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Regio- and *Trans*-Selective Ni-Catalyzed Coupling of Butadiene, Carbonyls, and Arylboronic Acids to Homoallylic Alcohols under Base-Free Conditions

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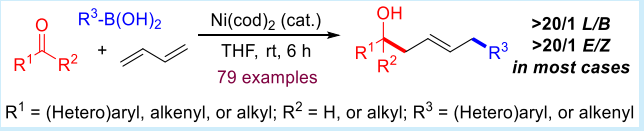
ABSTRACT: We herein report a Ni-catalyzed three-component coupling of 1,3-butadiene, carbonyl compounds, and arylboronic acids as a general synthetic approach to 1,4-disubstituted homoallylic alcohols, an important class of compounds, which have previously not been straightforward to access. The reaction occurs efficiently using a $Ni(cod)_2$ catalyst without any external base and ligand at ambient temperature and allows a highly regioselective and *trans*-selective 1,4-dicarbofunctionalization of feedstock butadiene in a single operation. This simple and practical protocol could apply to a comprehensive scope of substrates. The neutral conditions show extraordinary tolerance for even highly base-sensitive functional groups.



Homoallylic alcohols constitute a vital structural element that widely exists in many natural products and bioactive molecules.[1] Moreover, they are versatile synthetic intermediates that permit a variety of chemical transformations. Consequently, a tremendous amount of effort has been devoted to preparing homoallylic alcohols, and the most frequently utilized method is the addition of allylmetal reagents to carbonyls (Scheme 1a).[2] However, the allylmetal used generally needs to be pre-prepared, often through tedious multistep operations. In this context, it would be more desirable to use a readily available and stable allyl source instead of preformed sensitive allylmetal reagents. Butadiene, an abundant feedstock (production of ~13 × 10^6 tons/year) produced from petroleum cracking,[3] is an ideal allyl precursor. As such, various metal-catalyzed reductive (or borylative) butadiene−carbonyl coupling has been developed to prepare homoallylic alcohols (Scheme 1b).[4−7] However, these methods usually lead to 1,2-disubstituted homoallylic alcohols with the formation of one carbon−carbon (C−C) bond (Scheme 1a,b).[4,5] General methods for synthesizing 1,4-disubstituted homoallylic alcohols,[8] an important class of compounds, remain elusive.

We sought to develop a modular and general synthesis of 1,4-disubstituted homoallylic alcohols by a selective butadiene−carbonyl coupling through the direct construction of two C−C bonds.[9,10] We envisioned a nickel-catalyzed three-component coupling of butadiene, carbonyls, and carbon nucleophiles could afford homoallylic alcohols (Scheme 1c). Mechanistically, we envisaged that the oxa−nickelacycle intermediate[11] formed by the cyclometalation of diene and carbonyls could undergo transmetalation with a suitable carbon nucleophile to give an acyclic allyl−nickel complex. The subsequent reductive elimination at the terminal position

Scheme 1. Synthesis of Homoallylic Alcohols via (a) Carbonyl Allylation or (b and c) Butadiene−Carbonyl Couplings

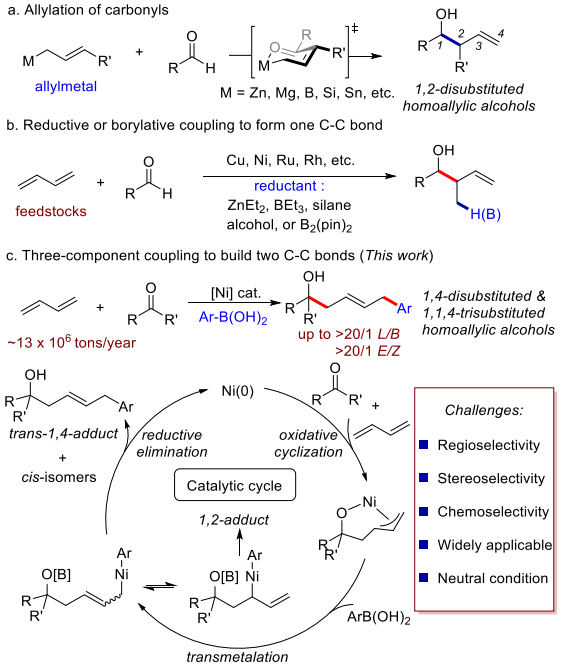


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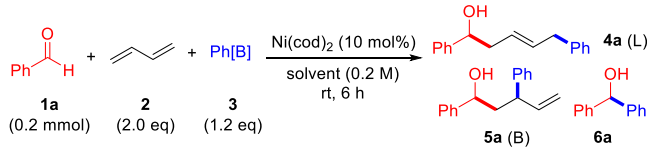
Table 1. Reaction Optimization



entry	Ph[B]	solvent	**4a** yield[a] (%) (*E*/*Z*)	**4a**/**5a**[a] (*L*/*B*)	**6a** yield[a] (%)
1	PhBpin	THF/H_2O (5/1)	52 (11/1)	13/1	0
2	PhBpin	THF	0		0
3	PhBpin	MeOH	54 (10/1)	13/1	2
4	$PhB(OH)_2$	MeOH	76 (10/1)	15/1	2
5	$PhB(OH)_2$	DMF	33 (5/1)	16/1	0
6	$PhB(OH)_2$	toluene	76 (>20/1)	10/1	13
7	$PhB(OH)_2$	dioxane	85 (>20/1)	14/1	4
8	$PhB(OH)_2$	THF	89 (86)[b] (>20/1)	>20/1	0

[a]Determined by ^{1}H NMR analysis. [b]Isolated yield.

could afford the desired *trans*-1,4-adduct. However, the high levels of chemo-, regio-, and stereocontrol would be nontrivial because of the competitive generation of the 1,2-adduct and *cis*-1,4-adduct as well as the direct addition of carbon nucleophiles to carbonyls. In 1999, Tamaru and co-workers reported a seminal work on a nickel-catalyzed three-component coupling of aldehydes, dienes, and organometallic reagents (basically Me_2Zn and Ph_2Zn) for the synthesis of homoallylic alcohols.[12] The narrow scope of organometallics, modest levels of selectivity, and functional group compatibility, however, significantly limit the synthetic utility.

In contrast, the relative stability and easy availability of organoboronic acids and esters have imparted good functional group tolerance and great operational simplicity to the Suzuki−Miyaura couplings, making it one of the most commonly used reactions in organic chemistry.[13] We felt that the use of arylboronic acids and esters instead of difficult-to-handle organometallic reagents would greatly facilitate the synthesis of homoallylic alcohols. Nevertheless, due to the low intrinsic nucleophilicity of organoboronic acid, strong bases are generally required to convert "transmetalation-inactive" metal(II) halide into "transmetalation-active" metal(II) alkoxide.[14] However, the addition of a base would promote competitive protodeboronation of organoboronic acid and be incompatible with base-sensitive functional groups, thus limiting the substrate scope.[15] We speculated the oxa−nickelacycle intermediate mentioned above that contains a Ni(II) alkoxide moiety would probably allow an efficient transmetalation of organoboronic acid without an exogenous base.[16] As part of our ongoing research on nickel catalysis,[17] we here report a base-free highly regio- and *trans*-selective Ni-catalyzed three-component coupling of butadiene, organoboronic acids, and carbonyl compounds. This protocol provides a general, efficient, and modular synthetic approach to 1,4-disubstituted and 1,1,4-trisubstituted homoallylic alcohols with an exceptionally broad substrate scope and an extraordinary tolerance to even highly base-sensitive functional groups (Scheme 1c).

We commenced our studies with the model reaction of butadiene, benzaldehyde, and phenylboronic acid pinacol ester (PhBpin) in the presence of a nickel catalyst [$Ni(cod)_2$]. We first tested various phosphine, and NHC ligands chelated nickel catalysts with or without the addition of a base, but none led to observation of the desired product **4a** (see the Supporting Information). To our delight, a simple $Ni(cod)_2$ catalyst in a THF/H_2O mixture under base- and ligand-free reaction conditions at ambient temperature was able to afford 1,4-disubstituted homoallylic alcohol [*trans*-1,4-adduct (**4a**)] in 52% yield with high levels of regio- and stereocontrol over the 1,2-adduct (13/1 *L*/*B*) and *cis*-1,4-adduct (11/1 *E*/*Z*) (Table 1, entry 1). The same conditions but in the absence of H_2O led to no conversions (entry 2). When MeOH was used as the solvent, results similar to those of the aqueous condition were obtained (entry 3). Using $PhB(OH)_2$ instead of PhBpin, the yield was improved to 76%. We found protic solvents were not necessary, and solvents would dramatically affect the yield and selectivity when $PhB(OH)_2$ was used as a coupling partner. While polar solvent DMF leads to low stereoselectivity (5/1 *E*/*Z*) and yield, arene and ether-type solvents (toluene and dioxane) gave **4a** in excellent stereocontrol (>20/1 *E*/*Z*) and high yields, accompanied by a substantial amount of byproduct via direct carbonyl addition (**6a**) (entries 4−8). Fortunately, THF was identified as the optimal solvent to furnish **4a** in 86% isolated yield with excellent regio- and stereoselectivity (>20/1 *E*/*Z*, >20/1 *L*/*B*), and with no observation of **6a** (entry 8). It is noteworthy that the mild and practical reaction condition is used at room temperature with no exogenous base, which might permit good functional group tolerance.

Under the optimized reaction conditions, we first examined the scope of this reaction using various aldehydes. As shown in Table 2, we found a wide variety of homoallylic alcohols were obtained in good to high yields with excellent regio- and stereoselectivity (>20/1 *E*/*Z*, >20/1 *L*/*B*) with very few exceptions. The reaction was not sensitive to the steric effect of the aldehyde substituent, and bulky 2,4,6-trimethyl benzaldehyde afforded the coupling product in high yield (**4c**). Aromatic aldehydes with electron-donating and -withdrawing groups were both suitable substrates (**4a**−**4z**). In particular, strong electron-deficient substrates (**4j**−**4l**) that might readily undergo direct carbonyl arylation were found to be compatible. Many functional groups such as ethers (**4d** and **4e**), a trifluoromethyl group (**4h**), a trifluoromethoxy group (**4i**), a cyano group (**4k**), an ester group (**4l**), and an alkynyl group (**4m**) were tolerated under this mild condition. Interestingly, aldehyde with a Bpin moiety was applicable (**4p**), suggesting the reaction could effectively differentiate arylboronic acid and esters. It is noteworthy that substrates with Cl and Br substituents were viable, indicating the method is orthogonal to traditional Suzuki−Miyaura reaction, and these handles provide opportunities for further manipulation (**4n**−**4p**).

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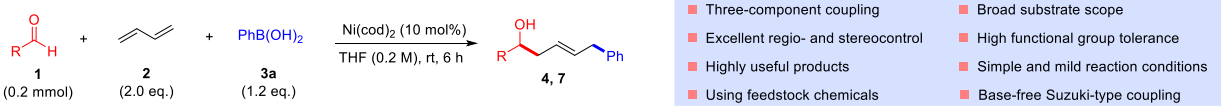
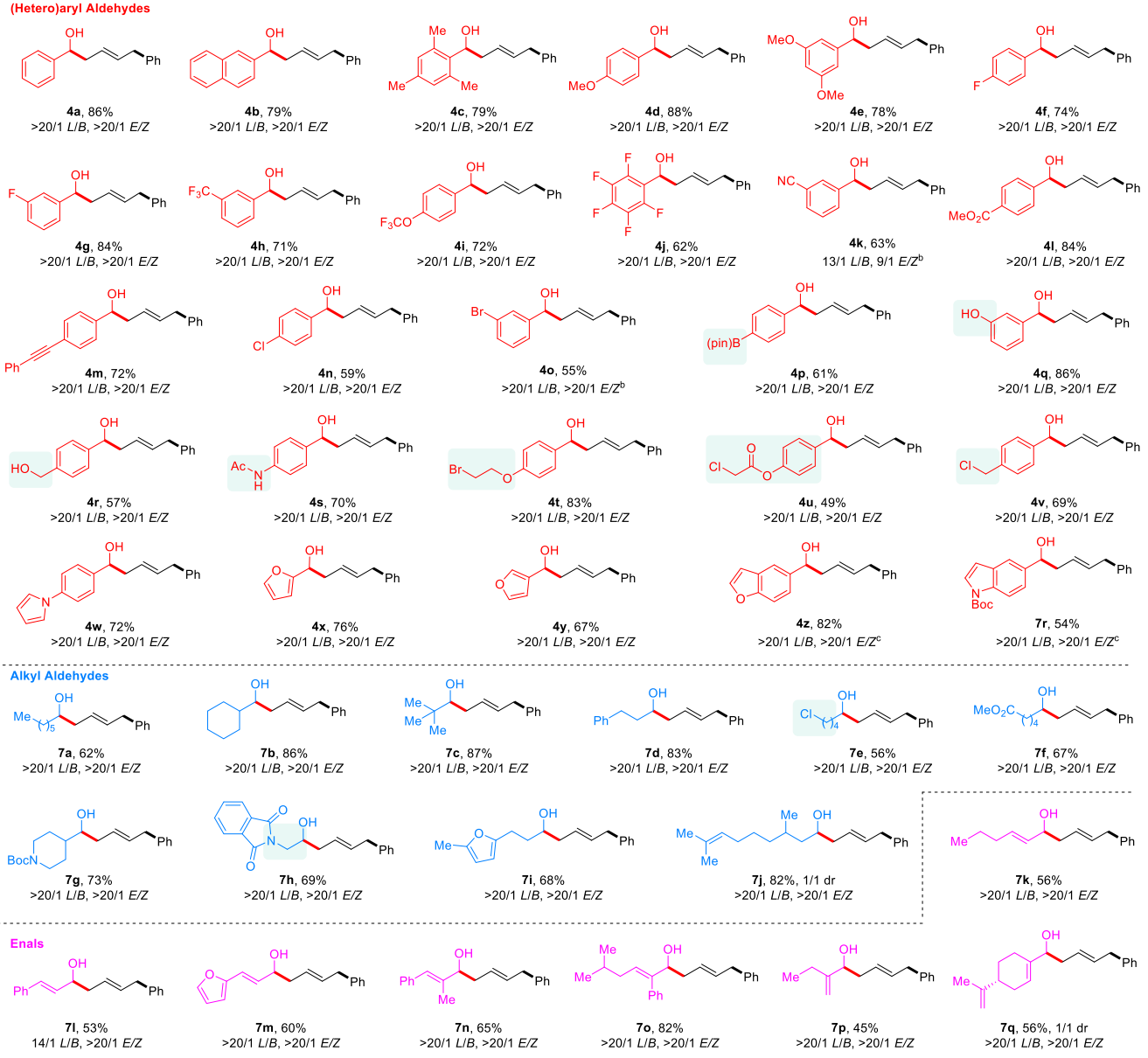
Table 2. Scope of Aldehydes[a]





[a]Yields of isolated products are shown. *E*/*Z* and *L*/*B* ratios were determined by ^{1}H NMR analysis of the crude products. [b]Using 2.0 equiv of aldehyde, 4.0 equiv of butadiene, and 1.0 equiv of $PhB(OH)_2$. [c]Using 0.2 equiv of $Ni(cod)_2$.

Moreover, heteroaromatic substrates, including furan, benzofuran, pyrrole, and indole derivatives, were also effective substrates (**4w**–**4z** and **7r**). Most remarkably, due to the mildness of the conditions, substrates containing acidic protons, such as phenols (**4q**), alcohols (**4r**), and secondary amides (**4s**), and other highly base-sensitive structures, including alkyl bromides (**4t**), benzyl chlorides (**4v**), and phenyl 2-chloroacetate (**4v**), that readily undergo undesired elimination, substitution, and hydrolysis reactions, are well-tolerated. Although more labile to undergo aldol reaction, aliphatic aldehydes also served as competent substrates furnishing products in high yields and excellent regio- and stereocontrol (**7a**–**7j**). Linear and α-branched aliphatic aldehydes all performed well (**7a**–**7d**). Functional groups, including an alkyl chloride, an ester, an amide, an alkene, and a carbamate, were all well-accommodated (**7e**–**7j**). Situations for enal substrates are more complicated, as enals readily undergo conjugate addition by nucleophiles and Diels–Alder reaction with diene. However, various enals with 1,1-, 1,2-, or 1,1,2-substitution patterns were all applicable to the coupling reaction to deliver alcohol products with both allyl and homoallyl substituents in moderate to high yields with high selectivity (**7k**–**7q**).

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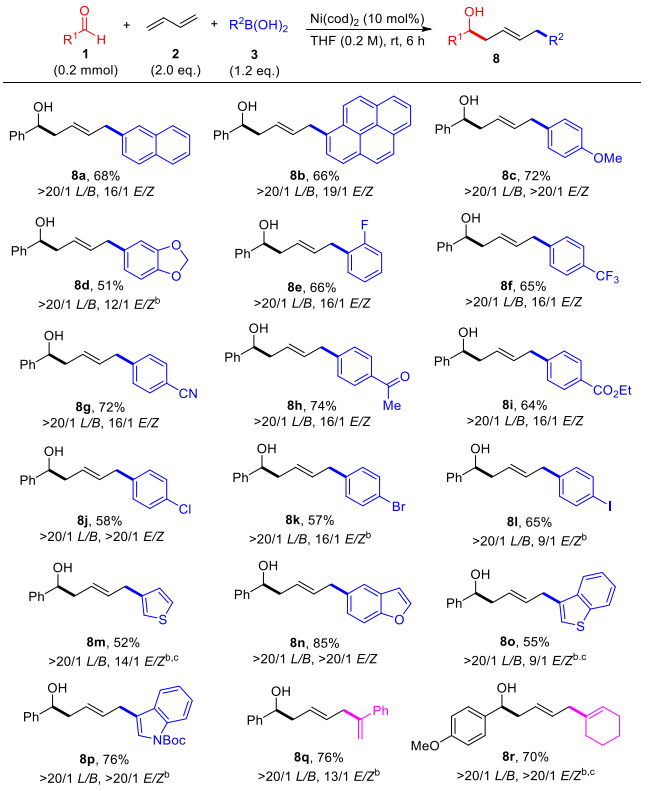
Subsequently, we explored the generality of the organoboronic acid coupling partners for this method. As shown in Table 3, various commercially available and stable organoboronic acids smoothly participated in the coupling reaction, affording homoallylic alcohols in outstanding regioselectivity (>20/1 *L*/*B*) and high to excellent *trans*-selectivity (9/1 to >20/1 *E*/*Z*). Sterically encumbered 1-pyrenylboronic acid could be applied (**8b**). Arylboronic acids with electron-donating and electron-withdrawing substituents were effective substrates (**8c**−**8i**). Functional groups, including ethers (**8c** and **8d**), a trifluoromethyl (**8f**), a cyano (**8g**), an acetyl (**8h**), an ester (**8i**), a fluoride (**8e**), a chloride (**8j**), a bromide (**8k**), an iodide (**8l**), and a carbamate (**8p**), could be readily incorporated. Various heteroaryl boronic acids, such as thiophene (**8m**), benzofuran (**8n**), benzothiophene (**8o**), and indole (**8p**), were competent substrates. Notably, alkenyl boronic acids served as effective coupling partners to provide products possessing skipped dienes (**8q** and **8r**),[18] which further enriched the diversity of homoallylic alcohol products.

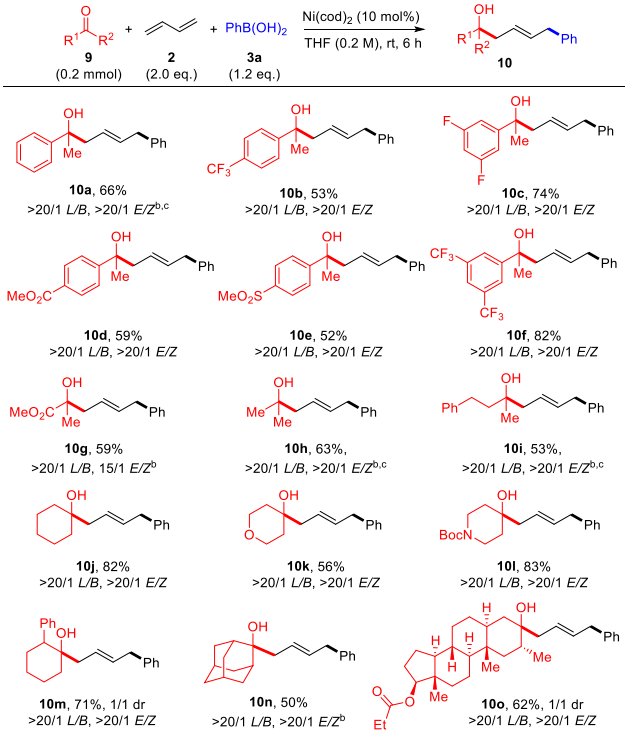
Table 3. Scope of Organoboronic Acids[a]



[a]Isolated yields are shown. *E*/*Z* and *L*/*B* ratios of the crude samples were determined by ^{1}H NMR analysis. [b]Using 0.2 equiv of Ni(cod)$_2$. [c]Using 4.0 equiv of butadiene.

Next, we surveyed the possibility of application of ketone substrates to the three-component coupling. Ketones are generally less reactive than aldehydes due to the attenuated electrophilicity and increased steric hindrance. Examples of Ni-catalyzed coupling (even reductive coupling) using ketones are rare, probably due to the problematic generation of the corresponding oxa−nickelacycle intermediate.[19] Indeed, the conversion of ketones was generally slower, and we observed, in some cases, the formation of a four-component coupling byproduct involving carbonyl, arylboronic acid, and two molecules of butadiene.[12a] However, despite these difficulties, a series of ketones could be successfully transformed into homoallylic tertiary alcohol products in good yields and exceptionally high regio- and stereoselectivity (Table 4, >20/1 *L*/*B*, >20/1 *E*/*Z* for most cases). For example, simple acetophenone (**10a**) and other aromatic ketones with electron-withdrawing substituents such as trifluoromethyl (**10b** and **10f**), fluoride (**10c**), ester (**10d**), and sulfonyl (**10e**) groups gave moderate to high yields with excellent regio- and stereoselectivity. Moreover, aliphatic ketones, including acetone (**10h**), benzylacetone (**10i**), and methyl pyruvate (**10g**), were suitable substrates. In addition to acyclic ketones, cyclic ketones such as cyclohexanones (**10j**), 4-tetrahydropyranone (**10k**), and 4-piperidinone (**10l**) as well as bulky adamantanone (**10n**) and dromostanolone (**10o**) derivatives performed well in this three-component coupling protocol delivering complex tertiary alcohols in a single operation.

Table 4. Scope of Ketones[a]



[a]Isolated yields are shown. *E*/*Z* and *L*/*B* ratios of the crude samples were determined by ^{1}H NMR analysis. [b]Using 0.2 equiv of Ni(cod)$_2$. [c]Using 1.0 equiv of **3a**, 3.0 equiv of **9**, and 2.0 equiv of **2**.

Importantly, we found this three-component reaction could be readily scaled up to gram scale (10 mmol) using even lower catalyst loadings; homoallylic alcohol product **4d** was obtained in high yield with very high levels of regio- and *trans*-selectivity, highlighting the practicality of the method (Scheme 2a). Interestingly, isoprene, a naturally abundant feedstock chemical (production of ∼8 × 10^5 tons/year),[20] could be applied in this protocol, affording homoallylic alcohol **4d′** in good yield with high selectivity (Scheme 2b). To further showcase the synthetic utility of the method, various transformations of the homoallylic alcohol product were conducted (Scheme 2c). For example, oxidation of hydroxy to carbonyl with Dess−Martin periodinane gave *β*,*γ*-unsatu-

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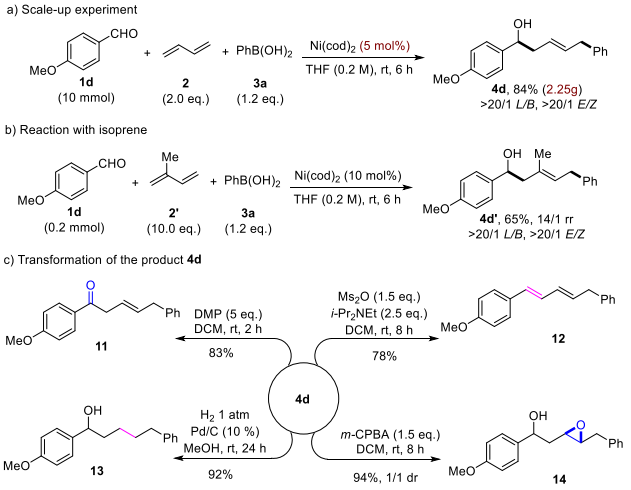
Scheme 2. Gram-Scale Reaction and Transformations of the Product



rated ketone **11** in high yield. Elimination of the hydroxyl group smoothly afforded a conjugate diene **12** with an absolute *trans,trans* configuration. The double bond of homoallylic alcohol can be easily hydrogenated to furnish a secondary alcohol **13**. The oxidation of alkene with *m*CPBA delivered an epoxide product **14** in high yield. Given the easy accessibility of substrates and the rich chemistry of homoallylic alcohols, the current coupling protocol would provide convenient and powerful means of building complex molecules from abundant butadiene.

In conclusion, we have developed a highly regio- and *trans*-selective Ni-catalyzed three-component coupling for a 1,4-dicarbofunctionalization of feedstock butadiene using carbonyls and organoboronic acids. A diverse variety of 1,4-disubstituted and 1,1,4-trisubstituted homoallylic alcohols were efficiently prepared in a single operation from stable and readily available substrates. These reactions could generally be applicable to various carbonyl compounds, including aromatic aldehydes, aliphatic aldehydes, enals, aromatic ketones, and aliphatic ketones. The mild and base-free protocol tolerated an exceptionally broad scope of functional groups.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00488.

Experimental procedures, characterization data, and copies of NMR spectra for all new products (PDF)

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Notes

The authors declare no competing financial interest.

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