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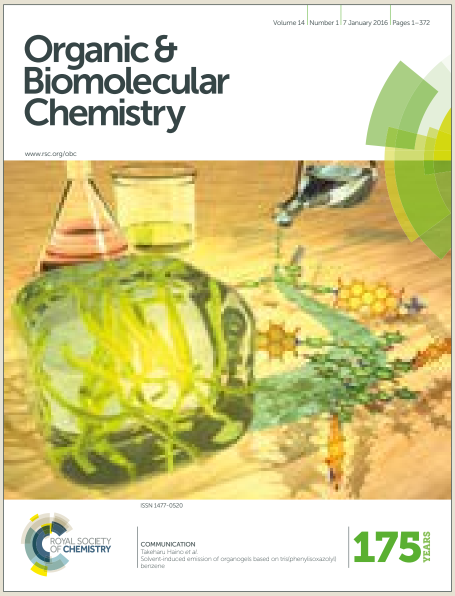

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# Application of 2-Aryl Indenylphosphine Ligand in the Buchwald-Hartwig Cross-Coupling Reactions of Aryl and Hereoaryl Chlorides under the Solvent-Free and Aqueous Conditions

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## Abstract

An efficient solvent-free protocol for the Buchwald–Hartwig cross-coupling reaction of aryl and heteroaryl chlorides with primary and secondary amines using the $Pd(dba)_2$/ligand **1** catalytic system has been developed. Notably, the catalytic system also efficiently catalyzed the reaction under aqueous conditions.

## Introduction

There has been a growing interest in developing cleaner and greener reactions for chemical transformations. It is one of the central subjects to develop efficient, environmental benefits and safe protocols for organic reactions, such as using water as a solvent or performing reactions without solvent.[1] The palladium-catalyzed Buchwald–Hartwig cross-coupling reaction is undoubtedly one of the most versatile tools for the formation of C–N bonds and has been widely applied in the pharmaceutical and fine-chemical industries.[2] Despite significant improvements in the amination of aryl chlorides, a comparably large amount of the palladium catalyst (>1 mol%), sensitive phosphine ligands and harmful and uneasily recoverable organic solvents, such as toluene and dioxane, still have to be used for the Buchwald–Hartwig cross-coupling reaction.[3-6]

The first example of a solvent-free Pd-catalyzed C–N cross-coupling reaction was reported in 2003 by Beletskaya et al.[7a] Meanwhile, the use of water in Pd-catalyzed C–N cross-coupling reactions was disclosed by Buchwald et al.[8a] Since then, several strategies for C–N cross-coupling reactions under solvent-free and aqueous conditions

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have been developed.[7–10] However, a number of challenges remain unresolved. For example, the coupling of the readily available and low-cost aryl and heteroaryl chlorides continues to pose difficulties with additives required to be added in some cases. We have recently developed a series of aryl-substituted indenyl phosphine ligands, which display excellent activity in Pd-catalyzed cross-coupling reactions.[11] Herein, we report the Pd(dba)$_2$/ligand **1** catalytic system, which exhibits high activity in the Buchwald–Hartwig cross-coupling reaction of aryl and heteroaryl chlorides with primary and secondary amines under solvent-free and aqueous conditions.

## Results and discussion

Initially, the reaction of chlorobenzene with aniline was investigated as a model reaction under solvent-free conditions for screening and optimization of the reaction conditions (Table 1). For example, 1.0 mol% of Pd(dba)$_2$, 2.0 mol% of ligand **1** and 1.4 equivalents of $^t$BuONa were used to obtained the coupling product in 71% yield (Table 1, entry 1), whereas low conversions were observed in the reaction with indenyl phosphine ligands **2** and **3** (Table 1, entries 2, 3). The temperature and reaction time was found to be crucial for a high yield in the reaction, the reaction conducted with 1.0 mol% of Pd(dba)$_2$ and 2.0 mol% ligand **1** gave 87% conversion at 110$^o$ C after 24 h (Table 1, entry 5). For comparison, several commercially available Pd sources, such as Pd(OAc)$_2$, Pd(acac)$_2$, PdCl$_2$(MeCN)$_2$ and PdCl$_2$ all provided disappointing results (Table 1, entries 6-9). Besides ligands **1**－**3**, various structurally diverse phosphine ligands were also examined for comparison. The reactions were carried out at 110$^o$ C for 24 h with Pd(dba)$_2$ as the catalyst precursor. Moderate conversions were generally observed in the cross-coupling reactions with ligands such as DiPPF, DPPF, DavePhos, CyJohnPhos, $^t$BuXPhos and SPhos (Table 1, entries 10-15), whereas the corresponding product was obtained in high yields with ligands RuPhos, $^t$BuDavePhos and XPhos (Table 1, entries 16-18).To further expand the application of this catalytic system, the optimized reaction conditions were established using Pd(dba)$_2$ (1.0 mol%)/**1** (2.0 mol%) as the catalyst, $^t$BuONa as the base at 110$^o$ C for 24 h.

With the optimized reaction conditions in hand, we then investigated the substrate scope of the Pd(dba)$_2$/ligand **1** catalytic system in the C–N cross-coupling reaction of aryl chlorides with amines. As shown in Table 2, chlorobenzene and aryl chlorides bearing an electron-donating group on the aromatic ring were proven to be suitable in the C–N cross-coupling reaction with various primary aryl amines and gave the desired products in moderate to good yield (52%–75%) (Table 2, entries 1–13). The reactions using 1-(4-chlorophenyl)ethan-1-one were also effective, albeit in giving the desired products in low to moderate yield (28%–59%) (Table 2, entries 14–17). It was observed that the reactions with aryl chlorides bearing an electron-donating group on the aromatic ring were more active. For example, *m*-toluidine reacted with 1-chloro-2-methylbenzene and 1-chloro-3-methylbenzene to give the corresponding products in 73% and 63% yield, respectively (Table 2, entries 5 and 10). However, *m*-toluidine reacted with 1-(4-chlorophenyl)ethan-1-one to give the desired product in only 28% yield (Table 2, entry 15). Additionally, the reactions of the secondary amine

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*N*-methylaniline with chlorobenzene, 1-chloro-2-methylbenzene, 1-chloro-3-methylbenzene and 1-(4-chlorophenyl)ethan-1-one gave the desired product in 75%, 73%, 64% and 28% yield, respectively (Table 2, entries 3, 7, 12 and 17). Morpholine also reacted smoothly to yield the corresponding C–N cross-coupling products in 29%–62% yield (Table 2, entries 4, 8 and 13).

To further extend the scope of our catalytic system, we carried out the reaction with various heteroaryl chlorides. As shown in Table 3, 2-chloropyridine, 3-chloropyridine, 8-chloroquinoline and 2-chloropyrazine successfully underwent the desired C–N cross-coupling reaction with anline, *m*-toluidine and 2-methoxyaniline to afford the corresponding products in moderate to good yields (44%–82%). Most of the reactions using the secondary amines *N*-methylaniline and morpholine also occurred smoothly to give the corresponding C–N cross-coupling products in moderate yield. However, the reactions of morpholine with 3-chloropyridine and 8-chloroquinoline only gave the desired product in 30% and 26% yield, respectively (Table 3, entries 10 and 19). Notably, the reaction of morpholine with 2-chloropyrazine gave the desired product in 75% yield (Table 3, entry 15).

Recently, performing organic transformations in or with water has gained increasing attention due to water being a cheap, green and safe solvent.[12, 13] However, little attention has been given to investigating the Buchwald–Hartwig cross-coupling reaction conducted under strictly aqueous conditions.[8–10] In general, additives including co-solvents and surfactants are required in the reaction.[9] The substrate scope is often limited in terms of the diversity of the amine substrates employed, and examples involving heteroaryl chlorides are scarce. Despite the Pd(dba)$_2$/ligand **1** catalytic system efficiently catalyzing the C–N cross-coupling reaction of various aryl and heteroaryl chlorides under solvent-free conditions, low yields were obtained in some cases. At the same time, we found the C–N cross-coupling reaction of chlorobenzene with aniline gave the corresponding product in 79% yield using the Pd(dba)$_2$/ligand **1**/$^t$BuONa catalytic system under aqueous conditions. Therefore, we then investigated the reaction of various aryl and heteroaryl chlorides with amines using the Pd(dba)$_2$/ligand **1**/$^t$BuONa catalytic system under aqueous conditions, the results are summarized in Table 4. All substrate pairings were successful in the C–N cross-coupling reaction and gave the desired products in moderate to good yield (50%–88%). Heteroaryl chlorides proved to suitable cross-coupling substrates as well as aryl chlorides (Table 4, entries 11-23). In addition, the secondary amines *N*-methylaniline and morpholine also reacted smoothly to give the corresponding C–N cross-coupling products in moderate yield (51%–79%). Interestingly, some reactions gave comparable yields to those observed in our investigations using solvent-free conditions, such as the reaction of 1-chloro-2-methylbenzene with *m*-toluidine (Table 2, entry 5 and Table 4, entry 4). Some reactions afforded higher yields under aqueous conditions, especially the reactions using 1-(4-chlorophenyl)ethan-1-one (Table 4, entries 9, 10). For example, a 28% yield was obtained in the reaction of 1-(4-chlorophenyl)ethan-1-one with *N*-methylaniline under solvent-free conditions, but it was dramatically increased to 60% yield under aqueous conditions (Table 2, entry 17 and Table 4, entry 10).

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## Conclusions

In summary, we have developed an efficient method to carry out the Buchwald–Hartwig cross-coupling reaction of aryl and heteroaryl chlorides with primary or secondary amines using the Pd(dba)$_2$/ligand **1** catalytic system under solvent-free conditions. Meanwhile, the reactions can also proceed smoothly using the same catalytic system under aqueous conditions with some reactions obtained in higher yields when compared with the solvent-free conditions. Further applications of this and related ligands in the development of more green metal-catalyzed transformations are currently in progress.

## Acknowledgements

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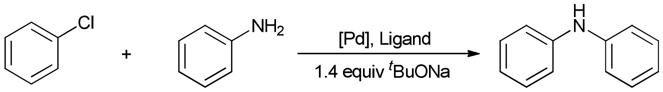
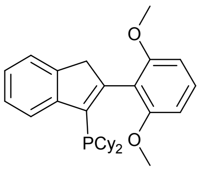
## Figure Legends

**Table 1.** Optimization conditions for the Buchwald-Hartwig cross-coupling reactions of chlorobenzene with aniline [a]



| Entry | [Pd] (mol%) | Ligand (mol%) | T (℃) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | Pd(dba)$_2$ (1.0) | **1** (2.0) | 100 | 20 | 71 |
| 2 | Pd(dba)$_2$ (1.0) | **2** (2.0) | 100 | 20 | 64 |
| 3 | Pd(dba)$_2$ (1.0) | **3** (2.0) | 100 | 20 | 61 |
| 4 | Pd(dba)$_2$ (0.1) | **1** (0.2) | 100 | 20 | 35 |
| 5 | Pd(dba)$_2$ (1.0) | **1** (2.0) | 110 | 24 | 87 |
| 6 | Pd(OAc)$_2$ (1.0) | **1** (2.0) | 110 | 24 | 33 |
| 7 | Pd(acac)$_2$ (1.0) | **1** (2.0) | 110 | 24 | 19 |
| 8 | PdCl$_2$(MeCN)$_2$ (1.0) | **1** (2.0) | 110 | 24 | 24 |
| 9 | PdCl$_2$ (1.0) | **1** (2.0) | 110 | 24 | 22 |
| 10 | Pd(dba)$_2$ (1.0) | **DiPPF** (2.0) | 110 | 24 | 61 |
| 11 | Pd(dba)$_2$ (1.0) | **DPPF** (2.0) | 110 | 24 | 68 |
| 12 | Pd(dba)$_2$ (1.0) | **DavePhos** (2.0) | 110 | 24 | 68 |
| 13 | Pd(dba)$_2$ (1.0) | **CyJohnPhos** (2.0) | 110 | 24 | 70 |
| 14 | Pd(dba)$_2$ (1.0) | **$^t$BuXPhos** (2.0) | 110 | 24 | 68 |
| 15 | Pd(dba)$_2$ (1.0) | **SPhos** (2.0) | 110 | 24 | 57 |
| 16 | Pd(dba)$_2$ (1.0) | **RuPhos** (2.0) | 110 | 24 | 85 |
| 17 | Pd(dba)$_2$ (1.0) | **$^t$BuDavePhos**(2.0) | 110 | 24 | 84 |
| 18 | Pd(dba)$_2$ (1.0) | **XPhos** (2.0) | 110 | 24 | 83 |

[a] Reaction conditions: chlorobenzene (2.5 mmol), aniline (3.0 mmol), [Pd] (1 mol% or 0.1 mol%), Ligand (2 mol% or 0.2 mol%) and $^t$BuONa (1.4 equiv, 3.5 mmol) at the required temperature for 20-24 h. [b] Isolated yield.



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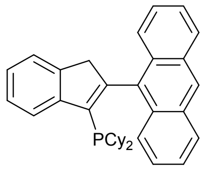

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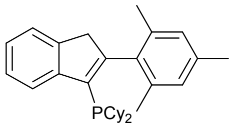

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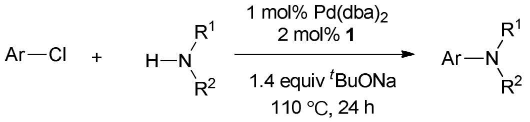
**Table 2.** Buchwald-Hartwig cross-coupling reactions of aryl chlorides with amines under solvent-free conditions$^a$



| Entry | ArCl | Amine | Product | Yield (%)$^b$ |
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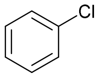
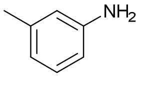
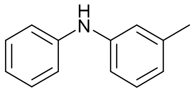
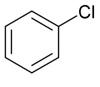
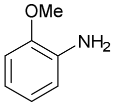
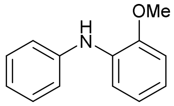
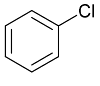
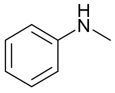
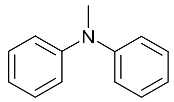
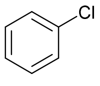
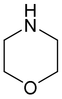
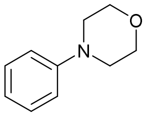
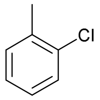
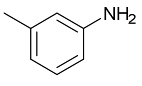
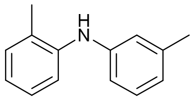
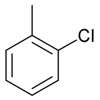
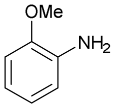
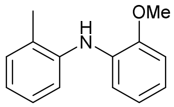
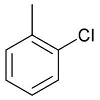
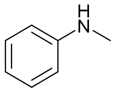
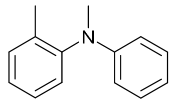
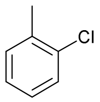
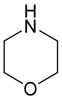
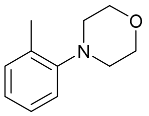
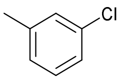
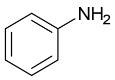
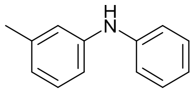
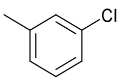
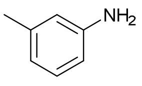
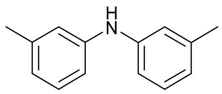
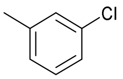
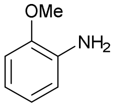
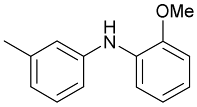
| 1 |  |  |  | 62 |
| 2 |  |  |  | 52 |
| 3 |  |  |  | 75 |
| 4 |  |  |  | 29 |
| 5 |  |  |  | 73 |
| 6 |  |  |  | 64 |
| 7 |  |  |  | 58 |
| 8 |  |  |  | 62 |
| 9 |  |  |  | 57 |
| 10 |  |  |  | 63 |
| 11 |  |  |  | 62 |

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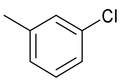
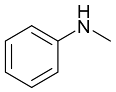
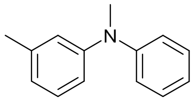
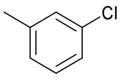
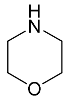
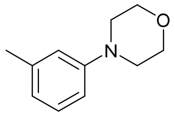
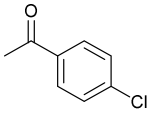
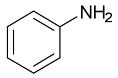
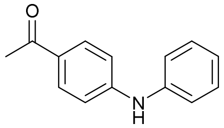
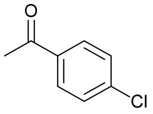
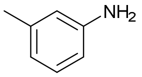
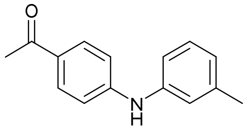
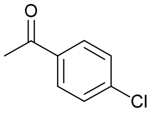
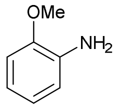
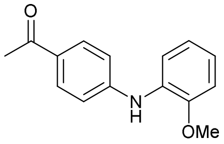
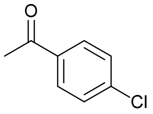
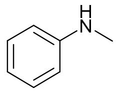
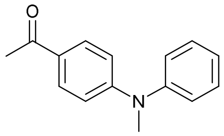
| 12 |  |  |  | 64 |
| 13 |  |  |  | 39 |
| 14 |  |  |  | 59 |
| 15 |  |  |  | 28 |
| 16 |  |  |  | 40 |
| 17 |  |  |  | 28 |

[a]Reaction conditions: ArCl (1.25 mmol), Amines (1.5 mmol), Pd(dba)$_2$ (1 mol%, 0.0125 mmol), ligand **1** (2 mol%, 0.025 mmol) and $^t$BuONa (1.4 equiv, 1.75 mmol) at 110 ºC for 24 h. [b]Isolated yield.

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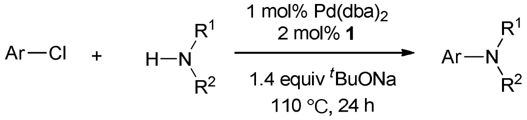
**Table 3.** Buchwald-Hartwig cross-coupling reactions of heteroaryl chlorides with amines under solvent-free conditions[a]



| Entry | ArCl | Amine | Product | Yield (%)[b] |
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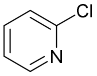
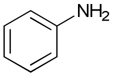
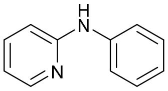
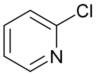
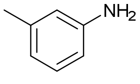
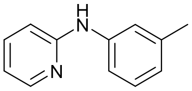
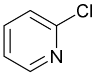
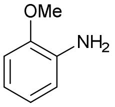
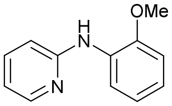
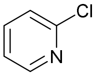
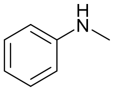
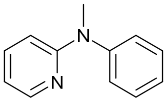
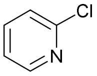
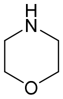
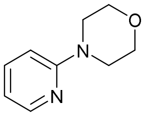
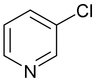
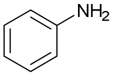
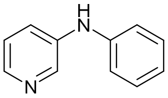
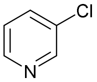
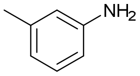
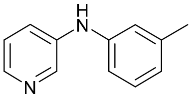
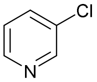
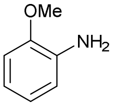
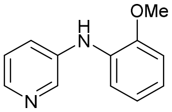
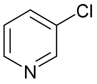
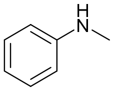
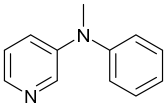
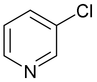
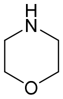
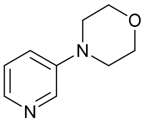
| 1 |  |  |  | 64 |
| 2 |  |  |  | 59 |
| 3 |  |  |  | 70 |
| 4 |  |  |  | 46 |
| 5 |  |  |  | 58 |
| 6 |  |  |  | 51 |
| 7 |  |  |  | 55 |
| 8 |  |  |  | 49 |
| 9 |  |  |  | 52 |
| 10 |  |  |  | 30 |

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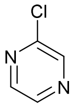
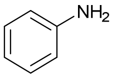
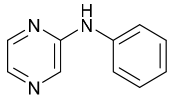
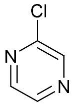
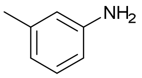
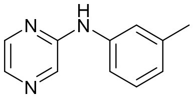
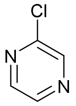
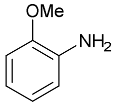
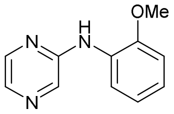
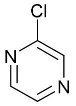
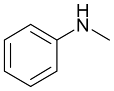
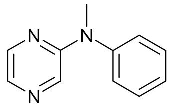
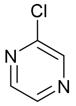
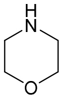
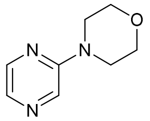
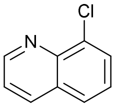
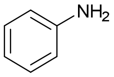
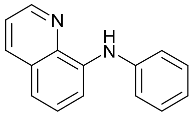
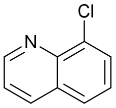
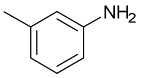
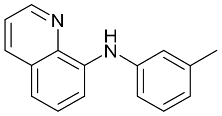
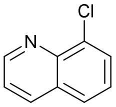
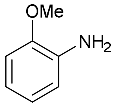
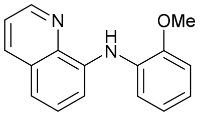
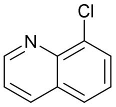
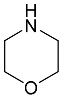
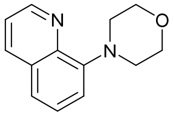
| 11 |  |  |  | 78 |
| 12 |  |  |  | 82 |
| 13 |  |  |  | 64 |
| 14 |  |  |  | 48 |
| 15 |  |  |  | 75 |
| 16 |  |  |  | 44 |
| 17 |  |  |  | 67 |
| 18 |  |  |  | 65 |
| 19 |  |  |  | 26 |

[a] Reaction conditions: heteroaryl chlorides (1.25 mmol), Amines (1.5 mmol), Pd(dba)$_2$ (1 mol%, 0.0125 mmol), ligand **1** (2 mol%, 0.025 mmol) and $^t$BuONa (1.4 equiv, 1.75 mmol) at 110 ºC for 24 h. [b] Isolated yield.

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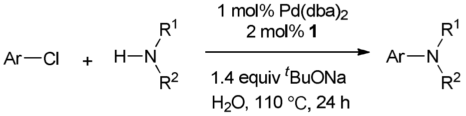
**Table 4.** Buchwald-Hartwig cross-coupling reactions of amines with aryl and heteroaryl chlorides under aqueous conditions[a]



| Entry | ArCl | Amine | Product | Yield (%)[c] |
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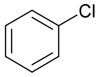
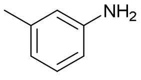
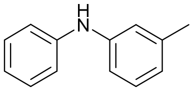
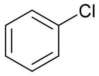
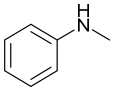
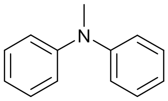
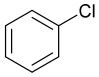
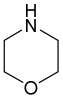
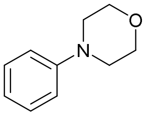
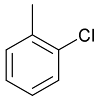
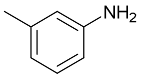
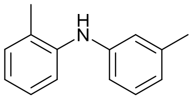
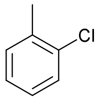
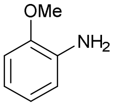
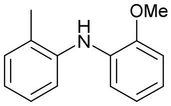
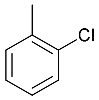
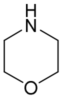
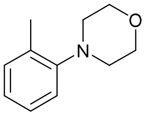
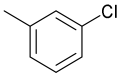
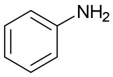
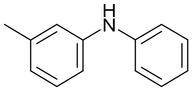
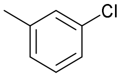
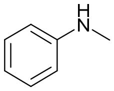
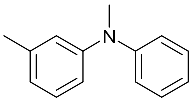
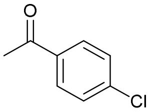
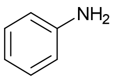
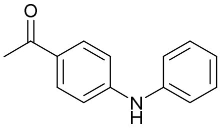
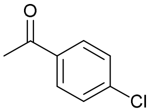
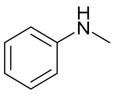
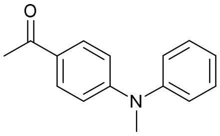
| 1 |  |  |  | 50 |
| 2 |  |  |  | 79 |
| 3 |  |  |  | 51 |
| 4 |  |  |  | 71 |
| 5 |  |  |  | 61 |
| 6 |  |  |  | 53 |
| 7 |  |  |  | 73 |
| 8 |  |  |  | 73 |
| 9 |  |  |  | 74 |
| 10 |  |  |  | 60 |

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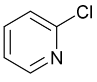
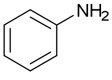
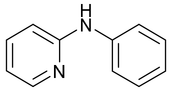
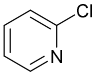
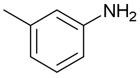
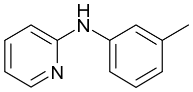
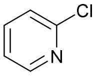
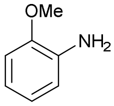
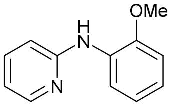
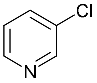
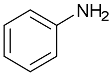
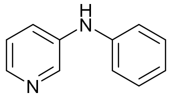
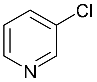
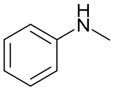
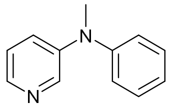
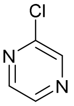
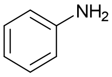
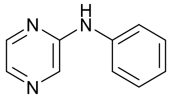
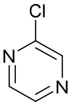
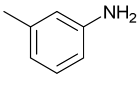
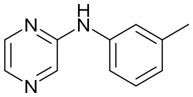
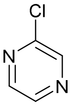
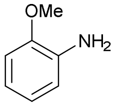
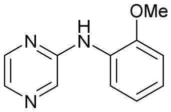
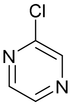
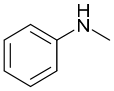
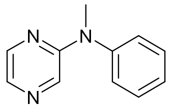
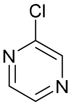
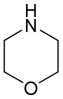
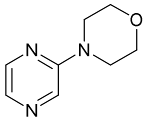
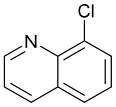
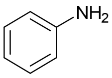
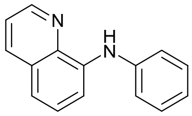
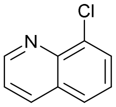
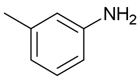
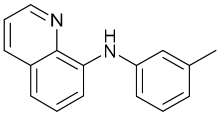
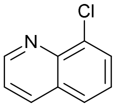
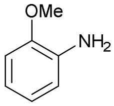
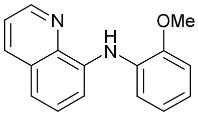
| 11 |  |  |  | 65 |
| 12 |  |  |  | 66 |
| 13 |  |  |  | 70 |
| 14 |  |  |  | 77 |
| 15 |  |  |  | 71 |
| 16 |  |  |  | 88 |
| 17 |  |  |  | 87 |
| 18 |  |  |  | 80 |
| 19 |  |  |  | 69 |
| 20 |  |  |  | 73 |
| 21 |  |  |  | 55 |
| 22 |  |  |  | 55 |
| 23 |  |  |  | 58 |

[a] Reaction conditions: $H_2O$ (0.05 mL), ArCl (1.25 mmol), Amines (1.5 mmol), $Pd(dba)_2$ (1 mol%, 0.0125 mmol), ligand **1** (2 mol%, 0.025 mmol) and $^t$BuONa (1.4 equiv, 1.75 mmol) at 110 ºC for 24 h. [b] Isolated yield.