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## Direct Liquid-Phase Amination of Phenols into Anilines and Cyclohexylamines

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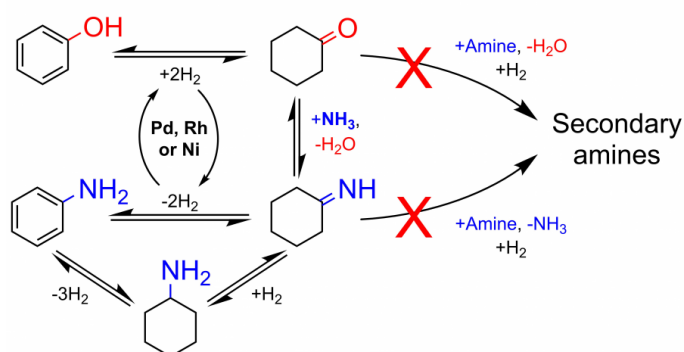
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## PURPOSE OF THE ABSTRACT

Anilines and cyclohexylamines are widely utilized as precursors for polymers, active pharmaceutical ingredients, fine chemicals, dyes and agrochemicals. Traditionally, these primary amines are obtained from arenes via multi-step processes, which display clear technological disadvantages such as hazardous synthesis routes and generation of toxic waste streams.[1] Phenols, on the other hand, are very attractive alternative starting materials since the overall transformation with ammonia (NH<sub>3</sub>) into anilines or cyclohexylamines only produce water as a by-product. Moreover, phenols are efficiently produced at low price and are also highly prevalent in renewable lignocellulosic biomass. Solid acidic catalysts have been used for the gas-phase transformation of phenol into aniline, but require high reaction temperatures and are quickly deactivated throughout the process. Alternatively, Ono et al. proposed a gas-phase transformation using supported noble metals in the presence of H<sub>2</sub> (scheme 1).[2] Even though moderate temperatures (250 °C) were applied, energy-intensive vaporization of phenol was still required and by-product formation was non-negligible. More recently, an interesting approach was proposed in which phenol is partially hydrogenated to cyclohexanone, which easily reacts with amines into an imine intermediate and (de)hydrogenated further into either N-substituted cyclohexylamines or anilines.[3-4] However, the production of primary amines remained a difficult challenge as by-product formation could drastically decrease product selectivity.

Herein, we report the first direct amination of phenol with NH<sub>3</sub> into primary amines (i.e. anilines and cyclohexylamines) in the liquid phase through an efficient one-step process. For this, a dedicated amination set-up was built in which gaseous NH<sub>3</sub> and H<sub>2</sub> can be added to a batch reaction mixture, allowing precise tuning of their concentrations in the liquid-phase. Both commercially available and self-prepared supported noble metals were able to catalyze this reaction in toluene or greener solvents, e.g., tert-amyl alcohol. While palladium (Pd) showed excellent selectivity towards anilines, rhodium (Rh) displayed a remarkable activity and selectivity towards cyclohexylamines.[5-6] As reactive imine intermediates are formed, it was shown that carefully controlling both H<sub>2</sub> and NH<sub>3</sub> partial pressures as well as reaction temperature were crucial to suppress by-product formation, viz. undesired secondary anilines and cyclohexylamines. As a result, aniline and cyclohexylamine yields were maximized (> 90%) in both cases. Finally, the scope for the direct amination of phenols was successfully expanded by converting a wide range of C-substituted phenols into their corresponding primary amines. In another part of this research, the use of non-noble metals, due to their abundance and low price, was also explored for the amination of phenols with either ammonia or amines. Particularly nickel (Ni), as an alternative to the expensive Rh, exhibited an outstanding selectivity (> 95%) towards the corresponding (N-substituted) cyclohexylamines at moderate reaction conditions.

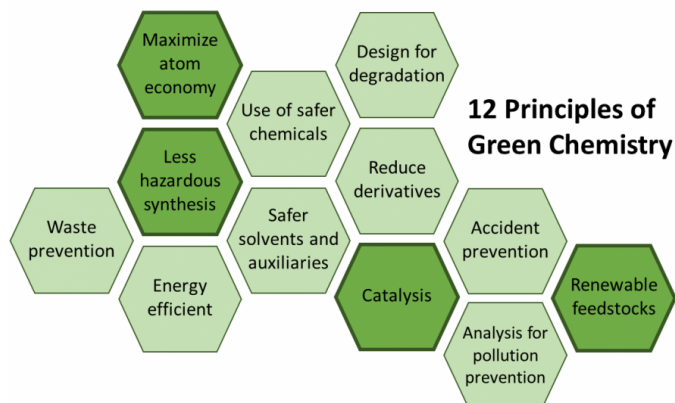
## FIGURES



**FIGURE 1**

Direct Amination of Phenol into Anilines and Cyclohexylamines

Phenol is partially hydrogenated to cyclohexanone, which quickly reacts with ammonia. The resulting cyclohexanimine is known to be very reactive and is either (in)directly dehydrogenated to aniline or hydrogenated to cyclohexylamine.



**FIGURE 2**

12 Principles of Green Chemistry

Highlighting the focus of this research regarding the production of primary amines.

## KEYWORDS

Amination | Phenol | Aniline | Cyclohexylamine

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