CHEMISTRY
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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201801241

Link to VoR: http://dx.doi.org/10.1002/chem.201801241

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Catalytic C-C bond-formation using a simple nickel precatalyst system: base– and activator–free direct C–allylation by alcohols and amines.**

Joseph B. Sweeney,[*,†] Anthony K. Ball,[¶] and Luke J. Smith[¶]*

Abstract: *A 'totally catalytic' nickel(0)-mediated method for base-free direct alkylation of allyl alcohols and allyl amines is reported. The reaction is selective for monoallylation, uses an inexpensive Ni(II) precatalyst system, and requires no activating reagents to be present.*

Catalytic bond-forming processes have become indispensible tools in all aspects of synthetic chemistry, for both academic and industrial chemists, and there has been a recent and increasing emphasis on methods which avoid catalysts derived from high-cost, non-abundant metals. Within the diverse research into the application of catalytic complexes used for synthesis and manufacturing, this has led to a focus on the use of nickel as a replacement for palladium in catalytic transformations. In addition to the cost advantages in using nickel, the differences in character of this more electropositive metal allow quite different opportunities for catalytic bond-formation compared with palladium, facilitating some chemical processes not available to the more expensive metal.[1] Notwithstanding these advantages, the adoption of nickel catalysis as an alternative to palladium has been slow, perhaps due to the comparative difficulty in handling Ni(0) complexes: the most widely used catalytic complex of nickel, $Ni(COD)_2$ is well-known to be highly air-sensitive, making it difficult to handle, and compromising the robustness and practicality of nickel-catalysed processes. To meet this obstacle, several elegant Ni(0) precatalysts systems have been developed to circumvent the use of $Ni(COD)_2$ using either synthesized precatalysts,[2] or combinations of simple nickel salts with stoichiometric reducing agents. Though several reports[3] have described the use of main group metals as *in situ* reducing agents to convert Ni(II) into catalytically active Ni(0), to our knowledge there has been no 'totally catalytic' combination (i.e., where the reducing agent is present in the same catalytic amount as the nickel component) and there are no reports of such a method being used in catalytic alkylation using allyl alcohols and amines. We report here an air-insensitive Ni(0)-catalyzed allylation process which is selective for monoallylation using allylic alcohols, and which employs an inexpensive nickel salt and equimolar elemental zinc as an effective precatalyst combination.

Catalytic alkylation of allylic acetates[4] and analogous reagents using Earth-scarce metal complexes is one of the most-employed synthetic methods for C-C bond formation, but traditional processes generate stoichiometric amounts of by-products (typically acids or their salts). The use of allylic alcohols and amines in such processes represents a more atom-economical transformation (since water or ammonia – in the case of primary allylamines – are the by-products), but the lower reactivity of these substrates typically demands the presence of stoichiometric amounts of activators (often Brønsted or Lewis acids).[5], [6] The ability of nickel complexes to mediate oxidative insertion into C-O and C-N bonds *without* the need for activating reagents has led to these catalysts being used in allylation using alcohols[7],[8] and amines; [7b], [9],[10] to date, the reported processes using alcohols have required $Ni(COD)_2$, and (where mixtures are possible[11]) often do not show selectivity for monoallylated products.[12]

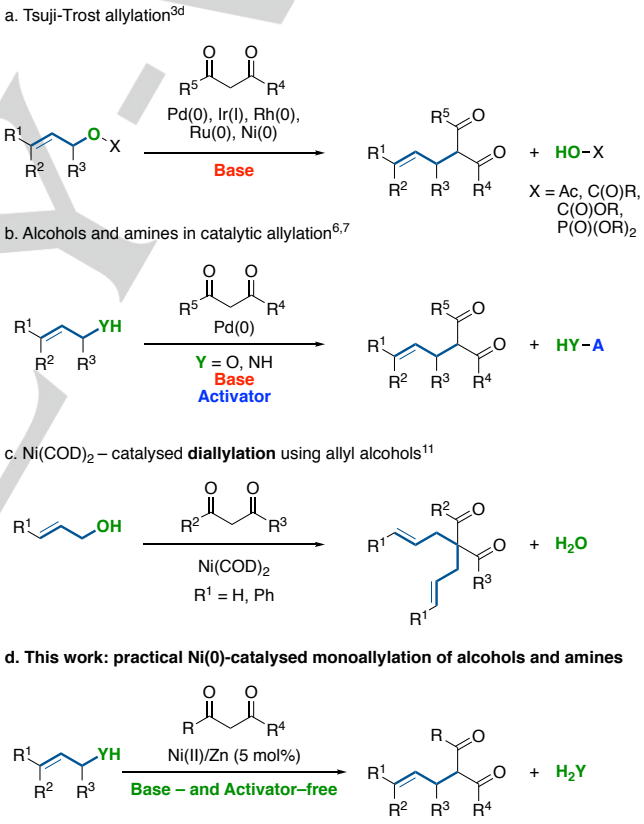

Figure 1: Catalytic allylation strategies.

We commenced our study with two aims: to develop a nickel-catalysed method using allyl amines or alcohols which delivered monoallylated products selectively, and to devise a means of accessing the crucial Ni(0) catalysts from an inexpensive, air-stable precursor. We chose to use $NiBr_2 \cdot 3H_2O$, one of the most inexpensive nickel salts,[13] as our nickel source, and elemental zinc as the reducing agent (due to its low toxicity compared to other metal reducing agents, such as manganese); as mentioned, key goals of our study were to reduce the amount of reducing agent to a low level, and to avoid the use of a base in the reaction, thereby simplifying still further the process.

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[**] We are grateful to the University of Huddersfield (A. B. and L. J. S.) for funding, and the Royal Society for an Industry Fellowship (J.B.S.).

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10.1002/chem.201801241

The first conditions examined proceeded with poor conversion, but in 50% yield based on recovered starting materials) (Figure 2).

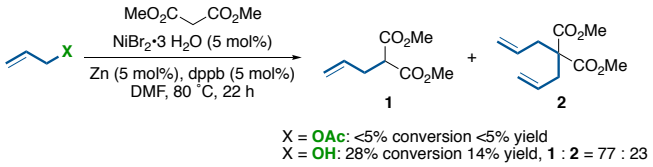
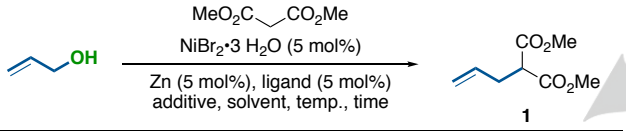


Figure 2. Ni(0)-mediated 'totally catalytic' allylation using allyl alcohol.

After an extensive analysis of the effects of variation in ligand, solvent and additive, the optimum conditions for the reaction of allyl alcohol with malonate were identified (Table 1, entry 16); using this reagent/catalyst combination, high selectivity for monoallylated product **1** was observed, in contrast to previously reported catalytic nickel allylation processes,[11] and despite the use of two equivalents of the nucleophile (used in excess to improve yield). Moreover, the relative stoichiometry in the process described here does not require large excesses of either reagent, or reducing agent, or ligand. These facts endow this method with enhanced utility, improved environmental impact and great practicality.

***Table 1*:** Reaction optimization

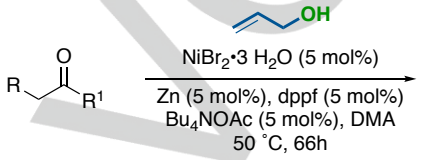


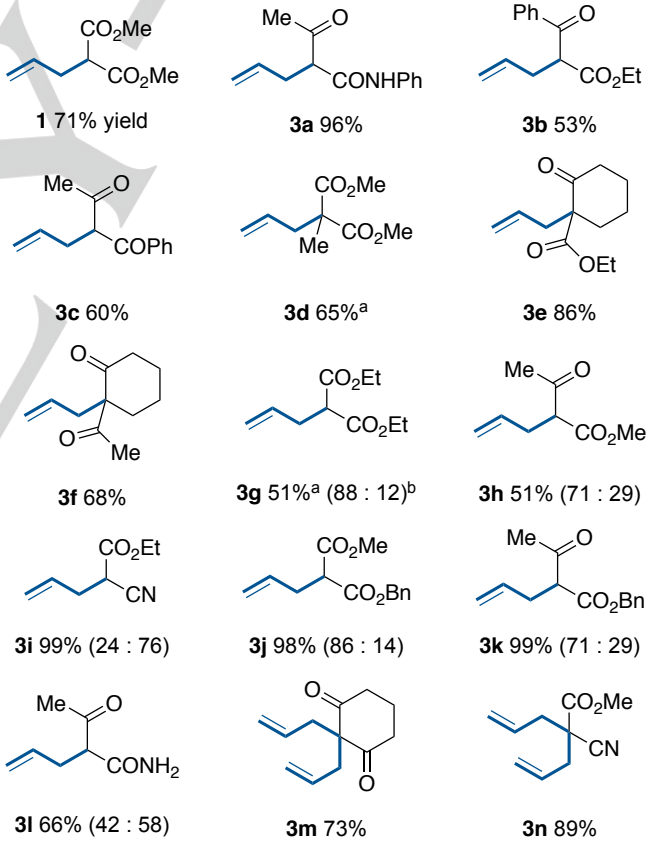
Entry	Ligand	Solvent	Temp	Time	Conv/%[a]	Yield/%[b]	Selectivity[c]
1	dppb	DMF	80 °C	18 h	28	50[d]	77:23
2	dppb	DMF	80 °C	96 h	50	60[d]	91:9
3	PPh_3	DMF	80 °C	96 h	<5	0	-
4	dppe	DMF	80 °C	96 h	<5	0	-
5	dppp	DMF	80 °C	96 h	<5	0	-
6	dppf	DMF	80 °C	96 h	90	58	82:18
7	XantPhos	DMF	80 °C	96 h	<5	0	-
8	BINAP	DMF	80 °C	96 h	<5	0	-
9	dppf	NMP	80 °C	96 h	<5	0	-
10	dppf	MeCN	80 °C	96 h	23	70[d]	>95:5
11	dppf	DMA	80 °C	66 h	>95	51	80:20
12	dppf	DMA	50 °C	66 h	75	41[d]	91:9
13	dppf	DMA	50 °C	66 h	35	37[d, e]	95:5
14	dppf	DMA	50 °C	66 h	70	44[d,f]	90:10
15	dppf	DMA	50 °C	66 h	>95	48[g]	85:15
16	dppf	DMA	50 °C	66 h	>95	71[g,h]	>90:10

[a] Estimated from ^{1}H NMR of crude product; [b] Isolated yield; [c] Monoallylated : diallylated (determined from ^{1}H NMR of crude product); [d] Yield based on recovered starting material; [f] 5 mol% AcOH present; [f] 5 mol% NH_4OAc present; [g] 5 mol% NBu_4OAc[14] present; [h] 2 eq. malonate used.

Armed with a robust, operationally simple method for selective nickel-catalysed monoallylation, we next examined the scope of the reaction, from the perspective of the nucleophilic component. Thus, a range of nucleophilic partners were tested using the optimized conditions, furnishing a library of allylation products **1** and **3a-n** (Table 2). As demonstrated by these data, there is a clear effect of CH acidity upon the product composition, with more acidic substrates more likely to deliver mixtures of products. H-bonding[15] seems to enhance diallylation (as seen in preparation of **3l**). There is also an effect of steric compression in the ester component: thus, whilst dimethyl malonate gives only monoallyl product **1**, larger esters tend to give (separable) mixtures of products (vide **3g** and **3j**). Quaternary centres can be created in the reaction, as shown by obtention of **3d**–**f** in good yields.

***Table 2*:** Scope of the Ni-catalysed allylation of nucleophiles with allyl alcohol



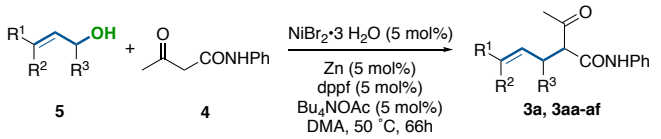


Reaction conditions: Allyl alcohol (1.0 mmol), nucleophile (2.0 mmol), $NiBr_2$•$3H_2O$ (0.05 mmol), dppf (0.05 mmol), $^n Bu_4NOAc$ (0.05 mmol) , zinc (0.05 mmol), DMA, 50 °C, 66 h, sealed vial. [a] reaction carried out at 80 °C; [b] Monoallylated : diallylated.

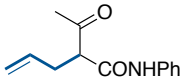
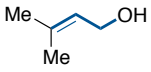
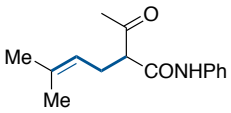
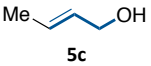
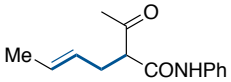
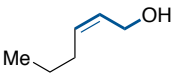
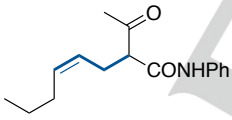
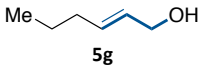
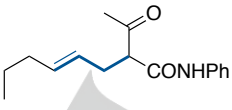
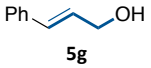
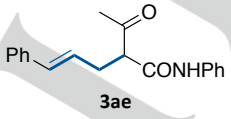
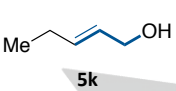
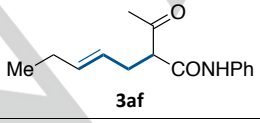
Having probed the scope of nucleophile in this nickel-catalysed processes, the reactions of a range of allyl alcohols with acetamide **4** were next examined: these transformations generally proceeded in good yields, and with complete selectivity for monoallylated

products (Table 3). In all cases, where possible, linear products were favoured over branched isomers (vide substrates **5b**, **5d** and **5h**, entries 3,5 and 9), and alkene stereochemistry was retained (entries 6 and 7). The obtention of the same products (**3aa**, **3ab** and **3ae**) from isomeric alcohols implies a common intermediate in each of these reactions.

Table 3: Scope of the Ni-catalysed allylation with various allyl alcohols



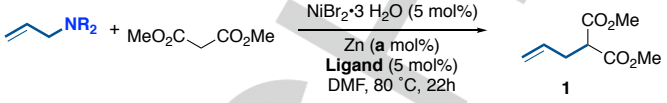
5 **4** **3a, 3aa-af**

Entry	Alcohol **5**	Product	Yield/%[a]
1		 **3a**	96
2	 **5a**	 **3aa**	73
3	 **5b**		27
4	 **5c**	 **3ab**	69
5	 **5d**		56
6	 **5e**	 **3ac**	54
7	 **5g**	 **3ad**	66
8	 **5g**		48
9	 **5h**	 **3ae**	94
10	 **5k**	 **3af**	73

Reaction conditions: Allyl alcohol (1.0 mmol), N-phenyl acetoacetamide (2.0 mmol), $NiBr_2$•$3H_2O$ (0.05 mmol), dppf (0.05 mmol), $^nBu_4NOAc$ (0.05 mmol) , zinc (0.05 mmol), DMA, 50 °C, 66 h, sealed vial; [a] Isolated yield.

Though palladium-mediated processes are well-known,[16] there are no reports of a general method for nickel-catalysed allylation reactions using allyl amines.[10] We were gratified, therefore, to observe that our method was also productive when using N,N-diethyl allylamine or allylamine itself as a π-allyl precursor (Table 4).

***Table 4*:** Ni-catalysed allylation using allylamine



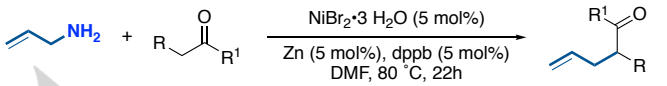
1

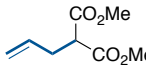
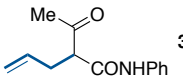
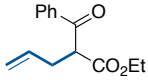
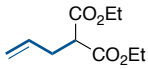
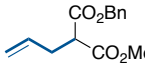
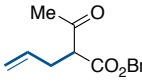
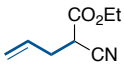
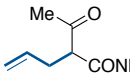
Entry	R	a	Ligand	Yield/%[a]	Selectivity[b]
1	Et	15	dppb	89	85:15
2	Et	10	dppb	80	85:15
3	Et	5	dppb	90	85:15
4	Et	5	dppb	74[c]	85:15
5	H	5	dppb	86	85:15
6	H	5	dppf	0[d]	–

[a] Isolated yield; [b] Monoallylated : diallylated; [c] $NiCl$•$6H_2O$ used; [d] Complex mixture of products obtained.

In the process using allylamine, mixtures of mono- and diallylated products were more often obtained, perhaps being a reflection of the relative basicity of the leaving group (an amide, rather than hydroxide), which more rapidly deprotonates the monoallylated product and thereby encouraging diallylation. Using a range of active methylene nucleophiles, allylamine reacted to give products of C-allylation (Table 5).

***Table 5*:** Scope of the Ni-catalysed allylation with allyl amine



Entry	R	R^1	Product	Yield %	Ratio[a]
1	CO_2Me	OMe	 **1**	89	71 : 29
2	CONHPh	Me	 **3a**	53	62 : 38
3	CO_2Et	Ph	 **3b**	30[b]	100:0
4	CO_2Et	OEt	 **3g**	75	73 : 27
5	CO_2Me	OBn	 **3j**	84	76 : 24
6	CO_2Bn	Me	 **3k**	40	100 : 0
7	CN	OEt	 **3i**	96	27 : 63
8	$CONH_2$	Me	 **3l**	23	30 : 70

Reaction conditions: Allyl amine (1.0 mmol), nucleophile (1.5 mmol), $NiBr_2$•$3H_2O$ (0.05 mmol), dppb (0.05 mmol), zinc (0.05 mmol),

DMF, 80 °C, 66 h, sealed vial. [a] Monoallylated : diallylated; [b] *N,N*-diethylallylamine used.

In summary, we have described a practical, scalable and cost-effective method for executing nickel-catalysed C-allylation reactions using readily available, inexpensive, air-insensitive reagents. The use of allyl alcohols and amines as substrates in such reactions offers significant advantages and can be easily applied to gram-scale preparations. We are currently engaged in exploring the mechanistic nuances and extending the boundaries of this highly practical catalytic process.

Keywords: • Catalytic • nickel • C-C bond formation • allylation • sustainable • quaternary

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Layout 2:

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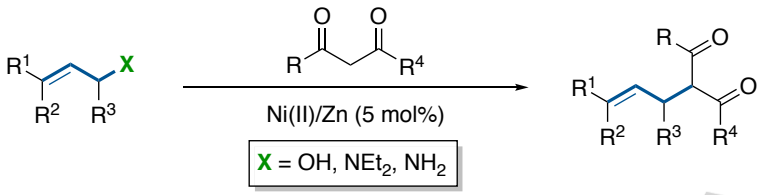

• Base – and activator–free • Inexpensive Ni(0) precatalyst system • > 30 examples

Abstract: A 'totally catalytic' nickel(0)-mediated method for base-free direct alkylation of allyl alcohols and allyl amines is reported. The reaction is selective for monoallylation, uses an inexpensive Ni(II) precatalyst system, and requires no activating reagents to be present.

Catalytic C-C bond-formation using a simple nickel precatalyst system: base– and activator–free direct C–allylation by alcohols and amines

Joseph B. Sweeney,* Anthony K. Ball, and Luke J. Smith

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