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SHORT COMMUNICATION

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Copper-Mediated 1,4-Diamination of 1,3-Butadienes

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A copper(II)-mediated diamination of 1,3-butadienes is reported. The reaction employs an inorganic base, copper dibromide as a reagent, and saccharin as the nitrogen source. The diamination proceeds for a series of 1,3-butadienes under relatively mild conditions with complete selectivity in favor of the 1,4-oxidation products.

Introduction

The diamination of unfunctionalized alkenes has recently emerged as a suitable route to establish vicinal diamines within a single, operationally simple oxidation reaction.[1] This work comprises both metal-mediated[2] and metal-catalyzed reactions.[3] In contrast to isolated alkenes, 1,3-butadienes have received significantly less attention, as, generally, conditions for the oxidative diamination of alkenes are not readily transferable to the substrate class of conjugated dienes. Shi developed a series of important 1,2-diamination reactions of 1,3-dienes under palladium and copper catalysis.[4] Our laboratory recently contributed an iodine(III)-mediated reaction that uses a combination of $PhI(OAc)_2$ and bistosylimide ($HNTs_2$) to transform conjugated dienes into diamines.[5] Although this metal-free method has its advantages, the reaction shows enhanced substrate dependence in the formation of 1,2- and 1,4-diamination products. Thus, a more general method for selective 1,4-diamination is still highly desirable.

1,4-Diamines are interesting compounds in their own right. For example 1,4-diaminobutane (putrescine, Figure 1) was recognized as an important natural polyamine, and together with its derivatives cadaverine, spermine, and spermidine became part of a group of substances deeply involved in cell proliferation, in vivo protein synthesis, programmed cell death, tumor prevention, and antiviral activities.[6,7] It has also been shown that the putrescine derivative (*E*)-1,4-diaminobut-2-ene (**A**) and its derivatives are of biological interest and have, for example, important fungicidal activity.[6,8] However, 1,4-diamination reactions are usually more difficult to accomplish than the corresponding vicinal diaminations. A pioneering example was provided by Bäckvall, who investigated the palladium-mediated diamination of butadiene and cyclohexadiene with dimethylamine as the nitrogen source. This work demonstrated that selective 1,4-diamination reactions between free nitrogen sources and 1,3-butadienes by using metal promoters could indeed be realized.[9]

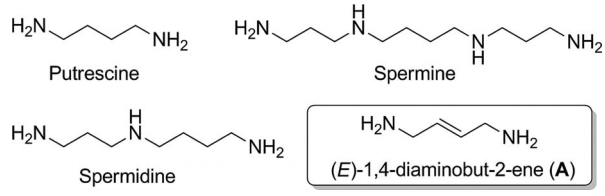

Figure 1. 1,4-Diamines as important building blocks.

Results and Discussion

In view of this important structural motif, we became interested in exploring alternative metal-based routes towards the 1,4-diamination of alkenes. A series of conditions was tested with 2-methyl-1,3-butadiene (**1a**) as the substrate (Table 1).

An initial attempt to employ palladium catalysis in the presence of copper(II) bromide (3 equiv.) as the terminal oxidant resulted in the isolation of desired diamine **2a** in 32% yield (Table 1, entry 1). However, a control experiment revealed that the same outcome was achieved in the absence of the palladium compound (Table 1, entry 2). The reaction was improved by using dry potassium phosphate as the base (Table 1, entry 3). In general, the reaction outcome was found to depend crucially on the exclusion of moisture. Upon successive increases in the temperature, the reaction went to full conversion to provide the product in 87% yield after column chromatography (Table 1, entries 4 and 5). Solvents other than DMF (Table 1, entries 6–8) and bases

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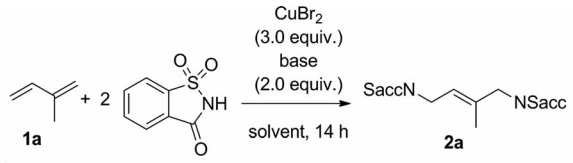
Table 1. Optimization of the copper-mediated 1,4-diamination of 1,3-butadienes (HNSacc = saccharin).



Entry	Base	Solvent	Temperature [°C]	Conv.[a] [%]	Yield[b] [%]
1[c]	$K_2CO_3 \cdot xH_2O$	DMF	25	40	32
2	$K_3PO_4 \cdot xH_2O$	DMF	25	40	32
3	K_3PO_4	DMF	25	75	64
4	K_3PO_4	DMF	35	80	72
5	K_3PO_4	DMF	50	100	87
6	K_3PO_4	MeCN	50	60	51
7	K_3PO_4	THF	50	<30	n.d.[d]
8	K_3PO_4	CH_2Cl_2	50	<30	n.d.[d]
9	K_2CO_3	DMF	50	75	62
10	$NaHCO_3$	DMF	50	60	48
11	Na_2HPO_4	DMF	50	75	62
12[e]	K_3PO_4	DMF	50	80	70
13[f]	K_3PO_4	DMF	50	<10	n.d.[d]
14[g]	K_3PO_4	DMF	50	<10	n.d.[d]
15[h]	K_3PO_4	DMF	50	70	0

[a] Determined by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy. [b] Yield of isolated product after column chromatography. [c] Reaction was performed with $Pd(OAc)_2$ (10 mol-%). [d] n.d.: not determined. [e] With $CuBr_2$ (2.0 equiv.). [f] With $CuBr_2$ (30 mol-%) under an atmosphere of molecular dioxygen. [g] With $Cu(OAc)_2$ (2.0 equiv.) instead of $CuBr_2$. [h] With phthalimide (2.0 equiv.) instead of saccharin (a complex product mixture was obtained).

other than K_3PO_4 (Table 1, entries 9–11) were found to be less effective. Decreasing the amount of copper(II) bromide resulted in a significant decrease in the chemical yield, as did an attempt to work under aerobic conditions with a substoichiometric amount of copper (Table 1, entries 12 and 13). Notably, the reaction depended on copper(II) bromide as the promoter. An attempt to replace this reagent by copper(II) acetate, which was introduced by Chemler for intramolecular diamination reactions,[2n,2o] did not result in any observable oxidation of **1a** (Table 1, entry 14). Attempts to employ phthalimide as an alternative nitrogen source under otherwise unchanged conditions did not lead to any observable diamination product (Table 1, entry 15).

As a result, it was decided to explore the scope of the 1,4-diamination reaction for different 1,3-butadienes (Table 2). 1,3-Butadiene (**1b**) itself was condensed into the reaction solution at low temperature. The sealed vessel was then warmed to room temperature over several hours. For this particular case, the reported yield of 41% is based on saccharin (Table 2, entry 2). As in the case of **1a**, exclusive 1,4-diamination was obtained. The same regioselectivity was observed for the diamination reactions of 1,3-octadiene (**1c**) and 1,3-pentadien-5-yl benzyl ether (**1e**; Table 2, entries 4,5). These compounds bearing aliphatic substituents had also generated 1,4-diamination products in previous iodine(III)-mediated reactions.[5a] The terpene myrcene (**1f**) underwent clean diamination of the 1,3-butadiene functionality to yield corresponding diamines **2f**/**2f′** as a 3:1 diastereomeric mixture. It is an important observation that the double bond remained untouched under the present conditions. In addition to the selective oxidation, the absence of any possible cyclization products was also noted. We were then pleased to observe that 1,3-butadienylarenes **1g**–**n** (Table 2, entries 6–12) and their derivatives (Table 2, entries 7–10) gave excellent yields of the intermolecular 1,4-addition products. For product **2g**, the 1,4-constitution was unambiguously assured by X-ray structure analysis (Figure 2).[10] This regioselectivity outcome is an exciting contrast to the case of iodine(III) chemistry, which usually favors the exclusive 1,2-addition onto the terminal position.[5] Under the present conditions, 1,4-diamination was obtained in all cases. For *para*-substituted arenes, good to excellent yields were obtained. We noted the formation of minor amounts of aminobromination products as side products in these cases.[11] These were formed as *N*-(1-bromo-4-arylbut-3-enyl) saccharins **3g**–**n**,[12] and their constitution was assigned through X-ray structure analysis of *p*-methoxy derivative **3i**.[10]

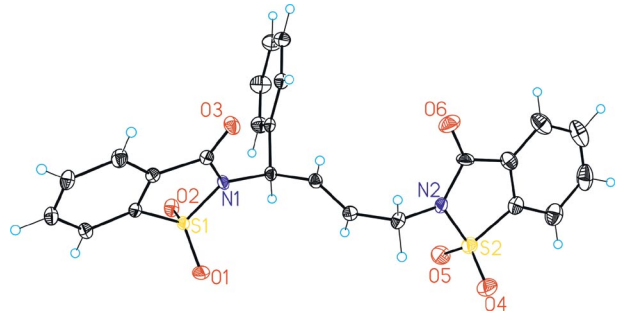
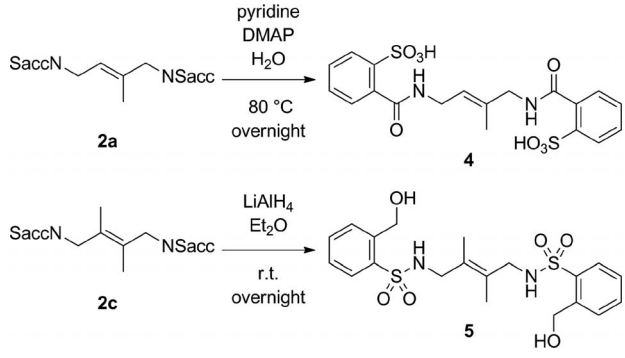


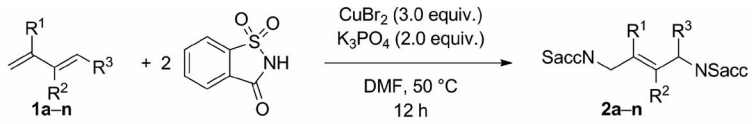
Figure 2. X-ray structure of **2f**.[10]

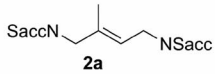
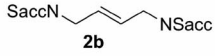
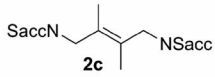
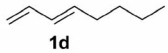
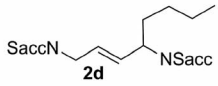
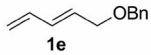
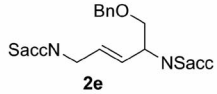
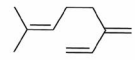
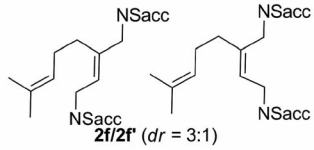
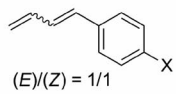
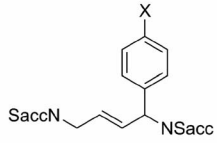
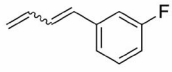
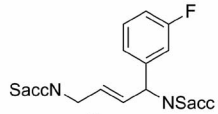
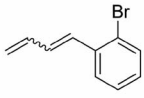
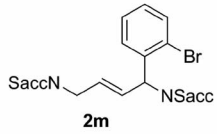
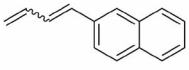
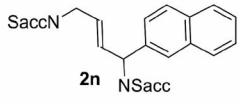
Given that we had experienced some problems with the removal of the saccharin moiety in the past, we undertook some preliminary investigations into its deprotection for the present case (Scheme 1).



Scheme 1. Selective cleavage reactions of saccharin in **2a**,**c**.

Table 2. Scope of the copper-mediated 1,4-diamination of 1,3-butadienes.



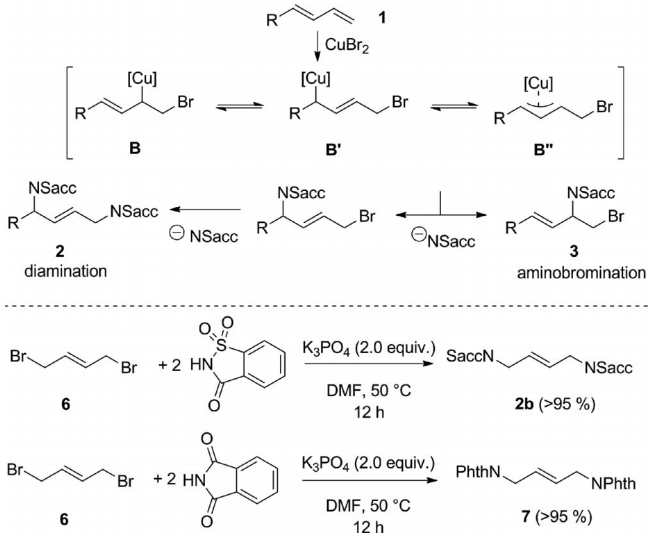
Entry	Substrate	Product	Yield[a] [%]
1	 **1a**	 **2a**	87
2[b]	 **1b**	 **2b**	41
3	 **1c**	 **2c**	64
4	 **1d**	 **2d**	71
5	 **1e**	 **2e**	75
6	 **1f**	 **2f/2f'** (*dr* = 3:1)	50
	 (*E*)/(*Z*) = 1/1		
7[c]	**1g**(X = H)	**2g**	76 (17)[d]
8	**1h** (X = Cl)	**2h**	78 (16)
9	**1i** (X = OMe)	**2i**	70 (24)
10	**1j** (X = F)	**2j**	44 (51)
11	**1k** (X = Me)	**2k**	88 (10)
12	 **1l**	 **2l**	34 (31)
13	 **1m**	 **2m**	48 (30)
14	 **1n**	 **2n**	48 (32)

[a] Yield of isolated product after column chromatography. [b] In condensed matter as a cosolvent, yield is based on saccharin. [c] 1,3-Butadienes **1g**–**n** were used as 1:1 mixtures of (*E*)/(*Z*) isomers. [d] Yield in parentheses refers to the corresponding aminobromination products **3g**–**n** (see text).

The synthetic utility of 1,4-diamination products **2** as suitable precursors to 1,4-diamine building blocks was investigated within some representative reactions. First, **2a** was treated with 4-(dimethylamino)pyridine (DMAP) and pyridine in water at 80 °C to afford product **4** in quantitative yield. This method allowed the saccharin ring to be selectively opened at the sulfamide side to afford amide **4**. Derivatives of **4** are recognized for their biologic properties such as their role in probiotic formulations[13] and for their proadhesin and nonadhesin properties.[14] Treatment of **2c**

with $LiAlH_4$ led to the opening of the saccharin ring with concomitant reduction of the carbonyl group to the alcohol, which resulted in product **5**, the structure of which was confirmed by X-ray structure analysis.[10] Derivatives of **5** are known for their biological properties, as, for example, their cytotoxic activity against human tumor cell lines.[7c] The full deprotection of the saccharin to the amine was previously reported, the first report of which was under acidic conditions with the use of HCl and another approach was through the use of CsF in DMF.[3f]

Although full mechanistic studies have to await future investigation, we did perform some control experiments to clarify major aspects. First, the formation of diamination products **2** and aminobromination products **3** is assumed to proceed through identical initial pathways.[15] We postulate an initial regioselective bromocupration of butadiene **1** with copper(II) bromide. This step should apparently not proceed through radical C–Br bond formation, as in the example of myrcene oxidation (Table 2, entry 6) no cyclization product was observed. The intermediate product should be 1,2- or 1,4-cuprate **B** or **B′**, respectively, which could be formulated as allyl cuprate **B′′** (Scheme 2). An alternative mechanism may be considered on the basis of the known decomposition of $CuBr_2$ into CuBr and elemental bromine.[16] However, subsequent formation of a dibromide species such as **6** as an intermediate prior to product formation through two nucleophilic allylic substitution reactions appears less probable. A control experiment revealed that **6** undergoes the expected formation of **2b** in the presence of saccharin and base; however, the same was observed for phthalimide, which in contrast to saccharin does not promote the diamination reaction under the copper-mediated conditions (Table 1, entry 19). Instead, direct nucleophilic displacement from **B**/**B′**/**B′′** is expected. This can either promote the formation of aminobromination product **3** upon nucleophilic substitution in **B** or promote the S_N2' addition to **B′**. Diamination product **2** would then arise from the alternative pathways (S_N2 addition to **B** and S_N2' addition to **B′**). Given that this process gives an allylic bromide, a second nucleophilic amination is feasible to provide observed diamination products **2**. This mechanistic proposal is also supported by the increased formation of aminobromination products for substrates **1l**–**n**. In these cases, the enhanced volume of the aromatic substituent should render the amination in the benzylic position less feasible, which would result in the observed decrease in the formation of the diamination product. The assumption of allylic copper intermediate **B′′** would also explain the observation that both (*E*)- and (*Z*)-**1n** lead to single (*E*)-configured product **2n**.[12] The nature of the copper in allylic intermediates **B**/**B′**/**B′′** is unclear at present. Owing to the observation that 3 equivalents of the copper(II) promoter are required for complete conversion, the involvement of higher copper aggregates or the formation of a copper(III) species may be concluded.[2o,17]



Scheme 2. Mechanistic proposal and control experiments.

Conclusions

In summary, we have developed a new copper-promoted 1,4-selective diamination of 1,3-butadienes. The reaction proceeds under mild conditions by using copper dibromide and saccharin as reagents and gives rise to a series of 1,4-diaminobut-2-enes. The reported reactivity should be of interest for the development of additional 1,4-difunctionalization reactions with the use of copper(II) promoters.

Experimental Section

General Procedure: A flame-dried Schlenk tube was charged with $CuBr_2$ (268 mg, 1.2 mmol, 3.0 equiv.), K_3PO_4 (170 mg, 0.8 mmol, 2.0 equiv.), saccharin (147 mg, 0.8 mmol, 2.0 equiv.), and dry DMF (2.0 mL) under a nitrogen atmosphere. The diene (0.4 mmol, 1.0 equiv.) was then added. After stirring for 12 h at 50 °C, the reaction mixture was cooled to room temperature and water (10 mL) was added. The copper salt was removed by filtration through Celite. The aqueous layer was extracted with dichloromethane (5× 7 mL), and the combined organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 4:1 to 1:1) to give the pure diamination product.

Supporting Information (see footnote on the first page of this article): Detailed experimental description; characterization data for all new compounds; details of the X-ray analyses; and copies of the ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra.

Acknowledgments

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