CHAPTER-IV  SECTION-I

*Synthesis and Characterization of Palladium incorporated CoFe$_2$O$_4$ Magnetic nanoparticles*
4.1.1 Introduction

Palladium, a 4d transition metal is considered to be the most versatile catalyst in organic synthesis due to its high activity and selectivity [1]. Chemical characteristic of Pd is similar to that of its 5d analog, platinum (Pt), with the most notable difference being that palladium is much more reactive than platinum. Palladium is known to exists in oxidation states (0), (I), (II) and (IV) in complexes. Almost all of the palladium complexes used as catalyst in organic synthesis are low-spin d^8, diamagnetic Pd(II) which normally has preference for soft donor ligands such as ethylene, phosphene etc. Nanoparticles of palladium and palladium containing intermetallic compounds have grown significant interest in many areas such as sensors, catalysis, active membranes etc. [2-4]. Palladium nanoparticles has gained considerable importance as catalyst in organic transformations because of its large surface area and hence more exposed the catalytic active sites compared to their homogenous counterparts. However, the separation and recycling the metal nanoparticles from the product is a major concern for a broad industrial application.

It is noteworthy that use of palladium incorporated magnetic nanoparticle can address the isolation and re-cycling problem encountered in many heterogenous and homogenous catalytic reactions [5-11]. The magnetic cores of these particles are
generally capped with suitable capping agents rendering their stability and dispersibility to organic solvent and for specific applications in catalytic reactions. In general, catalysts can be loaded onto MNP supports either by post modification of MNP shells or by co-precipitation during the MNP synthesis [12]. Recently, the functionalized MNPs have appeared as viable alternatives to conventional materials, as robust, readily available, high surface area heterogeneous catalyst support [13-15]. The magnetically nanosized palladium catalysts has been widely used in a variety of organic reactions and in most cases, palladium is immobilized on to the modified surface of the MNPs.

4.1.2 Review of Literature

Facile recovery and re-usability of catalysts is a task of great economic and environmental importance in reactions of industrial significance, especially when expensive and toxic metal particles are employed [16]. There are many approaches to separate and recycle metal nanoparticles from the reaction products in an easy and simple way such as immobilization on solid supports such as organic polymeric resin [17], inorganic support such as Pd/C, Pd/SiO₂, Pd/Al₂O₃ etc. [18-20]. However, in these immobilized catalysts, the rate limiting is a major factor due to large size of the catalyst bodies [21]. Thus, it is more realized to develop new catalyst with magnetic cores and their shell containing the catalytic species for ease of separation by external magnetic field [22]. Iron oxide nanoparticles such as magnetite (Fe₃O₄) and maghemite (γ-Fe₂O₃) are commonly used for both catalyst supports and biomedical applications [23]. However, other paramagnetic or ferromagnetic nanoparticles are less studied [24-28].
Although, the Fe$_3$O$_4$ could be easily prepared and has been efficiently utilized in many organic reactions, it is fairly reactive to acidic environment [22] and γ-Fe$_2$O$_3$ is also not thermally stable [29]. On contrary, the CoFeO$_4$ is a typical ferromagnetic oxide with spinel structure which have high thermal stability, large magnetic anisotropy, moderate saturation magnetization, remarkable chemical stability and mechanical hardness [30, 31] which would make it a good candidate for magnetic core.

The MNPs-supported catalysts have been efficiently used as heterogenous catalysts for a variety of organic transformations such as hydrogenation [8, 32-36], hydroformylation [5, 37], epoxidation [38], Friedel-Crafts benzylation and benzylation [39, 40], and coupling resections [41-44] e.g. Suzuki, Heck and Sonogashira coupling reactions etc.

A magnetically separable palladium catalyst was simply synthesized through a wet impregnation incorporating palladium nanoparticles and superparamagnetic Fe$_3$O$_4$ nanoparticles in KBH$_4$ solution, which is a highly efficient catalyst for the carbonylative Sonogashira coupling reaction of aryl iodides with terminal alkynes under phosphine-free conditions [44]. This catalyst is completely magnetically recoverable and can be reused with sustained selectivity and activity.

Magnetic nanoparticles-supported quaternary ammonium and phosphonium salts were prepared and evaluated as phase-transfer catalysts [45]. Some of them exhibited good activities that were comparable to that of tetra-$n$-butylammonium iodide. The catalysts were readily separated using an external magnet and reusable without significant loss of their catalytic efficiency.
Sato and Kawamura have prepared magnetic nanoparticle (MNP)-supported crown ethers and evaluated as catalysts for solid-liquid phase-transfer reactions [46]. The catalytic activities of the MNP supported crown ethers were comparable to those of unsupported crown ethers. After the reactions being over, the catalysts could be readily separated using an external magnet and reused without significant loss of catalytic efficiency.

The surface of magnetic ferrite nanoparticles (CoFe$_2$O$_4$) was coated with a Rh-based cationic complex, to make them homogeneously dispersible and thermodynamically stable without an excess amount of surface capping molecules in normal organic solvents [5]. The ferrite nanoparticle supported Rh catalyst showed very effective catalytic activity toward the hydroformylation reaction of olefins and could be easily recovered from the reaction mixture by magnetic decantation to be used for subsequent reactions.

Manorama et al. reported a facile route for Pd (0) immobilization on the surface of amine-terminated Fe$_3$O$_4$ and NiFe$_2$O$_4$ nanoparticles for a series of hydrogenation reactions [34]. The catalysts are completely recoverable with the simple application of an external magnetic field, and the efficiency of the catalyst remains unaltered even after 10 repeated cycles for each of the reactions. Yi et al. reported the synthesis of nano Pd on SiO$_2$-coated Fe$_2$O$_3$ and their application in the hydrogenation of nitrobenzene [47]. Y. Gao et al. prepared iron-oxide supported Pd nanoparticles for catalytic use in Suzuki, Heck and Sonogashira cross-coupling reactions [42]. Yoon and his coworkers developed for deposition of palladium nanoparticles with high dispersion and stability.
4.1.3 Present Work

Objective

Although in general, the surface coated MNPs offers good catalytic activity in many organic reactions, the coating may decrease magnetization and stability of the magnetic core by altering interparticle interactions which in turn reduce effective surface area and hence catalytic efficacy [49]. Although in comparison to other MNPs, Fe$_3$O$_4$ could be easily prepared and has been extensively studied in a variety of organic reactions, it is fairly reactive to acidic environment in liquid phase catalytic reactions and hence surface stabilizer is employed to protect from external environment [50]. Thus we intend to design a magnetic nano catalyst by directly incorporating catalyst species on the magnetic core to gain its maximum activity and stability in catalytic reaction. We wish to prepare Pd incorporated CoFe$_2$O$_4$ nanoparticles by addition of Pd NPs to the reaction mixture during synthesis of CoFe$_2$O$_4$ by co-precipitation method under ultrasonic irradiation without using any surface stabilizer.
4.1.4 Result and Discussion

The formation of Pd NPs was observed from UV-VIS spectrophotometric measurement (200-600 nm) in Fig. 4.1.1 and scanning electron microscope (SEM) in Fig. 4.1.2 with electron dispersive X-ray (EDX) analysis (inset b, Fig. 4.1.2). The complete disappearance of peak at 400 nm in the UV-VIS measurement revealed the full conversion of Pd (II) to palladium nanoparticles (Pd NPs) [51]. The SEM morphology visualized the presence of PEG-stabilized very uniform narrow size distributed Pd NPs with the elemental contributions from Pd, C and O in the EDX spectra. The cobalt ferrite magnetic nanoparticles (CoFe₂O₄ MNPs) were synthesized by a combined sonochemical and co-precipitation technique in aqueous medium without any surfactant or organic capping agent. The synthesis was carried out in an alkaline pH with repeated ultrasonic irradiation.

Fig. 4.1.1 UV-VIS spectra of (a) Pd(OAc)₂ in PEG-400, and (b) Pd NPs in spectra of Pd NPs.

Fig. 4.1.2 (a) SEM image and inset (b) EDX spectra of Pd NPs.
After determining the elemental composition of the black particles of $\text{CoFe}_2\text{O}_4$ formed at the initial stage by EDX analysis, the as-synthesized Pd NPs were added. The EDX analysis of Pd incorporated $\text{CoFe}_2\text{O}_4$ MNPs (Pd-$\text{CoFe}_2\text{O}_4$ MNPs) (Fig. 4.1.3) showed that the distribution of the elements (atomic percent) in the product was Co=11.03%, Fe=22.77%, O=65.06% and Pd=1.13%.

![EDX spectra of Pd-CoFe$_2$O$_4$ MNPs](image)

**Fig. 4.1.3** EDX spectra of Pd-CoFe$_2$O$_4$ MNPs

The iron/cobalt ratio in the nanocrystals by EDX was found to be 2.06 which is very much close to the atomic ratio in the formula $\text{CoFe}_2\text{O}_4$ with 1% Pd incorporation. We studied the morphology of the Pd-$\text{CoFe}_2\text{O}_4$ MNPs in transmission electron microscopy (TEM) and field emission scanning electron microscopy (FESEM) measurements. The particle sizes were also measured in FESEM micrograph and were found to be in the range of 40-50 nm. **Fig. 4.1.4** (a) shows the TEM image of Pd-CoFe$_2$O$_4$ MNPs deposited on carbon coated copper grid at a 0.2 μm resolution.
Fig. 4.1.4 (a) TEM image and (b) FESEM image of Pd-CoFe$_2$O$_4$ MNP

Fig. 4.1.5 shows the XRD of CoFe$_2$O$_4$ MNPs which indicates the presence of all the characteristic peaks with relative intensities of all patterns matching well with a cubic spinel structure (JCPDS–International center diffraction data, PDF cards 3-864 and 22-1086) [52, 53]. XRD measurement were carried out using Cu K$_\alpha$ radiation ($\lambda = 1.54178$ Å) and the samples were scanned from 10° to 70° (2θ) at the speed of 5°/min. The crystallite size for the nanoparticles obtained from the XRD pattern using scherer's formula [54] were found to be 40±5 nm.

Fig. 4.1.5 XRD of Pd-CoFe$_2$O$_4$ MNPs
The average particle sizes measured in FESEM and TEM micrograph (Fig.4.1.4) and were found to be consistent with the particle size obtained from XRD analysis. The crystalline nature of the synthesized nanoparticles was further inferred from HRTEM analysis with SAED pattern and shown in Fig. 4.1.6 (a) and (b).

![Fig.4.1.6](image) (a) SAED pattern and (b) HRTEM image of Pd-CoFe$_2$O$_4$ MNP

![Fig.4.1.7](image) M-H loop in VSM measurement of (a)CoFe$_2$O$_4$ MNP and (b) Pd-CoFe$_2$O$_4$ MNP at room temperature at ±2T

The SAED pattern in Fig.4.1.6.a showed the diffractions from the lattice planes of CoFe$_2$O$_4$ and Pd(0) (marked by star). The high resolution TEM (HRTEM) image allowed us, by means of Gatan DigitalMicrograph™ software, to obtain the Fourier transform from which lattice spacings of 2.32 and 1.97 Å were (experimental error, 5%) obtained for the Pd(0) and 4.43 Å for the CoFe$_2$O$_4$ MNPs. These lattice spacings, corresponding to the interplanar distance (1 1 1) and (2 0 0) of the Pd(0), are depicted by star (*) in Fig.4.1.6.b and (1 1 1) of the CoFe$_2$O$_4$ MNPs. The TEM and FESEM images of the Pd-CoFe$_2$O$_4$ MNPs (Fig.4.1.4) show that they are relatively uniform with an average size of 40-50 nm.
The magnetic properties of the as prepared Pd incorporated cobalt nanoparticles were investigated by VSM measurement. Fig. 4.1.7 (a) and (b) shows the M-H loops taken at room temperature with a maximum applied field of $\pm 2$ T. From the hysteresis loops both saturation magnetization ($M_s$) and coercivity values ($H_c$) were extracted. Coercivities of 1409 Oe and 1286 Oe were obtained from the extracted data of CoFe$_2$O$_4$ MNPs and Pd-CoFe$_2$O$_4$ MNPs with their corresponding saturation magnetization values of 52.6 and 72.8 emu$^{-1}$ respectively. Thus after Pd incorporation in CoFe$_2$O$_4$ MNPs the coercivity was slightly decreased whereas magnetization, $M_s$ is significantly increased.

Next, the surface area and porosity of the Pd-CoFe$_2$O$_4$ MNPs were measured using Brunauer-Emmett-Teller (BET) equation [55] following the Barrett-Joyner-Halanda (BJH) method [55]. From the N$_2$ adsorption-desorption isotherm of Pd-CoFe$_2$O$_4$ MNPs in Fig. 4.1.8, the BET surface area of the particles is 259.56 m$^2$g$^{-1}$ as calculated by linear part of the BET plot, which is much higher than CoFe$_2$O$_4$ nanoparticles prepared by conventional co-precipitation method [56]. The total pore volume at $P/P_0 = 0.98$ is 0.23 cm$^3$g$^{-1}$. The BET isotherm is of type II and H3 hysteresis loop (BDDT/IUPAC classification), characteristic of mesoporous adsorbents [57].
The as synthesized MNPs and their ethanolic dispersion formed by this ultrasound promoted co-precipitation methods are quite stable for longer period. The catalyst surface were further examined with the help of FT-IR spectra (Fig. 4.1.9), which shows two broad absorption peaks centered around 3419 cm$^{-1}$ and 1620 cm$^{-1}$ along with other characteristic peaks of spinel ferrite [58]. These two peaks are due to surface adsorbed water and due to creation of polar surface site. This may happens due to excessive ultrasonic treatment during synthesis of the MNPs in aqueous medium and the polar surface property of the MNPs accounts for stable dispersion in ethanol.
Fig. 4.1.9 FT-IR spectra of Pd-CoFe$_2$O$_4$ MNPs

Fig. 4.1.10 Magnetic separation of Pd-CoFe$_2$O$_4$ MNPs from ethanolic dispersion
4.1.5 Conclusion

In conclusion, a combined sonochemical-coprecipitation method has been developed for the synthesis of Pd incorporated CoFe$_2$O$_4$ magnetic nanoparticles in aqueous medium. Average sizes of the MNPs were found to be 40-50 nm and the particles were found to form stable dispersions in aqueous or alcoholic medium. Diffraction pattern of the nanoparticles indicates that the particles are spinel in nature. Surface area of the Pd-CoFe$_2$O$_4$ magnetic nanoparticles was found to be 259.56 m$^2$/g and total pore volume at P/Po = 0.98 is 0.23 cm$^3$/g.
CHAPTER-IV SECTION-II

Palladium incorporated CoFe$_2$O nanoparticles: a facile magnetic catalyst for Suzuki reactions under mild conditions
4.2.1 Introduction

The Suzuki reaction since its discovery in 1979 by Akira Suzuki and his group has been one of the most frequently studied reactions in organic synthesis for C-C bonds formation in particular to synthesize poly-olefins, styrenes and substituted biphenyls. The 2010 Nobel Prize in Chemistry was awarded to Suzuki for his discovery and development of this reaction in frontier areas. Suzuki et al. reported that in presence of base such as sodium methoxide, ethoxide, acetate and hydroxide reaction of an equimolar amount of (E)-1-hexenyl disiamyl borane in THF with (E)-1-bromo-2-phenylethene with 1 mol% of tetrais(triphenylphosphine) palladium gave (E,E)-1-phenyl-1,3-octadiene in decent yields (Scheme 2). Palladium finds its special interest in cross-couplings of aryl and vinyl halides with either olefins or organo metallic reagents, due to its tolerance towards a wide range of functional groups.

```
R^1C=CH + HBX_2 → R^1H \quad \text{PdL}_4, \text{Base}
```

\[ X_2 = (\text{Si})_2 \text{O} \]

Scheme 4.2.1
The Suzuki or Suzuki-Miyaura cross-coupling reaction of organic halides or triflates and boronic acids catalyzed by palladium is one of the most efficient methods for the selective construction of carbon-carbon bonds, in particular for the formation of biaryls [59, 60]. This reaction has gained prominence in recent years in the synthesis of pharmaceuticals, herbicides, natural products, and advanced materials [61].

4.2.2 Review of Literature

The use of Pd-catalyzed cross-coupling reactions has significantly increased among the methods to make C-C bonds and particularly Suzuki coupling has been intensively developed in recent times [62]. Several catalytic systems with a variety of ligands have been found to facilitate Suzuki cross-coupling reactions and great efforts have been made toward the development of efficient catalytic systems for the coupling in the past few years [63-73]. Phosphine ligands, ammonium and phosphonium halides and quarternary ammonium salts have been found to stabilize the Pd-catalysts via formation of zerovalent Pd species and accelerate the coupling in the reaction [74].

Recently, a variety of nanoparticle catalysts/support has been found to facilitate Suzuki cross-coupling reactions either in presence of ligand or ligand free conditions. A Pd NP catalyzed ligand-free Suzuki coupling reaction under aerobic conditions was reported [75]. The Pd NP was generated in situ in PEG-400 and the reaction was highly efficient for coupling aryl chlorides with phenylboronic acid in short times under mild conditions (Scheme 4.2.2).
Scheme 4.2.2

Pd NP catalyzed Suzuki cross-couplings of aryl bromides and chlorides were carried out in quaternary ammonium salts as solvents under mild conditions and with the recycling of the catalyst (Scheme 4.2.3) [76].

Scheme 4.2.3

A magnetic nanoparticle-supported homogeneous Pd catalyst was employed for promoting the Suzuki cross-coupling of an aryl halide on resins and an excessive arylboronic acid in solution [77]. The workup procedure of separating three components (the catalyst, product, and remaining arylborate) is a chromatography free process. The Pd catalyst was magnetically isolated and recycled from the reaction mixture by applying an external magnetic field.

Y. Gao and his co-workers employed the magnetic nanoparticle-supported Pd-N-heterocyclic carbenes (NHC) complexes for catalysis of a group of Suzuki cross-couplings of aryl halides with arylboronic acids (Fig. 4.2.1) [43, 80].
H. Yoon et al. prepared a highly stable Pd NP impregnated on nitrogen doped magnetic carbon nanoparticles and their catalytic performance was investigated for Heck, Suzuki, and Sonogashira coupling reactions [48].

Z. Yinghuai and his co-workers prepared a ultra small palladium(0) particles (less than 1 nm) on magnetic nanoparticle supports, in which immobilized auxiliaries were used as stabilizing ligands [78]. These catalysts were highly active for Suzuki cross-coupling and the catalyst can be easily separated using a magnet and reused several times with sustained activity.

4.2.3 Present Work

Objective

The palladium-catalyzed Suzuki coupling reaction is generally performed under an inert atmosphere because the catalytic species are sensitive to oxygen or moisture [79]. There are also several reports in the literature for the Suzuki coupling reaction which have the attractive attributes such as the commercial availability, the air and water stability, and the nontoxic nature of boronic acids and catalysts [80]. However, the effective catalyst separation and re-usability is still a challenge. Moreover, most of
these coupling reactions are ligand based reactions which is serious disadvantage from the points of green economy and green chemistry. Therefore, developing an efficient and ligand free reaction for Suzuki coupling with easy catalyst separation and re-usability under aerobic conditions is of our special interest. The objective of the present investigation is to apply the palladium incorporated magnetic nanoparticles as catalyst for the Suzuki cross-coupling reaction (Scheme 4.2.5) under mild conditions with the advantage of magnetic separation and re-usability of the catalyst.

\[
\text{R}^+_{-x} + n,_{0-uv} \rightarrow \text{y y y y y} \\
\text{R}: \text{H, Ph, CH}_3, \text{NO}_2 \quad \text{R}^+ : \text{H, NO}_2 \\
\text{X}: \text{I, Br}
\]

Scheme 4.2.5 Suzuki reaction catalyzed by Pd-CoFe\textsubscript{2}O\textsubscript{4} MNPs.

### 4.1.4 Result and Discussion

The catalytic activity of the synthesized Pd incorporated CoFe\textsubscript{2}O\textsubscript{4} NPs were examined for Suzuki cross-coupling reaction (Scheme 4.2.5). Initial experiments were performed for the reaction of iodobenzene with phenyl boronic acid in presence of a catalytic amount of CoFe\textsubscript{2}O\textsubscript{4} MNP. In general phospines are used as a promoting ligand for many Pd-catalysed reactions [81]. We have carried out the reaction under phosphine-free condition in ethanol at reflux temperature in presence of Na\textsubscript{2}CO\textsubscript{3} under aerobic conditions.
Scheme 4.2.6 Suzuki reaction catalyzed by Pd-CoFe$_2$O$_4$ MNPs

To standardize the reaction conditions, we performed a series of reactions with several bases, solvents, temperatures and catalyst concentration to obtain the best possible combination. Initially, the reaction was performed using 0.5 mmol of iodobenzene, 0.75 mmol of phenyl boronic acid, and 1.25 mmol Na$_2$CO$_3$ in presence of 1.6 mol% of Pd-CoFe$_2$O$_4$ MNP by refluxing in ethanol and monitored by TLC. The reaction was completed in 12 h with a yield of 81%. When the reaction was carried out in water and ethylene glycol (EG) under the same reaction conditions, yields were very low i.e. 30% and 20% respectively. The reactions were also carried out under the same conditions using different bases such as K$_2$CO$_3$, K$_3$PO$_4$ and CsCO$_3$ and the yields were 80%, 68% and 30% respectively (Table 4.2.1: entry 4, 5, 6). The yields were not satisfactory in water and aqueous ethanol under the same reaction condition. The reaction at room temperature was found to be very slow and completion of reaction was observed only after 52 h with 72% yield. The results for optimum reaction condition are summarized in Table 4.2.1.
Table 4.2.1 Suzuki reaction catalyzed by Pd incorporated CoFe₂O₄ MNPs (Pd-CoFe₂O₄ MNPs).a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst concentration</th>
<th>Solvent</th>
<th>Base</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.6 mol%</td>
<td>Ethanol</td>
<td>Na₂CO₃</td>
<td>Reflux</td>
<td>12</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>2.4 mol%</td>
<td>Ethanol</td>
<td>Na₂CO₃</td>
<td>Reflux</td>
<td>12</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>0.8 mol%</td>
<td>Ethanol</td>
<td>Na₂CO₃</td>
<td>Reflux</td>
<td>12</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>1.6 mol%</td>
<td>Ethanol</td>
<td>K₂CO₃</td>
<td>Reflux</td>
<td>12</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>1.6 mol%</td>
<td>Ethanol</td>
<td>K₂PO₄</td>
<td>Reflux</td>
<td>12</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>1.6 mol%</td>
<td>Ethanol</td>
<td>Cs₂CO₃</td>
<td>Reflux</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>1.6 mol%</td>
<td>aq.Ethanol</td>
<td>Na₂CO₃</td>
<td>Reflux</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>1.6 mol%</td>
<td>Water</td>
<td>Na₂CO₃</td>
<td>Reflux</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>1.6 mol%</td>
<td>Ethylene glycol</td>
<td>Na₂CO₃</td>
<td>Reflux</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>1.6 mol%</td>
<td>Ethanol</td>
<td>Na₂CO₃</td>
<td>30</td>
<td>52</td>
<td>72</td>
</tr>
</tbody>
</table>

*aReaction condition: Iodobenzene (0.5 mmol), phenyl boronic acid (0.75 mmol), base (133 mg), solvent (5 ml); bIsolated yield by column chromatography.

After optimizing reaction conditions, the scope of the catalyst was further investigated for a variety of aryl halidies and boronic acids and the results are summarized in Table 4.2.2.

Table 4.2.2 Suzuki reaction catalyzed by Pd-CoFe₂O₄ MNPa

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Boronic acid</th>
<th>Time (h)</th>
<th>Product(s)</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>B(OH)₂</td>
<td>12</td>
<td></td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>B(OH)₂</td>
<td>12</td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>B(OH)₂</td>
<td>6</td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>B(OH)₂</td>
<td>12</td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>B(OH)₂</td>
<td>12</td>
<td></td>
<td>92</td>
</tr>
<tr>
<td>No</td>
<td>Structure</td>
<td>Reaction Condition</td>
<td>Yield (isolated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>------------</td>
<td>---------------------</td>
<td>-----------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image1" alt="Structure 6" /></td>
<td>0.5 mmol of aryl halide, 0.75 mmol of boronic acid, 1.25 mmol of Na₂CO₃, 0.008 mmol of Pd-CoFe₂O₄ MNPs, 5 ml ethanol, reflux; isolated yield by column chromatography.</td>
<td>83%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="image2" alt="Structure 7" /></td>
<td></td>
<td>75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><img src="image3" alt="Structure 8" /></td>
<td></td>
<td>79%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td><img src="image4" alt="Structure 9" /></td>
<td></td>
<td>84%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td><img src="image5" alt="Structure 10" /></td>
<td></td>
<td>70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td><img src="image6" alt="Structure 11" /></td>
<td></td>
<td>85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td><img src="image7" alt="Structure 12" /></td>
<td></td>
<td>80%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Reaction condition: 0.5 mmol of aryl halide, 0.75 mmol of boronic acid, 1.25 mmol of Na₂CO₃, 0.008 mmol of Pd-CoFe₂O₄ MNPs, 5 ml ethanol, reflux; isolated yield by column chromatography.*

After completion of the reaction, an external magnet was applied to concentrate the catalyst on the side of the reaction vessel. The reaction mixture was decanted holding the magnet on outside of the flask. Thereafter, the flask was washed with ethanol and combined ethanol layer was concentrated in a rotary evaporator under reduced pressure. The crude product was purified by flash chromatography in 230-400 mesh size silica using hexane as eluent. The products were characterized by using IR, NMR and mass (ESI-MS) spectroscopy data.
After separation, the catalyst was dried in an oven at 120 °C for 6 h and kept under vacuum for 6 h before next cycle of reaction.

Fig. 4.2.2 $^1$H NMR of Biphenyl (entry 1&2)

Fig. 4.2.3 $^1$H NMR of 4-nitrobiphenyl (entry 5 and 9)
Fig. 4.2.4 $^1H$ NMR of 4, 4'-dimethylbiphenyl (entry 11)

Fig. 4.2.5 $^1H$ NMR of 4-methoxy-4'-methylbiphenyl (entry 12)
Fig. 4.2.6 ESI-MS of biphenyl (entry 1)

Fig. 4.2.7 ESI-MS of 3-methylbiphenyl (entry 2)
The reusability of the magnetic catalyst was also examined by carrying out repeated runs on the same batch of the used 10 mol% Pd-CoFe\(_2\)O\(_4\) MNP catalyst in Suzuki reaction of 4-methyl iodobenzene and phenyl boronic acid (Table 4.2.3). After each cycle, nanoparticles were magnetically separated, washed, dried and used directly for the next round of reaction. The yield was not significantly decreased in the regenerated catalyst even after four consecutive cycles. It was also evident from the SEM that, the morphology of the recovered MNPs remains unaltered (Fig. 4.2.8).

Table 4.2.3 Recyclability of Suzuki reaction with 1.6 mol\% regenerated Pd-CoFe\(_2\)O\(_4\) MNP catalyst.\(^a\):

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Yield at 6h (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>81</td>
</tr>
</tbody>
</table>

\(^a\)Reaction condition: 0.5 mmol 4-methyl iodobenzene, 0.75 mmol phenyl boronic acid, 1.25 mmol Na\(_2\)CO\(_3\), 5 ml dried ethanol, reflux; \(^b\)Isolated yield after column purification.

![Fig. 4.2.8 SEM image of Pd-CoFe\(_2\)O\(_4\) MNPs in (a) first and (b) fourth catalytic cycles](image)
4.2.5 Conclusion

Catalytic performance of palladium incorporated CoFe$_2$O$_4$ MNPs was examined for Suzuki coupling reactions. The reactions can be carried out using ethanolic dispersion of the catalyst under mild reaction conditions i.e ligand free and aerobic conditions with low catalyst loading (1.6 mol%). Unlike other Pd catalyzed Suzuki reactions, the catalyst was recovered by simple magnetic decantation and reusability was achieved up to four catalytic cycles with no significant loss of activity which will be of immense importance in industrial processes. Hence, these MNPs as catalysts are new development in using heterogenous catalysts for production of fine chemicals in liquid phase reactions.

4.2.6 Experimental Section

Typical procedure for the Suzuki coupling reaction

In a typical reaction, to a solution of 0.5 mmol of the aryl halide in 5 ml of dried ethanol was added 0.75 mmol of phenyl boronic acid, 0.133 g of Na$_2$CO$_3$ (1.25 mmol) followed by 0.002 g of the as-synthesized catalyst (1.6 mol% based on aryl halide). The mixture was then stirred under reflux condition in oil bath for 12 h. The reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the reaction mixture was cooled to room temperature and the catalyst (MNPs) was recovered by external magnet and washed with ethanol. The combined
organic layer was dried over anhydrous sodium sulfate (Na₂SO₄) and evaporated in a rotary evaporator under reduced pressure. The crude product was purified by flash chromatography on silica gel (230-400 mesh) with hexane as eluting solvent.

**Experimental data:**

**Entry 1&2 (Biphenyl)**

![Biphenyl structure](image)

$^1$H NMR (400MHz, CDCl₃): δ 7.57 (d, J= 9.6, 4H), 7.41 (t, J= 7.6, 4H), 7.31 (t, J= 7.4, 2H)

$^{13}$C NMR (400 MHz, CDCl₃): δ 141.6, 129.1, 127.6, 127.5

ESI-MS: m/z 154.07, 155.08

**Entry 3 (4-methylbiphenyl)**

![4-methylbiphenyl structure](image)

$^1$H NMR (400 MHz, CDCl₃): δ 7.59 (d, J= 7.6Hz, 2H), 7.49 (d, J= 6.8 Hz, 2H), 7.43 (t, J= 6.6, 2H), 7.33 (t, J= 8, 1H), 7.25 (d, J= 7.2, 2H), 2.41 (s, 3H)

$^{13}$C NMR (400 MHz, CDCl₃): δ 25.1, 127.6, 127.9, 128.1, 129.4, 130.0, 133.5, 136.7, 137.6

ESI-MS: m/z 168.09, 169.1
Entry 4 & 10 (3-methylbiphenyl)

![3-methylbiphenyl structure]

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38-7.44 (m, 4H), 7.341-7.34 (t, $J=8$, 2H), 7.57 (d, $J=8$Hz, 2H), 7.17-7.11 (m, 1H), 2.41 (s, 3H)

$^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 138.9, 135.6, 129.7129.6, 128.8, 128.3, 128.0, 125.5, 21.5

ESI-MS: $m/z$ 168.09, 169.10

Entry 5 & 9 (4-nitrobiphenyl)

![4-nitrobiphenyl structure]

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.26 (d, $J=9.2$Hz, 2H), 7.7 (d, $J=9.2$ Hz, 2H), 7.75 (d, $J=8$, 2H), 7.41-7.49 (m, 3H)

$^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$: 147.6, 147.1, 138.8, 129.2, 128.91, 127.8, 127.4, 124.1.

ESI-MS $m/z$: 199.06, 200.07

Entry 6 (4'-methyl-3-nitrobiphenyl)

![4'-methyl-3-nitrobiphenyl structure]

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.4 (s, 1H), 8.14 (d, $J=6.8$ Hz, 1H), 7.75 (d, $J=6.8$, 1H), 7.55 (t, $J=8$, 1H), 7.50 (d, $J=8.4$, 2H), 7.27 (d, $J=8$, 2H).
$^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 148.8, 137.4, 137.3, 134.1, 133.4, 130.2, 129.7, 127.8, 122.4, 120.1, 24.6

ESI-MS: m/z 213.07, 214.08

**Entry 7 (3, 4'-dinitrobiphenyl)**


$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.48 (s, J= 7.6Hz, 1H), 8.36 (d, J= 8.4Hz, 2H), 8.28 (d, J=8.4Hz, 1H) 7.93 (d, J= 6.8Hz, 1H), 7.77 (d, J= 9.2Hz, 2H), 7.66 (t, J=8.2Hz 1H),

$^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 148.8, 147.2, 142.5, 137.3, 134.1, 130.3, 128.7, 122.4, 121.5, 120.0

ESI-MS m/z: 244.04, 245.05

**Entry 8 (1-phenylnaphthalene )**


$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.44-7.90 (m, 12 H)

$^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 136.6, 136.2, 134.1, 133.1, 129.3, 128.2, 127.8, 127.2, 126.2, 125.1

ESI-MS: m/z 205.10, 204.09
Entry 11 (4, 4'-dimethylbiphenyl)

\[
\begin{array}{c}
\text{Entry 11 (4, 4'-dimethylbiphenyl)}
\end{array}
\]

\[
\begin{array}{c}
1^H \text{NMR (400 MHz, CDCl}_3\text{): } \delta 7.46 \text{ (d, } J = 8.4, 4H), 7.22 \text{ (d, } J = 7.6, 4H), 2.38 \text{ (s, 6H)}
\end{array}
\]

\[
\begin{array}{c}
1^3 \text{C NMR (400 MHz, CDCl}_3\text{): } \delta 137.3, 133.7, 129.7, 128.1, 24.3
\end{array}
\]

ESI-MS: \(m/z\) 182.10, 183.11

Entry 12 (4-methoxy-4'-methylbiphenyl)

\[
\begin{array}{c}
\text{Entry 12 (4-methoxy-4'-methylbiphenyl)}
\end{array}
\]

\[
\begin{array}{c}
1^H \text{NMR (400, CDCl}_3\text{): } \delta 7.50 \text{ (d, } J = 8.8, 2H), 7.22 \text{ (d, } J = 7.6, 2H), 6.95 \text{ (d, } J = 8 \text{ Hz, } 2H), 3.84 \text{ (s, 3H), 2.38 (s, 3H)}
\end{array}
\]

\[
\begin{array}{c}
1^3 \text{C NMR (400 MHz, CDCl}_3\text{): } \delta 159.1, 140.8, 133.7, 128.7, 128.1, 127.3, 126.6, 114.2, 55.5.
\end{array}
\]

ESI-MS: \(m/z\) 198.10, 199.11
CHAPTER-IV SECTION-III

Synthesis of Spirocycles using Palladium incorporated \textit{CoFe}_2\textit{O}_4 nanoparticle
4.3.1 Introduction

A range of alkaloids contains bi- or polycyclic structures [82]. In the context of the efficient search for drugs, natural products and their core structures can function as important leads [83, 84]. Classical strategies to such compounds involve the use of Mannich-type reactions, C-N-bond forming reactions, Michael additions, rearrangement reactions etc. Newer methods are based on ring closing metathesis reactions [85, 86] or other organometallic transformations. In this regard, the Buchwald-Hartwig arylation (equation 1) [87-90] and Buchwald etherification reaction [91, 92] (Scheme 4.3.1) seems very promising.

\[
\text{Br} + \text{HO-}R \xrightarrow{\text{Pd(0), ligand, base}} \text{O-}R
\]

Scheme 4.3.1
4.3.2 Review of literature

In general, spiro compounds [93, 94, 95] and nitrogen heterocycles such as pyridines [96], pyrroles [97], and pyrazolines [98] display good antimycobacterial activities. Spiro-compounds having piperidine sub-structures also shows excellent bioactivity [99].

In recent years a variety of synthetic strategies have been developed for the preparation of spirocyclic ethers [100]. These methods involves the re-arrangement, alkylation, ring closure of geminally distributed compounds, ring closing metathesis, other transition-metal-based processes, radical cyclisation or cycloaddition reactions as the key steps of forming spirocyclic ring.

Wang reported a method for the synthesis of spiro-ethers from dibenzofuran, lithium metal and TMED in dry ether under reflux condition and subsequently upon treatment with keyones or aldehydes at -78 °C treatment with further hydrolysis and dehydration steps [101].
4.3.3 Present Work

Objective

In the previous section, we have developed a new type of magnetic palladium catalyst for a carbon-carbon bond forming reaction. We intended to examine the scope of the catalyst for other organic transformations. Palladium compounds are known to catalyze the reaction between aryl halides and alcohols to form corresponding ether [91, 92]. The objective of the present investigation is to develop a new strategy for the synthesis of spirocycles via an intramolecular etherification reaction in presence of palladium ferrite catalyst (Scheme 4.3.2).

We plan to extend our methodology for the synthesis of some heteroatom containing spiro compounds.
4.3.4 Results and Discussion

To realise our goal for development of a new strategy for the synthesis of spirocycles, we synthesize a bifunctional molecule having both aryl bromide and tertiary-benzyl alcohol functionalities. This molecular skeleton serves as the starting material for making spiro-compounds. We have followed a strategy via the formation of ortho-bromophenyl lithium (Scheme 4.3.3) [102, 103]. Although we could synthesize the starting material successfully, the product yield was found to be low due to the formation of some undesired side products.

\[
\begin{align*}
\text{Scheme 4.3.3} & \\
& \\
&
\end{align*}
\]

Initially, we have carried out a series of experiments under different reaction conditions to find out the optimum reaction conditions. We have examined several solvents such as dioxane, toluene, DMF and ethanol (Table 4.3.1). Use of ethanol gave the best result in 24 h of reaction at 90 °C.
Table 4.3.1 Synthesis of spirocyclic ether

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Solvent</th>
<th>Ligand</th>
<th>Temp</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dioxane</td>
<td>1</td>
<td>90</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Dioxane</td>
<td>1</td>
<td>90</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>Dioxane</td>
<td>2</td>
<td>90</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>2</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>2</td>
<td>120</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Ethanol</td>
<td>2</td>
<td>90</td>
<td>80</td>
</tr>
</tbody>
</table>

After obtaining the most suitable reaction condition, we have extended the process to a variety of bromo-alcohols which are described in Table 4.3.2. Reactions were carried out in 0.2 mmol scale in presence of 2 mol % (based on substrate) of the catalyst. After completion of the reaction, the nano catalysts were separated with the aid of an external magnet.
Table 4.3.2: Synthesis of various spiro-compounds

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (a)</th>
<th>Product (b)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Substrate 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Substrate 6" /></td>
<td><img src="image12" alt="Product 6" /></td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Substrate 7" /></td>
<td><img src="image14" alt="Product 7" /></td>
<td>74</td>
</tr>
</tbody>
</table>
All the products were characterized by analyzing the NMR and mass (HR-MS) spectroscopic data.

Structural analysis of compound 6b was done using single crystal X-ray analysis (Fig. 4.3.1). The reflection data for the compound were collected at room temperature using a Bruker SMART CCD diffractometer. The SMART programme [104] was used for data acquisition and the collected data were integrated using SAINT [105] software. Empirical absorption corrections were applied using the programme SADABS [106]. Both structures were solved by direct method (SHELEX-97) and refined by full matrix least squares method using the programme SHELEX-97 [107]. Both programmes were used in Windows XP platform by utilizing the WinGX suite of programmes [108] that also facilitated the use of PLUTON [109] and ORTEP-III [110] for drawing the structural diagrams. All H atoms in both structures were found in different Fourier maps.
and were refined with isotopic atomic displacement parameters. The centrosymmetric settings of the space groups were ascertained on the basis of successful solution and refinement of the structures. Details of data collection and refinement for 6b are presented in Table 4.3.3 (Experimental section). Position coordinates and isotopic thermal parameters for all atoms in both structures are listed in Table 4.3.4 (Experimental section).

![Fig. 4.3.2 ¹H NMR of 7a (starting compound)](image)
Fig. 4.3.3 $^{13}$C NMR of 7a (starting compound)

Fig. 4.3.4 $^1$H NMR of 1b (product)
Fig. 4.3.5 $^{13}$C NMR of 1b (product)

Fig. 4.3.6 $^1$H NMR of 7b (product)
4.3.5 Conclusions

Some new spiro ethers have synthesized via intramolecular etherification reaction in presence of palladium incorporated cobalt ferrite magnetic nano catalyst. The reaction is efficient in ethanol at 90 °C to yield various spiro-ethers in good to high yield.
Experimental Section

Procedure for the synthesis of bromo-alcohols

To a stirred solution of 2-bromo-1-iodo benzene (0.57g, 2 mmol) in THF (20 mL), at -90 °C, was added drop wise, n-BuLi (0.8 mL of 2.5 molar solution in hexane, 2 mmol) via syringe. After 5 min at -90 °C, a solution of the cyclohexanone derivative (1.5 mmol) in THF (5 mL) was added drop wise. The reaction mixture was stirred at the same temperature for 3 h, quenched with aqueous NH₄Cl solution and the reaction mixture was allowed to attain room temperature. Organic solvent was removed under reduced pressure and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude product was purified by flash column chromatography (230-400 mesh silica gel) using petroleum ether-ethyl acetate mixture as eluent.

General procedure for the synthesis of spirocyclic ethers

To a mixture of 1-(2'-bromo-1,1'-biphenyl-2-yl)cyclohexanol derivative (0.2 mmol), 2-dicyclohexylphosphino-2'-((N,N-dimethylamino)-biphenyl (0.04 mmol) and NaO'Bu (0.5 mmol) in anhydrous ethanol (3 mL), in an oven dried schlenk tube, was added Pd-CoFe₂O₄ (0.001g, 0.004 mmol) under nitrogen atmosphere. The reaction mixture was sonicated for 10 min and then stirred in an oil bath at 90 °C for 24h. The reaction mixture was then cooled to room temperature, and the catalyst was separated by magnetic decantation. The solvent was evaporated and the residue was taken up in ethyl acetate (5 mL) and washed with saturated aqueous NH₄Cl. The organic phase was washed with brine and dried over Na₂SO₄ filtered and concentrated under reduced...
pressure. The residue was then purified by chromatography on silica gel using petroleum ether.

**Experimental data:**

**Entry 1a** (1-(2′-bromo-1,1′-biphenyl-2-yl)cyclohexanol)

![Chemical Structure](image)

IR (CHCl₃, cm⁻¹): v 3499, 3048, 2920, 1693, 1450, 1264, 1021, 751.

¹H NMR (400 MHz, CDCl₃): δ 0.92-1.2 (m, 2H), 1.31-1.45 (m, 2H), 1.45-1.64 (m, 3H), 1.64-1.8 (m, 3H), 6.88 (dd, J = 7.57, 1.27 Hz, 1H), 7.04-7.14 (m, 1H), 7.14-7.24 (m 3H), 7.24-7.35 (m, 1H), 7.49 (d, J = 7.83 Hz, 1H), 7.53 (d, J = 8.58 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 21.9, 25.4, 38.7, 39.1, 75.1, 124.0, 126.1, 126.4, 126.5, 127.8, 128.3, 130.8, 132.0, 132.2, 138.8, 145.4, 146.4

HRMS: Calculated for [M + Na]⁺ = 353.05115; found: 353.05111

**Entry 2a** (1-(2′-bromo-1,1′-biphenyl-2-yl)-4-tert-butylcyclohexanol)

![Chemical Structure](image)
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.78 (s, 9H), 0.83-0.94 (m, 1H), 1.25-1.41 (m, 2H), 1.44-1.57 (m, 2H), 1.64-1.74 (m, 1H), 1.76-1.95 (m, 3H), 6.92 (d, \(J = 6.57\) Hz, 1H), 7.1-7.17 (m, 1H), 7.18-7.30 (m, 3H), 7.33 (t, \(J = 7.9\) Hz, 1H), 7.50 (d, \(J = 8.08\) Hz, 1H), 7.57 (d, \(J = 8.09\) Hz, 1H).

\(^1\)3C NMR (400 MHz, CDCl\(_3\)): \(\delta\) 23.7, 27.6, 32.4, 39.2, 39.9, 47.4, 74.8, 124.0, 126.1, 126.4, 126.5, 127.8, 128.3, 130.8, 132.0, 132.3, 139.0, 145.5, 146.3.

HRMS: Calculated for [M + Na]\(^+\) = 409.11375; found: 409.113957

**Entry 3a** (1-\((2'\text{-bromo-1, 1'}\text{-biphenyl-2-yl})\text{cyclopentanol})

\[
\text{Mp: 82-83 °C}
\]

IR (KBr, cm\(^{-1}\)): \(\nu\) 3421, 2940, 1596, 1440, 1082, 996, 751.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.44-1.61 (m, 3H), 1.61-1.74 (m, 1H), 1.74-2.0 (m, 4H), 6.98 (dd, \(J = 7.32, 1.52\) Hz, 1H), 7.09-7.18 (m, 1H), 7.18-7.85 (m, 4H), 7.5 (dd, \(J = 7.83, 1.02\) Hz, 1H), 7.5 (d, \(J = 7.84, 1.01\) Hz, 1H).

\(^1\)3C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 23.1, 23.2, 39.8, 41.1, 84.1, 124.4, 126.4, 126.7, 127.8, 128.7, 131.7, 131.8, 132.3, 140.1, 143.5, 144.3.

HRMS: Calculated for [M + Na]\(^+\) = 339.03550; found: 339.03555
**Entry 4a** (1-(2'-bromo-1,1'-biphenyl-2-yl)-4-methylcyclohexanol)

![Structure of Entry 4a](image)

$^1$H (400 MHz, CDCl$_3$): $\delta$ 0.78 (d, $J = 5.6$ Hz, 3H), 1.15-1.30 (m, 3H), 1.32-1.57 (m, 2H), 1.60-1.88 (m, 4H), 6.89 (dd, $J = 7.6$ Hz, 1.3 Hz, 1H), 7.07-7.14 (m, 1H), 7.15-7.26 (m, 3H), 7.27-7.35 (m, 1H), 7.50 (d, $J = 8.08$ Hz, 1H), 7.53 (d, $J = 7.83$ Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 22.4, 30.4, 31.8, 38.7, 39.1, 74.7, 124.1, 126.1, 126.3, 126.4, 127.8, 128.3, 130.8, 132.0, 132.3, 138.9, 145.4, 146.4.


**Entry 5a** (1-(2'-bromo-1,1'-biphenyl-2-yl)-2-isopropyl-5-methylcyclohexanol)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.65-1.05 (m, 10H), 1.4-2.1 (m, 8H), 6.93 (d, $J = 8.1$ Hz, 1H), 6.98 (d, $J = 8.9$ Hz, 1H), 7.10-8.42 (m, 5H), 7.57 (d, $J = 8.1$ Hz, 1H).

$^{13}$C (100 MHz, CDCl$_3$): $\delta$ 18.4, 21.0, 22.2, 24.0, 27.0, 28.1, 35.3, 51.2, 77.2, 123.7, 125.6, 126.4, 126.6, 127.8, 128.0, 128.4, 131.6, 131.8, 139.3, 145.7, 146.2.

HRMS: Calculated for [M + Na]$^+$ = 409.11375; found: 409.11414.
Entry 6a (4-(2'-bromo-1,1'-biphenyl-2-yl)tetrahydro-2H-pyran-4-ol)

\[ \text{\textit{Entry 6a}} \]

\[ \text{\textit{Entry 7a}} \]

**Entry 6a** (4-(2'-bromo-1,1'-biphenyl-2-yl)tetrahydro-2H-pyran-4-ol)

\[
\begin{align*}
^1\text{H NMR}(400 \text{ MHz, CDCl}_3): & \ \delta 1.60-1.80 (m, 2H), 2.00-2.30 (m, 2H), 3.65-3.90 (m, 4H), 7.02 (dd, J= 1.5 Hz, 7.6Hz, 1H), 7.20-7.38 (m, 4H), 7.38-7.48 (m, 1H), 7.58 (d, J=8.08 Hz, 1H), 7.66 (d, J= 8.09 Hz, 1H). \\
^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3): & \ \delta 38.7, 39.2, 63.6, 72.6, 124.0, 126.3, 126.7, 126.8, 128.1, 128.7, 130.9, 132.2, 132.4, 139.0, 144.6, 144.7.
\end{align*}
\]

**HRMS:** Calculated for [M + Na]^+ = 355.03041; found: 355.030439

**Entry 7a** (\textit{tert}-butyl 4-(2'-bromo-1,1'-biphenyl-2-yl)-4-hydroxypiperidine-1-carboxylate)

\[
\begin{align*}
^1\text{H} (400 \text{ MHz, CDCl}_3): & \ \delta 1.37 (s, 9H), 1.6-1.75 (m, 3H), 1.75-1.90 (m, 1H), 3.6-3.7 (m, 1H), 3.7-3.9 (m, 3H), 6.92 (d, J= 7.6 Hz, 1H), 7.10-7.35 (m, 5H), 7.43 (d, J= 8.1 Hz, 1H), 7.56 (d, J= 7.8 Hz, 1H). \\
^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3): & \ \delta 28.4, 38.1, 38.5, 39.6, 39.7, 73.4, 79.3, 124.0, 126.3, 128.1, 128.7, 130.8, 132.2, 132.5, 138.9, 144.6, 144.7, 154.7.
\end{align*}
\]

**HRMS:** Calculated for [M + Na]^+ = 454.09883; found: 454.098632
Entry 1b (spiro[benzo[c]chromene-6,1'-cyclohexane])

```
          O
       /   |
      /     |
   Ph -- C -- C -- C
```

Mp: 79 °C

IR (KBr, cm⁻¹): ν 3048, 2921, 1631, 1425, 1266, 1092.

¹H NMR (400 MHz, CDCl₃): δ 1.13-1.28 (m, 1H), 1.48-1.66 (m, 4H), 1.68-1.90 (m, 3H), 1.98-2.12 (m, 2H), 6.86-7.01 (m, 2H), 7.10-7.32 (m, 4H), 7.64 (dd, J = 8.34, 1.52 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 21.6, 25.4, 34.7, 77.6, 118.0, 121.5, 122.3, 122.8, 122.9, 123.1, 127.5, 127.9, 129.0, 129.2, 139.9, 152.2.

HRMS: Calculated for [M + H]⁺ = 251.14304; found: 251.14313

Entry 2b (4'-tert-butylspiro[benzo[c]chromene-6,1'-cyclohexane])

```
          O
       /   |
      /     |
   Ph -- C -- C -- C
```

¹H NMR (400 MHz, CDCl₃): δ 0.86 (s, 9H), 0.96-1.11 (m, 1H), 1.52-1.70 (m, 6H), 2.06-2.16 (m, 2H), 6.88-6.98 (m, 2H), 7.10-7.30 (m, 4H), 7.65 (d, J = 7.8 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 22.3, 27.6, 32.6, 35.0, 47.1, 77.3, 118.0, 121.5, 122.3, 122.8, 122.9, 123.2, 127.5, 127.9, 129.1, 129.2, 139.7, 152.2.
HRMS: Calculated for [M + Na]$^+$ = 307.20564; found: 307.205828

**Entry 3b (spiro[benzo[c]chromene-6,1'-cyclopentane])**

![spiro[benzo[c]chromene-6,1'-cyclopentane]](image)

IR (CHCl$_3$, cm$^{-1}$): v 2928, 1619, 1429, 1249

$^1$H NMR (400 MHz, CDCl$_3$): δ 1065-1.80 (m, 2H), 1.81-1.98 (m, 4H), 2.10-2.24(m, 2H), 6.86 (dd, $J$ = 8.09, 1.02 Hz, 1H), 6.94 (dt, $J$ = 7.58, 1.02 Hz, 1H), 7.09-7.3 (m, 4H), 7.64 (dd, $J$ = 7.58, 1.02 Hz, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 23.9, 37.9, 88.6, 118.1, 121.6, 122.1, 122.8, 122.9, 123.2, 127.6, 127.8, 129.2, 129.6, 137.8, 152.9.

HRMS: Calculated for [M + H]$^+$ = 237.12739; found: 237.12736.

**Entry 4b (4'-methylspiro[benzo[c]chromene-6,1'-cyclohexane])**

![spiro[benzo[c]chromene-6,1'-cyclohexane]](image)

$^1$H NMR (400 MHz, CDCl$_3$): δ 0.98 (d, $J$ = 6.8 Hz, 3H), 1.21-1.31 (m, 2H), 1.76-2.07 (m, 7H), 6.90-6.97 (m, 2H), 7.12-7.17 (m, 1H), 7.20-7.30 (m, 3H), 7.64 (d, $J$ = 7.8 Hz, 2H).
$^{13}$C NMR (100 MHz, CDCl₃): $\delta$ 17.8, 26.6, 27.6, 29.7, 77.8, 118.0, 121.5, 122.4, 122.8, 123.1, 123.2, 127.5, 127.8, 129.1, 129.3, 139.8, 152.3.

HRMS: Calculated for [M + Na]$^+ = 287.14064$; found: 287.140616

**Entry 5b** (1-(2'-bromo-1,1'-biphenyl-2-yl)-2-isopropyl-5-methylcyclohexanol)

\[
\begin{align*}
\text{H NMR} & \quad (400 MHz, CDCl₃): \delta 0.78 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 7.1 Hz, 3H), 1.0-1.12 (m, 1H), 1.68-2.21 (m, 8H), 6.91-7.05 (m, 2H), 7.15-7.40 (m, 4H), 7.70-7.82 (m, 2H).
\end{align*}
\]

$^{13}$C NMR (400 MHz, CDCl₃): $\delta$ 18.2, 21.0, 22.0, 23.8, 27.5, 27.8, 35.1, 46.8, 47.0, 83.1, 117.6, 121.0, 121.6, 122.0, 122.6, 123.6, 127.1, 127.7, 129.2, 129.3, 138.7, 152.0.

HRMS: Calculated for [M + Na]$^+ = 329.18759$; found: 329.187618

**Entry 6b** (2', 3', 5', 6'-tetrahydrospiro[benzo[c]chromene-6,4'-pyran])

\[
\begin{align*}
\text{Mp.} & \quad 141-142 \, ^{\circ}C
\end{align*}
\]
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.88-1.97 (m, 2H), 1.98-2.09 (m, 2H), 3.73-3.82 (m, 2H), 3.88-4.0 (m, 2H), 6.93-7.01 (m, 2H), 7.13-7.20 (m, 2H), 7.22-7.32 (m, 2H), 7.63-7.70 (m, 2H).

\(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 35.0, 63.9, 75.7, 118.4, 122.4, 122.9, 123.2, 123.3, 123.5, 128.4, 128.6, 129.3, 129.9, 138.5, 152.1.

HRMS: Calculated for [M + Na]\(^+\) = 275.10425; found: 275.104247

**Entry 7b (tert-butyl \(1'H\)-spiro[benzo[c]chromene-6,4'-piperidine]-1'-carboxylate)**

![Chemical structure](image)

Mp: 127-128 °C

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.41 (s, 9H), 1.77-1.89 (m, 2H), 1.94-2.05 (m, 2H), 3.15-3.29 (m, 2H), 3.92-4.04 (m, 2H), 6.90-7.01 (m, 2H), 7.10 (7.20 (m, 2H), 7.20-7.32 (m, 2H), 7.62-7.70 (m, 2H)

\(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 28.5, 33.9, 39.4, 75.8, 79.5, 117.9, 122.0, 122.5, 122.7, 122.8, 123.1, 128.0, 128.2, 128.9, 129.5, 138.0, 151.6, 154.9

HRMS; Calculated for [M + Na]\(^+\) = 374.17266; found: 374.173028
Table 4.2.3 Crystal data and structure refinement for pp-8.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>pp-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C16 H13 O2</td>
</tr>
<tr>
<td>Formula weight</td>
<td>237.26</td>
</tr>
<tr>
<td>Temperature</td>
<td>296(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(1)/c</td>
</tr>
</tbody>
</table>
| Unit cell dimensions | \( a = 9.4431(6) \) Å  
\( b = 21.0773(14) \) Å  
\( c = 6.6800(4) \) Å  
\( \alpha = 90^\circ \)  
\( \beta = 101.874(4)^\circ \)  
\( \gamma = 90^\circ \) |
| Volume              | 1301.10(14) Å³ |
| Z                   | 4 |
| Density (calculated)| 1.211 Mg/m³ |
| Absorption coefficient | 0.079 mm⁻¹ |
| F(000)              | 500 |
| Theta range for data collection | 1.93 to 28.01° |
| Index ranges        | -12 ≤ h ≤ 10, -24 ≤ k ≤ 24, -8 ≤ l ≤ 8 |
| Refractions collected | 14480 |
| Independent refractions | 2880 [R(int) = 0.0774] |
| Completeness to theta = 28.01° | 91.5 % |
Refinement method

Data / restraints / parameters

Goodness-of-fit on F^2

Final R indices [I>2\sigma(I)]

R indices (all data)

Largest diff. peak and hole

Full-matrix least-squares on F^2

2880 / 0 / 172

0.809

R1 = 0.0552, wR2 = 0.1487

R1 = 0.1320, wR2 = 0.1696

0.395 and -0.194 eÅ^3

Table 4.2.4 Atomic coordinates \((x \times 10^4)\) and equivalent isotropic displacement parameters \((\text{Å}^2 \times 10^3)\) for pp-8. \(U(\text{eq})\) is defined as one third of the trace of orthogonalized \(U_{ij}\) tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(3)</td>
<td>3659(2)</td>
<td>6156(1)</td>
<td>2413(2)</td>
<td>56(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>1782(2)</td>
<td>6256(1)</td>
<td>-681(3)</td>
<td>46(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>4250(2)</td>
<td>6660(1)</td>
<td>-544(3)</td>
<td>44(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>5325(3)</td>
<td>6932(1)</td>
<td>-1410(3)</td>
<td>53(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>2695(2)</td>
<td>6661(1)</td>
<td>-1487(3)</td>
<td>42(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>6115(3)</td>
<td>6370(1)</td>
<td>2395(4)</td>
<td>59(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>319(2)</td>
<td>6240(1)</td>
<td>-1584(3)</td>
<td>58(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>1453(2)</td>
<td>5700(1)</td>
<td>2619(3)</td>
<td>63(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>4687(2)</td>
<td>6386(1)</td>
<td>1374(3)</td>
<td>48(1)</td>
</tr>
</tbody>
</table>

- 222 -
<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>°</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(8)</td>
<td>2096(2)</td>
<td>7060(1)</td>
<td>-3088(3)</td>
<td>53(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>2441(2)</td>
<td>5834(1)</td>
<td>1121(3)</td>
<td>48(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>2596(2)</td>
<td>4678(1)</td>
<td>3489(3)</td>
<td>79(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>-240(3)</td>
<td>6627(1)</td>
<td>-3228(3)</td>
<td>61(1)</td>
</tr>
<tr>
<td>C(17)</td>
<td>2952(2)</td>
<td>5213(1)</td>
<td>416(3)</td>
<td>57(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>7141(3)</td>
<td>6642(1)</td>
<td>1468(4)</td>
<td>63(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>6748(3)</td>
<td>6924(1)</td>
<td>-414(4)</td>
<td>60(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>644(3)</td>
<td>7042(1)</td>
<td>-3958(3)</td>
<td>58(1)</td>
</tr>
<tr>
<td>C(16)</td>
<td>3603(3)</td>
<td>4792(1)</td>
<td>2226(3)</td>
<td>67(1)</td>
</tr>
<tr>
<td>C(15)</td>
<td>2161(3)</td>
<td>5248(2)</td>
<td>4314(4)</td>
<td>75(1)</td>
</tr>
</tbody>
</table>

Table 4.2.5  Bond lengths [Å] and angles [°] for pp-8.
C(5)-C(4) 1.371(3)
C(7)-C(8) 1.386(3)
C(2)-C(3) 1.378(3)
C(2)-C(1) 1.381(3)
C(11)-C(10) 1.382(3)
C(14)-C(15) 1.525(3)
C(14)-C(13) 1.528(3)
C(8)-C(9) 1.376(3)
C(13)-C(17) 1.503(3)
O(2)-C(16) 1.415(3)
O(2)-C(15) 1.417(3)
C(10)-C(9) 1.368(3)
C(17)-C(16) 1.523(3)
C(3)-C(4) 1.371(3)

C(1)-O(3)-C(13) 114.44(15)
C(11)-C(12)-C(7) 119.0(2)
C(11)-C(12)-C(13) 122.4(2)
C(7)-C(12)-C(13) 118.53(19)
C(1)-C(6)-C(5) 116.9(2)
C(1)-C(6)-C(7) 118.39(19)
C(5)-C(6)-C(7) 124.7(2)
<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(4)-C(5)-C(6)</td>
<td>121.2(2)</td>
</tr>
<tr>
<td>C(8)-C(7)-C(12)</td>
<td>118.8(2)</td>
</tr>
<tr>
<td>C(8)-C(7)-C(6)</td>
<td>122.9(2)</td>
</tr>
<tr>
<td>C(12)-C(7)-C(6)</td>
<td>118.30(18)</td>
</tr>
<tr>
<td>C(3)-C(2)-C(1)</td>
<td>118.2(2)</td>
</tr>
<tr>
<td>C(10)-C(11)-C(12)</td>
<td>120.9(2)</td>
</tr>
<tr>
<td>C(15)-C(14)-C(13)</td>
<td>111.55(19)</td>
</tr>
<tr>
<td>C(2)-C(1)-C(6)</td>
<td>122.7(2)</td>
</tr>
<tr>
<td>C(2)-C(1)-O(3)</td>
<td>117.1(2)</td>
</tr>
<tr>
<td>C(6)-C(1)-O(3)</td>
<td>120.02(19)</td>
</tr>
<tr>
<td>C(9)-C(8)-C(7)</td>
<td>121.6(2)</td>
</tr>
<tr>
<td>O(3)-C(13)-C(17)</td>
<td>109.00(18)</td>
</tr>
<tr>
<td>O(3)-C(13)-C(12)</td>
<td>109.87(17)</td>
</tr>
<tr>
<td>C(17)-C(13)-C(12)</td>
<td>111.50(17)</td>
</tr>
<tr>
<td>O(3)-C(13)-C(14)</td>
<td>102.26(16)</td>
</tr>
<tr>
<td>C(17)-C(13)-C(14)</td>
<td>108.92(19)</td>
</tr>
<tr>
<td>C(12)-C(13)-C(14)</td>
<td>114.82(18)</td>
</tr>
<tr>
<td>C(16)-O(2)-C(15)</td>
<td>111.85(19)</td>
</tr>
<tr>
<td>C(9)-C(10)-C(11)</td>
<td>119.9(2)</td>
</tr>
<tr>
<td>C(13)-C(17)-C(16)</td>
<td>111.15(18)</td>
</tr>
<tr>
<td>C(4)-C(3)-C(2)</td>
<td>120.7(2)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(5)</td>
<td>120.2(2)</td>
</tr>
</tbody>
</table>
C(10)-C(9)-C(8)119.6(2)
O(2)-C(16)-C(17)111.18(19)
O(2)-C(15)-C(14)111.01(19)

Symmetry transformations used to generate equivalent atoms:

Table 4.2.6 Anisotropic displacement parameters (Å² x 10³) for pp-8. The anisotropic displacement factor exponent takes the form: 

\[-2\sum_{ij} U_{ij} x_i x_j + ... + 2 h k a^* b^* U_{ij} \]

<table>
<thead>
<tr>
<th></th>
<th>U₁₁</th>
<th>U₁₂</th>
<th>U₁₃</th>
<th>U₂₂</th>
<th>U₂₃</th>
<th>U₃₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(3)</td>
<td>54(1)</td>
<td>61(1)</td>
<td>49(1)</td>
<td>-2(1)</td>
<td>-1(1)</td>
<td>-9(1)</td>
</tr>
<tr>
<td>O(12)</td>
<td>40(1)</td>
<td>45(2)</td>
<td>51(1)</td>
<td>2(1)</td>
<td>6(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>42(1)</td>
<td>37(1)</td>
<td>52(1)</td>
<td>0(1)</td>
<td>8(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>52(2)</td>
<td>46(2)</td>
<td>60(1)</td>
<td>6(1)</td>
<td>13(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>42(1)</td>
<td>40(1)</td>
<td>44(1)</td>
<td>-1(1)</td>
<td>7(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>47(2)</td>
<td>61(2)</td>
<td>64(1)</td>
<td>3(1)</td>
<td>1(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>45(2)</td>
<td>67(2)</td>
<td>60(1)</td>
<td>3(1)</td>
<td>6(1)</td>
<td>-5(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>53(2)</td>
<td>78(2)</td>
<td>59(1)</td>
<td>0(1)</td>
<td>15(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>42(2)</td>
<td>45(2)</td>
<td>55(1)</td>
<td>3(1)</td>
<td>7(1)</td>
<td>-5(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>54(2)</td>
<td>49(2)</td>
<td>55(1)</td>
<td>7(1)</td>
<td>10(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>45(1)</td>
<td>43(2)</td>
<td>56(1)</td>
<td>2(1)</td>
<td>9(1)</td>
<td>-7(1)</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>C(2)</td>
<td>84(1)</td>
<td>69(1)</td>
<td>81(1)</td>
<td>25(1)</td>
<td>11(1)</td>
<td>-11(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>44(2)</td>
<td>80(2)</td>
<td>53(1)</td>
<td>-2(1)</td>
<td>-2(1)</td>
<td>6(1)</td>
</tr>
<tr>
<td>C(17)</td>
<td>60(2)</td>
<td>57(2)</td>
<td>51(1)</td>
<td>-9(1)</td>
<td>8(1)</td>
<td>-8(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>39(2)</td>
<td>64(2)</td>
<td>79(2)</td>
<td>-5(1)</td>
<td>0(1)</td>
<td>-4(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>48(2)</td>
<td>55(2)</td>
<td>80(2)</td>
<td>2(1)</td>
<td>18(1)</td>
<td>-5(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>56(2)</td>
<td>66(2)</td>
<td>50(1)</td>
<td>9(1)</td>
<td>4(1)</td>
<td>11(1)</td>
</tr>
<tr>
<td>C(16)</td>
<td>78(2)</td>
<td>61(2)</td>
<td>59(2)</td>
<td>6(1)</td>
<td>7(1)</td>
<td>10(2)</td>
</tr>
<tr>
<td>C(15)</td>
<td>63(2)</td>
<td>118(3)</td>
<td>48(1)</td>
<td>9(2)</td>
<td>20(1)</td>
<td>-14(2)</td>
</tr>
</tbody>
</table>
4.4 References


