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Room Temperature Palladium-Catalyzed Intramolecular Hydroamination of Unactivated Alkenes

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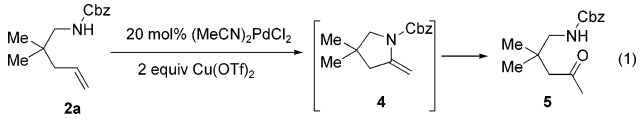
The direct addition of N−H bonds across alkenes and alkynes (hydroamination) is an efficient method for the formation of carbon−nitrogen bonds.[1] Although numerous catalysts for this transformation have been developed recently, the hydroamination of unactivated alkenes remains a significant challenge. Lanthanide and group 4 complexes are effective for hydroaminations of unactivated alkenes, but the low functional group tolerance and extreme air and water sensitivity of these catalysts severely limit their synthetic utility.[2] Recently, both platinum catalysts[3] and strong Brønsted acids[4] have been reported to catalyze inter- and intramolecular hydroaminations of alkenes. Unfortunately, elevated temperatures (85−150 °C) are required for reasonable reaction rates. Herein we report a *room temperature*, functional group tolerant Pd-catalyzed method for the intramolecular hydroamination of unactivated alkenes.

One of the complications of Pd-catalyzed additions to alkenes is the strong tendency for the alkylpalladium intermediates to undergo β-hydride elimination (Scheme 1).[5] We hypothesized that the use of a tridentate ligand would block the open coordination sites required for β-hydride elimination, and thereby prevent this process and promote alternate reactions of the alkylpalladium species. Stoichiometric studies of palladium complexes of bis(diphenylphosphinomethyl)pyridine have shown that β-hydride elimination is effectively inhibited by this ligand.[6] We therefore chose to investigate the catalytic activity of palladium complex **1** in the cyclization of amidoalkenes.

Reaction of protected aminoalkene **2a** using 20 mol % of Pd complex **1**, 40 mol % of $AgBF_4$, and 2 equiv of $Cu(OTf)_2$ at room temperature gave hydroamination product **3a** in 98% yield (Table 1). In contrast, reaction of **2a** in the absence of ligand (20 mol % of $PdCl_2(CH_3CN)_2$ and 2 equiv of $Cu(OTf)_2$) yielded Wacker oxidation product **5**, presumably via the intermediacy of enamide **4** (eq 1). This difference in reactivity strongly suggests that the tridentate ligand was effectively inhibiting β-hydride elimination.



(1)

Further optimization of reaction conditions revealed that the amount of $Cu(OTf)_2$ could be reduced with no effect on the yield of hydroamination product (Table 1). As little as 1 mol % of the palladium catalyst could be employed with minimal loss in yield. Toluene and CH_2Cl_2 were identified as equally suitable solvents for this transformation, but the use of coordinating solvents, such as CH_3CN, THF, or Et_2O, completely inhibited the reaction.

During early investigations, the reaction was found to be sensitive to the presence of water, resulting in inconsistent yields. Addition of a drying agent (K_2CO_3, $MgSO_4$, or powdered 3 Å sieves) to the reaction mixture easily and effectively solved this problem. This protocol allowed for complete conversion even using unpurified ("wet") commercial reagents and solvents.

Scheme 1. Tridentate Ligands Inhibit β-Hydride Elimination

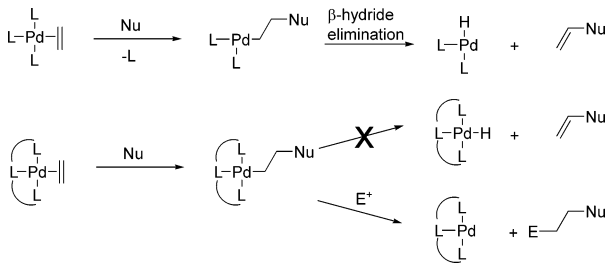
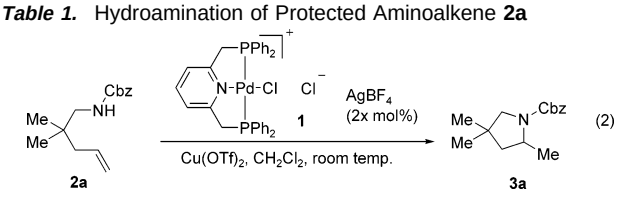


Table 1. Hydroamination of Protected Aminoalkene **2a**



(2)

entry	[Pd] (× mol %)	$Cu(OTf)_2$(mol %)	% yield (GC)
1	20	200	98
2	5	10	97
3	2.5	5	93
4	1	10	91
5	0.5	10	84

A variety of other ligands for palladium were assayed in the hydroamination of substrate **2a** (Chart 1). Interestingly, the original catalyst **1** was the only complex to catalyze the hydroamination reaction. Complexes of mono-, bi-, and even other tridentate ligands did not afford detectable amounts of product. It was especially surprising that the corresponding Pt complex **7** was also unreactive given the established reports of Pt-catalyzed hydroamination of unactivated alkenes.

Substrates bearing a variety of substituents on nitrogen were tolerated by catalyst **1** (Table 2). Amides and carbamates **2a**−**d** cyclize most readily. Despite the greater synthetic utility of the Cbz and Boc protecting groups, hydroaminations of carbamates are extremely rare.[7] It is particularly interesting that the acid-labile Boc protecting group survives these reaction conditions. Substrates bearing a tosyl substituent on nitrogen failed to cyclize. This selectivity is in contrast to that observed in the acid-catalyzed hydroamination reported by Hartwig, where only sulfonamides could be cyclized.[4a]

Other successful hydroamination reactions are depicted in Scheme 2. Formation of both five- and six-membered rings is facile, and the presence of *gem*-dimethyl substituents on the alkyl chain to promote ring closure is not required, as indicated by the cyclization of unsubstituted alkenes (eqs 4 and 5). Protected aniline **13b** was also a substrate for the hydroamination reaction, albeit in lower yield. The unprotected alcohol in **17a**,**b** did not effect the cyclization efficiency. Notably, all substrates in Scheme 2 contain functional groups that are unlikely to be compatible with lanthanide and group 4 hydroamination catalysts.

10.1021/ja060126h CCC: $33.50

Chart 1. Palladium Complexes that Do Not Catalyze Equation 2

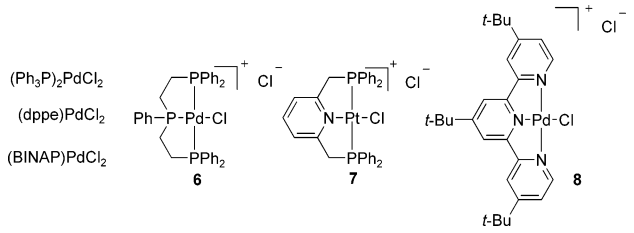
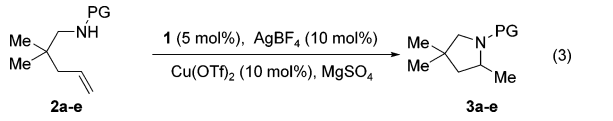
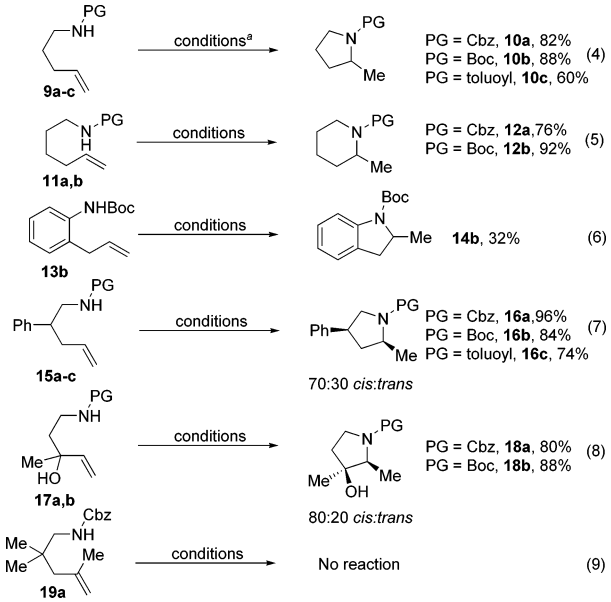


Table 2. Effect of Nitrogen Protecting Group on Hydroamination



PG	alkene	product	% yield (isolated)
Cbz	**2a**	**3a**	82
Boc	**2b**	**3b**	75
p-toluoyl	**2c**	**3c**	92
Ac	**2d**	**3d**	68
Ts	**2e**	**3e**	0

Scheme 2. Hydroaminations of Other Aminoalkenes[a]



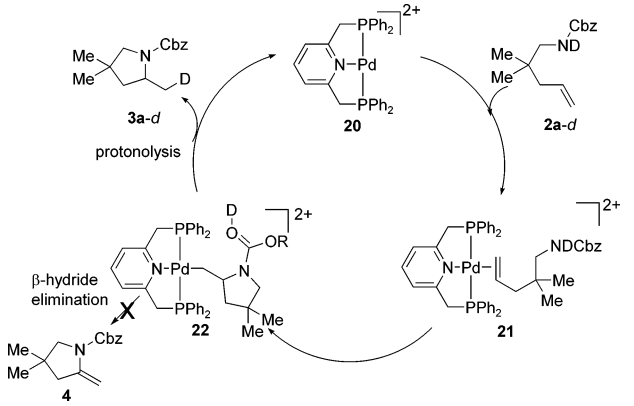
[a] Conditions: 5 mol % of **1**, 10 mol % of $AgBF_4$, 10 mol % of $Cu(OTf)_2$, $MgSO_4$.

Substrates bearing a stereogenic center in the tether gave moderate levels of diastereoselectivity. Under standard reaction conditions, phenyl-substituted substrates **15a**−**c** gave a 70:30 mixture of diastereomers, favoring the *cis* isomer.[8] Substrates **17a**,**b** were efficiently cyclized to give an 80:20 mixture favoring the *cis* diastereomer.

Recent reports have suggested that metal-catalyzed hydroamination reactions may be complicated by background reactions catalyzed by trace acids.[4,9] Several factors argue against such a pathway in this system. First, neither HOTf nor $HBF_4{\cdot}OEt_2$ catalyzes any appreciable reaction of substrate **2b** at room temperature. Second, 1,1-disubstituted alkene **19a**, which should be more active under acid-catalyzed conditions, does not cyclize at room temperature using catalyst **1**, presumably because it is prevented sterically from binding to the metal center.

The proposed reaction mechanism is illustrated in Scheme 3. Coordination of the alkene to the dicationic palladium complex activates the alkene toward nucleophilic attack by the amide or

Scheme 3. Proposed Mechanistic Cycle



carbamate to form alkylpalladium intermediate **22**. In the absence of the tridentate ligand, β-hydride elimination is facile, and the enamide product **4** is formed. With the tridentate ligand, β-hydride elimination is suppressed, and protonolysis of the Pd−C bond is favored. Consistent with this mechanism, the product of cyclization of deuterium-labeled substrate **2a**-*d* is deuterated exclusively at the terminal methyl group. Further investigations of the mechanism of this reaction are underway.

In conclusion, a mild and facile Pd-catalyzed intramolecular hydroamination of unactivated alkenes has been described. This reaction takes place at room temperature and is tolerant of synthetically useful acid-sensitive functional groups. The formation of hydroamination products rather than oxidative amination products is due to the use of a tridentate ligand on Pd which effectively inhibits β-hydride elimination.

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Supporting Information Available: Reaction conditions and experimental data for synthesis of all starting materials, catalysts, and cyclization products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) This compares favorably to the ratio observed in ref 2b (58:42).

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