Homoallylic Amines

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Palladium(II)-Catalyzed Intramolecular Hydroamination of 1,3-Dienes to Give Homoallylic Amines**

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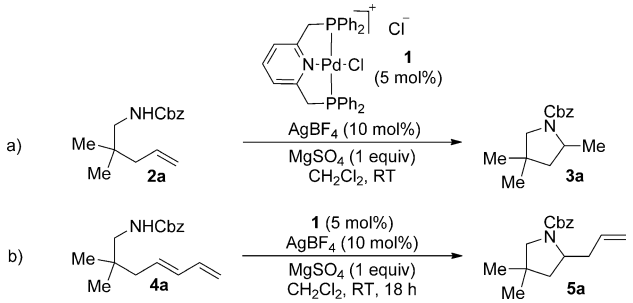
Nitrogen heterocycles are key features of many natural products and industrially relevant pharmaceuticals.[1] As a result, many methods for the construction of these core structures have been developed. In particular, the hydroamination of unsaturated hydrocarbons has arisen as a general and useful method for generating new carbon–nitrogen bonds in heterocycles because of its atom-economic nature and mild reaction conditions.[2] Numerous transition-metal and Brønsted acid hydroamination catalysts have been discovered.

The hydroamination of 1,3-dienes is a useful transformation, because the resulting aminoalkenes possess a handle for further functionalization. A major challenge for diene hydroamination catalysts is the controlled formation of one of the several possible regioisomeric products. In practice, the vast majority of reported diene hydroamination reactions are selective for the formation of allylic amines.[3] In particular, known hydroamination reactions catalyzed by nickel or palladium give exclusively allylic amines, owing to the intermediacy of an η^3-allyl complex.[4] Similarly, Brønsted acid catalyzed hydroamination reactions also generate allylic amines, as predicted by the stability of the intermediate allyl cation.[5] In contrast, the formation of homoallylic amines in hydroamination reactions is a more challenging task. A few hydroamination catalysts have been reported to give mixtures of allylic and homoallylic amines,[6] but only two reports on hydroamination catalysts that selectively give homoallylic amines have been published. Marks et al. described a Th catalyst that gives high selectivity for two substrates lacking substitution on the diene, but with a trisubstituted diene substrate, the selectivity was poor.[7] Yamamoto and coworkers discovered a carbaboranyl–Hg catalyst that exclusively afforded homoallylic amines from a range of sulfonamidodiene substrates.[8] In this case, the conversion of substrates with substituents on the diene moiety was not reported. Herein, we report a Pd catalyst for the hydroamination of dienes that exclusively gives homoallylic amines in excellent yields for a variety of diene substitution patterns.

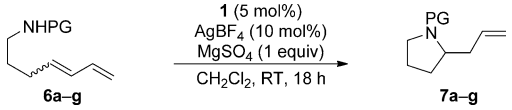
We previously reported a mild Pd-catalyzed intramolecular hydroamination of aminoalkenes that generated pyrrolidine, piperidine, and piperazine scaffolds (Scheme 1 a).[9] We hypothesized that the same Pd catalyst should also catalyze the hydroamination of dienes by a similar mechanism, and, by virtue of the increased reactivity of dienes, tolerate a greater range of substitution patterns. Initial studies began by subjecting protected aminodiene **4a** to the previously reported hydroamination conditions (Scheme 1 b). Encouragingly, this afforded a single isomer of the cyclization product in excellent yield. This isomer was identified as the homoallylic amine product **5a**, which arises from a 5-*exo* 1,2-addition. Exposure of a substrate without geminal backbone substitution to these conditions gave the product in equally high yields and regioselectivity (Table 1, entry 1), which established that this hydroamination catalyst is even active for substrates that do not benefit from Thorpe–Ingold effects.



Scheme 1. Pd-catalyzed intramolecular hydroamination reactions.

This reaction can be applied to substrates with a wide array of amine protecting groups (Table 1). Importantly, the

Table 1: Variation of the protecting group.



Entry	Protecting group[a]	Product	Yield [%]
1	Cbz (**6a**)	**7a**	>99 (95%)[b]
2	Boc (**6b**)	**7b**	76
3	*p*-toluoyl (**6c**)	**7c**	86
4	Ac (**6d**)	**7d**	>99
5	Ts (**6e**)	**7e**	73
6	4-Ns (**6f**)	**7f**	97
7	SES (**6g**)	**7g**	73

[a] For the *E*/*Z* ratios, see the Supporting Information. [b] 1.8 mmol scale. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, 4-Ns = 4-nitrobenzenesulfonyl, PG = protecting group, SES = 2-(trimethylsilyl)-ethanesulfonyl, Ts = *p*-toluenesulfonyl.

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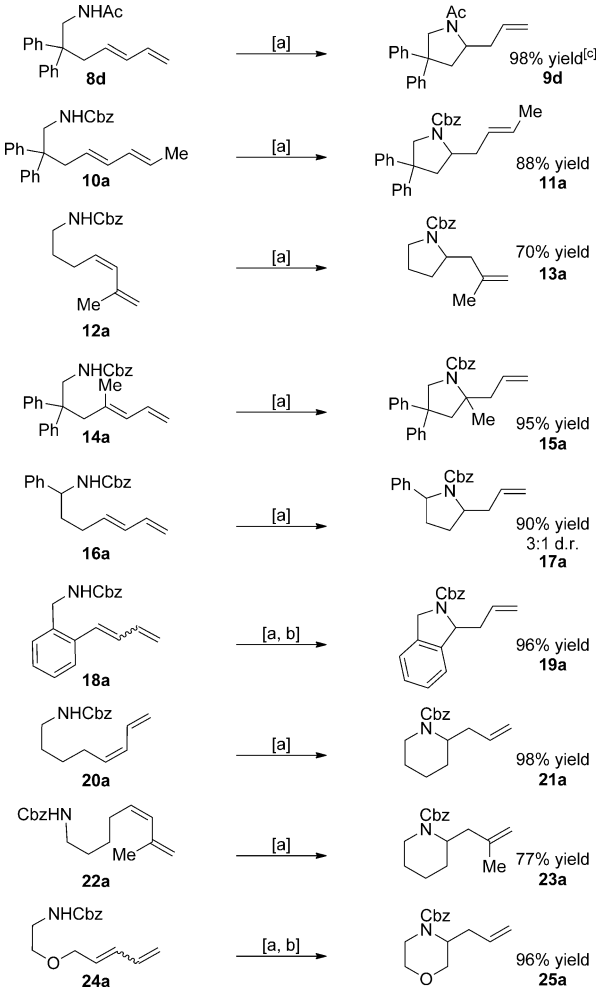
synthetically useful substrates that bear the carbamate protecting groups Cbz (**6a**) or Boc (**6b**) were successfully converted into the corresponding hydroamination products, which makes this the only catalytic system that gives homoallylic amines with these protecting groups. Amides also cyclized in good to excellent yields (**6c** and **6d**). Even sulfonamide-protected amines (**6e**–**6g**) underwent hydroamination under standard conditions, which is somewhat surprising given the previous failure of catalyst **1** to react with sulfonamidoalkenes.[9]

The effect of the diene substitution pattern on the regioselectivity of an intramolecular hydroamination had not been extensively explored, so we prepared the substituted dienes **10a**, **12a**, and **14a** with substituents at the 4, 3, and 1 positions of the diene, respectively. All three substrates cleanly underwent hydroamination, affording the allylpyrrolidine products in high yields (**11a**, **13a**, **15a**; Scheme 2). The excellent yield of **15a** shows that this method can be used to construct sterically hindered tetrasubstituted carbon centers. Other backbone substitution patterns and lengths were also tolerated, as isoindoline, piperidine, and morpholine heterocycles were isolated in >95% yield (**19a**, **21a**, **23a**, **25a**). Excellent regioselectivities (>20:1) were obtained in all cases.

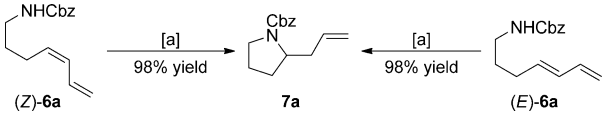
Although it is clear from Scheme 2 that both *E* and *Z* alkenes are capable of undergoing hydroamination, we tested whether the initial stereochemistry had any influence on the hydroamination reactivity. Hydroamination of (*E*)-**6a** and (*Z*)-**6a** gave the same products in identical yields (98%), illustrating that alkene stereochemistry has little effect on the outcome of hydroamination (Scheme 3).

Understanding the high selectivity for formation of the homoallylic amines in this system requires consideration of the key Pd–alkyl intermediate that arises from aminopalladation of the diene.[9c] To investigate this intermediate, a stoichiometric reaction of the Pd complex with substrate **8d** was performed in the presence of various bases. *N*,*N*-Dimethylaniline proved to be an appropriately strong and bulky base to allow the allyl intermediate **26** to be isolated as a yellow solid in 66% yield (Scheme 4). NMR spectroscopy confirmed that the allyl group was bound to the metal center in an η^1 fashion, and that palladium was bound to the distal terminus of the former diene moiety. Similar pincer-ligated Pd–allyl complexes have been shown to be preferentially of η^1 hapticity.[10] When complex **26** was treated with a Brønsted acid, hydroamination product **9d** was obtained, which is consistent with the intermediacy of this complex in the catalytic reaction. It appears that the regioselectivity observed in this hydroamination reaction arises from 1) initial 1,4 aminopalladation to form the less-substituted η^1-allyl complex **26**, followed by 2) regioselective S_E2' protonation of the Pd–allyl complex.[11]

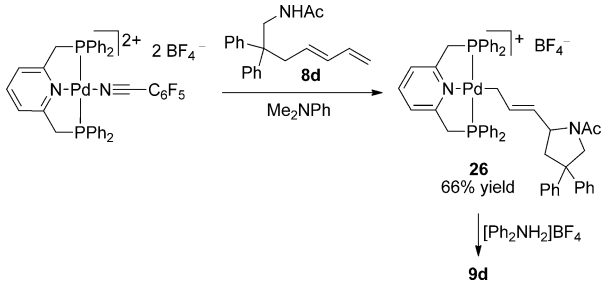
In conclusion, a palladium-catalyzed hydroamination of amino-1,3-dienes at room temperature has been developed that results in the formation of useful olefinic nitrogen heterocycles. Homoallylic amines were formed in high yields and with high selectivity. A wide variety of amine protecting groups could be employed, and various diene substitution patterns were tolerated. Finally, an η^1-allyl–palladium com-



Scheme 2. Substrate scope of the hydroamination. [a] **1** (5 mol%), $AgBF_4$ (10 mol%), $MgSO_4$ (1 equiv), CH_2Cl_2, RT, 18 h. [b] For the *E*/*Z* ratios, see the Supporting Information. [c] The same yield was obtained on both a 0.2 and a 2.0 mmol scale.



Scheme 3. Hydroaminations of *E* and *Z* dienes. [a] **1** (5 mol%), $AgBF_4$ (10 mol%), $MgSO_4$ (1 equiv), CH_2Cl_2, RT, 18 h.



Scheme 4. Formation of the η^1-allyl–Pd complex and protonolysis.

plex was isolated and shown to be a viable intermediate, which gave insight into the reaction mechanism.

Experimental Section

General hydroamination conditions for the reaction with **5a:** In a glove box, 2,6-bis(diphenylphosphinomethyl)pyridine dichloropalladium (**1;** 3.27 mg, 0.05 mmol), $AgBF_4$ (1.97 mg, 0.01 mmol), and $MgSO_4$ (12 mg, 0.1 mmol) were added to a round-bottomed flask. The flask was capped with a septum and removed from the glove box. The reaction mixture was placed under an atmosphere of nitrogen, and CH_2Cl_2 (0.5 mL) was added. A solution of the substrate (27.3 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) was added by syringe to the stirring mixture. The reaction was stirred overnight; then the mixture was filtered through a plug of celite. Purification by column chromatography (CH_2Cl_2) on silica gel afforded the pure product (26.0 mg, 95 % yield).

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[11] As the two regioisomeric η^1-allyl complexes are known to interconvert rapidly at room temperature (see Ref. [10]), we cannot rule out S_E2 protonation of the unobserved allyl isomer.

