Published in final edited form as:

Angew Chem Int Ed Engl. 2014 February 3; 53(6): 1664–1668. doi:10.1002/anie.201309134.

Allylic Functionalization of Unactivated Olefins with Grignard Reagents

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Abstract

Allylic functionalization of unactivated olefins with carbon nucleophiles is a powerful strategy for converting olefins into complex products. We report a general method for functionalizing olefins with aromatic, aliphatic, and vinyl Grignard reagents. In a one-pot process, olefins are oxidized by a commercially available reagent to allylic electrophiles, which undergo selective Cu-catalyzed allylic alkylation with Grignard reagents. Products are formed in high yield and regioselectivity.

Keywords

allylic compounds; copper; Grignard reaction; catalysis; alkenes

The functionalization of unactivated olefins with carbon nucleophiles is an attractive strategy for synthesizing value-added small molecules from inexpensive and abundant components of petrochemical feedstock (Scheme 1).^[1,2] It is quickly becoming an alternative approach to the Heck reaction for the conversion of simple terminal olefins into more complex products.^[3] Elegant examples of allylic alkylations have been reported with stabilized carbon nucleophiles,^[4] tethered carbon nucleophiles,^[5] diazoesters,^[6] and trifluoromethane donors.^[7] To complement these studies, we were interested in functionalizing unactivated olefins with Grignard reagents, which are a readily accessible and affordable class of diverse carbon nucleophiles.

Herein, we describe a general method for functionalizing unactivated olefins with aromatic, aliphatic, and vinyl Grignard reagents.^[8] This one-pot process is performed by the sequential addition of a stoichiometric oxidant, copper catalyst, and a Grignard reagent to unactivated terminal olefins, which are converted to internal olefins with high *E*-selectivity. In contrast to most Heck reaction protocols, our strategy exhibits broader scope in the coupling partner and does not require activated olefins for high levels of reactivity and selectivity in the formation of a single olefin isomer.^[9]

Allylic functionalization with carbon nucleophiles usually requires a stoichiometric oxidant to mediate the oxidation state of the metal in the catalytic cycle. We envisioned a

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

conceptually distinct approach, in which the stoichiometric oxidant could oxidize the unactivated olefin in the absence of a catalyst to a reactive intermediate, which would be susceptible to metal-catalyzed allylic substitution with Grignard reagents in the same reaction flask (Scheme 2). We were drawn to the metal-free allylic oxidation of unactivated olefins **1** with commercially available sulfurdiiimide reagent **2**. This chemistry was initially explored for the allylic amination of unactivated olefins through the [2,3]-rearrangement of allylic sulfinamide **3**.^[10,11] Motivated by early examples of metal-catalyzed couplings of allylic sulfides and sulfoxides with Grignard reagents,^[12] we were interested in exploiting sulfinamide **3** as a new class of electrophiles for metal-catalyzed allylic substitution. We now report the broad substrate scope and unique product selectivity exhibited by this novel strategy in allylic alkylation.

Our initial challenge in functionalizing olefins with Grignard reagents via sulfinamide **3** was the suppression of the facile [2,3]-rearrangement to allylic amine **5** in favor of the desired coupling with Grignard reagent **6** (Table 1). Sulfinamide **3a** was generated upon mixing olefin **1a** and sulfurdiiimide reagent **2** for 12 h at 4 °C in various solvents. This oxidized intermediate was subsequently cooled to –20 °C and treated with several low valent metals that typically generate electrophilic metal allyl intermediates **7** from allylic acetates, carbonates, and halides. Palladium, iridium, rhodium, and molybdenum catalysts did not yield the internal olefin **4a** in the presence or absence of various classes of ligands (entries 1–6). Gratifyingly, copper(I) salts emerged as promising catalysts for this process (entries 7–11).^[13] In the presence of copper(I) thiophene-2-carboxylate (CuTc), internal olefin **4a** was formed in 22% isolated yield (entry 7). The source of copper impacted the isolated yield of the desired product (entries 7–9). When CuTc was replaced with CuBr•SMe₂, olefin **4a** was produced in slightly greater yield (entry 9). Given the propensity for sulfinamide **3a** to undergo a facile [2,3]-rearrangement to allylic amine **5**, we hypothesized that the proper selection of solvent for the oxidation step was essential for the efficiency of the overall process. In Et₂O, sulfurdiiimide **2** and sulfinamide **3a** were largely insoluble, resulting in an inefficient oxidation reaction and subsequent allylic substitution with Grignard reagent **6** (entry 9). In DME, sulfurdiiimide **2** and sulfinamide **3a** were completely soluble, which caused significant [2,3]-rearrangement to allylic amine **5** before the reaction mixture was treated with copper and Grignard reagent (entry 10). A 1:1 mixture of DME:Et₂O produced the ideal environment for the formation and stability of sulfinamide **3a**, which was smoothly converted *in situ* to internal olefin **4a** (entry 11). Under these conditions, the desired product was isolated in 72% yield with high *E*-olefin selectivity (15:1) and complete regioselectivity.

With optimal reaction conditions in hand for the functionalization of unactivated olefins with Grignard reagents, we explored the substrate scope of this process (Table 2). A diverse range of aliphatic Grignard reagents could be utilized in this transformation without affecting the overall efficiency of the process (Table 2a, **4a–f**), including Grignard reagents with trimethylsilyl groups (**4e**) and remote stereocenters (**4f**). A hindered *t*-butyl Grignard reagent furnished the neopentyl internal olefin **4d**. When aryl Grignard reagents were employed in the reaction, the *in situ* conversion of sulfinamide **3** resulted in considerably lower yields, presumably because of side reactions between the highly reactive aryl Grignard reagents and byproducts from the oxidation reaction. Optimal yields were obtained

for the coupling of these aryl Grignard reagents after isolating sulfinamide **3** and adding catalytic amounts of radical scavenger TEMPO in the second copper-catalyzed step (**4g–i**). Notably, products **4g–i** formed with high *E*-allylic selectivity, which is distinct from the mixture of *E*-allylic and *E*-styrenyl products typically obtained through indiscriminate β -hydride eliminations under traditional Heck conditions,^[3] or the high *E*-styrenyl selectivity observed under modified Heck conditions recently reported by the Sigman group.^[14] Regardless of the Grignard reagent utilized in the reaction, we always isolated *E*-olefins as the major products (>20:1 in most cases).

We also examined an array of terminal olefins as substrates for coupling with *i*-butyl Grignard reagent (Table 2b). Unsaturated hydrocarbons furnished internal *E*-olefins in good yields (**4j–l**). This reaction was tolerant of several functional groups in the olefin, including alkyl chlorides (**4m**), silyl ethers (**4n**), carbonates (**4o**), and esters (**4p**). When terminal 1,1-disubstituted exocyclic olefins were employed, we obtained trisubstituted olefins (**4q–r**).

To highlight the synthetic potential of the functionalization of olefins with Grignard reagents, we synthesized a series of skipped dienes (Scheme 3). Although methods have been developed for the assembly of specific classes of skipped dienes,^[15] the allylic alkylation of unactivated olefins is not considered a general strategy for accessing these structures. This may be due to the difficulty in controlling the reactivity of multiple olefins in the skipped diene product for further undesired allylic alkylations. We recognized that our strategy for functionalizing olefins is uniquely suited for synthesizing skipped dienes, because we can control the reactivity of a single olefin in the presence of other unsaturation through a selective oxidation reaction with sulfurdiiimide **2**. We coupled terminal olefin **1a** with unsaturated Grignard reagents **8** and **10** to furnish skipped dienes **9** and **11**, respectively (Scheme 3a). We also converted various dienes **12a–d** to mono-alkylation products **14a–d** by selectively controlling the mono-oxidation reaction between one olefin in the substrates with one equivalent of sulfurdiiimide **2** (Scheme 3b). Finally, we controlled the mono- and di-alkylation between olefin **12c** and *i*-butyl Grignard reagent **15** by altering the relative equivalents of the two substrates, which resulted in the selective synthesis of skipped dienes **16** and **17** (Scheme 3c).

We have commenced a mechanistic examination of the copper-catalyzed functionalization of allylic sulfinamide **3** with Grignard reagents due to the distinct reactivity and product selectivity exhibited by this novel class of electrophiles. For example, while most copper-catalyzed Grignard additions to allylic electrophiles favor the S_N2' pathway to yield branched products,^[16] the allylic alkylation of sulfinamide **3** favored the S_N2 product under all the conditions we examined. In addition, the use of excess Grignard reagent was necessary to obtain a high yield of product (Scheme 4a). Most notably, in the presence of 2 equivalents of Grignard reagent **6**, we did not observe product formation, which suggests that Grignard reagents have a multifunctional role in the overall allylic substitution process. For example, one equivalent of Grignard reagent may initially react with allylic sulfinamide **3** prior to allylic substitution.^[12] Another equivalent of Grignard reagent may also react with the sulfonamide-containing byproduct after displacement with the Grignard reagent.^[17]

To probe the presence of free radical intermediates in the copper-catalyzed step, we isolated sulfonamide **3a** and subjected this intermediate to the copper-catalyzed allylic substitution conditions with varying amounts of TEMPO. When sulfonamide **3a** was coupled with phenylmagnesium bromide, olefin **4g** was isolated in 78% yield even in the presence of 2 equivalents of TEMPO, with no trace of adduct **18**. This observation suggests that the productive pathway may not proceed by free radical intermediates (Scheme 4b).^[18]

In conclusion, we have developed a one-pot functionalization of unactivated olefins with Grignard reagents. We demonstrated the conversion of terminal olefins to sulfonamide intermediates that are susceptible to highly selective nucleophilic substitutions with Grignard reagents. Overall, the process exhibited a broad substrate scope for unactivated olefins as well as Grignard reagents. The internal olefin products were formed in high yield as predominantly single olefin regioisomers and stereoisomers. Allylic sulfonamide **3** was unique in its ability generate predominantly S_N2 products under all the conditions examined so far, presumably via dialkyl π -allylcopper(III) complexes, which are known to favor the formation of S_N2 products over S_N2' products.^[13, 19] We exploited the controlled activation of olefins in polyunsaturated structures to synthesize a variety of skipped dienes, which are prevalent in natural products and are difficult to synthesize by known methods for allylic alkylation. We are currently expanding this strategy to include allylic functionalization with other nucleophiles to develop a diverse array of chemical transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support was provided by the W. W. Caruth, Jr. Endowed Scholarship, the Robert A. Welch Foundation (Grant I-1748), the National Institutes of Health (1R01GM102604-01), the Chilton Foundation Fellowship (H.B.), the University of Texas System Chemistry and Biology Training Grant (L.B.), and the Sloan Research Fellowship (U.K.T.).

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Scheme 1.
Allylic Functionalization of Unactivated Olefins

Scheme 2.
 General Approach to the Allylic Functionalization of Unactivated Olefins with Grignard Reagents

a) Synthesis of skipped dienes from olefin-containing Grignard reagents

b) Synthesis of skipped dienes from dienes

c) Control of mono-allylic alkylation and di-allylic alkylation

Scheme 3.

Synthesis of Skipped Dienes

[a] Yield calculated relative to sulfurdiiimide **2** as the limiting reagent.

a) Effect of Equivalents of Grignard Reagent

b) Evidence for a Non-Radical Pathway

Scheme 4.

Mechanistic Studies for the Copper-Catalyzed Coupling of Grignard Reagents and Allylic Sulfonamide **3**

Table 1

Optimization of Allylic Functionalization with Grignard Reagents

Entry	ML _n	Solvent	Yield (%)
1	Pd ₂ dba ₃ •CHCl ₃ ^a	Et ₂ O	< 5
2	[Pd(C ₃ H ₅)Cl] ₂ ^a	Et ₂ O	< 5
3	[Ir(cod)Cl] ₂ ^a	Et ₂ O	< 5
4	[Ir(cod)BF ₄] ^a	Et ₂ O	< 5
5	[Rh(cod)Cl] ₂ ^a	Et ₂ O	< 5
6	C ₇ H ₈ Mo(CO) ₃ ^{a,b}	Et ₂ O	< 5
7	CuTc	Et ₂ O	22
8	CuCl	Et ₂ O	6
9	CuBr•SMe ₂	Et ₂ O	25
10	CuBr•SMe ₂	DME	53
11	CuBr•SMe ₂	DME:Et ₂ O (1:1)	72

Reaction conditions: (Step 1) Olefin **1a** (1 equiv), sulfur diimide **2** (1.2 equiv), solvent (0.3 M). (Step 2) DME (0.2 M), ML_n (5 mol%), Grignard reagent **6** (4 equiv).

[^a] Metal complex was pretreated with (10 mol%) phosphine ligands, pyridine ligands, phosphoramidite ligands, or no ligand.

[^b] C₇H₈Mo(CO)₃ = cycloheptatriene molybdenum tricarbonyl.

Table 2

Substrate Scope

Reaction conditions: (1) Olefin **1** (1 equiv), sulfur diimide **2** (1.2 equiv), DME:Et₂O 1:1 (0.3 M). (2) DME (0.2 M), CuBr•SMe₂ (5 mol%), Grignard reagent (4 equiv).

[a] Intermediary adduct was filtered and isolated before treating with copper catalyst and Grignard reagent. In addition, 8 mol% TEMPO was utilized in the second step.