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Heterogeneous copper-catalyzed Grignard reactions with allylic substrates†

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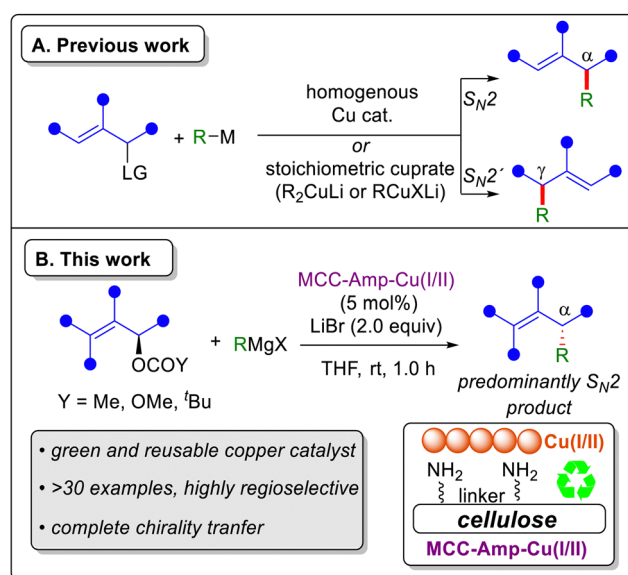
Herein, we present a highly efficient allylic substitution of carbonates with Grignard reagents using a reusable cellulose-supported nanocopper catalyst. This approach highlights the first instance of heterogeneous catalysis for the cross-coupling of allylic alcohol substrates with Grignard reagents. The method features high yields, excellent regioselectivity, and complete chirality transfer.

Transition-metal-catalyzed allylic substitution reactions are fundamental tools for construction of carbon–carbon bonds in organic synthesis.^{1–3} In particular, the enantiocontrolled version of these reactions are widely employed for the preparation of various chiral α -substituted alkenes.^{2,4} Significant progress over the years has led to the development of stereoselective palladium-catalyzed allylic substitutions with stabilized carbon nucleophiles, such as malonate carbanions.^{5,6} In contrast, copper catalysis^{2,7–9} enables the use of non-stabilized carbon nucleophiles, such as Grignard and organozinc reagents, offering a complementary approach to palladium catalysis. Traditionally, these Cu-catalyzed cross-coupling reactions have predominantly relied on homogeneous catalysis (or the use of stoichiometric cuprates), and the reactivity, regioselectivity (S_N2 versus S_N2'), and stereospecificity are influenced by several factors such as leaving group, copper source, reaction conditions, solvent and ligand (Scheme 1A).^{10–14}

Growing concerns about the environment and climate change have driven chemists to develop more sustainable and environmentally benign methodologies.¹⁵ Compared with homogeneous catalysis, heterogeneous catalysis presents a compelling alternative,^{16–18} offering advantages such as easier recovery, and reuse of metal catalysts as well as the production of cleaner products with lower heavy metal contamination.¹⁹ In our recent work, we developed a heterogeneous nanocopper

catalyst supported on modified microcrystalline cellulose (MCC), which demonstrated excellent performance in Alderene cyclization²⁰ and Crabbé type S_N2' propargylic substitution,²¹ both in terms of catalytic activity and sustainability. Expanding this sustainable system to a wider window of organic synthesis will be highly beneficial for a broader audience.

In the present study (Scheme 1B) we have developed a novel nanocopper-catalyzed Grignard reaction of allylic substrates leading to allylic substitution, where the previously reported heterogeneous nanocopper catalyst²¹ was successfully employed. We have demonstrated the practical advantages of the new heterogeneous catalytic method, including catalyst recovery and reuse, reduced heavy metal contamination, and improved environmental sustainability, offering a viable and greener alternative to traditional homogeneous methods.



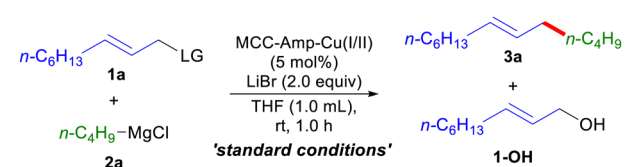
Scheme 1 Copper-catalyzed cross-coupling of allylic substrates with Grignard reagents: (A) previous work. (B) This work.

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Table 1 Optimization of reaction conditions^a


Entry	LG	Conditions	Yield% (3a, 1, 1-OH)
1	OAc (1a)	Standard	86, 0, 10
2	OCO ₂ Me (1a')	Standard	98, 0, 2
3	OCO ₂ Me (1a')	LiCl instead of LiBr	89, 7, 3
4	OCO ₂ Me (1a')	At 0 °C	95, 0, 3
5	OCO ₂ Me (1a')	Et ₂ O as solvent	95, 0, 2
6	OCO ₂ Me (1a')	No Cu catalyst	0, 65, 35
7	OCO ₂ Me (1a')	No LiBr additive	54, 35, 8
8	OPiv (1a'')	Standard	95, 0, 0

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), LiBr (0.4 mmol) and THF (1.0 mL) were used under N₂ atmosphere; yields were determined by ¹H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

The objective was to mimic the widely applied homogeneous copper-catalyzed allylic substitution reaction with Grignard reagents by the use of a heterogeneous nanocopper catalyst. Our initial investigations started by adapting the previously reported nanocopper catalytic system that was used with propargylic acetates.²¹ (*E*)-2-Nonenol derivatives were chosen as the model substrates together with *n*-butyl magnesium chloride. We were pleased to observe a complete conversion of **1a** (LG = OAc), yielding 86% of **3a** and 10% (*E*)-2-nonenol (Table 1, entry 1). Changing the leaving group of **1a** to carbonate **1a'** (LG = OCO₂Me) increased the yield to 98% without generating any significant side products (entry 2). Changing the additive to LiCl slightly decreased the yield (entry 3). Further control experiments (see ESI,[†] for details) indicate that LiBr plays a key role in enhancing the reaction, likely through the formation of more reactive Li-Grignard reagent complex (RMgX·LiBr).²² Performing the reaction at 0 °C resulted in a yield similar to that at room temperature (entry 4). Along with THF, diethyl ether also proved to be an efficient solvent for this allylic substitution reaction (entry 5). The use of the nanocopper catalyst was essential as its exclusion resulted in no product formation, with 65% of compound **1a'** remaining and with 35% of (*E*)-2-nonenol (entry 6) being formed. The presence of LiBr also proved important for reactivity as its omission reduced the yield to 54% along with 35% of **1a'** and 8% of alcohol **1-OH** (entry 7). Employing a bulkier pivalate ester leaving group (**1a''**) also proved to be highly efficient for this transformation (entry 8).

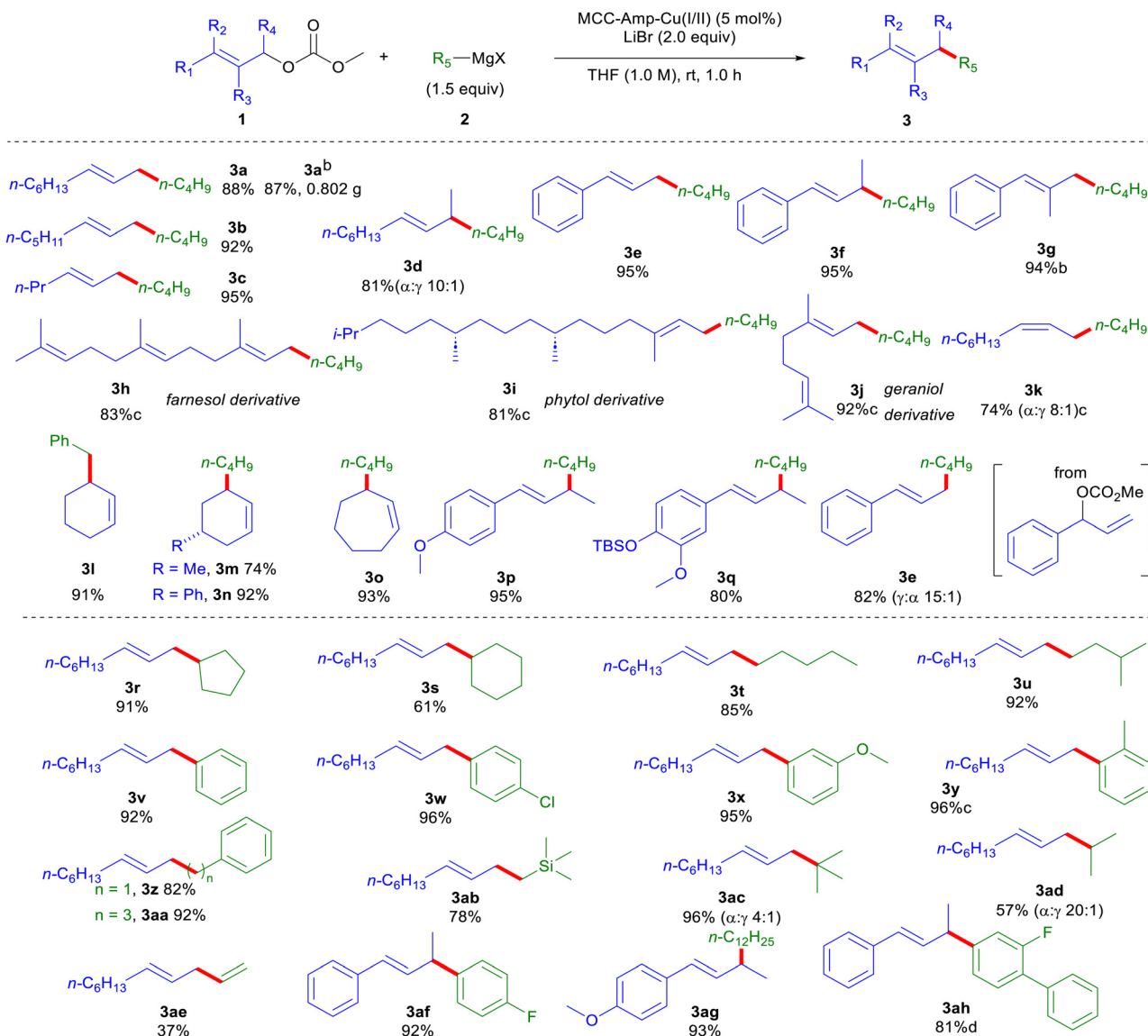
With the optimized reaction conditions in hand, the generality and scope of the protocol was explored (Scheme 2). Grignard reaction of allylic carbonate **1a** afforded **3a** with exclusive α -substitution in 88% yield. A similar yield (87%) of **3a** was obtained when the reaction was carried on a gram-scale. Comparable high yields of 92% and 95% of shorter chain olefin products **3b** and **3c**, respectively, were obtained from the corresponding allylic carbonates (**1b** and **1c**). An aliphatic

secondary alcohol derivative (**1d**) was suitable for this protocol, providing the desired product **3d** in 81% yield with minor amounts of γ -substituted product (α : γ 10:1). Extension of our methodology towards the cinnamyl system **1e** produced styryl derivative **3e** in 95% yield. A secondary cinnamyl carbonate **1f** underwent the reaction smoothly, and gave the corresponding targeted olefin **3f** in 95% yield. Then this reactivity was extended to the β -methyl substituted carbonate **1g**, which afforded product **3g** in 94% yield. The reaction was also extended to naturally abundant allylic alcohol analogs. The substituted product **3h**, obtained from farnesol derivative **1h**, was isolated in high yield. Likewise, phytol derived olefin **3i** was obtained in 81% yield from the corresponding carbonate derivative **1i**. Next, the carbonate derived from geraniol (**1j**) yielded the corresponding product **3j** in 92% yield. The *cis*-2-nonenol derivative **1k** was found to be amenable to the reaction conditions affording a mixture of internal and terminal (α : γ 8:1) olefins **3k**. Interestingly, the *cis* configuration was maintained in the reaction. The protocol was applied to cyclic allylic derivatives as well. The six-membered olefin derivatives **3l–3n** were obtained in high to excellent yield from **1l–1n** respectively, while seven-membered olefin **3o** was obtained in 93% yield from **1o**. We applied this method to electron-rich cinnamyl derivatives **1p** and **1q**, constructing cinnamyl derivative **3p** and **3q** in 95% and 80% yield respectively. The reaction with the carbonate derived from 1-phenylprop-2-en-1-ol resulted in γ -substituted derivative **3e** in 81% yield with a slight amount of α -substituted product (γ : α 15:1).

Subsequently, various Grignard reagents were examined under standard reaction conditions. Cyclic Grignard reagents like cyclopentyl (**2b**) and cyclohexyl (**2c**) were demonstrated to be efficient nucleophiles producing **3r** and **3s**, respectively in moderate to good yields. Also, aliphatic Grignard reagents (**2d**, **2e**) proved to be equally effective as nucleophiles providing olefins **3t** and **3u** in high yields. Next, aromatic Grignard reagents with neutral and different ring substitution were employed for this substitution reactions. Excellent yields of **3v**, **3w**, **3x** and **3y** were attained when unsubstituted (**2f**), 4-chloro substituted (**2g**), 3-methoxy (**2h**), and 2-methyl (**2i**) substituted phenyl Grignard reagents, respectively, were utilized under these reaction conditions. The benzyl (**2j**) and 3-phenylpropyl Grignard reagent (**2k**) exhibited satisfactory efficiency, forming **3z** and **3aa** in 82% and 92% isolated yields respectively. Subsequently, the trimethyl silyl-based Grignard reagent (**2l**) demonstrated moderate reactivity, affording **3ab** in 78% yield. However, employing the bulky *tert*-butyl magnesium chloride (**2m**) resulted in an excellent yield of 96%, nonetheless a 4:1 mixture of α - and γ -substituted regioisomers was observed. In case of isopropyl Grignard reagent (**2n**), moderate yield of **3ad** was observed with 20:1 ratio of regioisomers. In this instance, the cross-coupling reactions of a vinyl Grignard reagent (**2o**) with an allylic alcohol derivative (**1a'**), afforded 37% of non-conjugated diene derivative **3ae**.

Additionally, a cinnamyl carbonate derivative (**1af**) produced aryl substituted olefin **3af** in 92% yield. A long alkyl chain Grignard reagent (**2q**) performed well with cinnamyl derivative



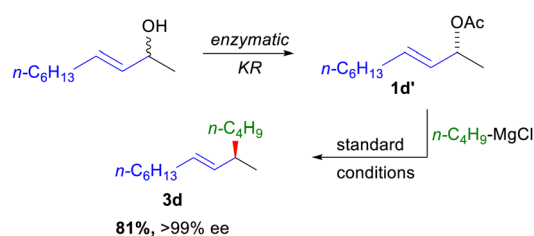


Scheme 2 Substrate scope of allylic substitution reaction. (a) Reactions conditions: **1** (0.2 mmol), **2** (0.3 mmol), THF (1.0 mL) were used under N₂ atmosphere, 1 h reaction time, isolated yields, regioisomeric ratios were determined from ¹H-NMR analysis. (b) Gram-scale reaction, 4 mol% catalyst loading. (c) **2** (0.4 mmol) was used, 15 h reaction time. (d) The allylic OAc substrate was used.

(**1p**) under the developed protocol providing **3ag** in high yield. Additionally, we applied our methodology to a previously reported drug precursor synthesis, successfully yielding desired compound **3ah** in 81% yield.²³

It is known that homogeneous copper catalysts offer transfer of chirality from enantioenriched allylic substrates,²⁴ and we therefore wanted to mimic this property with the heterogeneous catalyst used here (Scheme 3). Enantiopure acetate derivative (**1d'**) of allylic alcohol was obtained *via* enzymatic kinetic resolution.²⁵ Remarkably, under standard conditions, a complete chirality transfer was obtained for the corresponding allylic substitution product **3d** along with a high yield (81%).

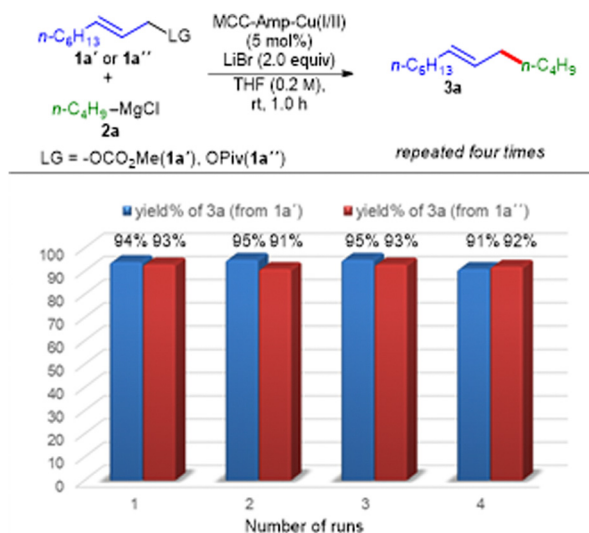
To further establish the sustainability of this protocol, we performed the model reactions with recycled catalyst several



Scheme 3 Chirality transfer experiment.

times using two different types of substrates (Scheme 4). In these cases, the catalyst recovered (washed with dry solvent) after each cycle *via* centrifugation was used directly for the next run. Both for carbonate (**1a'**) and pivalate (**1a''**) derivatives of





Scheme 4 Catalyst recovery experiment.

(*E*)-2-nonenol, the yields of **3a** were found to be maintained at a high level for at least four cycles when butyl magnesium chloride was employed under the standard reaction conditions.

In conclusion, we have utilized a cellulose supported nanocopper-catalyst to mimic the reactivity of homogeneous copper catalysis in nucleophilic substitution of allylic alcohol derivatives with Grignard reagents. A wide range of allylic alcohol derivatives including natural products were well-tolerated, providing the corresponding α -substituted product in high yields. Additionally, a variety of commercially available Grignard reagents proved to be efficient for this reaction. The broader application includes the complete chirality transfer similar to that with homogeneous copper catalysis. The efficient nanocopper catalyst used here can be recovered and reused for several times providing a green alternative with low metal contamination. The present work has shown that the heterogeneous nanocopper catalyst can efficiently mimic the homogeneous copper catalytic system, and the extension to Grignard reactions with allylic substrates has further increased the utility of the MCC-Amp-Cu in organic synthesis.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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