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# An Efficient Palladium-Catalysed Aminocarbonylation of Benzyl Chlorides

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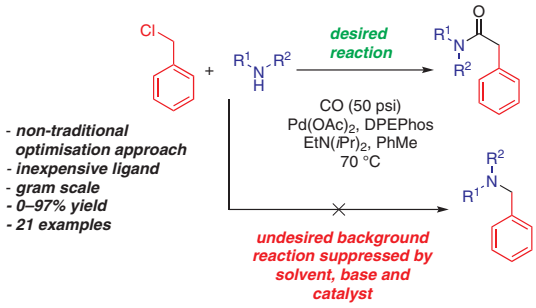


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**Abstract** An improved procedure for the aminocarbonylation of benzyl chloride derivatives using carbon monoxide and either primary or secondary amines has been developed. Studying the competing background alkylation reaction allowed the solvent and base to be selected for a simple catalyst screen, which, in turn, enabled the discovery of a method for the preparation of 2-arylacetamides under mild conditions, with minimal side-products using an inexpensive phosphine ligand. This non-traditional optimisation strategy allowed us to overcome the background alkylation, which has been cited as justification for the development of more complex and less atom-economical approaches.

**Key words** palladium catalysis, carbonylation, amides, reaction optimisation

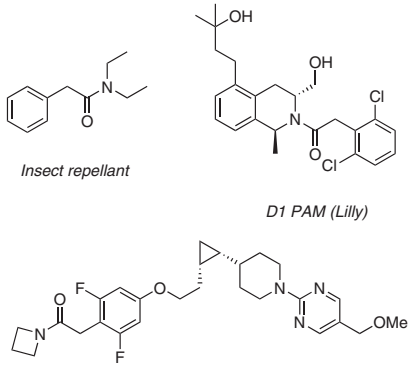
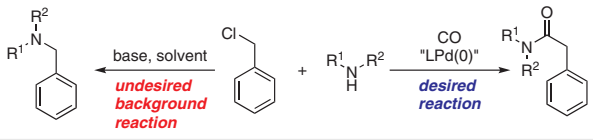



**Figure 1** A selection of biologically interesting 2-arylacetamides

2-Arylacetamides are useful synthetic intermediates[1] and can be found in some important biologically active compounds. Examples include the insect repellent *N*,*N*-diethylphenylacetamide (Figure 1),[2] as well as more highly elaborated amides from drug discovery projects such as the Lilly D1 Positive Allosteric Modulator[3] and Merck GPR119 agonist.[4]

During the course of one of our drug discovery programs a broadly applicable and robust method to prepare diverse 2-aryl acetamides was sought. Typically, 2-phenylacetamides are prepared from the corresponding acids, which themselves often require preparation, and so we sought a more modular method that utilises a broad array of available building blocks. Other methods are known but are not as straightforward and modular as was required for our program.[5]

Aminocarbonylation is a well-described and synthetically expedient method for the preparation of aryl amides from the corresponding aryl halide or pseudohalide and amine in the presence of carbon monoxide and a suitable catalyst.[6–14] Only a small number of examples have been reported for the aminocarbonylation of benzylic halides and those examples demonstrate the main challenge associated with overcoming the competing background alkylation of the amine and benzyl halide starting materials. This is frequently cited as justification of the development of alternate methods for the synthesis of 2-arylacetamides (Scheme 1).[15–19] This is in contrast to aminocarbonylation reactions of aryl halides, where the background amination is only problematic in substrates that are highly activated towards nucleophilic aromatic substitution.




**Scheme 1** Challenges associated with aminocarbonylation of benzyl halides
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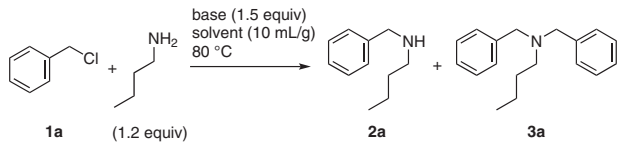
**Table 1** Survey of the Background Alkylation Reaction under the Influence of Bases and Solvents Commonly Used in Carbonylation Reaction[a]



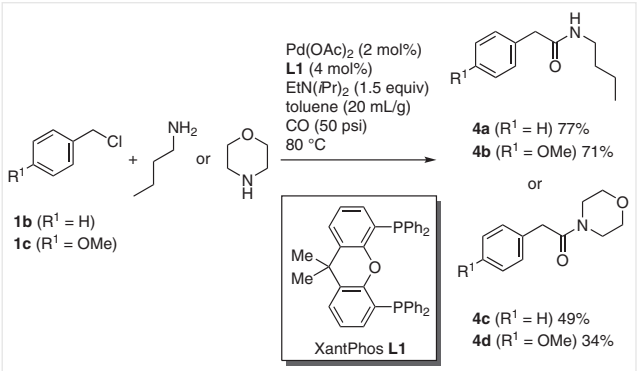

| Entry | Base | Solvent | 1 h | 3 h | 8 h |
|---|---|---|---|---|---|
| 1 | $Na_2CO_3$ | PhMe | 83:15:2 | 79:18:3 | 72:23:5 |
| 2 | EtN(*i*Pr)$_2$ | PhMe | 85:14:1 | 83:15:2 | 82:15:3 |
| 3 | $Na_2CO_3$ | 1,4-dioxane | 69:25:6 | 49:33:19 | 29:33:38 |
| 4 | EtN(*i*Pr)$_2$ | 1,4-dioxane | 73:22:5 | 56:30:14 | 37:32:32 |
| 5 | $Na_2CO_3$ | THF | 78:19:3 | 67:27:06 | 53:36:11 |
| 6 | EtN(*i*Pr)$_2$ | THF | 79:18:3 | 70:24:06 | 59:30:11 |
| 7 | $Na_2CO_3$ | MeCN | 11:36:53 | 3:35:62 | 0:35:65 |
| 8 | EtN(*i*Pr)$_2$ | MeCN | 4:46:50 | 0:46:54 | 0:46:54 |
| 9 | $Na_2CO_3$ | DMF | 6:37:58 | 0:36:64 | 0:35:65 |
| 10 | EtN(*i*Pr)$_2$ | DMF | 4:40:57 | 0:40:60 | 0:39:61 |

[a] Ratio = **1a**/**2a**/**3a**.

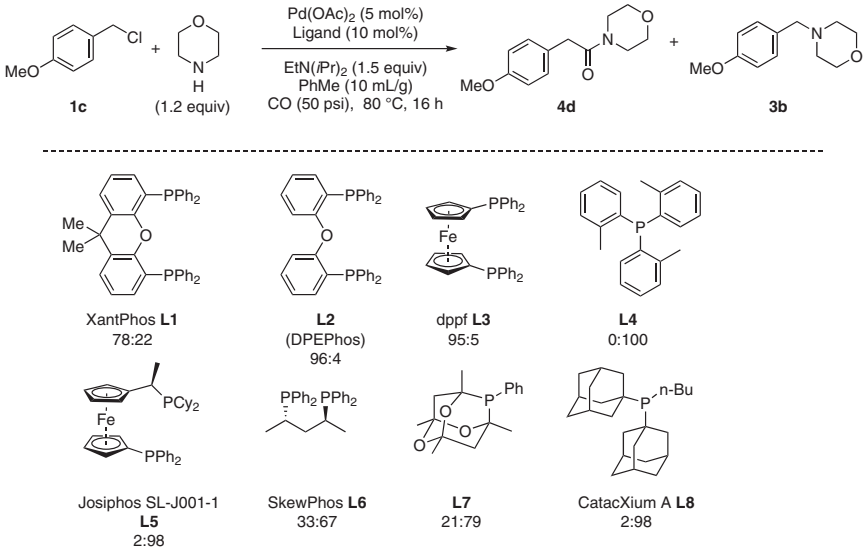
The conditions described by Troisi et al. demonstrate that, while this transformation can be achieved, the unproductive background reaction limits the utility and must be better controlled.[15] Furthermore, the scope of this transformation was not broadly explored and gaining additional insight into the effect of substitution on the benzylic portion would be critical for its application to the synthesis of interesting amides. A limited number of other examples[20,21] have been reported using $^{11}CO$ at high catalyst loadings[22,23] or CO surrogates[24–27] and were suggestive that a viable solution could be obtained.

Our approach for obtaining suitable conditions to effect this transformation was to study the background alkylation with various solvents and bases that are commonly employed in aminocarbonylation reactions[6–14] with the intent of identifying those in which the undesired alkylation is slowest. This approach afforded a reasonable expectation that a viable method could be found by subsequent screening around these conditions to identify potential catalysts and optimise solvent, base and ligand.

Our studies began by examining the inherent alkylation of *n*-butylamine with benzyl chloride (**1a**) with solvents and bases relevant to aminocarbonylation reactions (Table 1). This revealed that the extent of the background reaction was highly dependent on the solvent, and, to a lesser ex-




**Scheme 2** Proof of concept of aminocarbonylation reactions




**Scheme 3** Ligand screening to disfavour background reaction

tent, the base; we were encouraged to see that over a standard 8 h time course, the combination of toluene and EtN(*i*Pr)$_2$ left over 80% of the chloride unreacted (Table 1, entry 2).

When *n*-butylamine was reacted with 4-methoxybenzyl chloride (**1c**) under the same conditions, only 65% starting material remained after 8 h. Under identical conditions, benzyl bromide was completely consumed in the same period. These results suggested that the focus of our investigation should be limited to benzyl chlorides and that 4-methoxybenzyl chloride could be a more useful substrate for development of the aminocarbonylation conditions than benzyl chloride, as this provided a potentially more challenging background reaction to overcome.

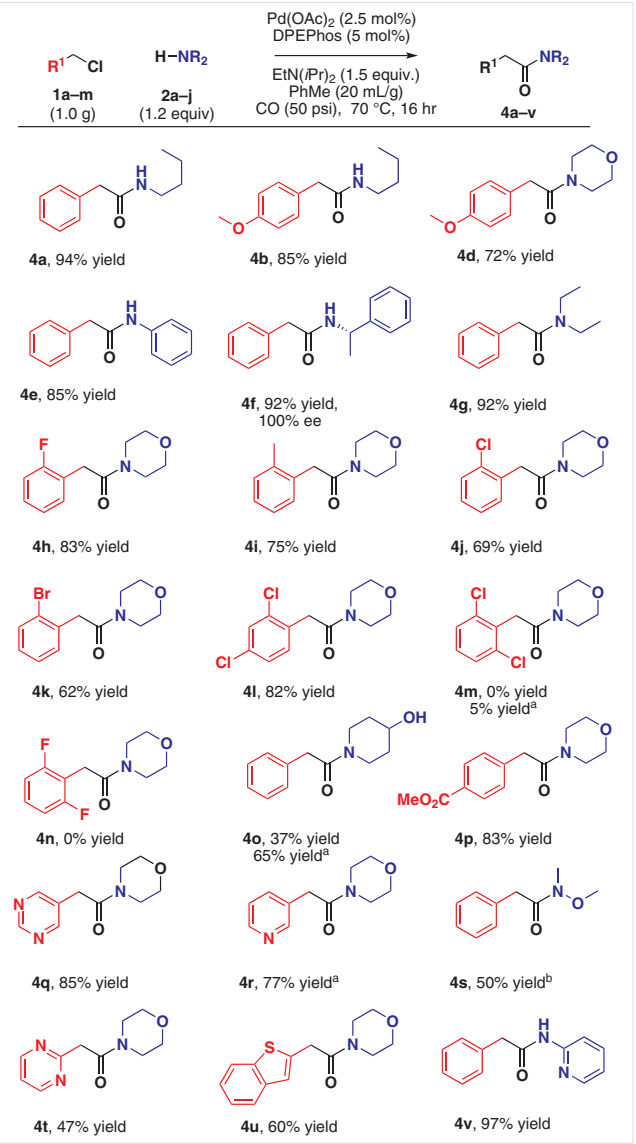
To confirm the hypothesis that the solvent/base combination could translate to useful conditions, preliminary aminocarbonylation reactions were attempted with Pd(OAc)$_2$ and Xantphos as the catalyst (Scheme 2). As expected, these performed well for benzyl chloride but with a lower yield for 4-methoxybenzyl chloride. To optimise this reaction, the carbon monoxide pressure and reaction temperature were varied (Table 2). These data suggested that the effects of pressure and temperature were subtle, and that further improvement of the reaction would likely come from optimization of the ligand.

The reaction was then further studied using 5 mol% Pd and a variety of commonly applied ligands to determine whether a more suitable ligand could be identified to overcome the background reaction (Scheme 3). DPEPhos (**L2**) was identified as the preferred ligand and the reaction was performed at 1 g scale to afford aminocarbonylation product **4d** in 72% isolated yield. The catalyst loading could be lowered to 2.5 mol% Pd without compromising the product/alkylation by-product ratio.

With these conditions in hand, we sought to better understand the scope and limitations of the method (Scheme 4).[28] These reactions worked broadly for a variety of (hetero)benzylic chlorides and amines. Electron-withdrawing and electron-donating groups were tolerated as were aryl halides. In the case of aryl bromide **4k**, some additional carbonylation of the ArBr was observed as a by-product.

Notably, while single *ortho*-substituents were tolerated, 2,6-disubstituted substrates proved challenging (**4m**). A range of amines were efficiently incorporated and although piperidin-4-ol gave a poor yield (**4o**) under the standard conditions, this could be overcome by using preformed catalyst. Highly nucleophilic amines, for example as in the preparation of Weinreb amide **4s** gave lower, but still useful, yields, as the rate of the background reaction was significantly increased.

In conclusion, by employing a non-traditional optimisation strategy we have successfully developed an efficient palladium-catalysed aminocarbonylation reaction of benzylic chlorides that uses an inexpensive ligand and works for a variety of interesting substrates. This reaction has often been cited as difficult to achieve efficiently and led to the development of more complex solutions.




**Scheme 4** Scope and limitations of the aminocarbonylation reaction. Isolated yields given. [a] $PdCl_2$(DPEPhos) used instead of Pd(OAc)$_2$ + **L2**. [b] HCl salt of amine used + additional EtN(*i*Pr)$_2$ (1.2 equiv).

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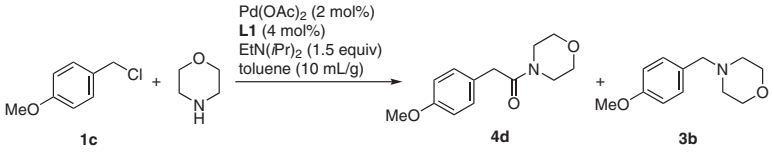
**Table 2** Effect of Temperature and Pressure on the Aminocarbonylation Reaction[a]




| CO pressure (psi) | Temperature (°C) | | |
|---|---|---|---|
| | 60 | 80 | 100 |
| 20 | 70:30 | 78:22 | 68:32 |
| 50 | 51:49 | 75:25 | 50:50 |
| 80 | 35:65 | 65:35 | 78:22 |

[a] Ratio **4d**/**3b** determined by HPLC analysis of the crude reaction mixture.

## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690786.

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(28) **General Procedure**: To a round-bottomed ACE glass pressure flask containing a magnetic stirrer was added toluene (20 mL), chloromethylbenzene (1.0 g, 7.9 mmol) and *N*,*N*-diisopropylethylamine (1.5 equiv). The mixture was degassed with subsurface nitrogen purge for 5 minutes. Palladium(II) acetate (2.5 mol%) and bis(2-diphenylphosphinophenyl)ether (5 mol%) were added, followed by the primary or secondary amine (1.2 equiv) to give a pale-yellow solution. The flask was purged with nitrogen, filled with carbon monoxide to 50 psig and heated at 70 °C with magnetic stirring overnight. The reaction mixture was cooled to ambient temperature and residual CO vented. The reaction mixture was partitioned between EtOAc (200 mL) and 10% aq. citric acid (2 × 30 mL). The organic layer was washed with water then brine, dried over $MgSO_4$, filtered and evaporated. The residue was loaded to the top of a silica gel plug with $CH_2Cl_2$ and eluted with a gradient of EtOAc in isohexane to afford the amide products.