4 Introduction

The present chapter deals with the catalytic application of Pd(NHC)Cl$_2$ complex in the regioselective C–H thiolation of 1-aryl-3-methyl-1H-pyrazol-5(4H)-ones using aryl thiols. The protocol was found to be simple, efficient and highly regioselective to afford the thiolation products in good to excellent yields. The structures of all the synthesized compounds have been well characterized by elemental analysis, FT-IR, NMR and mass spectrometry.

4.1 Regioselective C–H thiolation

Recently, the construction of C=S bond via direct activation of a C–H bond is one of the central themes in organic synthesis.$^1$ Great efforts have been made to develop new C–S bond-forming reactions.$^2,^3$ In this context, transition-metal-catalyzed regioselective C–H thiolation [sulfonylation] reactions have drawn much attention because aryl/hetero aryl sulfides are ubiquitous structural motifs, frequently found in biologically and pharmaceutically active compounds that are used to treat cancer, asthma, Alzheimer’s and Parkinson’s disease.$^4,^5$ They have also been approved as anti-HIV,$^5$ anti-inflammatory (AZD4407)$^6$ and agonists of GPR109A$^7$ (Figure 4.1).

**Figure 4.1** Pharmacologically active aryl/hetero aryl sulfides

Complexes and salts of nickel,$^6,^8$ copper,$^{11-13}$ palladium$^{14-18}$ and silver$^{19,20}$ have been employed as the efficient catalysts to synthesize this type of compounds using
C–H thiolation reactions. Among them, palladium catalyzed chelation-directed regioselective C–H thiolation reactions have attracted much interest due to its better efficacy and high turnover numbers.\textsuperscript{18, 21} Some of the recent reports for the transition-metal-catalyzed C–H thiolation reactions are described below.

Chen, Liu and co-workers developed an efficient nickel-catalyzed protocol for C–S cross-coupling through the regioselective thiolation of 2-aryl-1,2,3-triazole N-oxide C–H bonds using aryl or alkyl thiols or diphenyl disulfides as the thiolating agents (Scheme 4.1).\textsuperscript{6}

\textbf{Scheme 4.1} Nickel-catalyzed regioselective thiolation of 2-aryl-1,2,3-triazole N-oxide

\[
\text{NiSO}_4 \quad (\text{5 mol\%}) \quad \text{DMEDA, C}_{2}\text{H}_2\text{CO}_3 \quad \text{DMSO} \quad 60^\circ \text{C}, \text{12 h}
\]

Yang \textit{et. al.} developed an efficient nickel chloride-catalyzed and benzoic acid-promoted direct thiolation/sulfenylation of unactivated arenes using removable 2-(pyridine-2-yl)-isopropylamine as a directing group through the sp\textsuperscript{2} C–H bond functionalization process (Scheme 4.2).\textsuperscript{10}

\textbf{Scheme 4.2} NiCl\textsubscript{2}-catalyzed and benzoic acid-promoted direct thiolation/sulfenylation

Ranjit \textit{et. al.} reported the synthesis of a series of aryl- or alkylsubstituted 2-mercaptobenzothiazoles by direct thiolation of benzothiazoles with aryl or alkyl thiols via copper-mediated aerobic C–H bond activation in the presence of stoichiometric CuI, 2,2’ bipyridine and Na\textsubscript{2}CO\textsubscript{3} (Scheme 4.3).\textsuperscript{12}
Zhou and co-workers developed a highly efficient and environmentally friendly method for catalytic regiodselective thiolation of 2-arylimidazo[1,2-α]pyridines with diaryl disulfides by using Cul as the catalyst under air atmosphere (Scheme 4.4).\(^{13}\)

\[ \text{Scheme 4.4 Cul catalyzed regioselective thiolation of 2-arylimidazo[1,2-α]pyridines} \]

Nishihara and co-workers developed palladium-catalyzed direct thiolation of aryl C–H bonds in 2-arylpyridines with diphenyl disulfides or thiols. The reaction proceeded with ortho-selectivity. Thiolation was expected to be induced by pyridine ring as the directing group. (Scheme 4.5).\(^{14}\)

\[ \text{Scheme 4.5 Palladium-catalyzed direct thiolation of arenes 2-arylpymrdines} \]

Saravanan and Anbarasan accomplished a general protocol for palladium-catalyzed aryl-thiolation of various substituted unactivated arenes to synthesize diverse unsymmetrical diaryl sulfides in good yield employing electrophilic sulfur reagent \(2\) derived from succinimide (Scheme 4.6).\(^{15}\)
Pawliczek et al. reported palladium-catalyzed cyanothiolation of aryne precursors to access 1,2-thiobenzonitriles by using aryl thiocyanates as the cyanothiolating agent. The activation of carbon–sulfur bonds allowed aryne insertion into aryl thiocyanates to form new C–SAr and C–CN bonds in one step (Scheme 4.7).\(^{16}\)

**Scheme 4.7** Palladium-catalyzed cyanothiolation of aryne precursors

Li et al. developed a novel and efficient palladium-catalyzed cascade annulation/arylthiolation reaction to afford functionalized 3-sulfenylbenzofuran and 3-sulfenylindole derivatives in moderate to good yields from readily available 2-alkynylphenols and 2-alkynylamines in [Bmim]Cl ionic liquid (Scheme 4.8).\(^{17}\)

**Scheme 4.8** Palladium-catalyzed cascade annulation/arylthiolation reaction

Deng and co-workers reported a silver-mediated oxidative vinylic C–H bond thiolation of enamides by using diaryl disulfides to synthesize biologically precious chalcogenated olefins efficiently. The amide functionality acted as the intrinsic directing group for regioselective thiolation of the vinylic C–H bond (Scheme 4.9).\(^{19}\)
Yan and co-workers developed an efficient protocol for silver/copper-cocatalyzed direct thiolation/sulfenylation of 1-methoxynaphthalene with diaryl disulfides. The strategy exhibited excellent functional group tolerance and high regioselectivity (Scheme 4.10).²⁰

Scheme 4.10 Ag/Cu-catalyzed direct sulfenylation of 1-methoxynaphthalene

4.2 Objectives

After the careful perusal of the present literature, it was observed that Pd-catalyzed C–H thiolation of 1-aryl-3-methyl-1H-pyrazol-5(4H)-ones have not been reported yet. Therefore, our present study on C–H thiolation of the same compounds will not only lead to a new regioselective protocol, but also provide new analogues of the existing drug edaravone for immediate drug screening.

- To develop a novel and efficient protocol for the regioselective C–H thiolation of 1-aryl-3-methyl-1H-pyrazol-5(4H)-ones via C–H bond activation by employing a novel Pd(NHC)Cl₂ catalyst.

- To check the scope of the novel protocol to sustain effect of electron donating and withdrawing groups for synthesizing a good library of aryl sulfide derivatives of 1-aryl-3-methyl-1H-pyrazol-5(4H)-ones.

- To characterize all the synthesized compounds by elemental analysis, NMR, FTIR and mass spectrometry.
4.3 Results & Discussion

4.3.1 Optimization of reaction conditions

To optimize the reaction conditions, the screening reactions were performed with respect to the Pd-sources, bases and the solvents in the model reactions using 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one 1a (1.0 mmol) and thiophenol 2a (1.0 mmol). In the absence of palladium catalyst or base, only trace amounts of product 3a was obtained after 12 h (Table 1, entry 1 and Table 2, entry 1).

The effectiveness of the model reaction was found to be affected by various Pd-sources (Table 1). Among them, Pd(NHC)Cl$_2$ (5 mol %) was proved to be the best (Table 1, entry 5) as compared to other palladium species such as Pd(OAc)$_2$, Pd(PPh$_3$)$_4$ and PdCl$_2$ (Table 1, entries 2–4). Further increase in the catalyst loading did not affect the yield of 3a.

The efficiency of the reaction was also considerably affected by the choice of bases. Various inorganic bases including Na$_2$CO$_3$, K$_2$CO$_3$, Cs$_2$CO$_3$, NaOt-Bu, NaOAc and KOH were examined. Among the carbonate bases, K$_2$CO$_3$ was the optimal choice for the reaction (Table 2, entries 2–12). A loading of 1.5 equivalents K$_2$CO$_3$ was found to give the product 3a in 85% yield (Table 2, entry 6). The significant decrease in yield was observed by increasing the equivalents of K$_2$CO$_3$ (Table 2, entry 7). To investigate the effects of solvent, the model reaction was performed in various polar and non-polar solvents at 100 °C using 5 mol % Pd(NHC)Cl$_2$ as the catalyst and K$_2$CO$_3$ (1.5 eq.) as the
base. It was observed that DMF was found to be superior over the other organic solvents having 85% yield of 3a (Table 2, entry 6) in 3 h.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>mol %</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nil</td>
<td>-</td>
<td>12</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>5</td>
<td>5</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>5</td>
<td>6</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>PdCl$_2$</td>
<td>5</td>
<td>6</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>Pd(NHC)Cl$_2$</td>
<td>5</td>
<td>3</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>Pd(NHC)Cl$_2$</td>
<td>10</td>
<td>3</td>
<td>85</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (1 mmol), thiophenol (1.0 mmol), K$_2$CO$_3$ (1.5 eq.), Pd-source (5 mol%), DMF (2 mL) and 100 °C. $^b$All the reactions were monitored by TLC using hexane : ethyl acetate (1 : 1). $^c$Isolated yield

Table 2 Optimization of the reaction conditions for the synthesis$^a$ of 3a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Equivalent</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nil</td>
<td>-</td>
<td>DMF</td>
<td>12</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$CO$_3$</td>
<td>1.5</td>
<td>Toluene</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$CO$_3$</td>
<td>1.5</td>
<td>DMSO</td>
<td>5</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>K$_2$CO$_3$</td>
<td>1.5</td>
<td>Dioxane</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>K$_2$CO$_3$</td>
<td>1.5</td>
<td>AcOH</td>
<td>6</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>K$_2$CO$_3$</td>
<td>1.5</td>
<td>DMF</td>
<td>3</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>K$_2$CO$_3$</td>
<td>2.0</td>
<td>DMF</td>
<td>3</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>Na$_2$CO$_3$</td>
<td>1.5</td>
<td>DMF</td>
<td>5</td>
<td>77</td>
</tr>
<tr>
<td>9</td>
<td>Cs$_2$CO$_3$</td>
<td>1.5</td>
<td>DMF</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>NaOtBu</td>
<td>1.5</td>
<td>DMF</td>
<td>6</td>
<td>45</td>
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<tr>
<td>11</td>
<td>NaOAc</td>
<td>1.5</td>
<td>DMF</td>
<td>6</td>
<td>42</td>
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<tr>
<td>12</td>
<td>KOH</td>
<td>1.5</td>
<td>DMF</td>
<td>6</td>
<td>50</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (1 mmol), thiophenol (1.0 mmol), Base (1.5 eq.), Pd(NHC)Cl$_2$ (5 mol%), solvent (2 mL) and 100 °C. $^b$All the reactions were monitored by TLC using hexane : ethyl acetate (1 : 1). $^c$Isolated yield

All the reported work for C–H activation of 1a described pyrazol-5(4H)-one as the intrinsic ortho-directing group and C–H activation takes place at the aryl ring.$^{22-25}$ From our present observations, it was surprisingly noted that C–H thiolation occurred on pyrazole ring rather than aryl ring and as a result compound 3a was the actual product instead of 4a (Scheme 4.11). This might be due to the acidic nature of C$_4$-H of pyrazole ring (Scheme 4.13).
With the optimized reaction conditions in hand, the scope and generality of the approach for the regioselective C–H thiolation of 1-Aryl-3-methyl-1H-pyrazol-5(4H)-ones 1a-c (1.0 mmol) with various aryl thiols 2a-e (1.0 mmol) were examined (Table 3). The reaction of aryl thiols 2a-e bearing both electron-donating as well as withdrawing substituents in the para-position of the thiol group proceeded smoothly to provide the corresponding products of thiolation 3a-o in good to excellent yields. All the results are summarized in Table 3.

The effectiveness of the thiolation reaction was also checked by using unsubstituted as well as benzyl pyrazolones as substrates under same reaction conditions. The reactions of 3-methyl-1H-pyrazol-5(4H)-one 5a and 1-benzyl-3-methyl-1H-pyrazol-5(4H)-one 5b with 4-methylbenzenethiol 2b proceeded smoothly to give thiolation products 6a-b respectively in good yields (Scheme 4.12).

### Table 3 Pd(NHC)Cl₂ catalyzed regioselective C-H thiolation of 1-Aryl-3-methyl-1H-pyrazol-5(4H)-ones\(^a\) 1a-c

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compounds</th>
<th>R</th>
<th>R₁</th>
<th>R₂</th>
<th>Time(^b) (h)</th>
<th>Yield(^c) (%)</th>
<th>Melting point (°C) Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>-H</td>
<td>-H</td>
<td>-H</td>
<td>3.0</td>
<td>85</td>
<td>188-189</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>-H</td>
<td>-H</td>
<td>-CH₃</td>
<td>3.0</td>
<td>85</td>
<td>203-204</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>-H</td>
<td>-H</td>
<td>-OCH₃</td>
<td>4.0</td>
<td>82</td>
<td>200-201</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>-H</td>
<td>-H</td>
<td>-Cl</td>
<td>3.0</td>
<td>81</td>
<td>170-171</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>-H</td>
<td>-H</td>
<td>-Br</td>
<td>3.5</td>
<td>82</td>
<td>189-190</td>
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<tr>
<td>6</td>
<td>3f</td>
<td>-CH₃</td>
<td>-H</td>
<td>-H</td>
<td>3.5</td>
<td>82</td>
<td>190-192</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>-CH₃</td>
<td>-H</td>
<td>-CH₃</td>
<td>3.0</td>
<td>84</td>
<td>195-196</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>-CH₃</td>
<td>-H</td>
<td>-OCH₃</td>
<td>4.0</td>
<td>80</td>
<td>178-180</td>
</tr>
<tr>
<td>9</td>
<td>3i</td>
<td>-CH₃</td>
<td>-H</td>
<td>-Cl</td>
<td>3.0</td>
<td>79</td>
<td>183-184</td>
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<tr>
<td>10</td>
<td>3j</td>
<td>-CH₃</td>
<td>-H</td>
<td>-Br</td>
<td>3.0</td>
<td>83</td>
<td>193-194</td>
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<tr>
<td>11</td>
<td>3k</td>
<td>-H</td>
<td>-Cl</td>
<td>-H</td>
<td>4.0</td>
<td>81</td>
<td>171-172</td>
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<td>12</td>
<td>3l</td>
<td>-H</td>
<td>-Cl</td>
<td>-CH₃</td>
<td>3.0</td>
<td>80</td>
<td>180-181</td>
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<tr>
<td>13</td>
<td>3m</td>
<td>-H</td>
<td>-Cl</td>
<td>-OCH₃</td>
<td>4.0</td>
<td>80</td>
<td>177-178</td>
</tr>
<tr>
<td>14</td>
<td>3n</td>
<td>-H</td>
<td>-Cl</td>
<td>-Cl</td>
<td>3.0</td>
<td>83</td>
<td>176-177</td>
</tr>
<tr>
<td>15</td>
<td>3o</td>
<td>-H</td>
<td>-Cl</td>
<td>-Br</td>
<td>3.0</td>
<td>85</td>
<td>188-189</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 1-Aryl-3-methyl-1H-pyrazol-5(4H)-one (1 mmol), Aryl thiols (1.0 mmol), K₂CO₃ (1.5 eq.), Pd(NHC)Cl₂ (5 mol%), DMF (2 mL) and 100 °C. \(^b\)All the reactions were monitored by TLC using hexane : ethyl acetate (1 : 1). \(^c\)Isolated yield.
The mechanistic pathway for Pd(NHC)Cl₂ catalyzed regioselective C–H thiolation of 1a has been proposed to involve a Pd(II)–Pd(IV) catalytic cycle¹,¹⁴,¹⁸ (Scheme 4.13). First, substrate 1a tautomerized to 1a' in DMF and then K₂CO₃ may abstract the acidic proton of hydroxyl group to form intermediate A. A may then undergo coordination with Pd(NHC)Cl₂ to yield Pd(II) complex B, which after oxidative addition of thiophenol 2a forms a Pd(IV) intermediate C. Finally, the product 3a is obtained via reductive elimination from C leading to regeneration of the Pd(II) catalyst. The hydroxyl group at C₅ of pyrazole ring might have acted as the intrinsic directing group to produce compound 3a with exclusive regioselectivity due to ease of formation of complex B with Pd⁰⁺(NHC)Cl₂.
4.4 Experimental

4.4.1 General procedure for the regioselective thiolation of 1-aryl-3-methyl-1H-pyrazol-5(4H)-ones catalyzed by Pd(NHC)Cl$_2$

A mixture of 1-aryl-3-methyl-1H-pyrazol-5(4H)-one 1a-c (1 mmol), aryl thiol 2a-e (1.0 mmol), K$_2$CO$_3$ (1.5 mmol) and Pd(NHC)Cl$_2$ complex (5 mol %) in 2 mL DMF was magnetically stirred at 100 °C for specified time. The progress of reaction was monitored by TLC. After completion of the reaction, 20 mL of water was added to the reaction mixture followed by extraction with ethyl acetate. The collected organic phase was dried with anhydrous Na$_2$SO$_4$ and the solvent was removed under vacuum. The resulting residues were purified by chromatography on silica gel column by using hexane/ethyl acetate (20:1, v/v) as eluent to afford the pure desired products 3a-o.

4.5 Conclusion

We have developed a new strategy for the catalytic application of Pd(NHC)Cl$_2$ complex for the regioselective C–H thiolation of 1-Aryl-3-methyl-1H-pyrazol-5(4H)-ones using aryl thiols as thiolating reagents and K$_2$CO$_3$ as the effective base via C–H bond activation. The protocol was found to be simple, efficient, atom economic and highly regioselective to afford the target products in good to excellent yields. Moreover, the present study has not only led to the regioselectivity, but also provided important substructures of valuable drug candidates for the pharmacological screening.

4.6 Characterization

All the synthesized compounds were characterized well by spectroscopic techniques viz. $^1$H NMR, $^{13}$C NMR, FTIR and Mass spectrometry. The molecular structures and characterization data of all the synthesized compounds are given below in tabular form. The selected representative spectra of compounds 3g, 3l and 6a have been included at the end of the segment for perusal.
(3a) 3-methyl-1-phenyl-4-(phenylthio)-1H-pyrazol-5-ol

ESI-MS (m/z): 283.00 [M+H]$^+$

\[ \text{FTIR (KBr } \nu_{\text{max}}, \text{ cm}^{-1}) \ 3336, 2925, 1585, 1488, 1328, 1309, 1212, 1163, 1120, 1005, 823 \]

\[ ^{1}H \text{ NMR (400 MHz, CDCl}_3) : \delta \text{ (ppm) } 2.12 \text{ (s, 3H), 7.00 (d, } J = 8.0 \text{ Hz, 2H), 7.06 (t, 1H), 7.15 (d, } J = 7.2 \text{ Hz, 3H), 7.18 (d, } J = 4.0 \text{ Hz, 2H), 7.57 (d, } J = 8.0 \text{ Hz, 2H) } \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3) : \delta \text{ (ppm) } 11.8, 86.5, 121.2, 125.1, 125.3, 126.3, 126.4, 128.9, 135.0, 142.4, 148.8, 154.4 \]

Anal. Calcd. for C$_{16}$H$_{14}$N$_{2}$OS: C, 68.06; H, 5.00; N, 9.92. Found: C, 67.94; H, 4.90; N, 9.81%.

---

(3b) 3-methyl-1-phenyl-4-(p-tolylthio)-1H-pyrazol-5-ol

ESI-MS (m/z): 297.0 [M+H]$^+$

\[ \text{FTIR (KBr } \nu_{\text{max}}, \text{ cm}^{-1}) \ 3336, 2925, 1585, 1488, 1328, 1309, 1212, 1163, 1120, 1005, 823 \]

\[ ^{1}H \text{ NMR (400 MHz, CDCl}_3) : \delta \text{ (ppm) } 2.18 \text{ (s, 3H), 2.28 (s, 3H), 6.96 (d, } J = 8.0 \text{ Hz, 2H), 7.01 (d, } J = 8.0 \text{ Hz, 2H), 7.20 (t, 1H), 7.28-7.34 (m, 2H), 7.63 (d, } J = 7.6 \text{ Hz, 2H) } \]

Anal. Calcd. for C$_{17}$H$_{16}$N$_{2}$OS: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.75; H, 5.40; N, 9.38%.

---

(3c) 4-((4-methoxyphenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-ol

ESI-MS (m/z): 313.1 [M+H]$^+$

\[ \text{FTIR (KBr } \nu_{\text{max}}, \text{ cm}^{-1}) \ 3336, 2925, 1581, 1488, 1326, 1310, 1212, 1163, 1120, 1005, 823 \]

\[ ^{1}H \text{ NMR (400 MHz, CDCl}_3) : \delta \text{ (ppm) } 2.16 \text{ (s, 3H), 3.74 (s, 3H), 6.71 (d, } J = 4.0 \text{ Hz, 2H), 6.98-7.11 (m, 2H), 7.16 (d, } J = 8.0 \text{ Hz, 1H), 7.26 (d, 2H), 7.56 (d, } J = 4.6 \text{ Hz, 2H) } \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3) : \delta \text{ (ppm) } 12.0, 55.4, 87.1, 114.7, 121.1, 126.2, 128.0, 128.9, 136.8, 137.1, 146.0, 151.1, 154.5 \]

Anal. Calcd. for C$_{17}$H$_{16}$N$_{2}$O$_{2}$S: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.27; H, 5.13; N, 8.90%.
Chapter-4 | Pd(NHC)Cl₂ catalyzed regioselective thiolation

(3d) 4-((4-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-ol

**ESI-MS (m/z):** 316.9 [M+H]⁺

**FTIR** (KBr  νₘₐₓ, cm⁻¹) 3332, 2930, 1585, 1480, 1323, 1310, 1215, 1165, 1123, 1012, 823

**¹H NMR** (400 MHz, CDCl₃): δ (ppm) 2.08 (s, 3H), 6.83 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 7.14 - 7.24 (m, 3H), 7.51 (d, J = 7.6 Hz, 2H)

**¹³C NMR** (100 MHz, CDCl₃): δ (ppm) 11.4, 86.5, 121.1, 126.3, 126.4, 128.8, 128.8, 130.8, 136.5, 139.5, 148.0, 152.4

Anal. Calcd. for C₁₆H₁₃ClN₂O: C, 60.66; H, 4.14; N, 8.84. Found: C, 60.53; H, 4.09; N, 8.78%.

(3e) 4-((4-bromophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-ol

**ESI-MS (m/z):** 361.0 [M+H]⁺

**FTIR** (KBr  νₘₐₓ, cm⁻¹) 3340, 2938, 1588, 1481, 1330, 1315, 1218, 1160, 1120, 1011, 829

**¹H NMR** (400 MHz, DMSO-d₆): δ (ppm) 2.12 (s, 3H), 7.03 (d, J = 8.8 Hz, 2H), 7.28 (t, 1H), 7.48 (m, 4H), 7.75 (d, J = 7.6 Hz, 2H), 12.30 (s, 1H)

**¹³C NMR** (100 MHz, DMSO-d₆): δ (ppm) 12.7, 82.5, 118.1, 121.2, 126.2, 127.3, 129.4, 132.2, 136.1, 138.7, 148.0, 158.6

Anal. Calcd. for C₁₆H₁₃BrN₂O: C, 53.20; H, 3.63; N, 7.75. Found: C, 53.04; H, 3.53; N, 7.69%.

(3f) 3-methyl-4-(phenylthio)-1-(p-tolyl)-1H-pyrazol-5-ol

**ESI-MS (m/z):** 297.0 [M+H]⁺

**FTIR** (KBr  νₘₐₓ, cm⁻¹) 3339, 2930, 1581, 1480, 1333, 1312, 1220, 1165, 1123, 1008, 824

**¹H NMR** (400 MHz, CDCl₃): δ (ppm) 2.04 (s, 3H), 2.29 (s, 3H), 6.94 (d, J = 7.6 Hz, 2H), 6.99-7.04 (m, 3H), 7.11 (t, 2H), 7.38 (d, J = 8.0 Hz, 2H)

**¹³C NMR** (100 MHz, CDCl₃): δ (ppm) 11.4, 21.0, 85.0, 121.4, 124.9, 125.1, 128.7, 129.3, 133.9, 135.9, 138.0, 149.2, 152.1

Anal. Calcd. for C₁₇H₁₆N₂O: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.79; H, 5.38; N, 9.40%.
3-methyl-1-(p-tolyl)-4-(p-tolylthio)-1H-pyrazol-5-ol

**ESI-MS** (m/z): 311.0 [M+H]^+

**FTIR** (KBr, ν max, cm⁻¹): 3342, 2933, 1582, 1480, 1332, 1312, 1223, 1164, 1121, 1005, 829

**1H NMR** (400 MHz, CDCl₃): δ (ppm) 2.10 (s, 3H), 2.25 (s, 3H), 2.30 (s, 3H), 6.90 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H)

**13C NMR** (100 MHz, CDCl₃): δ (ppm) 11.7, 20.8, 21.0, 89.0, 121.3, 125.6, 129.6, 129.8, 133.7, 134.2, 134.9, 135.9, 147.8, 152.1

Anal. Calcd. for C₁₈H₁₈N₂O₃S: C, 69.65; H, 5.85; N, 9.02. Found: C, 69.49; H, 5.81; N, 8.86%.

4-((4-methoxyphenyl)thio)-3-methyl-1-(p-tolyl)-1H-pyrazol-5-ol

**ESI-MS** (m/z): 327.0 [M+H]^+

**FTIR** (KBr, ν max, cm⁻¹): 3340, 2930, 1585, 1482, 1331, 1310, 1225, 1168, 1119, 1010, 829

**1H NMR** (400 MHz, DMSO-d₆): δ (ppm) 2.12 (s, 3H), 2.28 (s, 3H), 3.70 (s, 3H), 6.87 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 12.02 (s, 1H)

**13C NMR** (100 MHz, DMSO-d₆): δ (ppm) 11.9, 21.0, 55.6, 85.5, 115.2, 128.1, 129.2, 129.8, 133.9, 135.9, 138.0, 158.0, 160.0

Anal. Calcd. for C₁₈H₁₈N₂O₂S: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.10; H, 5.38; N, 8.42%.

4-((4-chlorophenyl)thio)-3-methyl-1-(p-tolyl)-1H-pyrazol-5-ol

**ESI-MS** (m/z): 331.0 [M+H]^+

**FTIR** (KBr, ν max, cm⁻¹): 3345, 2931, 1583, 1485, 1335, 1313, 1228, 1168, 1120, 1018, 830

**1H NMR** (400 MHz, DMSO-d₆): δ (ppm) 2.11 (s, 3H), 2.33 (s, 3H), 7.23 (d, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 12.23 (s, 1H)

**13C NMR** (100 MHz, DMSO-d₆): δ (ppm) 12.7, 21.0, 84.4, 121.2, 127.0, 129.4, 129.9, 135.5, 136.2, 138.2, 150.0, 153.3

Anal. Calcd. for C₁₇H₁₅ClN₂O₂S: C, 61.72; H, 4.57; N, 8.47. Found: C, 61.62; H, 4.40; N, 8.41%.
(3j) 4-((4-bromophenyl)thio)-3-methyl-1-(p-tolyl)-1H-pyrazol-5-ol

ESI-MS (m/z): 374.2 [M+H]^+

FTIR (KBr \( \nu_{\text{max}}, \text{ cm}^{-1} \)): 3332, 2936, 1581, 1483, 1339, 1311, 1228, 1165, 1121, 1015, 823

\(^1H\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) (ppm) 2.17 (s, 3H), 2.35 (s, 3H), 6.90 (d, \( J = 7.6 \) Hz, 2H), 7.14 (d, \( J = 8.0 \) Hz, 2H), 7.30 (d, 2H), 7.51 (d, \( J = 7.6 \) Hz, 2H)

\(^13C\) NMR (100 MHz, CDCl\(_3\)): \( \delta \) (ppm) 12.7, 20.9, 84.3, 118.1, 118.9, 121.2, 126.5, 127.4, 130.5, 133.8, 138.5, 149.8, 156.6

Anal. Calcd. for C\(_{17}\)H\(_{15}\)BrN\(_2\)OS: C, 54.41; H, 4.03; N, 7.46. Found: C, 54.29; H, 4.01; N, 7.39%.

(3k) 1-(3-chlorophenyl)-3-methyl-4-(phenylthio)-1H-pyrazol-5-ol

ESI-MS (m/z): 316.2 [M+H]^+

FTIR (KBr \( \nu_{\text{max}}, \text{ cm}^{-1} \)): 3339, 2932, 1583, 1480, 1335, 1310, 1228, 1163, 1120, 1005, 826

\(^1H\) NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) 2.13 (s, 3H), 7.13-7.30 (m, 3H), 7.34 (d, \( J = 7.6 \) Hz, 2H), 7.39 (t, 1H), 7.51 (t, 1H), 7.77 (d, \( J = 8.4 \) Hz, 1H), 7.95 (s, 1H), 12.55 (s, 1H)

\(^13C\) NMR (100 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) 12.8, 82.1, 125.4, 125.5, 125.7, 127.6, 129.5, 129.9, 131.2, 133.8, 136.7, 138.6, 146.0 150.0

Anal. Calcd. for C\(_{16}\)H\(_{13}\)ClN\(_2\)OS: C, 60.66; H, 4.14; N, 8.84. Found: C, 60.56; H, 3.98; N, 8.65%.

(3l) 1-(3-chlorophenyl)-3-methyl-4-(p-tolylthio)-1H-pyrazol-5-ol

ESI-MS (m/z): 330.0 [M+H]^+

FTIR (KBr \( \nu_{\text{max}}, \text{ cm}^{-1} \)): 3342, 2930, 1580, 1484, 1338, 1315, 1228, 1160, 1128, 1015, 830

\(^1H\) NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) 2.12 (s, 3H), 2.23 (s, 3H), 6.99 (d, \( J = 8.4 \) Hz, 2H), 7.09 (d, \( J = 8.0 \) Hz, 2H), 7.32 (d, \( J = 8.0 \) Hz, 1H), 7.49 (t, 1H), 7.77 (d, \( J = 8.0 \) Hz, 1H), 7.85 (d, \( J = 4.0 \) Hz, 1H), 12.53 (s, 1H)

\(^13C\) NMR (100 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) 12.8, 20.9, 86.2, 118.9, 120.1, 125.6, 125.8, 130.1, 131.2, 133.8, 134.8, 135.0, 139.8, 148.9, 153.3

Anal. Calcd. for C\(_{17}\)H\(_{15}\)ClN\(_2\)OS: C, 61.72; H, 4.57; N, 8.47. Found: C, 61.63; H, 4.36; N, 8.39%.
### (3m) 1-(3-chlorophenyl)-4-((4-methoxyphenyl)thio)-3-methyl-1H-pyrazol-5-ol

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**FTIR** (KBr \( v_{\text{max}} \), cm\(^{-1} \)) 3340, 2933, 1581, 1480, 1340, 1318, 1230, 1162, 1129, 1013, 829

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) 2.14 (s, 3H), 3.70 (s, 3H), 6.95 (d, \( J = 8.8 \) Hz, 2H), 7.27 (d, 2H), 7.32 (d, 1H), 7.42 (t, 1H), 7.48 (d, 1H), 7.76 (s, 1H), 12.47 (s, 1H)

\(^1\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) 12.7, 55.6, 86.8, 115.3, 115.5, 125.6, 128.3, 128.8, 131.2, 132.5, 133.8, 137.1, 149.0, 155.6, 158.1

Anal. Calcd. for C\(_{17}\)H\(_{15}\)ClN\(_2\)O\(_2\)S: C, 58.87; H, 4.36; N, 8.08. Found: C, 58.76; H, 4.33; N, 8.01.

### (3n) 1-(3-chlorophenyl)-4-((4-chlorophenyl)thio)-3-methyl-1H-pyrazol-5-ol

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**FTIR** (KBr \( v_{\text{max}} \), cm\(^{-1} \)) 3338, 2922, 1588, 1492, 1332, 1311, 1213, 1170, 1122, 1026, 826

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) 2.22 (s, 3H), 7.00 (d, \( J = 8.4 \) Hz, 2H), 7.18-7.23 (m, 3H), 7.31 (t, 1H), 7.64 (d, \( J = 8.4 \) Hz, 1H), 7.78 (s, 1H)

\(^1\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) 12.8, 84.4, 120.1, 121.1, 125.6, 126.3, 126.4, 128.4, 129.8, 131.7, 133.8, 148.8, 155.4

Anal. Calcd. for C\(_{16}\)H\(_{12}\)Cl\(_2\)N\(_2\)OS: C, 54.71; H, 3.44; N, 7.98. Found: C, 54.59; H, 3.39; N, 7.86%.

### (3o) 4-((4-bromophenyl)thio)-1-(3-chlorophenyl)-3-methyl-1H-pyrazol-5-ol

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<th>ESI-MS (m/z):</th>
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**FTIR** (KBr \( v_{\text{max}} \), cm\(^{-1} \)) 3335, 2920, 1583, 1490, 1339, 1311, 1215, 1169, 1120, 1018, 823

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) 2.12 (s, 3H), 7.03 (d, \( J = 8.4 \) Hz, 2H), 7.33 (d, \( J = 8.0 \) Hz, 1H), 7.45-7.52 (m, 3H), 7.77 (d, \( J = 8.0 \) Hz, 1H), 7.86 (s, 1H), 12.63 (s, 1H)

\(^1\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) 12.8, 82.4, 118.1, 118.9, 120.1, 125.6, 127.4, 131.2, 132.2, 133.7, 138.5, 139.8, 149.0, 154.4

Anal. Calcd. for C\(_{16}\)H\(_{12}\)BrClN\(_2\)OS: C, 48.57; H, 3.06; N, 7.08. Found: C, 48.48; H, 2.96; N, 6.90%. 

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Chapter-4 | Pd(NHC)Cl\(_2\) catalyzed regioselective thiolation
**Chapter-4 | Pd(NHC)Cl₂ catalyzed regioselective thiolation**

### (6a) 3-methyl-4-(p-tolylthio)-1H-pyrazol-5-ol

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<td>220.8 [M+H]⁺</td>
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<tr>
<td><strong>FTIR</strong> (KBr)</td>
<td>( \nu_{\text{max}} ) cm(^{-1}): 3329, 2912, 1585, 1490, 1312, 1210, 1171, 1018, 823</td>
</tr>
<tr>
<td><strong>(^1^H) NMR</strong> (400 MHz, DMSO-d(_6)): δ (ppm)</td>
<td>2.10 (s, 3H), 2.22 (s, 3H), 6.90 (d, ( J = 8.0 \text{ Hz} ), 2H), 7.05 (d, ( J = 8.0 \text{ Hz} ), 2H), 9.8-12.2 (brs, 2H)</td>
</tr>
<tr>
<td><strong>(^1^C) NMR</strong> (100 MHz, DMSO-d(_6)): δ (ppm)</td>
<td>10.6, 20.8, 87.0, 125.6, 128.6, 129.9, 130.5, 134.4, 135.9, 144.8, 162.6</td>
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<td>Anal. Calcd. for C(<em>{11})H(</em>{12})N(_2)OS</td>
<td>C, 59.98; H, 5.49; N, 12.72. Found: C, 59.92; H, 5.41; N, 12.69%.</td>
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</table>

### (6b) 1-benzyl-3-methyl-4-(p-tolylthio)-1H-pyrazol-5-ol

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<td><strong>ESI-MS</strong> (m/z)</td>
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<tr>
<td><strong>(^1^H) NMR</strong> (400 MHz, DMSO-d(_6)): δ (ppm)</td>
<td>2.05 (s, 3H), 2.24 (s, 3H), 5.49 (s, 2H), 6.98 (d, ( J = 6.8 \text{ Hz} ), 2H), 7.11 (d, ( J = 8.0 \text{ Hz} ), 2H), 7.47-7.55 (m, 4H), 7.67 (t, 1H)</td>
</tr>
<tr>
<td>Anal. Calcd. for C(<em>{18})H(</em>{18})N(_2)OS</td>
<td>C, 69.65; H, 5.85; N, 9.02. Found: C, 69.61; H, 5.79; N, 8.98%.</td>
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</table>
$^1$H NMR spectrum of compound 3g (-OH/Deuterium exchange)

ESI-MS of compound 3g
Chapter-4 | Pd(NHC)Cl$_2$ catalyzed regioselective thiolation

$^{1}$H NMR spectrum of compound 3l

ESI-MS of compound 3l
Chapter-4 | Pd(NHC)Cl$_2$ catalyzed regioselective thiolation

$^1$H NMR spectrum of compound 6a

$^{13}$C APT spectrum of compound 6a
References: