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Complete List of Authors:	Bao, Hongli; University of Texas Southwestern Medical Center, Biochemistry Bayeh, Liela; University of Texas Southwestern Medical Center, Biochemistry Tambar, Uttam; University of Texas Southwestern Medical Center, Biochemistry

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ARTICLE TYPE

Regioselective and Diastereoselective Aminoarylation of 1,3-Dienes

Hongli Bao, Liela Bayeh, and Uttam K. Tambar*

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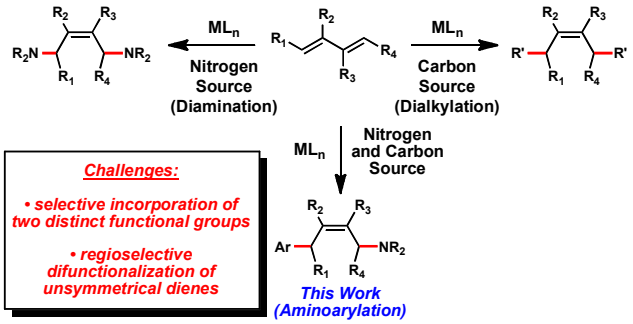
The 1,4-functionalization of dienes is a synthetically useful strategy for incorporating molecular complexity into a class of simple substrates. We report the aminoarylation of acyclic and cyclic 1,3-dienes via the sequential [4+2] cycloaddition with a sulfurdiimide reagent and copper-catalyzed allylic substitution with Grignard reagents. The regioselective and diastereoselective aminoarylation of unsymmetrical dienes is also presented, which highlights the utility of this method for generating products with multiple functional groups and stereocenters.

Introduction

The difunctionalization of 1,3-dienes is a powerful approach for installing two functional groups into an inexpensive and abundant class of hydrocarbons.[1] Efficient methods have been developed for the incorporation of two equivalents of the same nucleophile (e.g., diamination[2] and dialkylation,[3] Scheme 1). In contrast, selective difunctionalization with two distinct functional groups, such as carbon-based and nitrogen-based groups, remains rare.[4] Major challenges in the development of this type of transformation include: (1) selectivity for carboamination over diamination or dialkylation, and (2) regioselectivity and diastereoselectivity in the functionalization of unsymmetrical dienes.

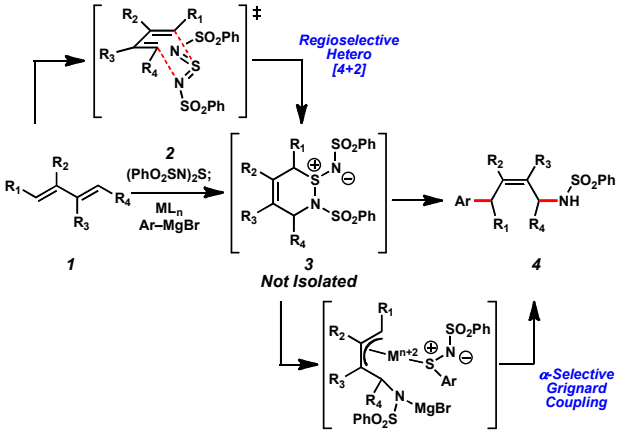
Herein, we describe a general method for the regioselective 1,4-aminoarylation of cyclic and acyclic dienes with Grignard reagents and a sulfurdiimide reagent. We also present examples of regioselective and diastereoselective aminoarylation. This process represents the first example of selectively converting simple 1,3-dienes into internal Z-olefins that are functionalized with aryl rings and sulfonamide.



Scheme 1 Selective Difunctionalization of 1,3-Dienes.

To address the aforementioned challenges in functionalizing dienes with two different functional groups, we envisioned a novel strategy that was based on the unique reactivity of sulfurdiimide **2** with unsaturated hydrocarbons (Scheme 2).[5] Our lab recently developed methods for the sulfurdiimide-mediated selective functionalization of terminal olefins with either carbon- or nitrogen-based groups.[6] We hypothesized that this reaction manifold would enable the simultaneous functionalization of 1,3-dienes, another class of unsaturated hydrocarbons, with carbon- and nitrogen-based groups through an unprecedented aminoarylation process.

Diene **1** would undergo spontaneous oxidation by sulfurdiimide **2** to generate [4+2] adduct **3**. Under properly selected conditions, sulfinamide **3** could be susceptible to metal-catalyzed allylic alkylation with aryl Grignard reagents.[7] The regioselectivity of the initial [4+2] cylcoaddition and the α-selectivity of the subsequent Grignard coupling would establish a selective difunctionalization of unsymmetrical dienes.



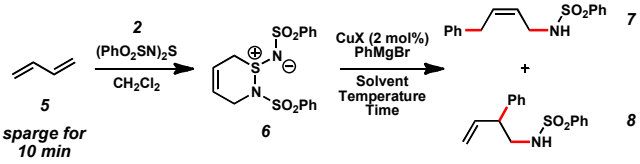
Scheme 2 Aminoarylation of 1,3-Dienes via Sulfinamide **3**.

Results and discussion

The proposed strategy for diene difunctionalization was initially evaluated for 1,3-butadiene **5** (Table 1). Sparging of sulfurdiimide **2** with butadiene for 10 minutes resulted in the efficient formation of cyclic sulfinamide **6**. In the absence of a metal catalyst, cycloadduct **6** did not yield coupled products **7** or **8** when treated with phenylmagnesium bromide (entry 1). Our

previous experience with the copper-catalyzed coupling of simple allylic sulfinamides and Grignard reagents suggested that copper complexes would be a reasonable starting point for the selective functionalization of cycloadduct **6**, despite the inherent differences between these two classes of substrates.[6] Copper(I) thio-phene-2-carboxylate (CuTc) exhibited a solvent dependent ability to catalyze the formation of aminoarylation products 7 and 8 (entries 2-4), with ethereal solvents such as DME proving to be optimal (entry 2). Despite the usual γ-selectivity of copper-catalyzed allylic alkylation systems,[8,9] cycloadduct **6** was transformed with high α-selectivity to product **7**.

Table 1 Optimization of 1,4-Aminoarylation.



Entry	CuX (2 mol%)	PhMgBr (equiv)	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]	7:8
1	–	3.0	DME	23	2	< 5	–
2	CuTc	3.0	DME	23	0.5	75	14:1
3	CuTc	3.0	CH_2Cl_2	23	2	< 5	–
4	CuTc	3.0	PhMe	23	2	< 5	–
5	CuCl	3.0	DME	23	0.5	60	15:1
6	$CuBF_4$	3.0	DME	23	0.5	67	9:1
7	$Cu(OTf)_2$	3.0	DME	23	0.5	70	10:1
8	CuI	3.0	DME	23	0.5	78	10:1
9	CuBr•SMe_2	3.0	DME	23	0.5	95 (82)[b]	20:1
10	CuBr•SMe_2	1.0	DME	23	0.5	21	20:1
11	CuBr•SMe_2	2.0	DME	23	0.5	45	20:1
12[c]	CuBr•SMe_2	3.0	DME	–78 to 23	0.5	88[b]	9:1

Reaction Conditions. Step 1: Sulfurdiimide **2** (1 equiv), solvent (0.2 M), 1,3-butadiene (sparge for 10 min and then stir for 10 min at 23 °C). Step 2: CuX (2 mol%), Ph–MgBr (3 equiv), solvent (0.2 M). [a] Two-step HNMR yield, with 1,4-dimethoxybenzene as an internal standard. [b] Isolated yield. [c] Two steps performed in one flask, without isolation of cycloadduct **6**.

After an examination of a series of copper sources (entries 5-9), CuBr•SMe2 was selected as the most effective catalyst (entry 9). Three equivalents of phenylmagnesium bromide were necessary for the efficient formation of aminoarylation product **7** (entries 10-11). Gratifyingly, without isolation of cycloadduct **6**, 1,3-butadiene **5** underwent selective difunctionalization in a single reaction flask in less than one hour to afford aminoarylation product **7**, which was isolated in 88% yield with 9:1 α-selectivity (entry 12). The product was generated with exclusive *Z*-olefin stereochemistry, which was a consequence of the preservation of olefin geometry in cycloadduct **6**. Although there are some reports of preserving olefin geometry in copper-mediated allylic alkylations,[10] potential for olefin isomerization exists due to the rapid equilibration between π-allyl Cu(III) and σ-allyl Cu(III) species and the subsequent reductive elimination via an enyl[σ+π]-type transition state.[11] Given the selective formation of *Z*-olefin aminoarylation products, we cannot rule out the possibility of coordination between the neighboring sulfonamide and copper.

We examined this efficient protocol for the aminoarylation of 1,3-butadiene with a series of aryl Grignard reagents (Table 2). The reaction was compatible with a range of *para*-substituted phenyl rings (entries 2-4). *Meta*- and *ortho*-substitution were also tolerated (entries 5-8). Polycyclic aromatic hydrocarbons were efficiently incorporated into the aminoarylation products (entries 9-10). Most notably, a heteroaromatic Grignard reagent was compatible with the transformation (entry 11). Interestingly, the scope of the aminoarylation of butadiene was limited to aryl Grignard reagents. The use of aliphatic Grignard reagents resulted in a selective aminosulfuration process (entries 12-13). Although we do not currently understand the origin of this distinct product selectivity for aliphatic Grignard reagents, the overall transformation represents a unique difunctionalization of dienes with carbon and sulfur functional groups.

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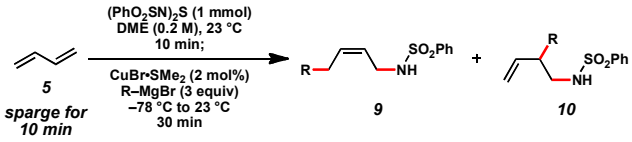
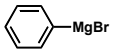
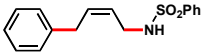
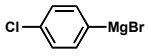
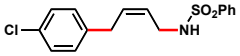
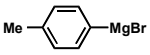
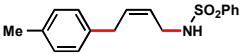
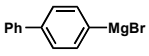
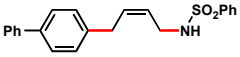
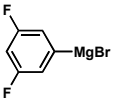
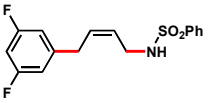
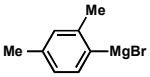
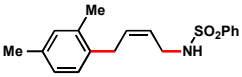
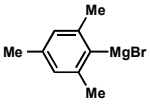
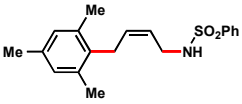
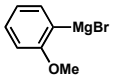
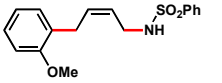
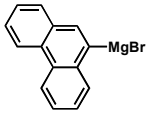
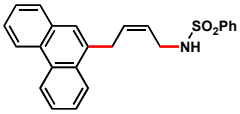
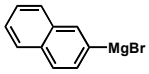
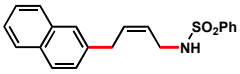
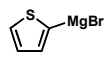
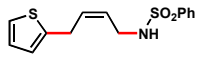
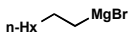
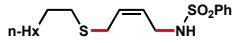
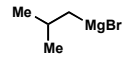
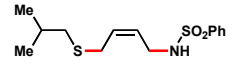
Table 2 Substrate Scope of Grignard Reagents.

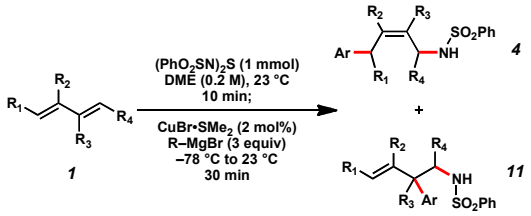


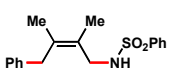
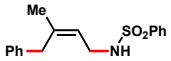
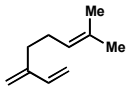
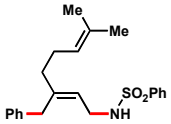
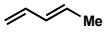
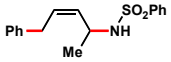
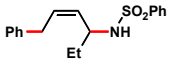
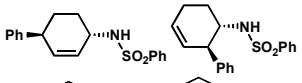
Entry	R–MgBr	Major Product (9)	Yield (%)[a]	9:10
1			88	9:1
2			82	9:1
3			87	7:1
4			89	5:1
5			66	5:1
6			56	10:1
7			32	>20:1
8			95	>20:1
9			81	>20:1
10			85	7:1
11			75	12:1
12			55	–
13			45	–

Reaction Conditions. Sulfurdiimide **2** (1 equiv), DME (0.2 M), 1,3-butadiene (sparge for 10 min and then stir for 10 min at 23 °C); $CuBr•SMe_2$ (2 mol%), R–MgBr (3 equiv). [a] Isolated yield.

We next explored the aminoarylation of substituted dienes, with the expectation that the difunctionalization of unsymmetrical substrates would occur in a regioselective manner (Table 3). Symmetrical 2,3-disubstitution of the diene did not affect the efficiency of the reaction (entry 1). Moreover, unsymmetrical 2-substituted dienes were converted to the aminoarylation products **4** as single regioisomers with exquisite α-selectivity (entries 2-3). The regioselectivity of the hetero-Diels-Alder reaction can be rationalized by frontier molecular orbital analysis of the concerted [4+2] cycloaddition between dienes **1** and sulfurdiimide **2**.[12] This argument for regioselectivity is supported by the selective formation of a single regioisomer when 1-substituted dienes were subjected to the reaction conditions (entries 4-5). Cyclic dienes were also efficiently functionalized, furnishing a mixture of the α-substituted and γ-substituted aminoarylation products (entries 6-7). The *anti* orientation of the phenyl ring and sulfonamide in the cyclic products is consistent with an oxidative addition of copper to the [4+2] cycloadduct with inversion, followed by reductive elimination with retention.[8]

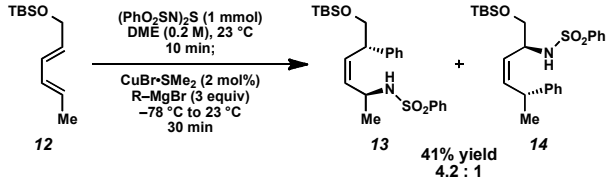
Table 3 Substrate Scope of 1,3-Dienes.



Entry	Olefin	Product	Yield (%)[a]	4:11
1			61	>20:1
2			77	>20:1
3			79	>20:1
4			80	>20:1
5			56	>20:1
6			90	4:1
7			85	5:1

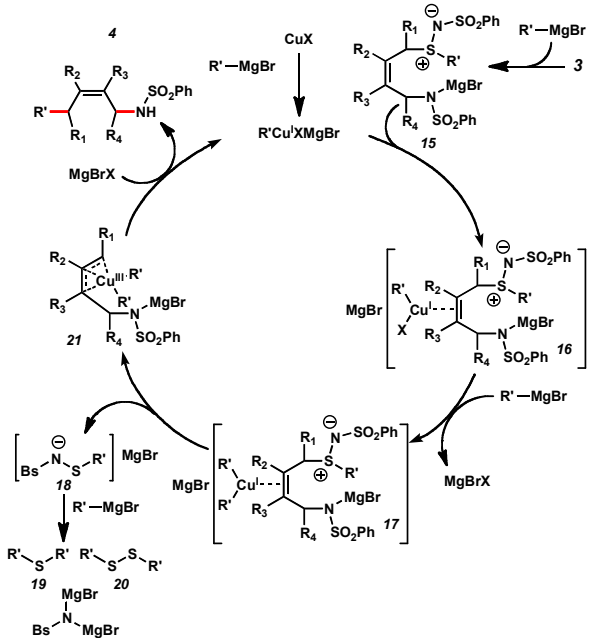
Reaction Conditions. Sulfurdiimide **2** (1 equiv), DME (0.2 M), diene **1** (1.5 equiv), stir for 10 min at 23 °C; $CuBr•SMe_2$ (2 mol%), R–MgBr (3 equiv). [a] Isolated yield.

To expand the synthetic utility of the 1,4-aminoarylation of dienes, we examined this method in a more stereochemically complex setting. We subjected 1,4-disubstituted unsymmetrical diene **12** to the optimized reaction conditions, which generated acyclic products with two stereocenters (Scheme 3). To our delight, our method for aminoarylation yielded predominantly regioisomer **13** (4.2:1 ratio), which was attributed to the subtle inductive differences of the silyl ether and methyl group in the [4+2] cycloaddition with sulfurdiimide **2**. In addition, both regioisomers **13** and **14** were isolated as single diastereomers, which was consistent with a diastereoselective [4+2] cycloaddition followed by a stereospecific copper-catalyzed arylation.[13]



Scheme 3 Regioselective and Diastereoselective Aminoarylation of Acyclic 1,3-Dienes.

We propose the mechanism depicted in Scheme 4 for the copper-catalyzed allylic substitution step. One equivalent of Grignard reagent initially reacts with [4+2] cycloadduct **3** to generate activated allylic sulfimide **15**. The susceptibility of sulfinamide **15** to nucleophilic attack is similar to the proposed reactivity of allylic sulfoxides in the presence of Grignard reagents.[14] Sulfimide **15** and the organocuprate reagent form π-complex **16**. While analogous π-complexes of other allylic electrophiles undergo facile oxidative addition with monoalkylcuprates followed by selective S_N2'-type displacement with Grignard reagents to form branched products,[8] we surmise that the unique leaving group in π-complex **16** renders this intermediate stable to oxidative addition. A second equivalent of Grignard reagent is necessary for the formation of the more reactive dialkylcuprate **17**, which proceeds through an oxidative addition pathway to π-allylcopper(III) complex **21** and sulfimide leaving group **18**. Byproduct **18** is decomposed by a third equivalent of Grignard reagent,[15] which is consistent with the requirement of 3 equivalents of Grignard reagent in the allylic functionalization protocol. Dialkyl π-allylcopper(III) complexes such as **21** (where R_1=H) are known to favor the formation of α-products over γ-products,[8,16] which may account for the regioselective generation of internal olefin **4** over terminal olefin **11** for unsymmetrical acyclic dienes (Table 3, entries 2-5).



Scheme 4 Mechanism of copper-catalyzed allylic substitution step.

Conclusions

In summary, we have developed a regioselective and diastereoselective aminoarylation of acyclic and cyclic 1,3-dienes with a sulfurdiimide reagent and aryl Grignard reagents. The high selectivity in product formation is a result of regioselective [4+2] oxidation of unsymmetrical substrates followed by α-selective copper-catalyzed allylic alkylation. Overall, this process converts 1,3-dienes into aminoarylation products with three new functional groups (an aryl ring, a sulfonamide, and a *Z*-olefin), which can be further manipulated to generate complex molecules efficiently from a simple class of starting materials. The utility of the aminoarylation reaction in complex natural product synthesis and the development of an enantioselective aminoarylation process are currently under investigation.

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Notes and references

The University of Texas Southwestern Medical Center at Dallas, Department of Biochemistry, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9038, USA. Fax: +1-214-648-8856; Tel: +1-214-648-0580; E-mail: Uttam.Tambar@utsouthwestern.edu

† Electronic Supplementary Information (ESI) available: Experimental details, compound characterization data, and spectra. See DOI: 10.1039/b000000x/

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