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Formamide as a Superior Nitrogen Nucleophile in Palladium(II) Mediated Synthesis of Imidazolidines

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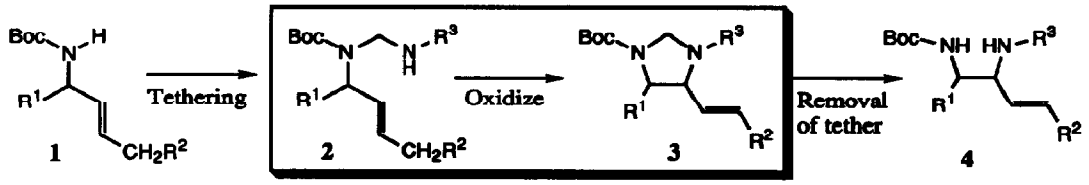
Abstract: Formamides emerge as superior nitrogen nucleophiles in palladium(II) catalyzed oxidative 5-*exo* cyclizations of formaldehyde aminals derived from *N*-Boc protected allylic amines. The product imidazolidines are readily transformed into protected vicinal diamines.

The successful concept of the "detachable connection" approach employing a tethered oxygen nucleophile in the synthesis of vicinal aminoalkenols from allylic amines using palladium(II) catalysis was recently demonstrated by us.[1] The key oxidative 5-*exo* cyclization of *N,O*-hemiacetals to oxazolidines ensured high regio- and stereoselectivities. With $Pd(OAc)_2$ as the catalyst, molecular oxygen was used as a clean stoichiometric oxidant without the need for a co-oxidant.[2] Dimethyl sulfoxide, used as the solvent, bears a unique character in this remarkable process by inducing the formation of "giant" palladium clusters which are most likely the catalytically active species.[3]

Our present efforts involve the application of similar methodology to the synthesis of vicinal diamines, as depicted in Scheme 1. In this communication we report several Pd(II) catalyzed oxidative cyclizations in which different tethered nitrogen nucleophiles are incorporated into imidazolidines **3**. As suitable precursors for these cyclizations aminals of type **2** were prepared from *N*-Boc protected allylic amines **1**,[4] formaldehyde and a protected nitrogen source. Their reactivities towards the oxidative cyclization conditions are reported. Furthermore, the convenient conversion of one imidazolidine into the corresponding diamine is described.



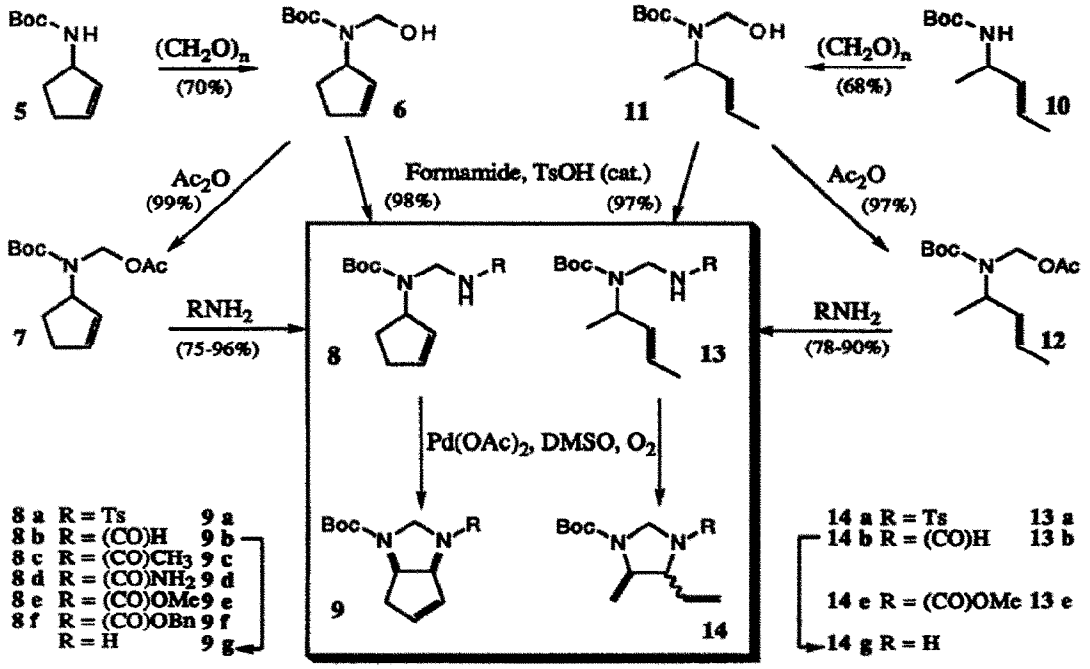
Scheme 1. "Detachable connection" approach to allylic diamines

Organometal-based techniques such as intramolecular aminopalladation,[5] amidopalladation and palladium mediated amidocarbonylation of monoolefins[6,7,8] dienes[9] and allenes[10] for the synthesis of five and six membered nitrogen containing heterocycles have been widely adopted. Acetamides and, especially, *p*-toluenesulfonamides were the first nitrogen nucleophiles reported to be successful in 5-*exo* cyclizations.[6] Since then, carbamates and urea derivatives have also been applied[7,8] and have often been found superior to p-

toluenesulfonamides but sometimes inferior.[7c] The optimum balance between nitrogen nucleophilicity and acidity apparently varies from case to case.

Two parent allylic carbamates were selected for testing different nitrogen nucleophiles. *N*-Boc-2-cyclopentenylamine **5** was chosen because its hemiacetals were found to be the most reactive[1,2,3] towards Pd(II) mediated 5-*exo* cyclization. More flexible aminals derived from the open chain *N*-Boc-3-pent-2-*(E)*-enylamine **10** were expected to be less reactive. In addition, steric induction by the methyl group could be observed in the formation of the corresponding imidazolidine **14**. These substrates would enable us to discriminate between the different nitrogen nucleophiles in terms of both reactivity and stereoselectivity.

Scheme 2 shows the preparation of the aminals.[11] Reaction of the parent carbamates **5** and **10** with paraformaldehyde and cesium carbonate[12] in dioxane (60 °C, 2 h) gave *N*-hydroxymethylcarbamates **6** and **11**, respectively, in good yields. These *N,O*-hemiacetals were stable at room temperature and were purified by flash chromatography (silica gel, ethyl acetate / hexanes). Treatment of **6** and **11** with a catalytic amount of *p*-toluenesulfonic acid in formamide directly gave formamide aminals **8b** and **13b**, respectively, *via* the *N*-acyliminium ions in excellent yields. Acetoxymethyl carbamates **7** and **12** obtained from the hemiacetals (Ac_2O, DMAP, pyridine, 0 °C) were similarly converted into aminals by reaction with acetamide (**8c**), methyl carbamate (**8e**, **13e**), benzyl carbamate (**8f**) or *p*-toluenesulfonamide (**8a**, **13a**) in dichloromethane (reflux, 20 h) in the presence of a catalytic amount of PPTS, or with urea (**8e**) in acetic acid (50 °C, 2 h).



Scheme 2. Preparation and Oxidative Cyclization of Aminals

The aminals **8** and **13** were converted to their corresponding imidazolidines **9** and **14** under standard oxidative cyclization conditions[2] using $Pd(OAc)_2$ (0.05 equiv) and one atmosphere of molecular oxygen. The

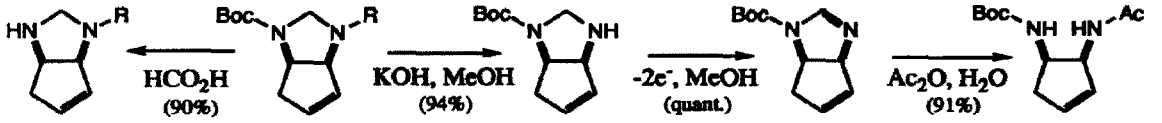
results of these reactions are summarized in Table 1. With the rigid cyclopentenyl derivatives urea (**8d**) surprisingly turned out to be the least reactive nucleophile. Acetamide (**8c**) and carbamates (**8e,f**) gave satisfactory results but were found to be less reactive than formamide (**8b**) and *p*-toluenesulfonamide (**8a**). With the more flexible pentenyl derivatives, however, formamide (**13b**) emerged as the most successful nucleophile. Stereoselectivities were found to be equally moderate with formamide and *p*-toluenesulfonamide (**13a**) and poor with methyl carbamate (**13e**). An additional advantage of the use of formamide as the nitrogen source is the facile mono deprotection of cyclization products **9b** and **14b** to the *N*-Boc imidazolidines **9g** and **14g**, respectively, by mild hydrolysis (KOH, MeOH, 94%).

Table 1. Results of the Oxidative Cyclizations of Aminals.

Aminal	mp (°C)[11]	Reaction Time (h)[a]	Yield (%)[b]	Imidazolidine	mp (°C)[11]	Isomer Ratio[c]
8 a	105-107	1	71	**9 a**	143-144	
8 b	67-69	2	86	**9 b**	-	
8 c	70-72	4	70	**9 c**	104-106	
8 d	119-120	4*	95 (68)	**9 d**	-	
8 e	62-63	4	83	**9 e**	-	
8 f	71-73	4	84	**9 f**	-	
				9 g	94-95	
13 a	76-78	4*	98 (66)	**14 a**	-	(35/65)
13 b	-	2	90	**14 b**	-	(35/65)
13 e	45-47	4*	98 (50)	**14 e**	-	(47/53)

[a] Conditions: 5% $Pd(OAc)_2$, O_2, DMSO (0.2 M), 65-70 °C. Times given refer to complete reactions unless marked with an asterisk. [b] Yields refer to isolated and purified (column chromatography) compounds. Recoveries of uncompleted reactions are followed between brackets by the conversion reached. [c] *Cis/trans;* stereochemistry was established by means of ^1H NMR NOE experiments.

The *N*-Boc imidazolidines **9e** and **9f** were also mono deprotected (Scheme 3) with the purpose of facilitating removal of the methylene tether. However, we were unable to convert imidazolidines **14g**, **17**, or **18** into the corresponding vicinal diamines by acid or base mediated hydrolysis. We therefore turned to electrochemistry once again[1] for removal of the tether. Anodic oxidation in methanol mediated by a catalytic amount of NaCl[13] surprisingly yielded amidine **15** quantitatively. Attempts to prepare the corresponding amidines from imidazolidines **17** and **18** in a similar way failed.



17 R = CO_2Me
18 R = CO_2Bn

9 (R = CHO) **14 g**

15 (mp 57-58 °C)

16 (mp 142-144 °C)

Scheme 3. Synthesis of mono protected imidazolidines and diamine

Conversion of amidine **15** to protected diamine **16** was finally achieved by reaction with acetic anhydride[14] in acetic acid/water (1:1).

In conclusion, we have demonstrated the advantages of formamide as a nitrogen nucleophile in palladium catalyzed synthesis of imidazolidines because of (1) its high reactivity and (2) the ease of its deprotection and thereby the feasibilty of stereocontrolled synthesis of vicinal diamines. This class of compounds have found widespread use as chiral ligands in asymmetric reactions[15,16] and chiral derivatizing reagents for determination of enantiomeric composition.[17] We are currently applying the methodology presented here to the synthesis of a wider variety of vicinal diamines.

Acknowledgement

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