## Section A

# *"Pd-Catalyzed transfer hydrogenation (CTH) using recyclable polymer-supported formate (PSF): Efficient and chemoselective reduction of nitroarenes"*

## I.A.1: Present Work: Background, Objectives and Strategy

Reduction of organic compounds is important synthetically both in the laboratory and in industry. Reduction generally means that the addition of hydrogen to an unsaturated bond or substitution of a group by hydride ion. Reduction of multiple bonds using molecular hydrogen ($H_2$) in presence of metal catalyst (generally heterogeneous Pd on charcoal or any other homogeneous metal catalysts) has long been known to be a robust procedure. The catalytic transfer hydrogenation reaction can be generalized as follows:

$$DHx + nA \xrightarrow[\text{solvent}]{\text{catalyst}} nAHx + D \qquad (1)$$

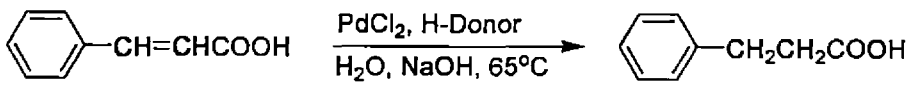
The donor compound DHx can be, in principle, be any organic compound whose oxidation potential is sufficiently low so that the hydrogen transfer can occur under mild conditions. At higher temperatures, especially in the presence of catalysts, almost any organic compound can donate hydrogen (catalytic cracking), but this has little potential for controlled synthesis.

Of all the methods available for addition of hydrogen to organic compounds, heterogeneous catalytic transfer reactions have been relatively underutilized. This lack of popularity can be traced to the relatively meager success of much of the earlier research which suggested that the technique was of only limited scope and could provide only modest yields of products. The earlier pioneering work by Braude[170] was largely ignored because of poor yields and long reactions times, but the situation has changed considerably following the appearance[171] of stimulating review and the introduction of greater catalyst loadings and different hydrogen donors.[172] Another reason for the underutilization of transfer reduction has been very successful exploitation of molecular hydrogen and hydrides for reduction of organic compounds.

The most popular H–donors are alcohols, including chiral ones, and formic acid.[173] More recently, formic acid and its salts such as ammonium formates, potassium formate, alkyl–ammonium formates, in particular triethylammonium formate (TEAF), have proven to be useful sources of hydrogen, due to their solubility in organic solvents.[174] Since dehydrogenation of formic acid derivatives is an irreversible and exothermic process,[175] this usually overwhelms the energetic

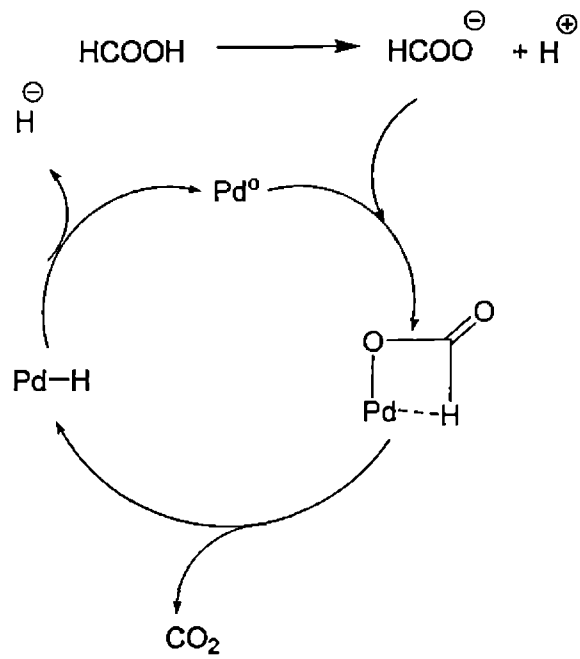
requirement of the reduction process. The use of such H–donors is recommended in reactions where unfavorable energetic balances are expected. Arterburn *et al.*[176] reported a convenient, effective method for the reduction of unsaturated carboxylic acids using non–pyrophoric catalyst $PdCl_2$, HCOOH and NaOH base in water (Scheme 57).

Scheme 57




A plausible mechanism of metal (palladium) catalyzed decomposition of formic acid or its salt is given below (Scheme 58). Formic acid gets ionized into $H^+$ and $HCOO^-$ in reaction medium. Then the formate anion ($HCOO^-$) is adsorbed on the active site of palladium catalyst and liberates $CO_2$ together with Pd–H, which supplies $H^-$ (hydride) that is actually responsible for transfer hydrogenation reaction.

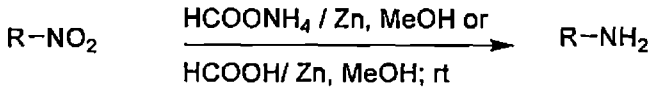
Scheme 58




With the aid of CTH aliphatic and aromatic nitro compounds are selectively reduced to corresponding amine in good yields. Cyclohexene, α–phellandrene, formic acid and its salt are used extensively as H–donor for the reduction of nitro

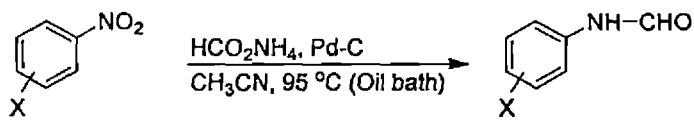
group. Gowda *et al.*[177] have developed the selective reduction of nitro group to corresponding amine as follows (Scheme 59).

Scheme 59



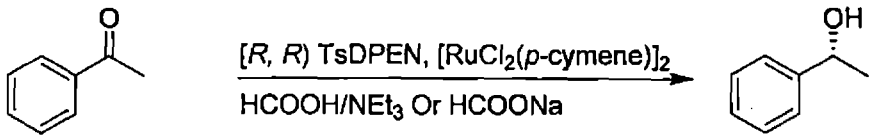

Formanilides have been widely used in the synthesis of biologically active compounds[178] such as N,N–diaryl ureas,[61a] cancer chemotherapeutic agents[178] and quinolone antibacterial.[179] N–Formyl compounds are lewis bases, which are known to catalyze allylation[181] and hydrosilylation.[182] Pratap and Baskaran[183] made an interesting observation that ammonium formate in an aprotic solvent like acetonitrile can function as a formylating agent[184] apart from being a source of hydrogen. Based on this observation, they have developed a novel and highly selective procedure (Scheme 60) for the direct conversion of aryl nitro compounds to formanilides in acetonitrile under CTH conditions.

Scheme 60




Asymmetric transfer hydrogenation, which affords chiral compounds, is one of the most important enantioselective catalytic transformations because of its high enantioselectivity, high product yield and operation simplicity. During the last decades thousands of chiral catalysts have been developed for a great variety of enantioselective transformations, and many of them are known to be highly effective.[185] Asymmetric transfer hydrogenation with ruthenium complexes has recently emerged as an effective approach to asymmetric carbonyl reduction,[186] although metal complexes of samarium,[187] rhodium,[188] iridium[186d,189] have been used successfully. Recently, Lui *et al.*[190] reported ruthenium catalyzed asymmetric transfer hydrogenation of ketones (Scheme 61) in HCOOH/$NEt_3$, as well in water with $HCO_2Na$ as a hydrogen source, in later combination they used sodium dodecyl sulfate as the phase transfer catalyst. They used (*R,R*)–N–(p–tolylsulfonyl)–1,2–diphenylethylene diamine as a chiral ligand [TsDPEN].

Scheme 61




99% Conversion
97% ee

The selective reduction of functional groups is a common need in organic synthesis. Catalytic transfer hydrogenation (CTH) with the aid of a stable hydrogen donor is a useful alternative method to catalytic hydrogenation by molecular hydrogen.[171a,175,191] The use of a H–donor has some advantages over molecular hydrogen since it avoids the risks and the constraints associated with hydrogen gas as well as the necessity for pressure vessels and other equipment. Formic acids and its salts are frequently employed as hydrogen donor in CTH reactions. Formate anion supported on a polymer backbone acts as a stable hydrogen donor.[192] Ammonium formate that acts as a H–donor in CTH reaction often leads the N–formyl derivatives[184] when nitro group is treated with ammonium formate in presence of Pd catalyst.

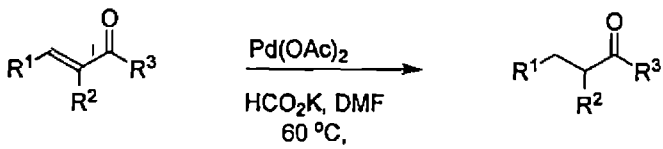
## I.A.2: Present Work: Results and Discussion

From the above discussion on catalytic transfer hydrogenation (CTH), it is established that hydrogenation using molecular hydrogenation, which requires special apparatus, the $H_2$ gas of high purity, might be avoided by using this alternative technique. Although several organic and inorganic compounds have been shown to be useful as H–donors in CTH, formic acid and its salts have occupied a major part of transfer hydrogenations.

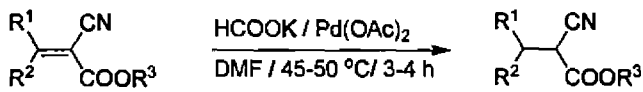
Although ammonium formate ($HCOONH_4$) has been employed as H–donor for the reduction of different functionality, researches from Cacchi's group[192] and from our laboratory[193] have shown that potassium formate (HCOOK) is a better choice than ammonium formate. Cacchi *et al.* reported that a combination of palladium acetate and potassium formate [$Pd(OAc)_2$/HCOOK] is a convenient alternative reductant for selective reduction of α,β–unsaturated carbonyl compounds to corresponding saturated carbonyl compounds (Scheme 62). On the other hand, reduction of conjugated nitriles and cyano ester using molecular hydrogen or

palladium catalyzed hydride–transfer afforded reduction of cyano group as well.[171a] To overcome such problems we used the combination of potassium formate and palladium acetate in DMF for the selective reduction of α, β–unsaturated cyano ester, possessing other sensitive functional groups, into corresponding saturated cyano ester scheme 63.

Scheme 62




Scheme 63




$R^3$ = Et, Sn(nBu)$_3$

Problems associated with using $HCOONH_4$, such as byproducts originated from reaction with ammonia, sublime–able nature etc., which might cause further reactions with the products,[183] (page 46) could be avoided by replacing with HCOOK. With the advent of immobilized techniques employed successfully in various organic transformations, we were looking for a simple and efficient polymer–supported H–donor to be used in CTH. We reasoned that such supported reagent could be used in excess to drive the reaction to completion and thereafter be separated from the reaction mixture by simple filtration. Various functionalized polymers have emerged as potential solid supports as tools for immobilization of reagents/catalysts. Literature reports reveal that while polymeric supports have been used for anchoring several reducing agents such as borohydrides,[49,50,51] tin hydrides[194] etc., solid supported H–donors have rarely been employed in CTH. To be more specific, ion–exchange resins have rarely been used to immobilize any suitable H–donor, except one report by Desai and Danks.[64] They reported that polymer (ion–exchange resins) supported formate can be used in Rh(I) catalyzed reduction of cinnamic acids (described in page no. 20). But their method lacks general applications and optimization with substrates bearing other reducible groups and other multiple bonds.[64]

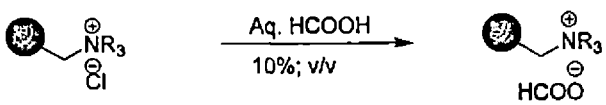
While exploring this area of research, we chose to use commercially available inexpensive Amberlite resins in its chloride form. Amberlite IRA® 900 (or IRA® 420) Cl ion–exchange resin is a cross–linked polymeric resin of styrene and divinylbenzene (1–2%). Functionally, it is aminomethyl polystyrene and its mechanical robustness, chemical inertness and facile functionalization are some of the attractive features of choice. The PSF (Polymer Supported Formate) was prepared by rinsing Amberlite resin (IRA® 420, Chloride form) packed in a column with 10% formic acid solution repeatedly until the washing gave negative response to chloride ion (Scheme 64). Finally the solid surface was washed several times with water and then dried under vacuum. The Amberlite resin formate was initially characterized by FT–IR spectral data, and compared with the corresponding absorption data of other salts (Table 1).

Table 1

| Entry | Symmetric Stretching ($\nu_{max}$) $cm^{-1}$ | Anti–symmetric Stretching ($\nu_{max}$) $cm^{-1}$ |
|---|---|---|
| $HCOONH_4$ | 1354 | 1595 |
| HCOOK | 1348 | 1593 |
| PSF | 1344 | 1593 |

The resulting resin formate when treated with catalytic amount of palladium acetate (2 mol% with respect to substrate) in DMF, an efficient reductant is generated that can be used for the reduction of nitroarenes (Scheme 65).

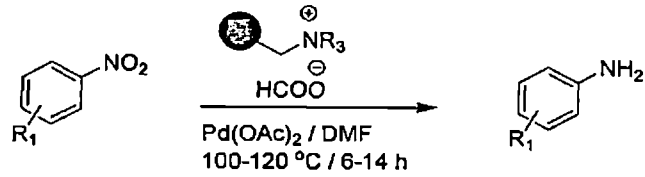
Scheme 64




Amberlite® IRA 420
Chloride form taken in water

Amberlite IRA 420
Formate form

Scheme 65

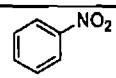
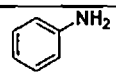
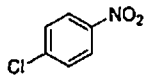
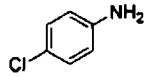
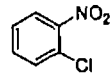
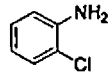
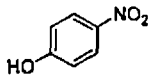
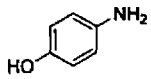
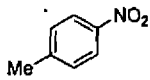
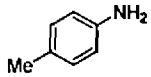
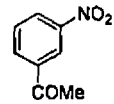
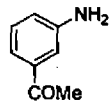
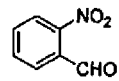
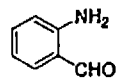
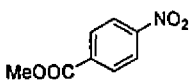
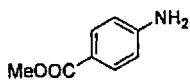
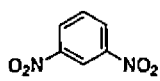
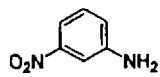
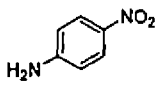
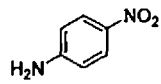
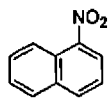
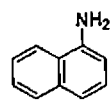
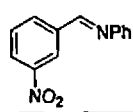
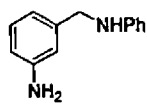



Reduction of nitroarenes to anilines is a synthetically important transformation, both in the laboratory and in industry.[195] A large number of methods have therefore been developed for the reduction of nitro groups. The reagents that are generally employed for the reduction include catalytic hydrogenation[196] with Pd/C, Raney Ni and $PtO_2$ or dissolving metal reduction, for example, with Sn/HCl,[197] Fe/HCl[198] and Fe/AcOH.[199] Reduction of aromatic nitro compounds with indium powder in ethanolic ammonium chloride[200] or $SmI_2$[201] results in selective reduction. Most of these methods require high pressure, specific hydrogenation apparatus, harsh reaction conditions or use of expensive metals and therefore lack the desired generality for true synthetic utility. Moreover, poor selectivity was reported in the reduction of aromatic nitro compounds bearing other potentially reducible groups such as carbonyl and halogen substituents.

The reduction of nitro group was carried out using 2 mol% $Pd(OAc)_2$ and formylated (aminomethyl)polystyrene (PSF) in a minimum quantity of DMF at 100–120 °C for 6–14 hours (Table 2). After filtration, extraction with ether followed by chromatographic purification afforded the desired anilines in good yields. The anilines in most cases were identified by comparison of spectroscopic data and/or melting points with literature values. Initially, reduction of nitrobenzene leading to aniline was performed in 82% yield. Concomitant reductive elimination of halogen on aromatic nucleus is often associated with transfer hydrogenation[202] and therefore poor selectivity was observed in the reduction of aromatic nitro compounds bearing halogen substituent. In our conditions, however, *o*– and *p*–chloronitrobenzene underwent reduction of the nitro group chemoselectively leading to corresponding chloroanilines in 71% and 77% yield respectively. *p*–Nitrophenol and *p*–nitrotoluene also underwent smooth reduction of the nitro group leading to the desired anilines. The selective and rapid reduction of nitro groups in the presence of carbonyl functionalities is also a highly valuable transformation in organic synthesis. The development of an efficient solid phase–bound reagent to achieve this goal has attracted considerable effort recently. We therefore investigated reduction of *m*–

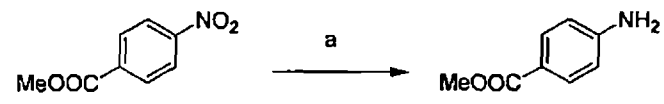
nitroacetophenone, *o*–nitrobenzaldehyde and methyl *p*–nitrobenzoate. The results showed that the formylated (aminomethyl)polystyrene (PSF) can effect highly efficient reduction of nitro groups in the presence of carbonyl functionalities. In transfer reduction of polynitrobenzenes, it was reported that use of much greater proportions of catalyst to substrates afforded only aminonitroarenes.[191C] In a typical case, dinitroarenes (*o*–, *m*–, *p*–) are reported to yield corresponding nitroanilines in 90% yields. At our hand, reduction of *p*–dinitrobenzene gave *p*–nitroaniline in 92% yield and further reduction to *p*–diaminobenzene was not possible. Previously, we[48] observed reduction of the C=N bond of imine using PSF and catalytic $Pd(OAc)_2$. The imine bearing a nitro group was examined under this condition and we obtained reduction of nitro group in addition to the imino group.

Table 2

| Entry | Nitroarene | Temp (°C)/ Time (h) | Anilines | Yield[b], (%) |
|---|---|---|---|---|
| 1 |  | 100 / 8 |  | 82 |
| 2 |  | 110 / 8 |  | 77 |
| 3 |  | 120 / 12 |  | 71 |
| 4 |  | 100 / 10 |  | 78 |
| 5 |  | 100 / 8 |  | 70 |
| 6 |  | 110 / 8 |  | 85 |
| 7 |  | 120 / 14 |  | 66 |
| 8 |  | 100 / 6 |  | 90 |
| 9 |  | 110 / 10 |  | 92 |
| 10 |  | 120 / 12 |  | No reaction |
| 11 |  | 110 / 10 |  | 77 |
| 12 |  | 100 / 12 |  | 66 |

In order to explore the efficiency and stability of the H–donor (PSF), recycling was examined with methyl *p*–nitrobenzoate as a substrate. Reduction proceeds to completion giving excellent yields through three successive recycle runs (Table 3). It should be noted that after separation of the Amberlite resin at the end of the three successive runs, the PSF can be easily generated and could be reused in further reductions.

Table 3




| Run | 1 | 2 | 3 |
|---|---|---|---|
| Yield (%) | 90 | 90 | 84 |
| Time/ h | 6 | 7 | 8 |

[a] Reagents and conditions: 2 mol% $Pd(OAc)_2$/ PSF (0.5 g/1 mmol nitro compound)/ DMF (1 ml)/ 100 °C.

## I.A.3: Conclusion

In summary, we have demonstrated that polymer–supported formate (PSF) can efficiently perform reduction of nitroarenes leading to anilines under palladium–catalyzed transfer hydrogenation conditions in small–scale reactions. The procedure is chemoselective for nitro group; and several other potentially reducible functionalities such as ketone, aldehyde, ester, and halide substituents on aromatic ring remain unaffected. Other advantages are clean work–up, high yields, and reusability of the PSF for at least three times and regeneration of PSF by reusing the recovered resin.

## I.A.4.A: Experimental Section: General

All reactions were performed in screw cap sealed tubes flashed with nitrogen. The minimal reaction times were determined by monitoring TLC of the reaction mixture. Silica gel (60–120 mesh) was used for chromatographic purifications. DMF was dried by distillation over $P_2O_5$. $^1$H–NMR and $^{13}$C–NMR were recorded at 300 MHz and 75 MHz respectively using Bruker AV–300 spectrometer. TMS was used as an internal standard and NMR spectral values are reported in ppm unit. Amberlite® IRA–420 $Cl^-$ standard grade (14–52 mesh) and palladium acetate were purchased from commercial suppliers and were used directly.

## I.A.4.A: Preparation of Polymer Supported Formate (PSF)

Anion exchange resin (Amberlite® IRA–420 $Cl^-$) was packed on a column and washed with water for two to three times. 10% aq. solution of formic acid was passed through it at slow rate of flow until washing gave the negative response to chloride ion ($AgNO_3$). The resin beads were washed with water for several times and dried

under vacuum. The resin thus obtained was then used for transfer hydrogenation reaction.

### I.A.4.B: General Procedure for Reduction of Nitroarene to Aniline

To a mixture of nitroarene (2 mmol) and palladium acetate (0.04 mmol, 2 mol%) in freshly distilled DMF (2 ml) was added PSF (1 g) and the reaction mixture was purged with $N_2$ for 2–3 min. The screw–cap tube was tightened and placed in a pre–heated oil bath for several hours (Table 2). After completion of the starting material as analyzed by TLC, the reaction mixture was taken in water, filtered through a cotton–bed and washed with ether. The ethereal layer was washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated. The residue was purified either by column chromatography over silica gel or by crystallization to afford the desired aniline.

### I.A.4.C: Spectral Analysis of Compounds

Entry 1: Aniline

Reaction temp: 100 °C; Time: 8 h,

Yield: 82%, (obtained as liquid); IR (neat): $\nu_{max}$ 3379, 2924, 2854, 1605, 1496, 1280 $cm^{-1}$.

Entry 2: 4–Chloroaniline:

Reaction temp: 110 °C; Time: 8 h,

Yield: 77%; (solid) mp 69–70 °C, (lit[203] mp 70-71 °C); IR (nujol): $\nu_{max}$ 3379, 2920, 2862, 1612, 1490, 1458, 1373, 1281 $cm^{-1}$.

Entry 3: 2-Chloroaniline

Reaction temp: 120 °C, Time: 12 h;

Yield: 71% (obtained as liquid); IR (neat): $\nu_{max}$ 3368, 2914, 2862, 1510, 1458 $cm^{-1}$.

Entry 4: 4–Aminophenol:

Reaction temp: 100 °C, Time: 10 h;

Yield: 78%; (solid) mp 184-185 °C, (lit[203] mp 186 °C); IR (nujol): $\nu_{max}$ 3340, 3294, 2910, 2854, 1612, 1512, 1466, 1380 $cm^{-1}$; $^1H$ NMR (300 MHz, CDCl3): $\delta$ = 6.28 (d, $J$ = 8.24 Hz, 2H), 6.19 (d, $J$ = 8.24 Hz, 2H), 3.00 (bs, 2H); $^{13}C$ NMR (75 MHz, CDCl3): $\delta$ = 148.85, 138.41, 115.58, 115.22.

Entry 5: 4–Toluidine:

Reaction temp: 100 °C, Time: 8 h,

Yield: 70%; (solid) mp 45–46 °C,(lit[203] mp 45 °C); IR (nujol): $\nu_{max}$ 3390 $cm^{-1}$; 1H NMR (300 MHz, CDCl3): δ = 6.97 (d, *J* = 8.24 Hz, 2H), 6.61 (d, *J* = 8.24 Hz, 2H), 3.52 (bs, 2H), 2.24 (s, 3H); 13C NMR (75 MHz, CDCl3): δ = 143.7, 129.6, 127.6, 115.2, 20.3.

Entry 6: 3–Aminoacetaphenone:

Reaction temp: 110 °C; Time: 8 h,

Yield: 85%; Recrystallized from ethanol, yellow plates; mp 98 °C; lit[203] mp 97-99 °C, IR (neat): $\nu_{max}$ 3480, 3371, 2910, 2854, 1712, 1670, 1458, 1377 $cm^{-1}$; $^1$H–NMR ($CDCl_3$, 300 MHz): δ = 7.33–7.19 (m, 2H), 6.87(dd, 1H, *J*=2.4 &1.2 Hz), 6.85 (dd, 1H, *J* = 2.4 & 1.2 Hz), 3.85 (s, 2H), 2.54 (s, 3H); $^{13}$C–NMR ($CDCl_3$, 75 MHz): δ = 198.5, 146.9, 138.3, 129.4, 119.7, 118.7, 114.0, 26.6.

Entry 7: 2–Amino benzaldehyde

Reaction temp: 120 °C; Time: 14 h,

Yield: 66%, (obtained as liquid); $^1$H–NMR ($CDCl_3$, 300 MHz): δ = 9.85 (s, 1H), 7.65 (m, 1H), 7.44–7.10 (m, 2H), 6.87 (d, 1H, *J* = 8Hz), 4.05 (s, 2H).

Entry 8: Methyl 4–aminobenzoate

Reaction temp: 100 °C; Time: 6 h,

Yield: 90%, (solid) mp 115 °C; IR (neat): $\nu_{max}$ 3460, 3371, 2915, 2858, 1690, 1604, 1458, 1377, 1288 $cm^{-1}$; $^1$H–NMR ($CDCl_3$, 300 MHz): δ = 7.84 (d, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 8.7 Hz, 2H), 4.1 (br s, 2H), 3.84 (s, 3H); $^{13}$C–NMR ($CDCl_3$, 75 MHz): δ = 167.13, 151.0, 131.0, 119.3, 114.0, 51.5.

Entry 9: 3–Nitroaniline

Reaction temp: 110 °C, Time: 10 h;

Yield: 92%, (pale yellow solid), mp 110–111 °C; lit[203] mp 114 °C; IR (nujol): $\nu_{max}$ 3433, 2915, 2858, 1624, 1519, 1458, 1350 $cm^{-1}$.

Entry 11: 1–Aminonapthalene

Reaction temp: 110 °C, Time: 10 h;

Yield: 77%, (solid), mp 49–50 °C; IR (nujol): $\nu_{max}$ 3390, 2900, 2854, 1624, 1458, 1377 $cm^{-1}$.

Entry 12: N-(3-Aminobenzyl)benzeneaminne

Reaction temp: 100 °C, Time: 12 h;

Yield: 66%; (solid); IR (nujol): $\nu_{max}$ 3400, 2935, 2850, 1614, 1530, 1450, $cm^{-1}$; $^1$H–NMR ($CDCl_3$, 300 MHz): δ = 7.20–7.15 (m, 2H), 7.09-7.04 (m, 1H), 6.78–6.74 (m, 1H), 6.64–6.55 (m, 3H), 6.5 (s, 1H), 6.41-6.38 (m, 1H), 4.46 (s, 2H), 4.0 (bs, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 147.2, 141.7, 118.2, 129.6, 129.4, 115.0, 118.6, 117.3, 113.5, 48.5.