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Copper-catalyzed allylic substitution of nitroallyl derivatives with Grignard reagents

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Grignard reagents engage with nitroallyl derivatives in the presence of copper(I) salts to promote allylic substitution of the nitro group. The reaction is particularly effective with aryl Grignards and unsubstituted nitroallyl compounds but is also applicable to diversely substituted nitroallyl derivatives and both alkyl and vinyl Grignards. A mechanism involving a Cu(I)/Cu(III) catalytic cycle is proposed for this transformation.

Owing to the strong electron-withdrawing nature of the nitro group, aliphatic nitro compounds readily undergo α-deprotonation and subsequent C–C bond formation under mild conditions, making them versatile intermediates in synthesis.[1] Subsequent reduction of the nitro group to the corresponding primary amine provides efficient access to five- and six-membered nitrogen heterocycles.[2] Alternatively, depending on the substitution pattern at the α-position, the relatively weak C–NO_2 bond can undergo fragmentation, resulting in the extrusion of a nitrite species.[3]

The ability of nitroallyl derivatives to serve as surrogates for allylic acetates or carbonates in Tsuji–Trost reactions with carbon-, nitrogen-, and sulfur-based nucleophiles was first recognized by Hegedus, Tamura, and Ono using palladium catalysts (Fig. 1A).[4a–c] Despite several applications building on these seminal studies,[4d–f] the use of nitroallyl compounds as electrophiles in transition-metal catalyzed allylations are rare. In this context, we recently demonstrated that copper(I) salts could catalyze the substitution of nitroallyl derivatives with B_2pin_2, providing efficient access to allyl boronic esters (Fig. 1B).[5] Building on this reactivity, we sought to evaluate whether copper catalysts could mediate analogous substitutions with other nucleophiles, including Grignard reagents. While Grignards are well known to participate in copper-mediated allylic substitution of ethers and carboxylates,[6] the extension to nitroallyl electrophiles is not trivial as competitive nucleophilic addition to the nitro group typically predominates, leading to hydroxylamine or amine byproducts (Fig. 1C).[7] Herein, we report a copper-catalyzed allylic substitution of nitroallyl derivatives with Grignard reagents, enabling selective C–C bond formation with concomitant nitrite elimination (Fig. 1D).

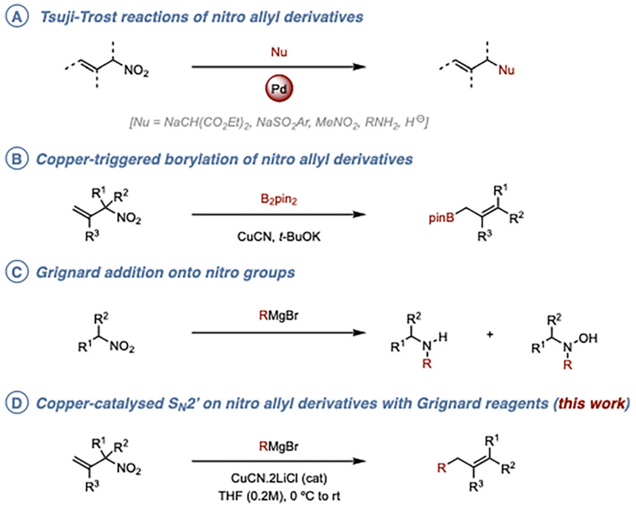

Fig. 1 Addition of nucleophiles onto nitro and nitroallyl derivatives.

Allylic nitro derivatives are readily accessible from simple nitroalkanes. Condensation with aldehydes followed by elimination furnishes nitroalkenes, which can be deprotonated and functionalized with a range of electrophiles to enable α-substitution at the nitro group. As a representative example, symmetrical nitro diester **1a** was prepared in four steps from nitromethane, methyl acrylate, and acetaldehyde.[5] Selection of **1a** minimizes stereochemical complexity in the Grignard addition while simultaneously probing the compatibility of ester functionality under the reaction conditions.

Treatment of **1a** with 4-chlorophenylmagnesium bromide (2a, 2.0 equiv.) at 0 °C in the presence of CuI (10 mol%)

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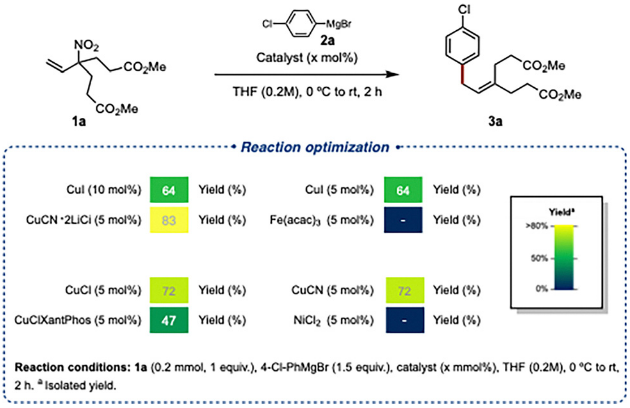

Reaction conditions: **1a** (0.2 mmol, 1 equiv.), 4-Cl-PhMgBr (1.5 equiv.), catalyst (x mmol%), THF (0.2M), 0 °C to rt, 2 h. [a] Isolated yield.

Fig. 2 Reaction optimization.

afforded the desired diester **3a** in 63% NMR yield. Reducing the amount of Grignard reagent to 1.5 equiv. or the CuI loading to 5 mol% had little effect on the reaction outcome (Fig. 2). In contrast, lowering the reaction temperature (CuI, −20 or −78 °C) completely suppressed coupling after 2 h. Modest improvements were observed upon replacement of CuI with CuCl or CuCN, although 4,4′-dichlorodiphenyl was consistently detected as a homocoupling byproduct. Optimal results were obtained using the more soluble CuCN·2LiCl complex, delivering **3a** in 83% yield (82% isolated). These conditions were therefore adopted for subsequent studies.

The scope of the allylic substitution was first evaluated using a series of aromatic and aliphatic Grignard reagents with nitroallylic derivative **1a**. As shown in Fig. 3, arylmagnesium bromides underwent efficient coupling to afford substituted diesters **3a–j** in moderate to good yields. The reaction proved largely insensitive to the electronic properties of the aryl group with comparable efficiencies observed for both electron-rich and electron-poor substrates. Likewise, substitution at the 2-, 3-, or 4-position had minimal effect on reactivity, as illustrated by the similar outcomes obtained with mesityl and phenylmagnesium bromides. Heterocyclic Grignard reagents, such as 2-thienyl- and 3-pyridylmagnesium bromides (not shown), failed to deliver any substituted products. In contrast, vinyl- and styrylmagnesium bromides reacted efficiently with 1a to afford dienyl esters **3k** (54%) and **3l** (31%) in moderate yields. Reactions with alkylmagnesium reagents also proved challenging. For example, methylmagnesium bromide gave **3m** in only 22% yield, likely due to competing direct addition onto the nitro group *versus* Cu-catalyzed allylic substitution. Consistent with this hypothesis, increasing the copper loading from 5 to 50 mol% improved the yield to 43%, highlighting the delicate balance between nucleophile reactivity and catalyst control.

The reaction scope was next evaluated with respect to the nitroallyl precursor using 4-methoxyphenyl magnesium bromide as the aryl Grignard, except for **3u** for which the 4-chloro analogue was used (Fig. 4). The efficiency of the Grignard addition proved highly sensitive to the substitution pattern on the terminal alkene. While the reaction with **1a** proceeded efficiently at 0 °C, introduction of a methyl group at the terminal position led to a more sluggish reaction, affording **3u** in only 17% isolated yield and 50% conversion. Increasing the Grignard loading to 3 equiv. and the copper catalyst to 10 mol% slightly improved the yield (30%), however the product was formed along with a significant amount of 4,4′-dichloro-1,1′-biphenyl (**4**). Homocoupling of aryl Grignard reagents to biphenyl derivatives is a well-known transition-metal-catalysed process often promoted by an oxidant such as O_2. In the present system, we attribute this side reaction to the nitrite anion released during the allylic substitution, consistent with observations made in our previous borylcupration

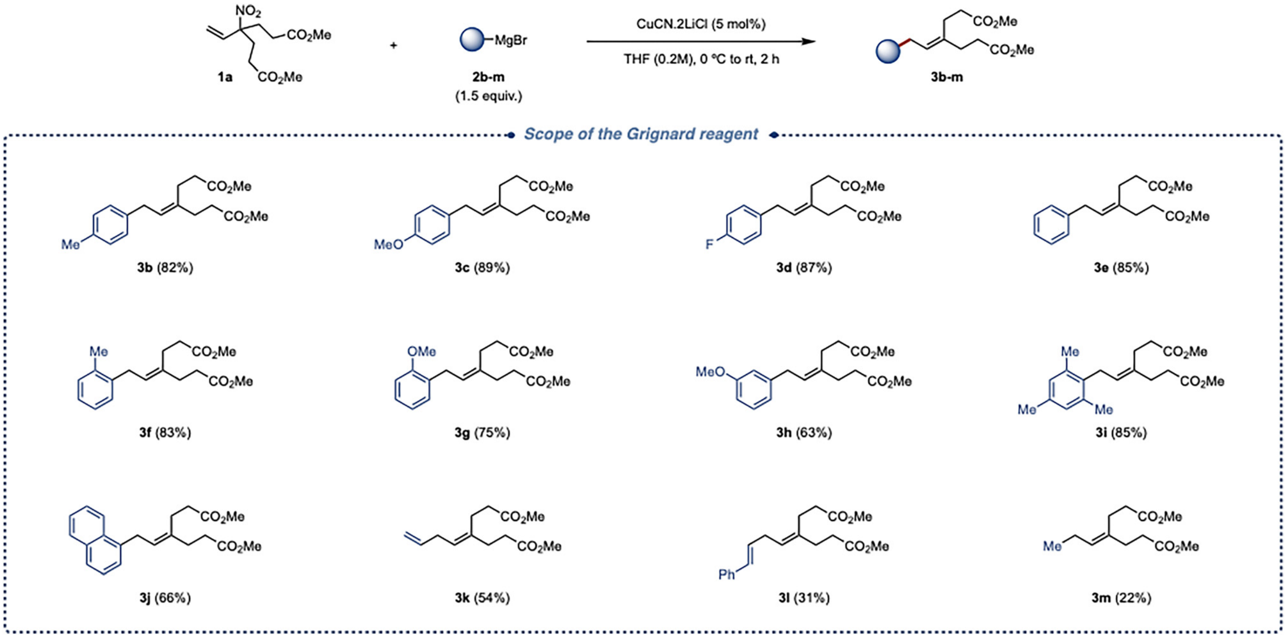

Fig. 3 Grignard scope. All reactions were carried out on a 0.2 mmol scale.

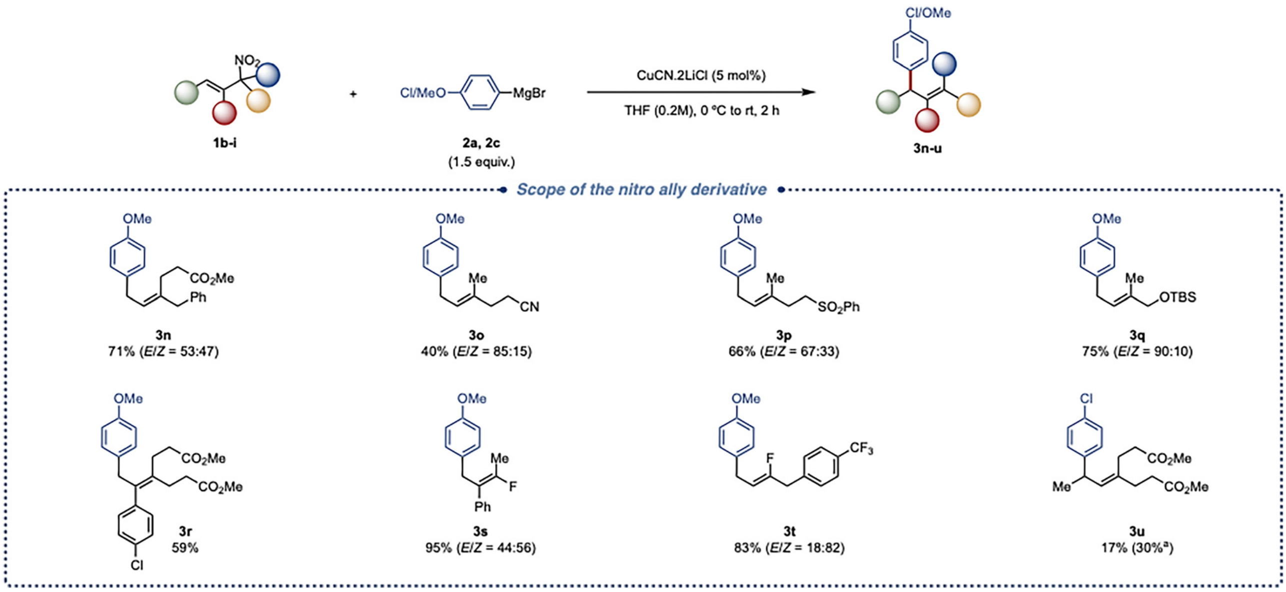

Fig. 4 Substrate scope. All reactions were carried out on a 0.2 mmol scale. [a]Reaction run using 3 equiv. of Grignard reagent and 10 mol% of the copper catalyst.

of nitroallyl derivatives.[5] The oxidizing potential of nitrite toward Grignard reagents under these conditions was confirmed by treatment of 4-chlorophenylmagnesium bromide with a stoichiometric amount of potassium nitrite in THF (Fig. 5A). The presence of terminal substituents on the alkene likely slows down the kinetics of the reaction with the intermediate arylcopper derivative, making it more susceptible to further reaction with the oxidant and arylmagnesium bromide. While terminal substituents are poorly tolerated, the alkene can be functionalized with an additional aromatic ring, as shown by the formation of **3r** in 59% isolated yield. We also prepared several unsymmetrical nitroallyl compounds to investigate the diastereoselectivity of the elimination step. As illustrated by the various examples in Fig. 4, the diastereoselectivity is primarily influenced by the size of the substituents. Hence, while **3n** was obtained with a poor *E*/*Z* selectivity, using a smaller methyl group compared to a cyanoethyl- (**3o**, 40%, *E*/*Z* = 85 : 15) or to a phenylsulfonylethyl group (**3p**, 40%, *E*/*Z* = 67 : 33) lead to higher selectivities, with preferential formation of the *Z* isomer. Fluorine-containing nitroallyl derivatives such as **1g** and **1h** were also prepared to evaluate whether the addition of the Grignard reagent, here 4-methoxyphenyl magnesium bromide, would promote a defluorination process rather than the elimination of the nitro group. Similar to what we observed in our previous borylation study,[5] only nitro elimination was detected, resulting in the formation of **3s** and **3t** in 95 and 83% yield, respectively.

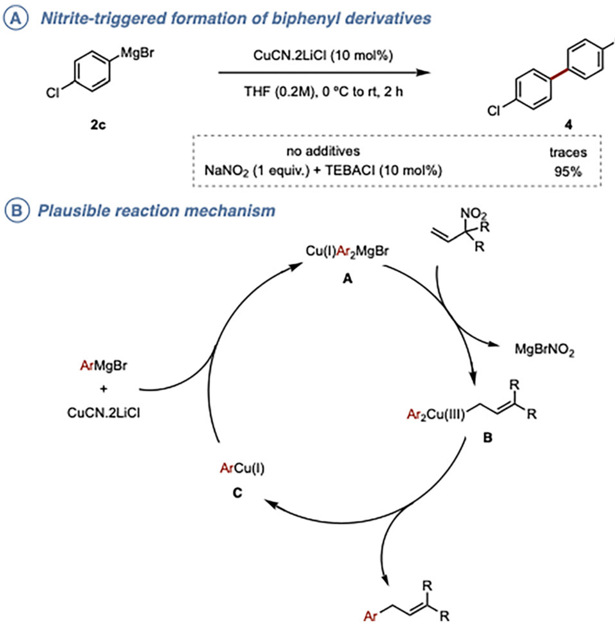

Fig. 5 Mechanistic considerations. [TEBACl = tetraethylbenzylammonium chloride].

The strong influence of the substitution pattern on the alkene together with previous studies on the addition of Grignard reagents onto allylic esters[6e] suggest a reaction mechanism involving a Cu(I)/Cu(III) catalytical cycle. This mechanism is consistent with the formation of bis-aryl derivatives as side products. The latter may be formed either directly from the Cu(III) allyl intermediate **B** or by an oxidation of the Cu(I)Ar_2MgBr intermediate **A** by the nitrite in solution leading to an Ar_2Cu(III)X species which may lead to the bis-aryl by reductive elimination (Fig. 5B).

In conclusion, we have successfully demonstrated the first copper-catalysed substitution of nitroallyl derivatives by Grignard reagents. This work builds on our previous studies, including the cuproborylation of nitroallyl compounds[5] and earlier research using alkyl lithium derivatives and stoichiometric amounts of copper(I) salts.[8] The ability to achieve similar transformations using catalytic amounts of copper and Grignard reagents, rather than alkyl lithium, is particularly significant. Not only does this approach reduce the quantity of transition metal required, but it also remains compatible with sensitive functional groups, such as esters. Following these successful additions of B_2pin_2 and Grignards, we plan to explore the reactivity of other nucleophiles to gain a comprehensive understanding of the full scope of the copper-catalysed allylic substitution of nitroallyl derivatives.

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Conflicts of interest

There are no conflicts of interest to declare.

Data availability

The datasets supporting this article have been uploaded as part of the supplementary information (SI). Supplementary information: full experimental procedures and characterization data for all compounds are provided. See DOI: https://doi.org/10.1039/d6cc00637j.

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