Ligand-Enabled Ni-Catalyzed Dicarbofunctionalization of Alkenyl Alcohols

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Here, an alcohol-directed 1,2-dicarbofunctionalization of alkenyl alcohols has been realized with aryl/alkenyl boronic acids and alkyl halides as the coupling partners. This reaction was enabled by a commercially available bulky 3-amyl *β*-diketone (Amacac) ligand, that enhancing the reactivity and suppressing many competitive processes. With alcohol as a weak native directing group, this protocol delivers 1,2-arylalkylated and 1,2-alkenylalkylated alcohols with high efficiency, high regioselectivities, a broad substrate scope, and exceptional functional group tolerance. Notably, this methodology facilitates the modular synthesis of biologically active compounds and key alcohol-containing synthetic intermediates. Preliminary mechanistic studies shed light on the neutral coordination of alcohol functionality to nickel catalyst and the origin of regioselectivity.

The development of efficient methods for the construction of carbon-carbon and carbon-heteroatom bonds is central and long-term goal of organic chemistry. In this context, alkene difunctionalization provides tremendous opportunities for simultaneously installing various functional groups across a carbon-carbon double bond in a single operation, which represents one of the most powerful and efficient tools for increasing the molecular complexity.[1,2] In comparison to previous advances with activated alkenes bearing polarized double bond, the difucntionalization of unactivated alkenes with diminished electronic and steric bias, is more challenging due to the low reactivity, poor regiochemical control, and many inevitable competing processes.[3-6] To overcome aforementioned challenges, many efforts have been devoted to directing group-assisted difunctionalization of unactivated alkenes, and the majority of those employed strong coordinated ones, including bidentate 8-aminoquinoline[3a-3f,3i] and 2-picolinic acid[3g-3h], monodentate

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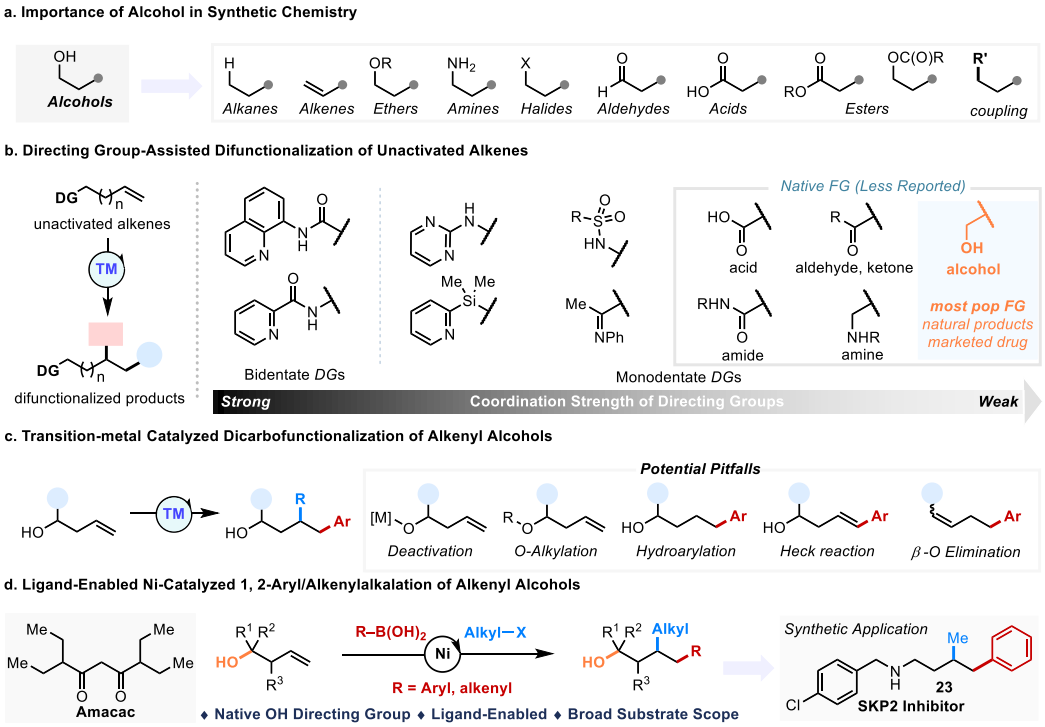
pyrimidine[4c], pyridine[4d], imine[4e-4f,4j], and sulfonamide[4g,4k] etc. (Scheme 1b). One significant direction in this area is to develop difucntionalization reactions of unactivated alkenes with native functional (amide[5a,5j,5k], acid[5c], ketone[5e,5f], amine[5h, 5j, 5k], etc.) group as a weak directing group pioneered by Engle group[5a-d], which is a more appealing and efficient approach omitting two extra steps for auxiliary installation and removal.

Given that alcohol is the most frequent functional group found in bioactive natural products[7a] and marketed drugs[7b], and is versatile synthetic intermediate with a middle level of carbon oxidation state with massive synthetic applications,[7] the access alcohol-containing architectures via difunctionalization of alkenyl alcohols is highly fascinating (Scheme 1a). The main obstacles to develop the difunctionalization reaction with alcohol as the native directing group are their low binding affinity for transition metals, and their conformational flexibility relatively to more commonly used native functional group, such as acid and amide. Despite of remaining challenges, the Engle group[5c] reported a breakthrough 1,2-carboamination of alkenyl alcohols with nickel catalysis. Very recently, our group[5g] demonstrated a Ni-catalyzed 1,2-hydroxylarylation of homoallyl alcohols enabled by a bulky β-diketone ligand. To the best of our knowledge, the dicarbofunctionalization of alkenyl alcohols has not been disclosed, despite the installation



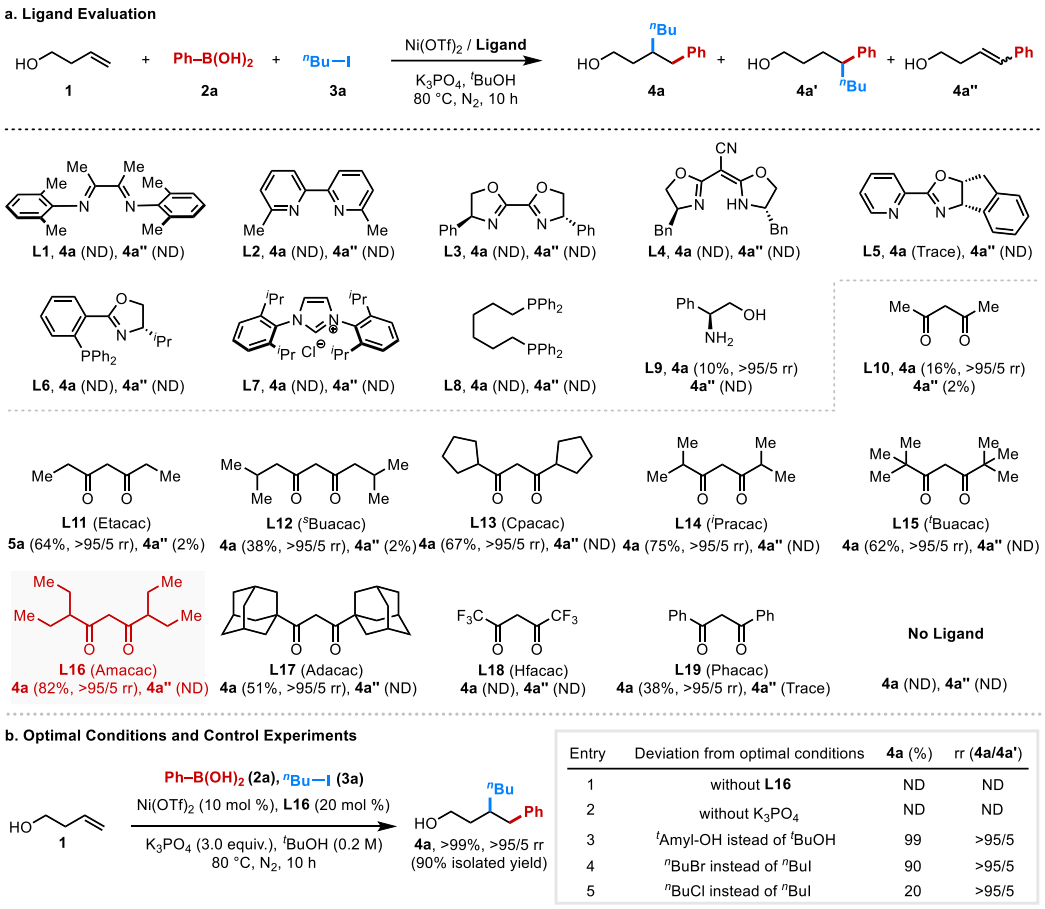
Scheme 1. Synopsis for Ligand-Enabled Ni-Catalyzed 1,2-Dicarbofunctionalization of Alkenyl Alcohols.

of two carbofunctionalilities on alkenyl alcohols provides tremendous opportunities for molecule derivation, but also constitutes substructures of bioactive molecules. In addition to well-known challenges for dicarbofunctionalization of unactivated alkenes, the installation of alkyl group in the dicarbofunctionalization event with alcohols via transition metal catalysis is even more challenging, as the etherification of free hydroxyl group with alkyl halides is highly feasible (Scheme 1c). The alcohols[8] and alkyl halides[9] could facilitate the formation metal-hydride species, thus initiating undesired hydrofunctionalization reactions.

Here, we reported a Ni(II)-catalyzed 1,2-arylalkylation and 1,2-alkenylalkylation of alkenyl alcohols in a regioselective manner with alcohol group as the native directing group (Scheme 1d). The identification of a commercially available and cheap 3-amyl β-diketone (Amacac) ligand is crucial for the success to this reaction, enabling the efficient coordination of alcohol by altering the Lewis acidity of the nickel catalyst. This reaction exhibits excellent regioselectivity, good functional group tolerance and a broad substrate scope of aryl/alkenyl boronic acids, alkyl halides and alkenyl alcohols, including complex natural products. The synthetic utility of this reaction has been demonstrated by the derivatizations of resulted arylalkylated alcohols, and the efficient preparation of two key synthetic intermediates and a biologically active compound. The obtained single crystal of alkenyl alcohol-coordinated $Ni(Amacac)_2$ also confirms the coordination model of alcohol with nickel catalyst.

Results and discussion

To explore the feasibility for Ni-catalyzed arylalkylation of alkenyl alcohols, we initiated our study by using 3-buten-1-ol (**1**), phenyl boronic acid (**2a**) and *n*-butyl iodide (**3a**) as the model substrates. In the presence of various widely explored ligands, including diamine (**L1**), bipyridine (**L2**), bisoxazoline (**L3**), Box (**L4**), py-oxazoline (**L5**), and Phox (**L6**), NHC ligand (**L7**), and diphosphine ligand (**L8**), this reaction could not proceed by using $Ni(OTf)_2$ as the catalyst precursor and K_3PO_4 as the base, while a weak coordinated amino alcohol ligand **L9** resulted in 10% yield (Scheme 2a). Taking consideration of bulky acac-type ligand could modulate the reactivity and selectivity in Ni-catalyzed hydrofunctionalization and difunctionalization reactions[5g,8f] by enhancing migratory insertion efficiency and stabilizing the resulted



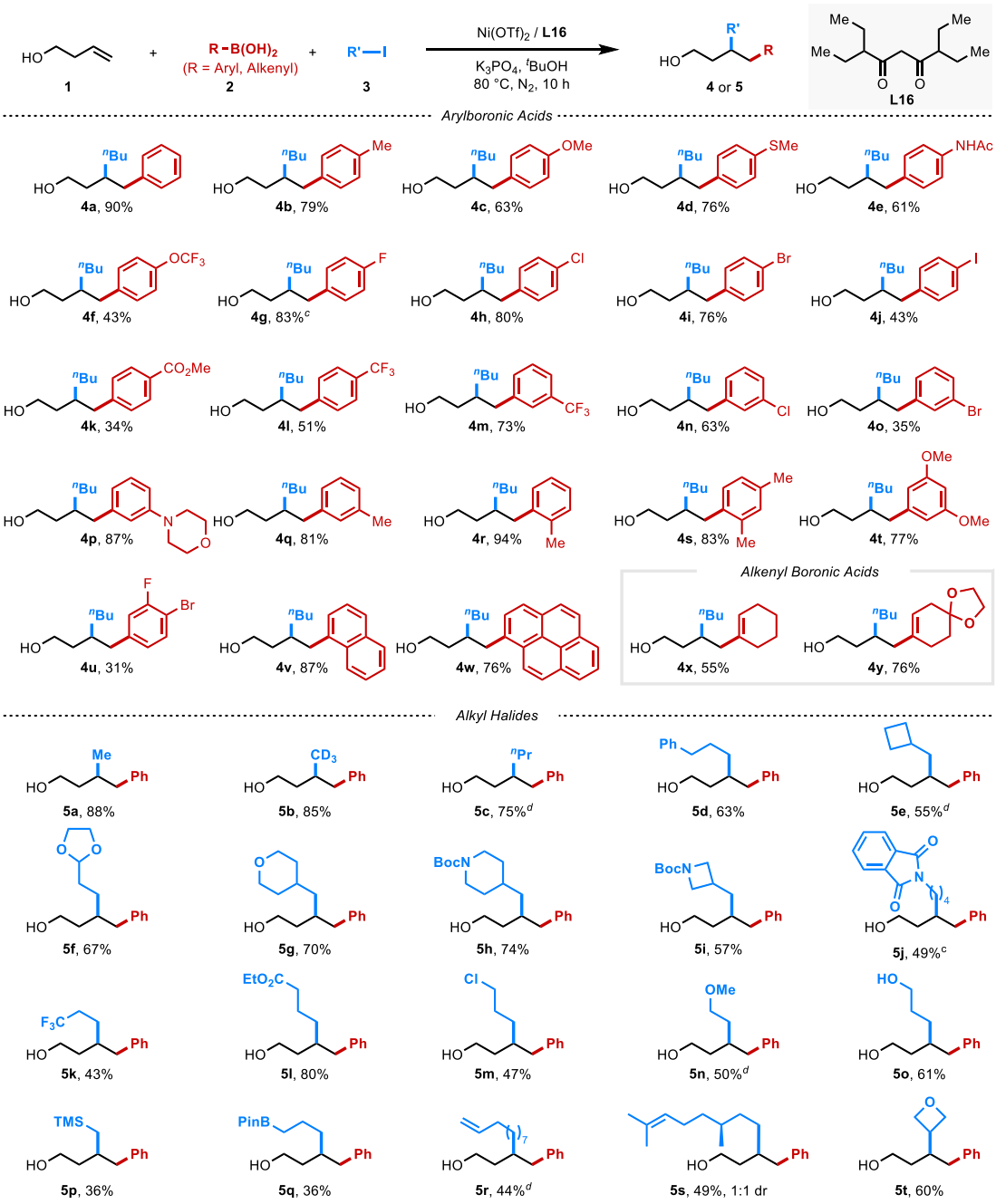
Entry	Deviation from optimal conditions	**4a** (%)	rr (**4a**/**4a'**)
1	without **L16**	ND	ND
2	without K_3PO_4	ND	ND
3	^{t}Amyl-OH istead of ^{t}BuOH	99	>95/5
4	^{n}BuBr instead of ^{n}BuI	90	>95/5
5	^{n}BuCl instead of ^{n}BuI	20	>95/5

Scheme 2. Ligand Evaluation, Optimal Reaction Conditions and Control Experiments.

carbon-Ni(II) species, a series of acac-type ligands were evaluated. Gratifyingly, simple acac ligand (**L10**) afforded the desired 1,2-arylalkylated product in 16% yield with excellent regioselectivity. Following this lead, systematically evaluation of *β*-diketone ligands was carried out. In general, significant increase of yield was observed by increasing the steric hindrance on acac-type ligands (**L10**-**L17**). Switching the methyl group to ethyl group (**L11**) resulted in 64% yield with high regioselective control, and ^{i}Pracac ligand **L14** gave the desired product in 75% yield with excellent regioselectivity. Replacement of the *iso*-propyl by *tert*-butyl (^{t}Buacac, **L15**) and 1-adamantyl (Adacac, **L17**) group led to the inferior results (**L15**, 62% yield; **L17**, 51% yield). Gratifyingly, a newly developed *β*-diketone ligand bearing a 3-amyl group (Amacac, **L16**) improved the yield of this reaction to 82% NMR yield with excellent regioselectivity (>95/5 rr). Similar to our previous acac-type ligand enabled functinoalizations of unactivated alkenes and internal alkenes, the electron-deficient *β*-diketone ligand (Hfacac, **L18**) shut down this reaction. Interestingly, the

aryl-substituted *β*-diketone ligand **L19** could also provide the desired arylalkylated product in 38% yield and excellent regioselectivity, indicating the potential of aryl-substituted *β*-diketone ligands in nickel-catalyzed functionalizations of alkenes. Upon systematical optimization of reaction parameters, the yield was improved to over 99% ^{1}H NMR yield (90% isolated yield) with >95/5 rr by conducting this reaction with 10 mol % of $Ni(OTf)_2$, 20 mol% of **L16**, 1.5 equivalent of **2a** and 3.0 equivalent of K_3PO_4 under N_2 atmosphere (For details, see supporting information). It is worth noting that the reaction could not proceed in the absence of ligand, which underscores the vital role of bulky *β*-diketone ligand in this reaction (Scheme 2b). The control experiments unveiled that all reaction parameters are crucial for this reaction. Both alkyl iodide and alkyl bromide are effective coupling partner for this alcohol-directed 1,2-arylalkylation reaction, while alkyl chloride is less reactive.

With the optimal conditions in hand, the generality of this alcohol-directed nickel-catalyzed 1,2-dicarbofunctionalization of unactivated alkenes has been evaluated. As shown in Scheme 3, this reaction presents high level of compatibility with both aryl boronic acids and alkyl halides (Scheme 3). Aryl boronic acids bearing both electron-donating and electron withdrawing substituents at the *para*-position all proceeded smoothly, providing the arylalkylated products in moderate to excellent yields with excellent regioselectivities. The *meta*- and *ortho*-substituted arylboronic acids are also compatible with this procedure. Notably, this protocol is not sensitive to steric hindrance of arylboronic acids, as the arylboronic acid bearing ortho-substituents didn't significantly affect the outcomes. In addition, a series of functional groups are well tolerated, including methyl, methoxy, thiosether, acetylamide, trifluoromethoxy, fluoro (**2g**), chloro (**2h**), bromo (**2i**) and iodo (**2j**), ester (**2k**), trifluoromethyl (**2l**, **2n**), morphine (**2p**) etc. Multi-substituted phenyl boronic acids (**2s**-**2u**) and polycyclic arylboronic acids (**2v**-**2w**) afforded the corresponding arylalkylated products in moderate to high yields. Of note, alkenyl boronic acids were also effective, furnishing alkenylalkylated products in good yields (**2x**-**2y**) and excellent regioselectivities.



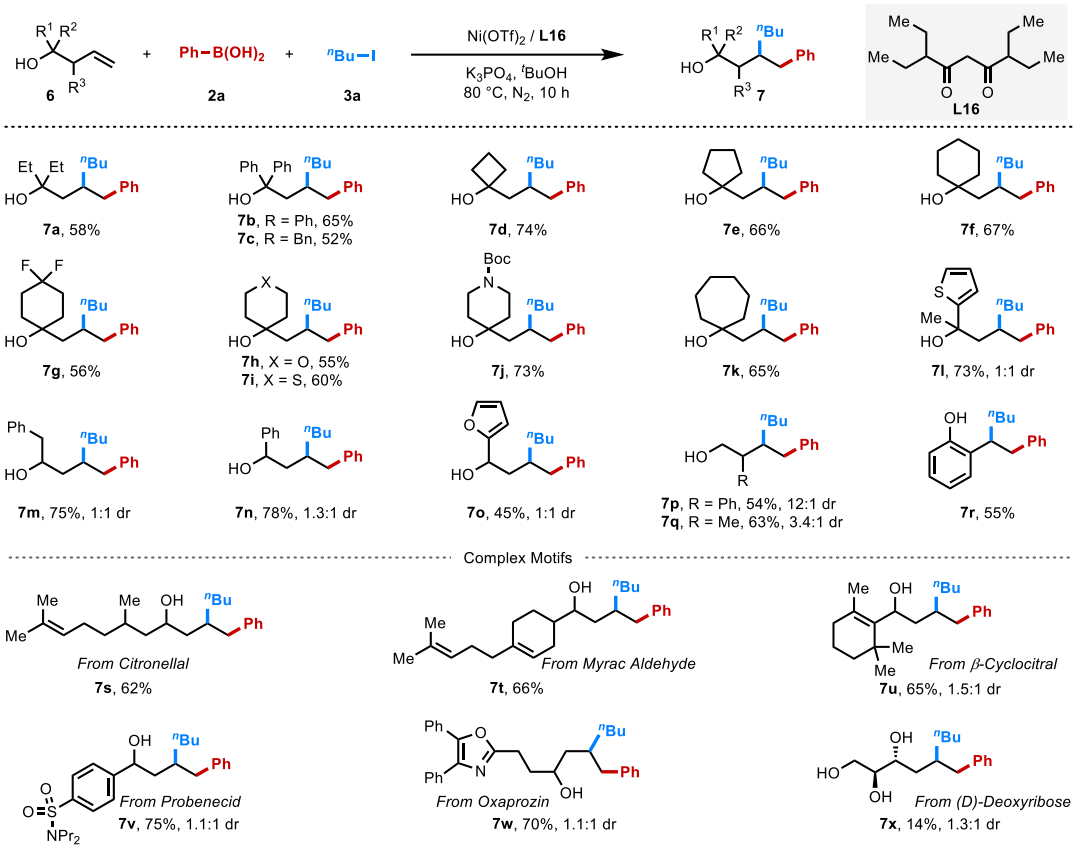
Scheme 3. Substrate Scope with Respect to Arylboronic Acids and Alkyl Halides.[a,b] [a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol, 1.5 equiv.), **3** (0.4 mmol, 2.0 equiv), $Ni(OTf)_2$ (7.1 mg, 10 mol %), **L16** (8.5 mg, 20 mol %), K_3PO_4 (127.4 mg, 3.0 equiv.), ^{t}BuOH (1.0 mL), 80 °C, 10 hours. [b]Isolated yield, rr > 95/5, and the rr and dr values were determined by ^{1}H NMR analysis. [c]rr = 92/8. [d]Alkyl bromide was used instead of alkyl iodide.

Next, the substrate scope with respect to alkyl halides was investigated. With alkyl iodides and bromides, a wide range of primary alkylating reagents bearing various functional groups were investigated, providing the desired arylalkylated products (**5a-s**) in moderate to excellent yields and excellent

regioselectivities. In addition to the installation of methyl group with methyl iodide, deuterated methyl group could also be easily introduced with excellent yield (**5b**). The tolerance of heterocycle-containing alkylating reagents is noteworthy, which highlights the generality of the current protocol (**5g-i**). Phthalimide-protected 4-bromobutan-1-amine gave the corresponding product in 49% yield (**5j**). Note that phthalimide protecting group could be readily converted to free aliphatic amine by hydrolysis. In case of the alkylating reagent bearing both iodo and chloro groups, the alkylation occurred at the more reactive site, providing the alcohol product bearing chloro group (**5m**). The mild conditions in this protocol resulted in the tolerance many reactive functional groups, including acid-sensitive acetal, free hydroxyl, trimethylsilyl, and BPin. The alkyl bromide bearing a terminal alkene functionality could also afford the arylalkylated product (**5r**) in 44% yield, which indicates the crucial role of hydroxyl directing group for the high activity. Notably, cyclic secondary alkyl iodide (**3t**) was also reactive, while tertiary alkyl halides were ineffective probably because of steric hindrance.

A series of alkenyl alcohols were examined using phenyl boronic acid (**2a**) and *n*-butyl iodide (**3a**) as the coupling components. As depicted in Scheme 4, this ligand-enabled catalytic approach was effective for primary, secondary, and tertiary primary alkenyl alcohols, affording corresponding arylalkylated products smoothly in moderate to high yields. The substituents for tertiary alcohols (**7a-l**) didn't significantly affect the outcomes of this reaction, despite of the weak coordination ability of bulky tertiary hydroxyl group. Secondary alcohols bearing both alkyl and aryl group gave similar outcomes (**6m** vs **6n**). In addition, primary alcohols with 2-substituents were investigated. Although 2-methyl butenol (**6q**) gave 64% yield with 3.4/1.0 of diastereoselectivity, 2-phenyl butenol (**6p**) afforded the desired product with excellent diastereoselectivity (12/1 dr). Besides, more acidic phenolic hydroxyl group could also serve as viable native directing groups, delivering the desired product **7r** in 55% yield. This reaction provides a potentially powerful disconnection for complex structure-containing natural products and drug molecules, particularly since the alcohol precursors can readily be synthesized via the nucleophilic addition of ketones or aldehydes with Grignard reagents or organozinc reagents. Alkenyl alcohols derived from complex motifs, including natural products (**6s-u**) and drugs (**6v-w**), were successfully transformed to arylalkylated products in 62-75% yields and excellent regioselectivities. It is noteworthy that, D-deoxyribose derivative **6x** bearing

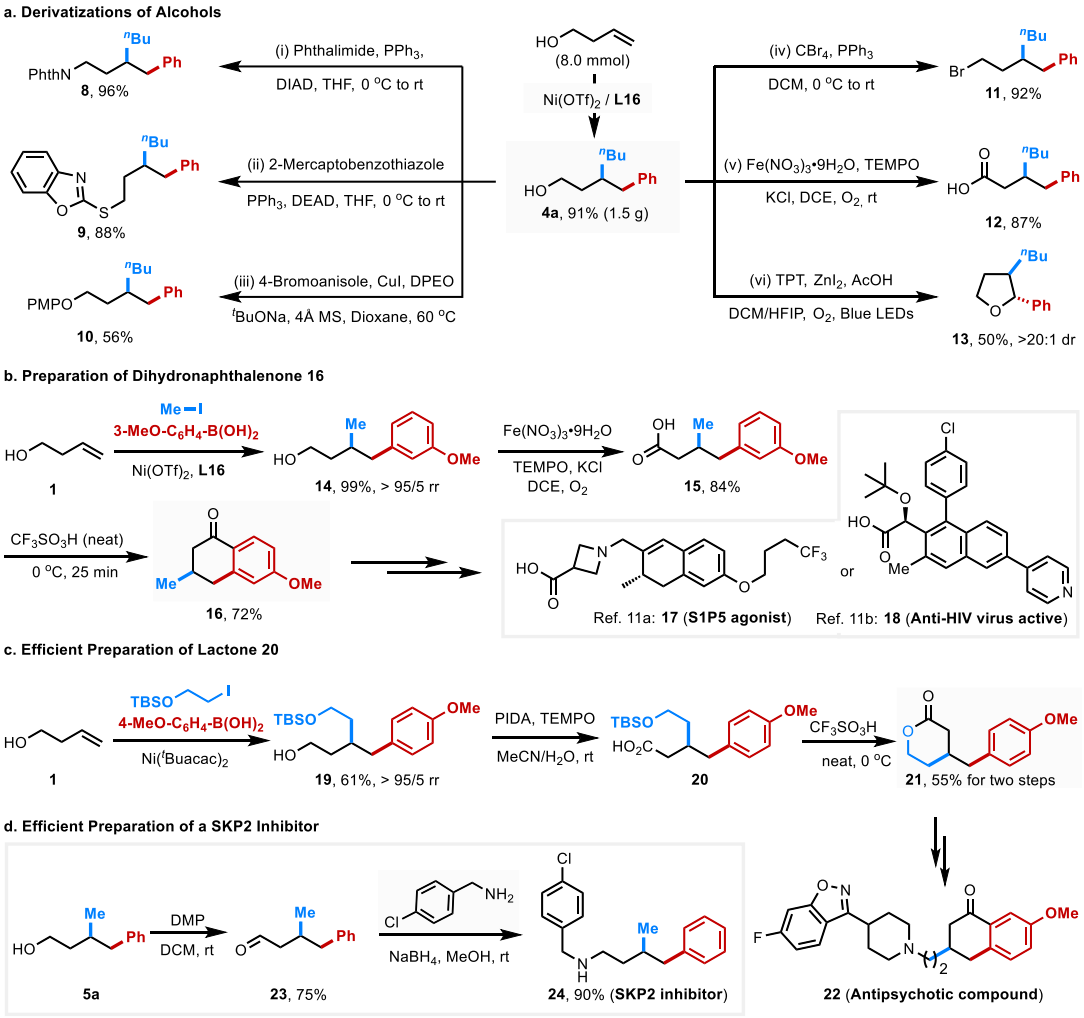
three unprotected hydroxyl groups didn't totally shut down this reaction, albeit with 14% yield, which underscores the generality of this protocol.



Scheme 4. Substrate Scope with Respect to Alkenyl Alcohols.[a,b] [a]Reaction conditions: 6 (0.2 mmol), 2a (0.3 mmol, 1.5 equiv.), 3a (0.4 mmol, 2.0 equiv.), $Ni(OTf)_2$ (7.1 mg, 10 mol %), L16 (8.5 mg, 20 mol %), K_3PO_4 (127.4 mg, 3.0 equiv.), ^{t}BuOH (1.0 mL), 80 °C, 10 hours. [b]Isolated yield, rr > 95/5, and the rr and dr values were determined by ^{1}H NMR analysis.

To illustrate the practicability of this protocol, we have conducted this reaction on 8.0 mmol scale using 5.0 mol% of $Ni(OTf)_2$ and 10 mol% of Amacac (**L16**). Notably, the yield increased to 92% without a decrease of regioselectivity (Scheme 5a). Since alcohols are versatile intermediates in organic synthesis, we next carried out derivatizations starting from alcohol **5a**. The hydroxyl functionality could be readily converted to corresponding amide (**8**), thioether (**9**) in excellent yields via Mitsunobu reaction. A PMP protected ether **10** was formed in 56% yield via Cu-catalyzed carbon-oxygen bond formation (Ullmann-Ma reaction).[10a] The alkyl bromide **11** was prepared in 92% yield under classic Appel reaction conditions. Moreover, alcohol **5a** could be easily oxidized to acid (**12**) via Fe-catalyzed oxidation reported by Ma and

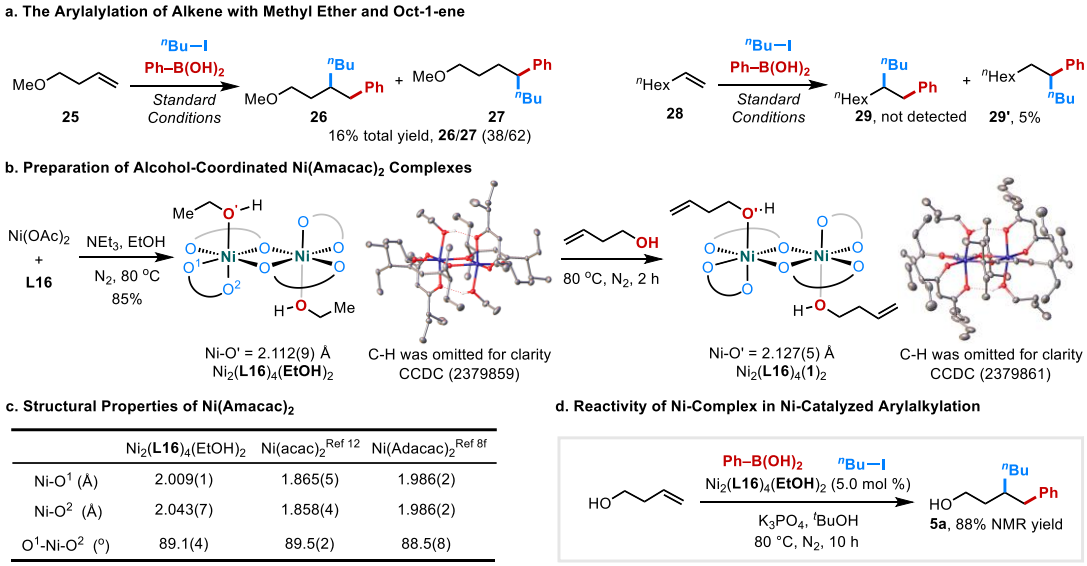
co-authors.[10b] Under photoirradiation, **5a** was converted into a five-membered cyclic ether (**13**) with high diastereoselectivity via intramolecular C–O formation.[10c]



Scheme 5. Gram-Scale Reaction, Derivatization, and Synthetic Applications

In addition to the diverse derivatizations of alcohol demonstrated above, we further established our protocol could be used as a pluripotent intermediate for the efficient synthesis of key intermediates or bioactive compounds. Dihydronaphthalenone **16** is the key intermediate for the synthesis of bioactive compounds **17** (S1P5 Agonist)[11a] and **18** (Anti-HIV virus active)[11b], which could be efficient prepared in three steps with 60% total yield starting from the commercially available and cheap 3-butenol **1** (Scheme 5b). Notably, this cyclic ketone **16** requires 5 steps from ethyl 3-methyl-4-oxocrotonate[11a] or 2-methoxyphenylacetone[11b]. Latone **21**, a key intermediate for the synthesis of a potential antipsychotic compound **22**,[11c] could also be accessed via ligand-enabled Ni-catalyzed arylalkylation of 3-butenol,

oxidation, and intramolecular lactonization (Scheme 5c). In addition, a SKP2 inhibitor **24**[11d] could be efficient prepared in 68% total yield via DMP oxidation and sequential reductive amination from alcohol **5a** (Scheme 5d). These newly established synthetic routes are not only step-economical, but also provide synthetic approaches that are amenable toward rapid structural diversification of the arylalkylation products for drug discovery.

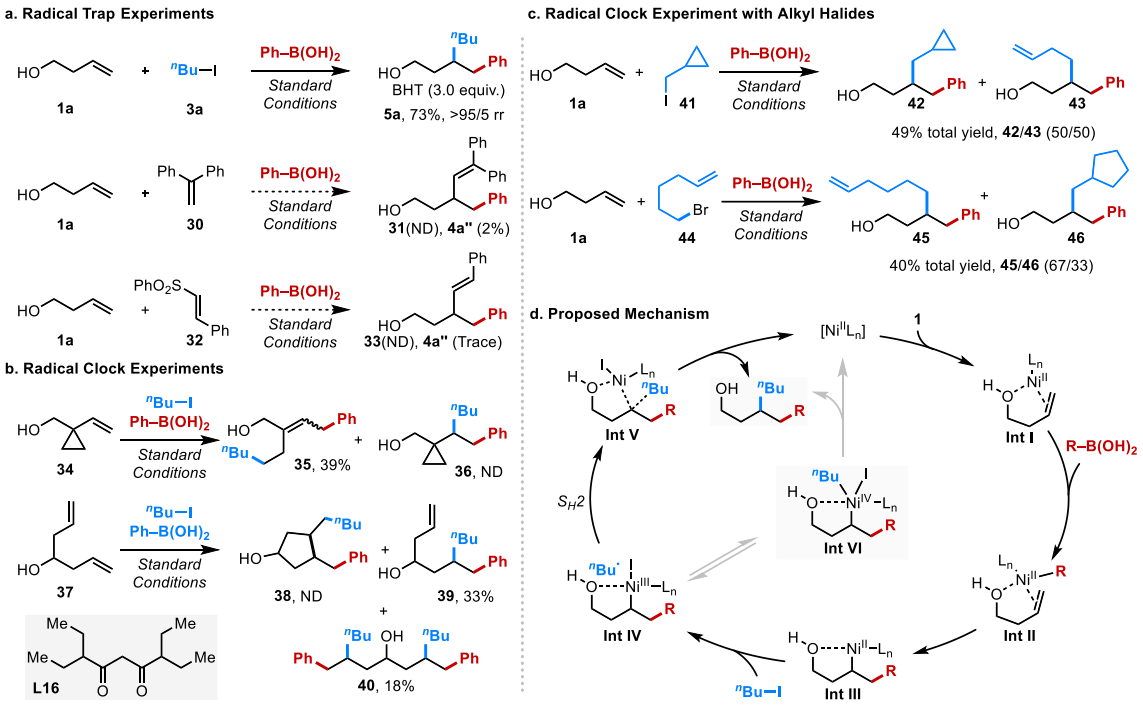


	Ni_2(**L16**)$_4$(EtOH)$_2$	Ni(acac)$_2$[Ref 12]	Ni(Adacac)$_2$[Ref 8f]
Ni-O^1 (Å)	2.009(1)	1.865(5)	1.986(2)
Ni-O^2 (Å)	2.043(7)	1.858(4)	1.986(2)
O^1-Ni-O^2 (°)	89.1(4)	89.5(2)	88.5(8)

Figure 1. The Role of Hydroxyl Group in Ni-Catalyzed 1,2-Dicarbofunctionalization.

To further understand the role of hydroxyl group in this newly development of ligand-enabled Ni-catalyzed 1,2-dicarbofunctionalization of alkenyl alcohols, the control experiments with protected alcohol were carried out first. Alkenyl methyl ether only gave a mixture of regio-isomers (38/62 rr) with a decrease of yield (16% total yield) (Figure 1a). Notably, the removal of alcohol functionality resulted in the formation of sole 1,1-arylalkylated product in very low yield (5% yield). Those observation indicates the indispensable role of native hydroxyl functionality in the control of regioselectivity and enhancement of migratory insertion efficiency as a weak directing group. To gain more information of this newly developed bulky 3-amyl acac-type ligand (**L16**), the complex of Ni(Amacac)$_2$ was synthesized following the known procedure[12]. This elementary analysis and X-ray analysis disclosed a Ni(Amacac)$_2$ dimmer with the coordination of EtOH (Figure 1b). The length of Ni–O is longer than that in Ni(acac)$_2$[12] and even longer than that in Ni(Adacac)$_2$[8f] (Figure 1c), which indicates a weaker coordinating ability of our newly developed

3-pentyl *β*-diketone ligand in comparison with known acac ligands. The week coordination of bulky *β*-diketone ligand resulted in a more acidic nickel catalyst, which could bond to free alcohol tightly. Moreover, we have tested the efficiency of the Ni complex Ni_2(**L16**)$_4$$(EtOH)_2$ in Ni-catalyzed arylalkylation of alkenyl alcohols, and this precursor shows high catalytic reactivity (88% NMR yield) (Figure 1d). To further understand the coordination model of alcohol with Ni(II) complex, we have obtained 3-butenol coordinated nickel complex [Ni_2(**1**)$_2$(**L16**)$_4$] and confirmed its structure by X-Ray crystallography. Of note, substrate **1** coordinates to Ni center via the neutral hydroxyl group (Ni–O˙, 2.13 Å), which proves free hydroxyl group to be reliable directing group in alkene difunctionalization (Figure 1b).



Scheme 6. Mechanistic Studies and Proposed Mechanism

To gain deep insights of this reaction, we carried out a series of mechanistic studies. Only Heck-type byproduct **4a''** was formed in the absence of *n*-butyl iodide **3a** indicates the alkyl halides might not affect the migratory insertion of alkene to aryl-Ni(II) species generated by the transmetalation of arylboronic acid (For details, see supporting information). Given the alkyl-Ni(II) species might to produce alkyl radicals and corresponding Ni(I) species via a homolytic process in the presence of bipyridine ligand, we next conducted the radical capturing experiments with BHT, 1,1-diphenylenthylene, and (*E*)-(2-

(phenylsulfonyl)vinyl)benzene. As listed in Scheme 6a, radical inhibitor BHT could not suppress the formation of arylalkylation product. In addition, the replacement of *n*-butyl iodide with 1,1-diphenylethylene (**30**) or (*E*)-(2-(phenylsulfonyl)vinyl)benzene (**32**) resulted in trace amount of Heck product **4a''** instead of arylalkenylation product. Those control experiments indicates the formation an alkyl radical from alkyl-Ni(II) intermediate **Int III** is unlikely be involved in our bulky *β*-diketone ligand-participated reaction, probably due to the strong anionic ligand could stabilize the alkyl-Ni(II) intermediate. Although the reaction with (1-vinylcyclopropyl)methanol (**34**) as substrate afforded ring-opening product **35** in 39% yield, the radical clock experiments with 1,6-heptadien-4-ol (**37**) only gave the mono-arylalkylated product **39** (33% yield) and diarylalkylated product **40** (18% yield), instead of the formation of cyclized product **38** (Scheme 6b). Those outcomes further confirm the generation of alkyl radical via the homolytic cleavage of alkyl-Ni(II) species is undesired in our catalytic system.

Furthermore, the use of cyclopropyl iodide (**41**) gave a mixture of cyclopropylmethylated product **42** and ring-opening product **43** in 49% total yield with a ratio of 50/50, which indicates an alkyl radical might be involved in the catalytic cycle from alkyl halide. To further confirm this observation, we have conducted the reaction with 6-bromohex-1-ene (**44**), affording both acyclic (**45**) and cyclic products (**46**) in 40% total yield and a ratio of 67/33 (Scheme 6c). On the basis of the above experimental observations and literature precedents, we hence hypothesized the generated alkyl radical form alkyl halides might happen via XAT (halogen atom transfer)of alkyl-Ni(II) species with alkyl halides. The arylalkylated product might be formed by a S_H2 process, according to the observation by Molander[13a], Koh[13b] and Macmillan[13d]. However, the formation of high-valent Ni(IV)[14] species via a radial recombination and further reductive elimination could not be fully ruled out by current mechanistic experiments. Based on preliminary mechanistic studies, a plausible mechanism of this Ni-catalyzed arylalkylation of alkenyl alcohols was proposed, as presented in Scheme 6d. alkyl-Ni(II) species (**Int III**) could be efficient formed via transmetalation, and sequential migratory insertion. The product could be generated via XAT with alkyl halides, followed by a S_H2 process, along with the regeneration of Ni(II) catalyst.

In summary, a Ni-catalyzed arylalkylation of alkenes using free hydroxyl as native directing group was realized, affording 1,2-arylalkylated and 1,2-alkenylalkylated products in high yields and high regioselectivities. And the key to this three-components cross-coupling reaction is utilizing bulky *β*-diketone ligand. This protocol could tolerate a wide range of substrates with excellent functional group tolerance, and open new an avenue for the efficient preparation of alcohol-containing synthetic intermediates and bioactive compounds.

Methods Summary

General Procedure for Nickel-Catalyzed 1,2-Aryl/Alkenylalkylation of Alkenyl Alcohols: To an oven-dried 8-mL vial equipped with a Teflon-coated magnetic stir bar were added boronic acid **2** (0.3 mmol, 1.5 equiv.), and transferred into the glovebox, followed by addition of $Ni(OTf)_2$ (7.1 mg, 10 mol%) and K_3PO_4 (127.4 mg, 3.0 equiv.). The vial was sealed using a cap with PTFE cap liner and moved outside of the glovebox. Next, **L16** (8.5 mg, 20 mol%), **1** (0.2 mmol, 1.0 equiv.), anhydrous ^{t}BuOH (1.0 mL) and **3** (0.4 mmol, 2.0 equiv.) were added under N_2 atmosphere. The reaction mixture was then stirred at 80 ℃ (500 rpm) for 10 h. After cooling to room temperature, the mixture was passed through a pad of silica gel with EtOAc as the eluent to remove nickel and insoluble precipitate. The resulting solution was concentrated under reduced pressure. The residue was then purified by silica gel chromatography or preparative thin-layer chromatography as mentioned. The ratio of 1, 2-/1, 1-regioselectivity was determined by crude ^{1}H NMR.

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Competing Interests The authors declare no competing interests.

Data Availability X-ray structural data of compound Ni_2(**L16**)$_4$(EtOH)$_2$ and [Ni_2(**1**)$_2$(**L16**)$_4$] is available free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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