Nickel-Catalyzed Suzuki Cross Couplings with Unprotected Allylic Alcohols Enabled by Bidentate NHC/Phosphine Ligands

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Abstract

Cross couplings between simple allylic alcohols and aryl and vinyl boronic acids are efficiently catalyzed by nickel(0) catalysts and bidentate *N*-heterocyclic carbene/phosphine ligands. The bidentate nature of the ligand is shown to extend catalyst lifetime and enable high yields of the corresponding cross coupling products. X-ray crystallography confirms the bidentate nature of the ligand scaffold. Multistep cross coupling-alkene/alkyne insertions reactions are also conducted and the bidentate nature of the substrate makes the pendant phosphine of the ligand unnecessary.

Key Words: Nickel catalysis, bidentate ligand, Suzuki reaction, alcohol electrophile, allylic arylation

Cross coupling reactions of simple, unprotected allylic alcohols represent a highly useful and atom economic process that precludes the need for activation of the electrophile substrate.[1] Factors including the acidic nature of the O–H bond, the stability of undesired M-alkoxide complexes and the poor leaving group ability and basicity of the alcohol electrophile have made cross couplings with unprotected alcohols challenging to achieve. Thus, allylic carbonates, sulfonates, acetates, phosphonates, or halogens are typically employed in allylic functionalization reactions, which add undesirable synthetic steps.[2] Recent advances in cross couplings with unprotected allylic alcohols have in general required the use of expensive noble

metal catalysts such as iridium,[3] ruthenium,[4] rhodium,[5] or palladium[1,6] (Figure 1). Nickel, on the other hand, represents an ideal catalyst for these transformations due to its relatively low cost and high abundance. Nickel-catalyzed allylic aminations,[7] alkylations,[8] and Negishi cross couplings[9] with unprotected allylic alcohols have been demonstrated, but nickel-catalyzed C-C bond forming Suzuki-Miyaura reactions with unprotected alcohol electrophiles have not been reported to date.[10]

Nickel catalysis is rapidly becoming a staple of modern organic chemistry.[11] A significant challenge with nickel catalysts is that nickel(0) complexes are generally unstable and readily decompose during catalysis, leading to short catalyst lifetimes. Nickel *N*-heterocyclic carbene (NHC) complexes have found widespread application in nickel catalysis due to their relatively high stability.[12] In this report, we demonstrate that nickel NHC complexes are efficient catalysts for Suzuki reactions with unprotected allylic alcohols (Figure 1). Importantly, traditional monodentate NHC ligands are shown to enable efficient catalysis, but the resulting catalytic species rapidly decompose under the reaction conditions, leading to low substrate conversions. Our results show that bidentate NHC/phosphine ligands increase catalyst stability, extend catalyst lifetime, and lead to high yields in Suzuki cross couplings with simple allylic alcohols, including for multistep cyclization/cross coupling reactions.

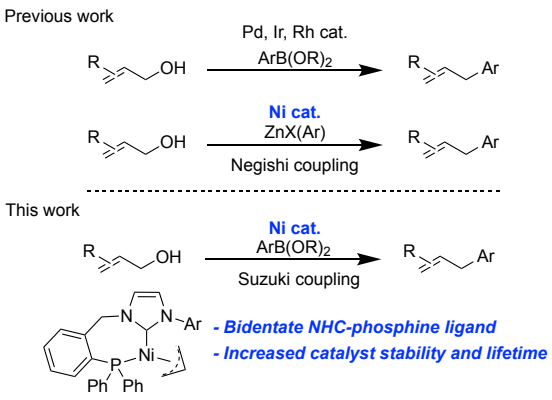
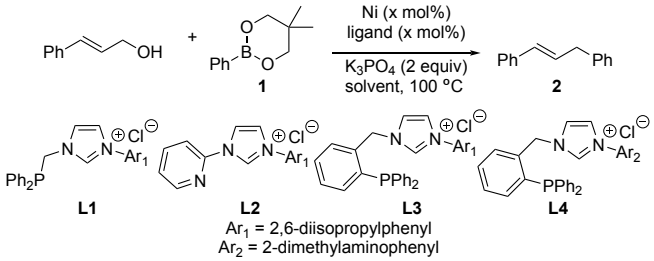


Figure 1. Nickel-catalyzed cross coupling reactions of unprotected allylic alcohols, including with NHC/phosphine bidentate ligands.

We began our studies into nickel-catalyzed Suzuki reactions with allylic alcohols by investigating the activity of NHC and phosphine ligands traditionally used in nickel catalysis.[11] For example, in the cross coupling of cinnamyl alcohol and phenylboronic ester **1,** iPrHCl (1,3-bis(2,6-diisopropylphenyl)imidazolium chloride)[11] or dppf (1,1'-bis(diphenylphosphino)ferrocene)[7] provided only 23% and 46% conversion to product **2**, respectively (Table 1, entries 1–2). In monitoring the kinetics of the reaction with either ligand, we observed that conversion rapidly approached the observed levels in about 1 h and then the reaction would stall, suggesting catalyst deactivation or decomposition. We wondered whether use of a bidentate ligand would increase catalyst stability and prevent catalyst deactivation.[13] Thus, we synthesized and utilized a variety of bidentate NHC ligands in the cross coupling reaction. Importantly, when ligands **L1**–**L4** were employed, conversion dramatically improved in all cases, with Ligands **L3** and **L4** giving the highest conversion (entries 3–6). One important observation we made was that while catalysis slowed down slightly when a bidentate ligand was employed, catalyst lifetime was greatly extended, enabling full conversion in the reaction. In continuing optimization studies, we found that the reaction proceeded most effectively

when acetonitrile was used as solvent (entries 7–10). Having discovered a much more stable catalytic species, we found that catalyst loading could be dramatically lowered while maintaining high reaction yields. For example, with 1.25 mol% catalyst, 91% yield was obtained in just 10 h (entries 11–14). Importantly, when IPrHCl and PPh_3 were used in concert in the

Table 1. Optimization Studies.



Entry[a]	Ligand	Mol% Ni	Solvent	% Yield
1	dppf	10	MeCN	46
2[b]	IPrHCl	10	MeCN	23
3	**L1**	10	MeCN	68
4	**L2**	10	MeCN	70
5	**L3**	10	MeCN	72
6	**L4**	10	MeCN	73
7[c]	**L3**	10	toluene	51
8	**L3**	10	dioxane	31
9	**L3**	10	DMF	78
10	**L3**	10	EtOH	51
11[d]	**L3**	10	MeCN	89
12[e]	**L3**	5	MeCN	92
13[f]	**L3**	2.5	MeCN	92
14[g]	**L3**	1.25	MeCN	91
15[h]	IPrHCl	10	MeCN	20

a) Reactions run using 0.02 mmol [(TMEDA)Ni(*o*-tolyl)Cl], 0.02 mmol *t*-BuOK, 0.2 mmol allylic alcohol, 1.5 equiv boronic ester, and 2.0 equiv K_3PO_4 at 100 °C for 1.5 h unless otherwise noted. All reaction proceeded with >100:1 selectivity for the linear product unless otherwise noted. b) IPrHCl = 1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride. c) Branched:linear ratio = 20:1. d) Run for 3 h. e) Run at 1M in allylic alcohol for 10 h. f) Run at 2.0M for 10 h. g) Run at 4.0M for 10 h. h) PPh_3 (10 mol %) was added to the reaction. Dppf = 1,1′-Bis(diphenylphosphino)ferrocene

reaction (entry 15), no improvement in the reaction conversion was observed, indicating that the bidentate nature of the NHC phosphine ligand was necessary in order to observed enhanced catalyst stability in this case.[14]

We next sought to gain better understanding of the structure of our nickel catalyst species. We therefore grew X-ray quality single crystals of a nickel(II) allyl species with ligand **L3**. X-Ray analysis confirms that the proposed nickel(II) allyl intermediate is cationic in nature with the phosphine bound to the nickel in a pseudo square planar arrangement (Figure 2).[13] This supports our hypothesis that the pendant phosphorous ligand helps stabilize the nickel catalyst under the reaction conditions. In our catalyst, the NHC portion of the ligand helps create a sufficiently electron-rich nickel center to enable oxidative addition into the weakly electrophilic C–O bond. We believe that the bidentate nature of the ligand helps prevent deactivation of the unstable nickel(0) intermediate by shielding the catalyst against aggregation with other nickel(0) centers. Importantly, this Ni(II) allyl species is an active catalyst in the cross-coupling reaction and provided identical rates and yield (10 mol% cat, 89% yield, 3 h) as when the Ni(II) precatalyst ([(TMEDA)Ni(*o*-tolyl)Cl]) and **L3** are employed (see table 1, entry 11).

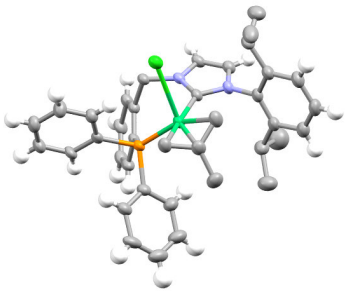


Figure 2. Single-crystal X-ray analysis of NiCl(methallyl)**L3** complex.

Having established the high reactivity of our nickel NHC/phosphine catalyst, we began to explore the substrate tolerance of the transformation by changing the structure of the allylic

alcohol (Figure 3). Various allylic alcohols can be employed as electrophiles in the transformation, including electron rich and electron poor cinnamyl alcohols (**2a**–**2e**). In all cases, >100:1 regioselectivity for aryl addition at the less hindered carbon was observed. Unsubstituted (**2h**) and alkyl substituted (**2i, 2j**) allylic alcohols also react in high yield. We were pleased to find that secondary alcohols also provide the desired product in high yield (**1f**–**1g**). In the case of product **2f**, the regioselectivity for addition of the phenyl group proximal to the methyl groups was also high (>100:1), suggesting significant electronic effect on the regioselectivity as well. When isomeric 1-phenyl-2-propen-1-ol was used instead of cinnamyl alcohol, the linear cross coupling product **2a** was isolated as the only observed product (96% yield). Heterocycles such as pyridines (**2k**) and thiophenes (**2l**) are also tolerated in this reaction.

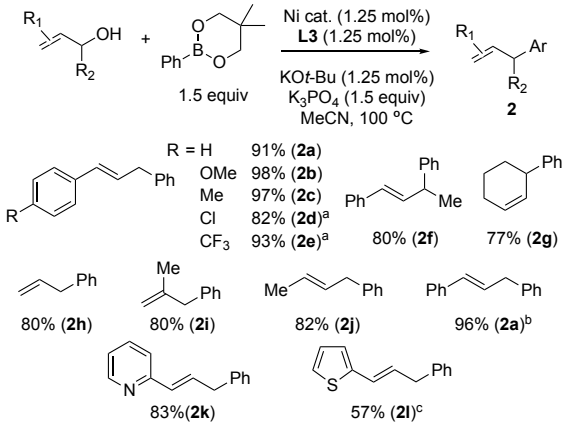


Figure 3. Substrate scope for allylic alcohol coupling partner. a) Reaction run with 2.5 mol% Ni and 2.5 mol% **L3**. b) 1-phenyl-2-propen-1-ol was used as starting material. c) Reaction run with 5 mol% Ni and 5 mol% **L3**.

We also varied the boronic ester partner in the cross coupling and found very wide substrate tolerance (Figure 4). Para, meta, and sterically hindering ortho substituents are all tolerated in the reaction (**3a**–**3c**). Electron donating (**3a**–**3d**) and electron withdrawing (**3e**–**3h**)

phenyl substituents are amenable to the reaction, as are naphthalenes (**3i**) and vinyl boronic esters (**3j**). Importantly, a variety of heterocyclic boronic esters, including pyridines (**3k**), furans (**3l**), and indoles (**3m**) also perform well in the cross coupling to generate the corresponding allylic heterocycles.

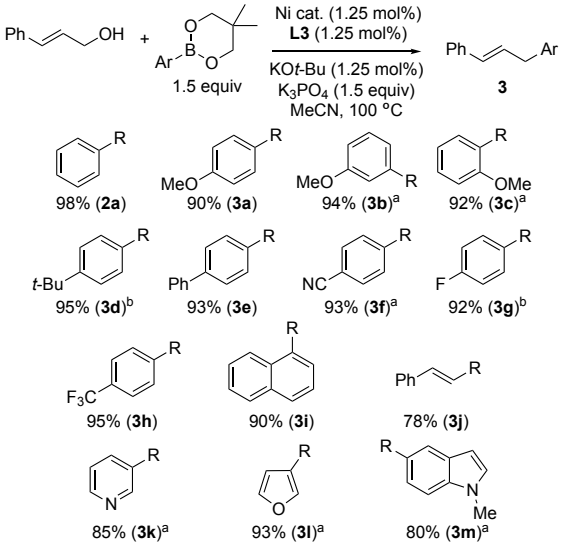


Figure 4. Substrate scope for boronic ester coupling partner. a) Reaction run with 2.5 mol% Ni and 2.5 mol% L3. b) Reaction run with 5 mol% Ni and 5 mol% L3.

In order to expand the synthetic utility of this nickel-catalyzed Suzuki cross coupling, we also investigated tandem cyclization/cross coupling reactions with pendant alkyne insertion partners (Figure 5).[6d] Interestingly, with these bidentate substrates, we found that catalysis with our bidentate ligand **L3** was sluggish and led to only modest yields of the insertion products (30–40% yield). However, when we employed the monodentate NHC ligand IPrHCl, reaction rates increased and high yields could be obtained. We hypothesized that the bidentate nature of the substrate played the same role as the pendant phosphine in NHC ligand **L3**. Thus, when bidentate substrates are employed, the catalyst lifetime is extended and the

insertion reaction accelerated by binding the alkyne to the metal center. In this tandem cyclization/cross coupling reaction, we found that a variety of bidentate substrates efficiently led to the cyclized product, including with N-tosyl amine (**4a**–**4b**), malonate (**4c**), and ether tethers (**4d**).

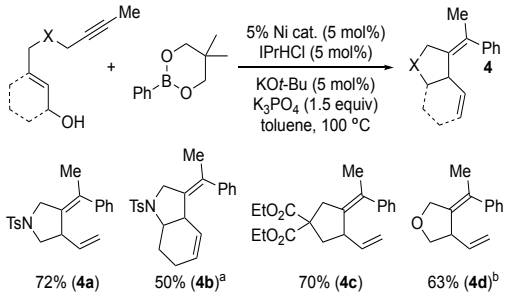


Figure 5. Tandem cyclization/cross coupling reaction. a) Run with $Ni(cod)_2$. b) Ligand **L2** was employed in MeCN.

In conclusion, we have developed an efficient nickel-catalyzed Suzuki cross coupling methodology that employs simple, unprotected allylic alcohols as electrophilic coupling partners. These results expand the current repertoire of nickel-catalyzed transformation and provide a convenient method for generating allylic arene and heteroarene products. In addition, our catalytic method rivals similar methods developed with more expensive noble metal catalysts, in terms of product yield and catalyst loading.[6b,6d] Key to obtaining high yields in these transformations is the use of bidentate NHC/phosphine ligands that extend catalyst lifetime and allow reactions to proceed with as little as 1.25 mol% nickel catalyst. In addition, efficient tandem cyclization/cross coupling reactions were developed that lead to synthetically valuable carbocyclic and heterocyclic ring systems. The application of this class of bidentate NHC/phosphine ligands to nickel catalysis could provide a general solution to the low stability and short catalyst lifetime often observed with nickel(0) complexes.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental Procedures, spectral data for new compounds, X-ray crystal data (PDF).

Notes

The authors claim no competing financial interest.

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Abstract Figure