Palladium-Catalyzed Amination of 1-Bromo- and 1-Chloro-1,3-butadienes: A General Method for the Synthesis of 1-Amino-1,3-butadienes

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Dedicated to Dr. Joe P. Richmond on the occasion of his 60th birthday.

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: 1-Amino-1,3-butadienes, interesting substrates for [4+2] cycloadditions, are prepared by Pd-catalyzed cross-coupling of secondary amines with readily available 1-halodienes. The optimized catalytic system employs $Pd_2(dba)_3$ as metal source and XPHOS as supporting ligand. The reaction proceeds in very high yields with 1-bromo-1,3-butadienes, and also with the less reactive 1-chloro-1,3-butadienes. Moreover, the range of amines that can be incorporated includes aromatic amines, and cyclic and acyclic aliphatic amines.

Keywords: amination; aminodiene; cross-coupling; enamine; palladium

1-Amino-substituted-1,3-butadienes are a very interesting class of enamines due to their high reactivity in [4+2] cycloaddition reactions.[1,2] The presence of the electron-donor amino substituent enhances the reactivity of the diene, and directs the regioselectivity and the stereoselectivity of the cycloaddition.[3] Moreover, the amino substituent attached at the diene skeleton may have even more additional interest. On the one hand, it may serve as a chiral auxiliary in the cycloaddition if a chiral amine is employed.[4] On the other hand, the amino substituent can be preserved in the molecule after the cycloaddition and used to build more elaborate structures, such as amino-substituted cyclohexanes[5] or nitrogen-containing heterocycles.[6] However, in spite of the potential interest of this class of dienes, very few methods have been described for their preparation. While there are several reliable approaches for the synthesis of dienamides (*N*-acyl-substituted systems), few procedures, other than the well-established condensation of α,β-unsaturated aldehydes with secondary amines,[7,8] have been reported for the synthesis of 1-aminodienes. However, the former methodology, and most of the alternative approaches, usually lack generality in both the structure of the dienic moiety and of the amino substituent, and also stereoselectivity in the amino-substituted double bond.[9]

We have disclosed recently a new method for the synthesis of enamines by Pd-catalyzed cross-coupling of secondary amines with alkenyl halides.[10] This methodology, which is an extension of the well developed Buchwald–Hartwig amination of aryl halides,[11,12] allows for the preparation of enamines with high regio- and stereoselectivity. Moreover, the application of this reaction to 2-chloro-1,3-butadienes has led to a new and very efficient method for the synthesis of 2-amino-1,3-butadienes.[13] Continuing with our interest in the application of the cross-coupling reaction of alkenyl halides with amines, we decided to focus on the preparation of 1-aminodienes. In this communication, we report our progress in the development of a general and stereoselective method for the synthesis of this particular class of enamines.

In a preliminary set of experiments we investigated the coupling of the readily available bromodiene **1a**[14] with morpholine **2a** under a set of different catalytic combinations (Scheme 1). The reactions were carried out in toluene, in the presence of NaO-*t*-Bu as base, $Pd_2(dba)_3$ as metal source, and several ligands which are known to promote C–N bond forming reactions with aryl and alkenyl bromides. Based on our previous experience in the amination of alkenyl bromides, the study was restricted to commercial and air-stable phosphane ligands and included the bidentate ligands BINAP and XANTPHOS, as well as Buchwald's electron-rich biphenyls, 2-dicyclohexylphosphino-2′-dimethylamino biphenyl (DavePhos)[15] and X-PHOS[16] (Scheme 1). The results are presented in Table 1.

As expected from our previous studies in the cross-coupling of amines with alkenyl bromides, all these cat-

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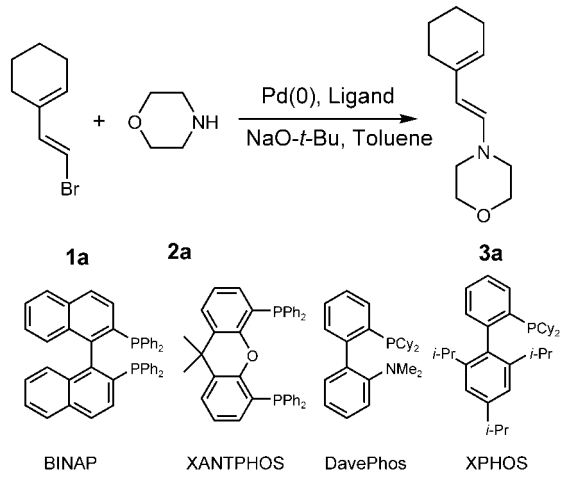
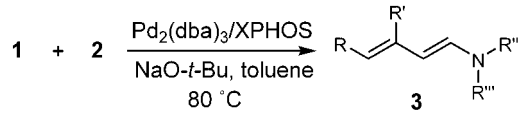
Table 1. Influence of the ligand and reaction conditions in the cross-coupling of **1a** and **2a**.[a]

Entry	Mol % of Pd	Ligand	T [°C]	t [h]	Conversion [%][b]
1	2[c]	BINAP	80	6.5	100
2	2	XANTPHOS	80	6.5	88
3	2	DavePhos	80	6.5	100
4	2	XPHOS	80	6.5	100
5	1	BINAP	80	3.5	28
6	1	DavePhos	80	3.5	61
7	1	XPHOS[d]	80	3.5	100
8	1	XPHOS	25	21	13
9	0.2	XPHOS	80	21	66

[a] General reaction conditions: 0.5 mmol of bromodiene **1**; 0.5 mmol of morpholine **2**; 2:1 molar relationship Pd:ligand; 1.4 equivs. of NaO-*t*-Bu; 2 mL of toluene.
[b] Determined by GC.
[c] $Pd(OAc)_2$ was used as metal source.
[d] 1:1 molar relationship of Pd:ligand.



Scheme 1. Coupling reaction of bromodiene **1a** and morpholine **2a** under different catalytic conditions.



Scheme 2. Synthesis of 1-amino-1,3-butadienes **3** by Pd-catalyzed cross-coupling of amines **2** with 1-halo-1,3-butadienes **1**.

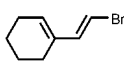
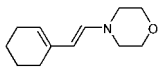
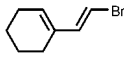
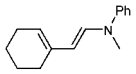
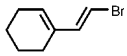
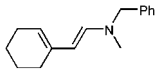
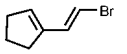
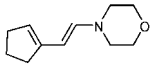
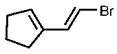
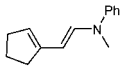
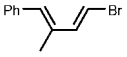
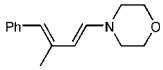
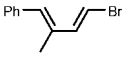
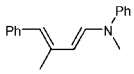
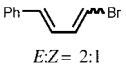
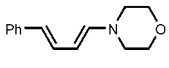
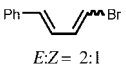
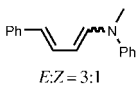
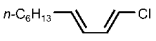
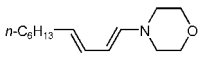
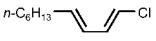
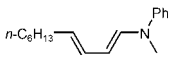
alytic systems promoted the reaction quite efficiently, giving rise to the desired 1-aminodiene **3a** with good to excellent conversion when the reactions were effected at 80 °C using 2 mol % of Pd (entries 1 to 4). More demanding reaction conditions established the Pd(0)/XPHOS combination as the more active catalyst (entries 5–7). Moreover, by using this catalytic system, the coupling reaction could be run to completion in 3.5 h at 80 °C with 1 mol % of Pd (entry 8). A decrease in the catalyst loading to 0.2 mol % gave rise to a substantial decrease in the reaction rate (66% of conversion after 21 h) while the reaction at room temperature proceeded with only 13% conversion after 21 h of reaction. Additional experiments revealed that the Pd:ligand molar ratio can be reduced to 1:1 without loss of catalytic activity. The optimized reaction conditions were applied thereafter to a set of different halodienes **1** and amines **2** (Scheme 2, Table 2).

The coupling reaction with bromodienes **1a – c** proceeded smoothly under the reaction conditions previously developed for most of the examples studied (Table 2) involving a cyclic aliphatic amine (entries 1, 4, 6), an acyclic aliphatic amine (entry 3), as well as an aromatic amine (entries 2, 5, 7), giving rise to the desired 1-aminodienes **3** with very high yields.

With regard to the stereoselectivity of the process, the reactions with dienes **1a**–**c**, (pure *E*-bromoalkenes) afforded the *E*-enamines again as pure isomers as deduced by the ^{1}H NMR spectra of the resulting dienes. Interestingly, when the coupling reaction was carried out with bromodiene **1d**,[17] which consisted in a 2:1 mixture of *E:Z* bromoolefins, we observed double bond isomerization to obtain the corresponding *(E,E)*-aminodiene as a pure stereiosomer when morpholine **2a** was used (entry 8), and a 3:1 ratio of the *(E,E)* and *(Z,E)* isomers, respectively, when the reaction was carried out with *N*-methylaniline **2b** (entry 9).[18] Clearly, in both cases the less stable *(Z)*-enamines undergo isomerization into the more stable (*E*) isomers.

The work-up of the reactions involved dilution of the reaction mixture with hexanes, filtration through celite and removal of the solvents under reduced pressure to afford the desired 1-aminodienes as nearly pure materials as judged by ^{1}H and ^{13}C NMR. This is an important characteristic of this reaction taking into account that conventional purification methods involving aqueous work-up or chromatography are not applicable to enamines, as they tend to hydrolyze rapidly.

Table 2. 1-Aminodienes prepared.[a]

Entry	Halodiene	Amine	Aminodiene	*t* [h]	Yield [%][b]
1				3.5	96
	1a	**2a**	**3a**		
2				4	88
	1a	**2b**	**3b**		
3				4	88
	1a	**2c**	**3c**		
4				3	86
	1b	**2a**	**3d**		
5				3	88
	1b	**2b**	**3e**		
6				3	96
	1c	**2a**	**3f**		
7				3	94
	1c	**2b**	**3g**		
8[c]	 *E*:*Z* = 2:1		 *E*:*Z* > 95:1	5	88
	1d	**2a**	**3h**		
9[c]	 *E*:*Z* = 2:1		 *E*:*Z* = 3:1	5	90[e]
	1d	**2b**	**3i**		
10[d]				2	98
	1e	**2a**	**3j**		
11[d]				2	95
	1e	**2b**	**3k**		

[a] See experimental section for reaction conditions.
[b] Isolated yields.
[c] $Pd(OAc)_2$/BINAP was used as catalytic system.
[d] Reaction conducted at 90 °C.
[e] See ref.[18]

We also examined the participation of the less reactive 1-chlorodiene **1e**.[19] As indicated in Table 2 (entries 10, 11), when the coupling reactions were carried out at 90 °C and using 1 mol % of Pd the enamines were isolated again with quantitative yields and as pure *E*-isomers. It is worth noting that the coupling reaction with chlor-

odienes does not require harsher conditions or longer reaction times than with bromodienes. Moreover, 1-chlorodienes are readily available through several methods, among them various cross-coupling protocols involving commercially available 1,2-dichloroethylene;[20] therefore, the present methodology may represent a very simple entry into structurally diverse 1-amino-1,3-butadienes.

In conclusion, we have reported a new methodology, which represents a fairly general method for the synthesis of 1-amino-1,3-butadienes from readily available substrates, 1-bromo- and 1-chloro-1,3-butadienes. Given the usefulness of 1-amino-1,3-butadienes in cycloaddition processes, we believe that the reaction presented herein may be of great applicability in synthetic organic chemistry.

Experimental Section

General Remarks

All reactions were carried out under nitrogen atmosphere in an RR98030 12 place Carousel Reaction Station™ from Radleys Discovery Technologies, equipped with gas-tight threaded caps with a valve, cooling reflux head system, and digital temperature controller. Toluene, pentane and hexanes were continuously refluxed and freshly distilled from sodium/benzophenone under nitrogen. $Pd_2(dba)_3$ and $Pd(OAc)_2$ were purchased from Strem Chemical co. and used without further purification. All phosphane ligands used are commercially available from Strem or Aldrich and were used without further purification. NaO-*t*-Bu was purchased from Aldrich Chemical Co., stored in a flask purged with nitrogen and weighted in the air. Bromodienes **1a** and **1b** were prepared as described in the Supplementary Information. The synthesis of 1-bromo-3-methyl-4-phenyl-1,3-butadiene **1c** and 1-bromo-4-phenylbutadiene **1d** was adapted from a known procedure[17] and is detailed in the Supplementary Information. GC analysis were performed with a GC Agilent Technologies 6890N instrument. NMR spectra were recorded at 300 or 200 MHz for ^1H and 75 or 50.3 MHz for ^{13}C, with tetramethylsilane as internal standard for ^1H and the residual solvent signals as standard for ^{13}C. Chemical shifts are given in ppm. Mass spectra were obtained by EI (70 eV).

General Procedure for the Cross-Coupling of 1-Halodienes 1a–d with Secondary Amines 2; Synthesis of 1-Aminodienes 3a–k

A carousel reaction tube under nitrogen atmosphere was charged with XPHOS (0.01 mmol, 1 mol %), tris(dibenzylideneacetone)dipalladium(0) (0.005 mmol, 1 mol %), sodium *tert*-butoxide (1.4 mmol) and toluene (4 mL). After 1 minute, the halodiene **1** (1 mmol) was added and the reaction mixture was stirred for 2 additional minutes, when the amine **2** (1 mmol) was added. The system was heated (80 °C for bromodienes or 90 °C for chlorodienes) with stirring until the starting halide had been completely consumed as judged by GC analysis. The mixture was allowed to cool to room temperature, taken up in dry pentane or hexanes (15 mL), and filtered through celite. The solvents were evaporated under reduced pressure. The residue was redissolved in dry hexanes (15 mL), filtered again through celite, concentrated under reduced pressure and dried under high vacuum to afford a residue which consisted of the essentially pure 1-aminodiene **3**.

4-[(1*E*)-2-Cyclohexenylvinyl]morpholine (3a): HRMS: calcd. for $C_{12}H_{19}ON$: 193.1461; found: 193.1460; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.61-1.68$ (m, 4H), 2.09–2.12 (m, 4H), 2.87–2.93 (m, 4H), 3.72–3.77 (m, 4H), 5.26 (d, $^3J_{trans} = 14.2$ Hz, 1H), 5.48 (s, 1H), 6.03 (d, $^3J_{trans} = 14.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 23.05$ (CH_2), 23.14 (CH_2), 25.25 (CH_2), 26.06 (CH_2), 49.49 (CH_2), 66.77 (CH_2), 106.88 (CH), 122.27 (CH), 134.70 (C), 136.82 (CH).

***N*-[(1*E*,3*E*)-Deca-1,3-dienyl]-*N*-methylbenzenamine (3k):** HRMS: calcd. for $C_{17}H_{25}N$: 243.1981; found: 223.1980; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.92-0.94$ (m, 3H), 1.32–1.37 (m, 8H), 2.08–2.13 (m, 2H), 3.19 (s, 3H), 5.44–5.53 (m, 2H), 6.10 (dd, $^3J_{trans} = 15.0$ Hz, $^3J = 10.4$ Hz, 1H), 6.82 (d, $^3J_{trans} = 13.5$ Hz, 1H), 6.92–7.03 (m, 3H, arom. H), 7.28–7.31 (m, 2H, arom. H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 14.06$ (CH_3), 22.60 (CH_2), 28.86 (CH_2), 29.89 (CH_2), 31.75 (CH_2), 32.87 (CH_2), 35.03 (CH_3), 104.95 (CH), 117.04 (CH), 120.62 (CH), 126.62 (CH), 129.06 (CH), 129.12 (CH), 134.84 (CH), 147.34 (C).

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