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**Title:** A simple, broad-scope nickel(0) precatalyst system for direct amination of allyl alcohols.

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# A simple, broad-scope nickel(0) precatalyst system for direct amination of allyl alcohols.**

*Joseph B. Sweeney,* Anthony K. Ball, Philippa A. Lawrence, Mackenzie C. Sinclair, and Luke J. Smith*

***Abstract.*** *The preparation of allylic amines is traditionally accomplished by reaction of amines with reactive electrophiles, such as allylic halides, sulfonates or oxyphosphonium species; such methods involve hazardous reagents, generate stoichiometric waste streams, and often suffer from side-reactions (such as over-alkylation). We report here the first nickel-catalysed direct amination of allyl alcohols which enables allylation of primary, secondary and electron-deficient amines, using an inexpensive Ni(II)-Zn couple, without need for glove-box techniques. Under mild conditions, primary and secondary aliphatic amines react smoothly with a range of allyl alcohols, giving secondary and tertiary amines efficiently. This 'totally catalytic' method can be also applied to electron-deficient nitrogen nucleophiles with effective results; the practicality of the process has been demonstrated in an efficient, gram-scale preparation of the calcium antagonist drug substance flunarizine (Sibelium®).*

Metal-catalysed allyl transfer processes are powerful synthetic tools, enabling reaction of suitable precursors with a wide range of nucleophiles. Originally dominated by the use of palladium catalysts,[1] the area has been the subject of intense attention from the synthetic chemistry research community, and a diverse range of metals catalysts have now been demonstrated to be effective in these reactions,[2] using both carbon and heteroatom nucleophiles to access a plethora of functional materials, including allyl amines. Allylic amines themselves are valuable and versatile chemical commodities, both as synthetic intermediates[3] (Figure 1a), medicinal chemistry commodities[4] (Figure 1b) and as commercial products (such as squalene monooxygenase inhibitors terbinafine **1** and naftifine **2**, and the anti-migraine calcium antagonist flunarizine Sibelium® **3**, Figure 1c). The traditional method for manufacture of allylamines is via nucleophilic reaction of amines with reactive allylating agents, such as halides, sulfonates or oxyphosphonium species:[5] the tendency to over-alkylation, combined with the inherent reactivity of all of these reagents, and generation of stoichiometric amounts of waste presents significant challenges to synthetic chemists, especially when large-scale preparations are needed. There has, therefore, been considerable interest in the development of catalytic methods for N-allylation (Figure 1d), and a diverse range of methods has been reported for metal-catalysed allylic amination using traditional electrophiles (acetates, halides, sulfonates, carbonates, phosphonates and related compounds). Since covalently activated allylic substrates inevitably generate stoichiometric amounts of waste by-products, there has been a developing interest in the use of allyl alcohols (from which the primary by-product is water) to minimize waste streams. Whilst the first methods reported for the use of allyl alcohols in catalytic amination processes required the use of stoichiometric additives as activating reagents,[7] more recent studies have led to the development of practical methods for metal-catalysed allylation in the absence of additives.[8] Accompanying the drive to minimise waste streams in catalytic processes, there has been an increasing emphasis on the development of methods which avoid high-cost, non-abundant catalytic metals; this, in turn, led to a concomitant focus on the use of nickel[9] as a replacement for palladium in catalytic transformations. In addition to the economic advantages in using nickel, the differences in character of this more electropositive metal allow quite distinct opportunities for catalytic bond-formation compared with palladium, facilitating chemical processes not available to more expensive metals. Notwithstanding these advantages, the adoption of nickel catalysis as an alternative to palladium is complicated by the comparative difficulty in handling Ni(0) complexes: the most widely used catalytic nickel complex, $Ni(COD)_2$, is highly air-sensitive, (usually necessitating

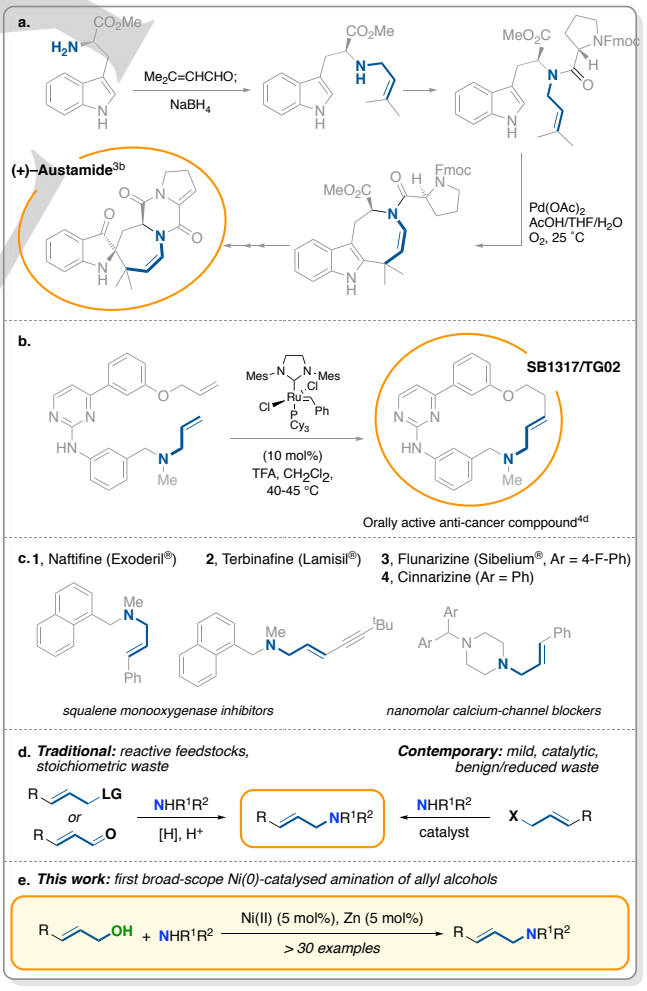


***Figure 1***: Utility and preparation of allylamines.

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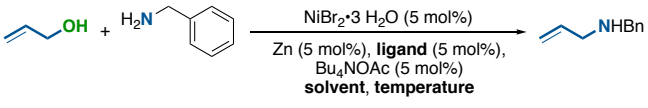



| Entry | Ligand | Solvent | Temp/°C | Yield/%[a] |
|---|---|---|---|---|
| 1 | None | DMA | 65 | <5[b] |
| 2 | $PPh_3$ | DMA | 65 | <5 |
| 3 | $(o\text{-Tol})_3P$ | DMA | 65 | <5 |
| 4 | SPhos | DMA | 65 | <5 |
| 5 | BINAP | DMA | 65 | 17 |
| 6 | dppe | DMA | 65 | <5 |
| 7 | dppp | DMA | 65 | <5 |
| 8 | dppb | DMA | 65 | 18 |
| 9 | dppf | DMA | 65 | 65 |
| 10 | dppf | DMF | 65 | 30 |
| 11 | dppf | NMP | 65 | 27 |
| 12 | dppf | 2-MeTHF | 65 | <5 |
| 13 | dppf | PhMe | 65 | 16 |
| 14 | dppf | MeCN | 65 | 32 |
| 15 | dppf | Dioxane | 65 | 21 |
| 16 | dppf | DMA | 50 | 27 |
| 17 | dppf | DMA | 80 | 40[c] |
| 18 | dppf | DMA | 65 | <5[d] |
| 19 | dppf | DMA | 65 | <5[e] |
| 20 | dppf | DMA | 65 | 27[f] |

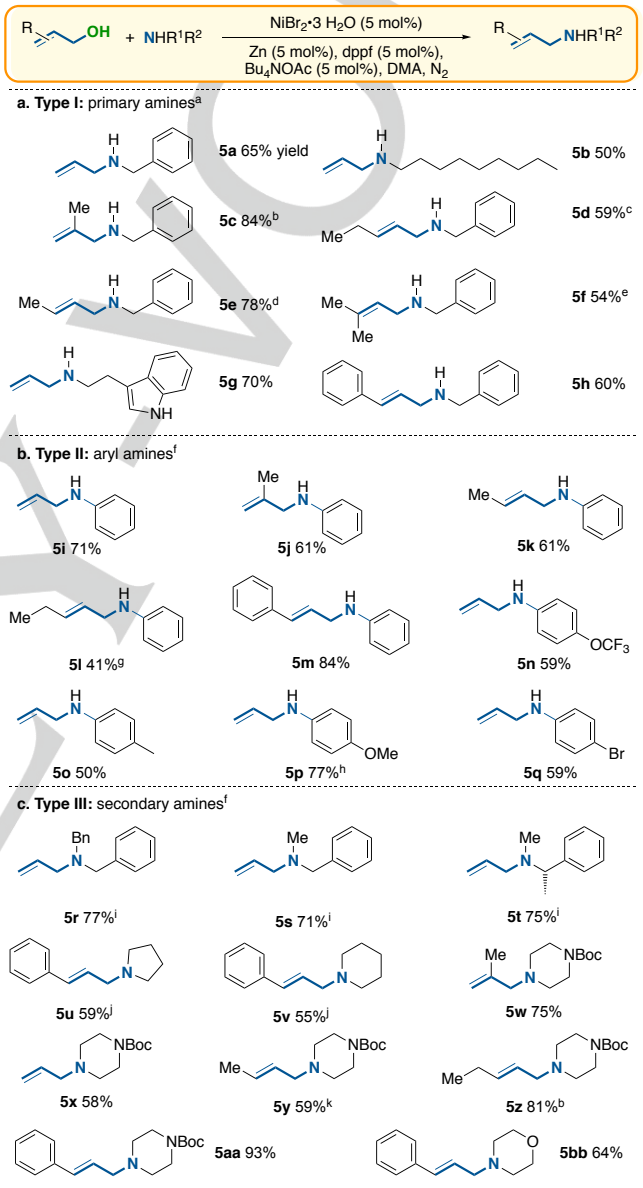
Reaction conditions: Alcohol (1.0 mmol), amine (2.0 mmol), $NiBr_2$•$3H_2O$ (0.05 mmol), dppf (0.05 mmol), $^n$$Bu_4NOAc$ (0.05 mmol), Zn (0.05 mmol), $N_2$, 66 h; [a] Isolated Yield; [b] not detectable by $^1$H NMR; [c] accompanied by 20% diallylated product; [d] 0% $NiBr_2$•$3H_2O$; [e] 0% Zn; [f] 0% $^n$$Bu_4NOAc$

***Table 1***: 'Totally-catalytic' allylic amination: reaction screening

use of a glove-box), and limiting the broad adoption of nickel catalysis. There has, therefore, been intense interest in the development and use of alternatives, and several elegant Ni(0) precatalyst system aiming to address this challenge have been developed.[10] The use of main group metals as *in situ* reducing agents to convert Ni(II) into catalytically active Ni(0) has also been described,[11] typically employing superstoichiometric amounts of reducing agent: we were keen to develop a 'totally catalytic' combination (i.e., where the reducing agent is present in the same substoichiometric amount as the nickel catalyst); though nickel catalysts can mediate amination using non-activated allyl alcohols as substrates, the reported methods require experimental conditions (such as non-commercial catalysts, use of glove-box conditions,[12, 13] or neat reactions[13]) which restrict the scalability of the processes. Moreover the reported methods are limited in scope, with no nickel-catalysed method described which can be applied to less-nucleophilic amino components (such as imides or sulfonamides).

We therefore set out to devise and implement a practical method for nickel-catalysed amination of allyl alcohols which used inexpensive, commercially-available catalysts, did not require glove-box or similar technologies, was broadly applicable (to both nucleophilic and electron-deficient amine nucleophiles) and could be carried out on gram-scale, using simple apparatus. We report here a practical catalytic system for allylic amination by alcohols, using an inexpensive Ni(0) precatalyst system (Figure 1e): this is both the first reported nickel-catalysed method to facilitate allylation of both nucleophilic and electron-deficient nitrogen nucleophiles, and the first allylic amination process using Ni(0) catalysts generated *in situ* from a simple Ni(II) salt. The method is also truly 'catalytic' in reducing agent, further minimizing the waste footprint of the process.

We chose $NiBr_2$•$3H_2O$, due to its low cost and ready availability, and zinc as the reducing agent, due to its low toxicity compared to other metal reducing agents; the data obtained from the initial screening study is summarised in Table 1. Thus, whilst monodentate ligands were ineffective, we were pleased to observe that the combination of $NiBr_2$•$3H_2O$ and Zn (both at 5 mol% loading) mediated N-allylation in the presence of diphosphanes (Table 1, entries 5, 8 and 9), with best results obtained using dppf (entry 9). A solvent screen (entries 10-15) indicated dimethyl acetamide (DMA) to be optimal; both the nickel salt and zinc were necessary for reaction (entries 18 and 19) and $Bu_4NOAc$ was important to maximise yield (cf. entries 9 and 20).




Reaction conditions: Alcohol (1.0 mmol), amine (2.0 mmol), $NiBr_2$•$3H_2O$ (0.05 mmol), dppf (0.05 mmol), $^n$$Bu_4NOAc$ (0.05 mmol), Zn (0.05 mmol), $N_2$, 66 h; [a.] Reaction carried out at 65 °C; [b.] E:Z = 88:12 (SM >95% E); mono-:diallylated = 60:40; [c.] E:Z = 85:15 (SM >95% E); linear:branched = 83:17; [d.] E:Z = 80:20 (SM E:Z = 90:10); linear:branched = 83:17; [e.] linear:branched = 70:30; [f.] Reaction carried out at 50 °C; [g.] E:Z = 88:12 (SM >95% E); [h.] mono-:diallylated = 87:13; [i.] Reaction carried out at 25 °C; [j.] Reaction carried out at 80 °C; [k.] E:Z = 80:20 (SM E:Z = 90:10).

***Figure 2.*** Ni(0)-mediated totally catalytic amination of allyl alcohols.

Armed with an efficient method, we next turned to an examination of the scope of the reaction, firstly using aliphatic amines as nucleophiles; thus, as summarised in Figure 2, we were pleased to observe that a broad range of amines reacted smoothly under the

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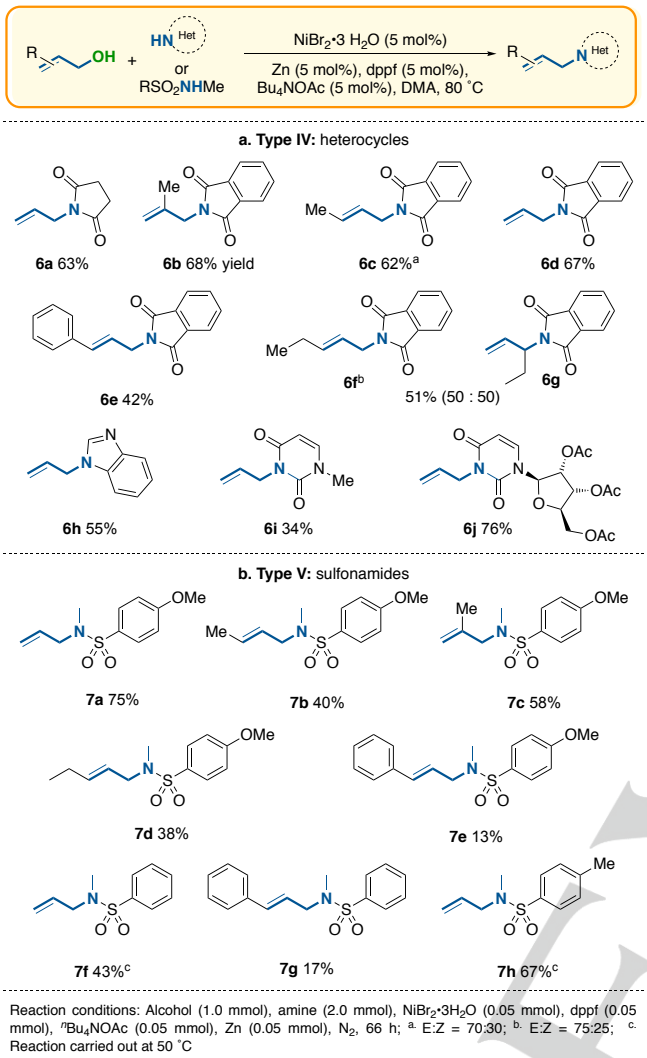



Reaction conditions: Alcohol (1.0 mmol), amine (2.0 mmol), $NiBr_2$•$3H_2O$ (0.05 mmol), dppf (0.05 mmol), $^nBu_4NOAc$ (0.05 mmol), Zn (0.05 mmol), $N_2$, 66 h; [a] E:Z = 70:30; [b] E:Z = 75:25; [c] Reaction carried out at 50 °C

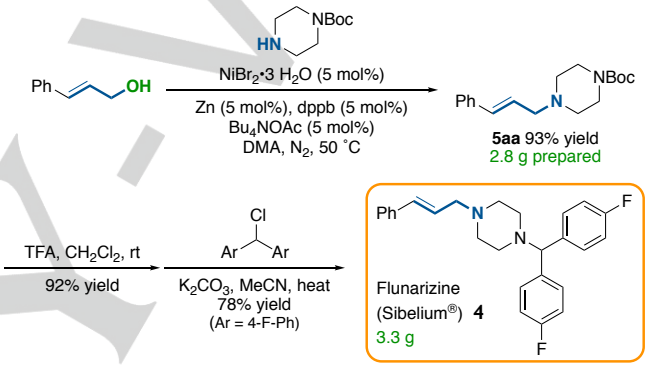
***Figure 3.*** Ni(0)-catalysed amination using electron-deficient nucleophiles.

conditions identified by the screening process. Primary aliphatic amines ('Type I', Figure 2a) reacted to give monoallylated products **5a–h** selectively (with a preference for reaction at the aliphatic nitrogen in tryptamine, giving **5g**), whilst primary aryl amines (Type II, Figure 2b) reacted at a slightly lower temperature to give products **5i-q**. Secondary amines (Type III, Figure 2c) reacted to give exclusively tertiary amines **5r-5ab**; no over-allylation was observed in the latter reactions, in contrast to traditional processes using reactive allyl electrophiles.

When we commenced our study, there was no reported method for Ni-catalysed amination which could be applied to both nucleophilic and electron-deficient substrates, meaning that demonstrating effectiveness using these substrates would be a powerful validation of our method. We were again pleased, therefore, to observe conversion of a range of electron-deficient nitrogen heterocycles (Type IV substrates) under the reactions conditions (Figure 3a), giving allylated products **6a-6j**. Of particular note is the reaction of triacetyl uridine, which proceeded smoothly to give N-allylated uridine **6j** in excellent yield.

The breadth of the scope of the allylation of electron-deficient nitrogen nucleophiles was further probed by reacting Type V substrates – sulfonamides– under the totally catalytic conditions, giving products **7a–7h**[14] (Figure 3b).[15]

A key advantage of using alcohols rather than the corresponding halides is the ability to avoid unpleasant characteristics of alternative reagents (such as allylic halides), and this is of particular importance for large-scale and industrial processes; the need for glove-box conditions can also compromise translation of catalytic processes into an industry paradigm, and so we sought to exemplify the applicability of this method to gram-scale synthesis of a marketed drug substance, choosing calcium-channel blocker flunarizine (Sibelium®) **4** as an exemplar target. Thus in a three-step sequence, this API could be accessed on multigram-scale with the key nickel-catalysed amination reaction proceeding in 93% yield (Scheme 1); this provides an excellent demonstration of the robust capabilities of the totally catalytic Ni(II)-Zn couple, and its ease of use to access end user-relevant chemical commodities.




***Scheme 1.*** Gram-scale totally catalytic synthesis of Sibelium® **4**

In summary, we have described a practical, scalable method for executing nickel-catalysed N-allylation reactions using readily available, inexpensive, air-insensitive catalysts and reagents. The use of allyl alcohols as substrates, and an inexpensive Ni(II) salt as a precatalyst offers significant practical advantage, the method has broad scope, and can be applied to gram-scale preparation of a marketed drug substance. We are currently engaged in extending the application of this truly catalytic process to other transformations.

**Keywords:** • Catalytic • nickel • C-N bond formation • amination • allylation • sustainable

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14. Since similar yields are obtained for the reactions of unsubstituted and (electron-donating) para-methoxy substrates with cinnamyl alcohol as substrate, the yields are assumed to be lower because of steric rather than electronic reasons.
15. It was noteworthy that primary sulfonamides were unreactive under the reaction conditions, presumably due to their tendency to form stable Ni(II)-sulfonamides complexes (see, for instance: G. Estiu, M. E. Chacón Villalba, G. E. Camí, G. A. Echeverria, D. B. Soria, *J. Mol. Struct.* **2014**, *1062*, 82 – 88).

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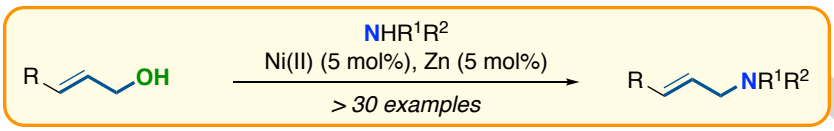


**• simple procedure • gram-scale • broad scope**

**Abstract:** The preparation of allylic amines is traditionally accomplished by reaction of amines with reactive electrophiles, such as allylic halides, sulfonates or oxyphosphonium species; such methods involve hazardous reagents, generate stoichiometric waste streams, and often suffer from side-reactions (such as over-alkylation). We report here the first nickel-catalysed direct amination of allyl alcohols which enables allylation of primary, secondary and electron-deficient amines, using an inexpensive Ni(II)-Zn couple, without need for glove-box techniques. Under mild conditions, primary and secondary aliphatic amines react smoothly with a range of allyl alcohols, giving secondary and tertiary amines efficiently. This 'totally catalytic' method can be also applied to electron-deficient nitrogen nucleophiles with effective results; the practicality of the process has been demonstrated in an efficient, gram-scale preparation of the calcium antagonist drug substance flunarizine (Sibelium®).

**A simple, broad-scope nickel(0) precatalyst system for direct amination of allyl alcohols.**

Joseph B. Sweeney,* Anthony K. Ball, Philippa A. Lawrence, Mackenzie C. Sinclair, and Luke Smith

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