, $J$ = 7.2 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 162.1, 155.2, 147.0, 136.1, 134.4, 134.0, 129.3, 129.1, 127.4, 127.2, 126.8, 120.9, 45.8, 30.8, 19.9, 13.5.

3-Butyl-2-(thiophen-2-yl)quinazolin-4(3H)-one (3.23e):$^{28}$

Appearance: Pale yellow oil.

Isolated yield: 67%, 190 mg).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.23 (dd, $J$ = 7.8, 0.6 Hz, 1H), 7.71-7.62 (m, 2H), 7.47 (dd, $J$ = 5.1, 0.9 Hz, 1H), 7.42 (m, 1H), 7.38 (dd, $J$ = 3.6, 0.9 Hz, 1H), 7.09 (dd, $J$ = 5.1, 3.6 Hz, 1H), 4.17-4.08 (m, 2H), 1.66 (dd, $J$ = 7.5, 5.1 Hz, 2H), 1.26 (dt, $J$ = 14.7, 7.5 Hz, 2H), 0.83 (t, $J$ = 7.5 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 162.2, 150.1, 147.1, 136.7, 134.3, 129.0, 128.8, 127.4, 127.3, 127.1, 126.8, 120.6, 45.9, 31.0, 20.0, 13.6.

3-Phenethyl-2-phenylquinazolin-4(3H)-one (3.23i):$^{13d}$

Appearance: Colorless crystalline solid.

Isolated yield: 75% (244 mg).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.41-8.31 (m, 1H), 7.78 (qd, $J$ = 8.4, 4.2 Hz, 2H), 7.59-7.43 (m, 4H), 7.42-7.31 (m, 2H), 7.19 (dd, $J$ = 4.8, 1.8 Hz,
3H), 6.88 (dd, J = 6.6, 3.0 Hz, 2H), 4.19 (dd, J = 9.0, 6.6 Hz, 2H), 2.92 (t, J = 9.0 Hz, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 162.2, 156.1, 147.2, 137.7, 135.3, 134.4, 129.8, 128.8, 128.6, 127.8, 127.5, 127.1, 126.7, 126.6, 47.6, 34.7.

2-(4-Methoxyphenyl)-3-phenethylquinazolin-4(3H)-one (3.23j):$^{29}$

![Structure](image)

Appearance: Colorless crystalline solid.

Isolated yield: 80% (284 mg).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.39-8.33 (m, 1H), 7.82-7.70 (m, 2H), 7.52 (m, 1H), 7.36-7.30 (m, 2H), 7.23-7.16 (m, 3H), 7.03-6.97 (m, 2H), 6.95-6.90 (m, 2H), 4.29-4.20 (m, 2H), 3.89 (s, 3H), 2.97-2.88 (t, J = 9.0 Hz, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 162.4, 160.7, 156.1, 147.2, 137.8, 134.4, 129.4, 128.8, 128.6, 127.8, 127.5, 126.9, 126.7, 128.6, 120.8, 114.1, 55.5, 47.6, 34.7.

2-(4-Chlorophenyl)-3-phenethylquinazolin-4(3H)-one (3.23k):$^{29}$

![Structure](image)

Appearance: Colorless crystalline solid.

Isolated yield: 86% (309 mg).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.37 (m, 1H), 7.79 (m, 1H), 7.71 (m, 1H), 7.55 (m, 1H), 7.49-7.44 (m, 1H), 7.44-7.42 (m, 1H), 7.26-7.24 (m, 1H), 7.24-7.14 (m, 4H), 6.94-6.84 (m, 2H), 4.25-4.14 (m, 2H), 2.98-2.88 (t, J = 9.0 Hz, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 162.1, 155.1, 147.0, 137.6, 136.0, 134.6, 133.7, 129.3, 129.0, 128.8, 128.7, 127.5, 127.3, 126.8, 120.9, 47.6, 34.6.

2-(Furan-2-yl)-3-phenethylquinazolin-4(3H)-one (3.23l):$^{13d}$

![Structure](image)

Appearance: Colorless crystalline solid.

Isolated yield: 69% (218 mg).
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.34 (d, $J = 8.1$ Hz, 1H), 7.84-7.71 (m, 2H), 7.68 (s, 1H), 7.57-7.47 (m, 1H), 7.34-7.22 (m, 5H), 7.11 (d, $J = 3.3$ Hz, 1H), 6.63 (dd, $J = 3.3$, 1.8 Hz, 1H), 4.45 (dd, $J = 9.6$, 6.9 Hz, 2H), 3.13 (t, $J = 9.0$ Hz, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 162.2, 147.9, 147.4, 146.2, 144.2, 138.2, 134.4, 128.8, 128.7, 127.6, 127.2, 126.8, 126.7, 120.8, 115.4, 112.1, 47.1, 35.2.

**Diphenylmethanol (III):**

![Structure of Diphenylmethanol](image)

Appearance: Colorless crystalline solid.

Isolated yield: 98% (180 mg).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.32 (d, $J = 1.8$ Hz, 1H), 7.31-7.27 (m, 4H), 7.27-7.22 (m, 3H), 7.22-7.15 (m, 2H), 5.77 (s, 1H), 2.22 (s, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 143.9, 128.6, 127.6, 126.7, 76.2.

### 3.4.12. Computational Details

The DFT studies were carried out using M06-2X functional as implemented in Gaussian 09.$^{30}$ M06-2X functional is proved to be efficient and reliable for organic systems.$^{31}$ All the reactant, intermediates and product structures were energy minimized using 6-31g (d, p) basis in the acetonitrile solvent simulated by the integral equation formulism polarizable continuum model (IEF-PCM). There is no significant effect of solvent on energetics. Harmonic frequency analysis was carried out at the same level of theory to confirm optimized geometry as minima with no negative frequency, or transition state structures with one negative frequency. Natural bond orbital (NBO) analyses were performed with the same level of theory to assign atomic charges. To know the role of NHC (Cat) in C–H activation, the nucleophilicity index (N) and electrophilicity index ($\omega$) were calculated and analysed as global reactivity indices.
Specifically, the nucleophilicity index (N) introduced by Domingo and co-workers can be used to estimate the global nucleophilicity index, which is based on HOMO energies obtained within the Kohn–Sham scheme\textsuperscript{32a} and defined as $N = E_{\text{HOMO(Nu)}} - E_{\text{HOMO(TCE)}}$. In the nucleophilicity scaling, tetracyanoethylene (TCE) is taken as a reference to compute the nucleophilicity of organic compounds.\textsuperscript{32b} The global electrophilicity character of a molecule is measured by the electrophilicity index, $\omega$, following equation, $\omega = \mu^2/2\eta$, in terms of the electronic chemical potential $\mu$ and the chemical hardness $\eta$. Both quantities may be obtained in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, $E_H$ and $E_L$, as $\mu = (E_H + E_L)/2$ and $\eta = E_L - E_H$. 
3.5. Representative Spectra

$^1$H and $^{13}$C NMR Spectra of Compounds

9H-xanthen-9-one

3.8f
3.6. References


