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CHLORIDE EFFECT ON THE PALLADIUM-CATALYZED ALLYLIC SUBSTITUTION VS ELIMINATION OF CYCLIC VINYLOXAZOLIDINONES AND OXAZOLINES

Gregory R. Cook* and P. Sathya Shanker

Department of Chemistry, North Dakota State University, Fargo, ND 58105

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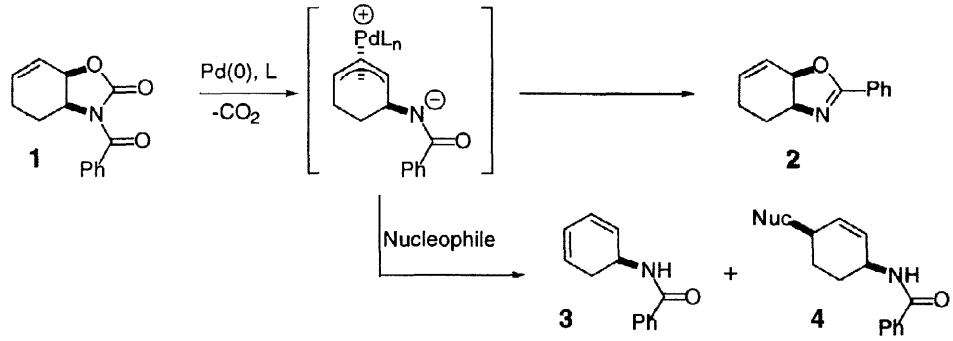
Abstract: The introduction of catalytic amounts of lithium chloride, or the utilization of chloride containing catalyst sources completely inhibited elimination in the Pd-catalyzed allylic substitution of vinyloxazolidinones and oxazolines. © 1998 Elsevier Science Ltd. All rights reserved.

The palladium-catalyzed allylic substitution reaction has become an important methodology for the selective introduction of a variety of functional groups.[1] A number of leaving groups, including allylic halides, acetates, carbonates, phosphates, and carbamates, are tolerated in this process. A prevalent difficulty in the substitution reaction is competing formation of 1,3-dienes by β-hydride or general base-promoted elimination of the π-allyl palladium intermediate.[2] It is known that additives can have a dramatic effect on the course of allylic substitution reactions.[3,4,5] To our knowledge, there is only one report of the influence of halides on the Pd-catalyzed elimination process.[6] We wish to report here our investigation of the allylic substitution of vinyloxazolidinones and oxazolines, and the dependence of chloride on the course of the reaction.

SCHEME



We have recently shown that 5-vinyloxazolidinones participate in palladium-catalyzed substitution reactions.[7] Thus, treatment of oxazolidinone **1** with a Pd(0) catalyst (scheme) afforded oxazoline **2** via oxidative insertion, decarboxylation, and intramolecular cyclization of the amide oxygen. We have studied the allylic substitution of **1** and **2** with external nucleophiles as well. Successful substitution was dependent upon the presence of chloride ion, as the competing elimination reaction predominated without it in the presence of basic amine nucleophiles. When oxazolidinone **1** was treated with catalytic $Pd_2dba_3CHCl_3$ and Ph_3P in the presence of benzylamine at ambient temperature, the oxazoline **2** and diene **3** were obtained in a 10:90 ratio, respectively (table 1, entry 1).[8] Interestingly, when diethyl malonate was used as the nucleophile (entry 2), **1** was completely converted to **2** with no formation of diene **3**, even when the fully deprotonated malonate salt was utilized at elevated temperatures (entry 3). Changing the ligand from monodentate triphenylphosphine to the bidentate bis(diphenylphosphino)propane (dppp) afforded the substitution product **4** with benzylamine, however, the major

fax: 701-231-8831, email: grcook@plains.nodak.edu

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product was still diene **3** (63:37). Acetonitrile, a more coordinating solvent, changed the product distribution to favor **4** (entry 5).

A dramatic effect was observed when π-allylpalladium chloride was employed as the catalyst. Only the substituted product **4** was produced in the reaction. Reasoning that the large change may have to do with the presence of chloride ion in solution, we repeated the reaction utilizing the dba catalyst with the addition of a catalytic amount of lithium chloride. As anticipated, diene **3** was not observed and **4** was produced (entry 7).

Table 1: Ligand effects in the allylic substitution of oxazolidinone **1**[a]

Entry	Ligand (mol%)	Nucleophile	Solvent	T (°C)	Ratio[g] 2 : 3 : 4
1	Ph_3P (20)	$BnNH_2$	CH_2Cl_2	25	10 : 90 : 0
2	Ph_3P (20)	$CH_2(CO_2Et)_2$	CH_2Cl_2	25	100 : 0 : 0
3	Ph_3P (20)	$NaCH(CO_2Et)_2$	THF	65	100 : 0 : 0
4	dppp (10)	$BnNH_2$	THF	60	0 : 63 : 37[b]
5	dppp (10)	$BnNH_2$	CH_3CN	60	0 : 32 : 68[c]
6[a]	dppp (10)	$BnNH_2$	THF	25	0 : 0 : 100[d]
7	dppp (10)-LiCl (36)	$BnNH_2$	THF	60	0 : 0 : 100[e]

[a]All reactions were run for 20 hrs with 2.5 mol% $Pd_2dba_3CHCl_3$ with the exception of entry 6 in which $[\pi\text{-}C_3H_5PdCl]_2$ (2.5 mol%) was utilized. [b]Combined yield 94%. [c]Combined yield 93%. [d]Isolated yield 86%. [e]The yield of **4** was low due to side reactions promoted by lithium coordination. The major products were the debenzoylated oxazolidinone and benzylbenzamide.

The addition of LiCl had a deleterious effect on the reaction with oxazolidinone **1**, however, as it promoted debenzoylation of **1** via acyl trasfer to benzylamine. Therefore, the chloride effect on the allylic substitution was investigated with oxazoline **2**, in which the benzoyl group was not labile. The results are summarized in table 2. Interestingly, in the presence of benzylamine, **2** did not react at room temperature (entry 1). This was in contrast to the room temperature reaction of the oxazolidinone **1**, and indicated that oxazolines are less easily ionized by Pd(0) catalysts. Heating the reaction at 60 °C for 6 hrs afforded both the diene and substituted products (ratio of **3**:**4**, 74:26). With 24 mol% LiCl added to the reaction, substitution proceeded slowly at room temperature (entry 4) to give a 80:20 ratio of **2**:**4** after 20 hrs. Heating the reaction at 60 degrees for 20 hrs gave **4** as the only product in 87% isolated yield. The diene **3** was not detected in any amounts when LiCl was present.

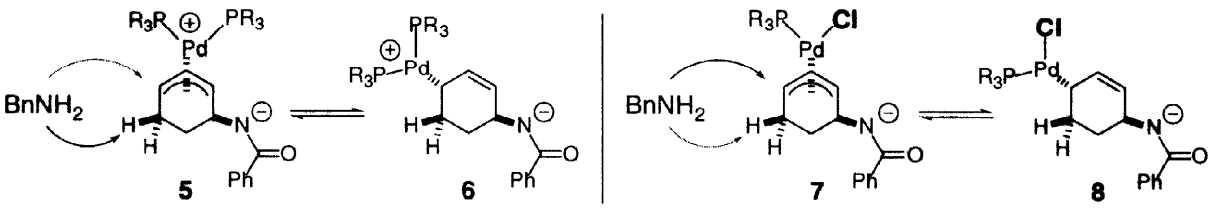
Table 2: Ligand effects in the allylic substitution of oxazoline **2**[a]

Entry	LiCl (mol%)	t (h)	T (°C)	Ratio[g] 2 : 3 : 4
1	none	20	25	100 : 0 : 0
2	none	6	60	0 : 74 : 26
3	24	20	25	80 : 0 : 20
4	24	6	60	38 : 0 : 62
5	24	20	60	0 : 0 : 100[b]

[a]All reactions were run with benzylamine as the nucleophile, 2.5 mol% $Pd_2dba_3CHCl_3$, and 10 mol% dppp in THF. [b]Isolated yield 87%.

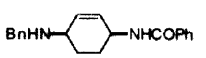
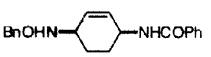
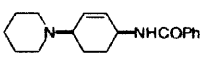
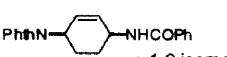
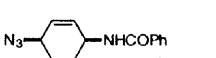
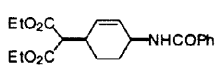
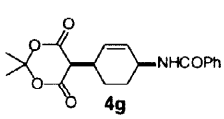
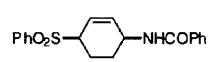
A mechanism which is consistent with our results may involve a base-promoted ($BnNH_2$) anti-elimination or a β-hydride elimination of the π- (**5**) or σ-allyl (**6**) intermediate.[9] The cationic nature of the Pd in the zwitterionic intermediates would increase the acidity of the adjacent hydrogens or increase the propensity for β-hydride elimination. In the presence of chloride ion,[6,10] the charge on the Pd is neutralized via displacement of a

phosphine ligand (**7** or **8**). This would result in a lowered acidity of the adjacent hydrogens permitting nucleophilic addition to compete favorably with elimination. The chloride coordination may also alter the π-σ equilibration of **7** and **8** to favor the π-complex **7** reducing β-hydride elimination via σ-complex **8**.



When the chloride containing catalyst was employed, allylic substitution of either **1** or **2** could be carried out with a variety of nucleophiles in high yield (table 3). Thus, benzylamine, *O*-benzylhydroxylamine, and piperidine nucleophiles afforded differentially protected diamine derivatives **4a-c** with complete stereo- and

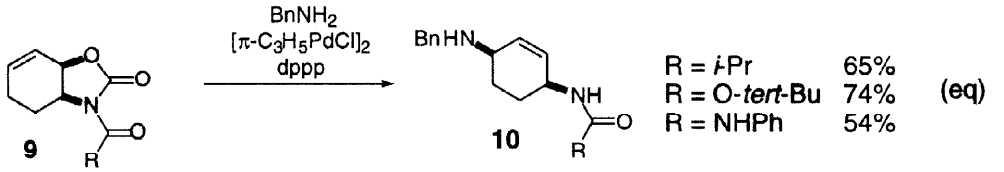
Table 3. Allylic substitution of **1** and **2**[a]

Entry	Substrate	Nucleophile (eq)	Solvent	t (h)	Product[g]	Yield[b]
1	**2**	$BnNH_2$ (3)	CH_3CN	5	 **4a**	99%
2	**1**	$BnNH_2$ (3)	CH_3CN	20	**4a**	86%
3	**2**	$BnONH_3Cl$ (2)[c] Et_3N (3)	CH_2Cl_2 - H_2O (2 : 1)	24	 **4b**	81%
4	**2**	piperidine (2)	CH_3CN	1.5	 **4c**	96%
5	**2**	phthalimide (1.2) potassium phthalimide (0.2)	THF	1	 **4d** + 1,2 isomer (1.9 : 1)	92%
6	**1**	phthalimide (1.2) potassium phthalimide (0.2)	THF	4	**4d** + 1,2 isomer (1.7 : 1)	91%
7	**2**	$TMSN_3$ (2)	CH_2Cl_2	20	 **4e** + 1,2 isomer (1 : 2.2)	*d*
8	**2**	$TMSN_3$ (2)	CH_2Cl_2	20	**4e** + 1,2 isomer (1 : 2.4)	95%[e]
9	**2**	$CH_2(CO_2Et)_2$ (2) NaH (0.5)	CH_3CN	1	 **4f**	80%
10	**2**	$NaCH(CO_2Et)_2$ (2)	THF	0.5	**4f**	83%
11	**2**	Meldrum's acid (1.5) NaH (0.2)	THF	20	 **4g**	72%
12	**1**	$PhSO_2Na$ (1.5) Bu_4NBr (0.1)	CH_2Cl_2 - H_2O (2 : 1)	4	 **4h**	97%

[a]All reactions were run with 2.5 mol% $[\pi\text{-}C_3H_5PdCl]_2$ and 10 mol% dppp at room temperature unless otherwise noted. [b]Isolated yields after column chromatography. [c]Reaction run at 40-45 °C. [d]Reaction only proceeded to 30% conversion. [e]*o*-Diphenylphosphinobenzamide (20 mol%) was used as the ligand.

regioselectivity. The use of phthalimide and azide led to mixtures of 1,2- and 1,4-regioisomers, but in excellent yields. Carbon and sulfur nucleophiles also performed well in the substitution reaction.

The *N*-benzoyl group was not necessary for successful allylic substitution. Although *N*-alkyl substituted oxazolidinones would not react under the Pd(0)-catalyzed conditions, a variety of *N*-acyl substrates could be aminated with benzylamine (eq). Isobutyroyl, *tert*-butylcarbonate, and carbamido substituents all reacted to give the substituted product in good yield.



In conclusion, we have shown that cyclic vinyloxazolidinone and oxazoline substrates participated in the palladium-catalyzed allylic substitution with a variety of nucleophiles. The reaction was sensitive to variations in the ligand. Bisphosphine ligands were required for successful substitution, and the presence of chloride inhibited competing elimination reactions.

Acknowledgments: We thank NSF (OSR 9452892) and North Dakota State University for support.

References and Notes

1. For recent reviews, see: (a) Hegedus, L. in *Organometallics in Synthesis*; Schlösser, M., Ed.; J. Wiley: New York, **1994**; pp 385-459. (b) *Palladium Reagents and Catalysis*; Tsuji, J.; Ed.; Wiley: New York, **1995**. (c) Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (d) Guibé, F. *Tetrahedron* **1998**, *54*, 2967.
2. (a) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, 2075. (b) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, 2301.
3. For a recent report of iodide influencing the regioselectivity in a Pd-catalyzed allylic alkylation, see: Kawatsura, M.; Uozumi, Y.; Hayashi, T. *Chem. Comm.* **1998**, 217.
4. The addition of LiCl to π-allyl palladium intermediates has been known to alter the stereochemistry of acetate addition via displacement of acetate from the Pd. (a) Bäckvall, S. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 4959. (b) Bäckvall, J. E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619.
5. An anion effect on enantioselectivity in the Pd-catalyzed allylic amination has been reported. Burckhardt, U.; Maumann, M.; Togni, A. *Tetrahedron Asymm.* **1997**, *8*, 155.
6. It has been reported that allylic chlorides would not undergo Pd-catalyzed elimination where the analogous allylic acetates would. Addition of TMSCl and Bu_4NCl also inhibited elimination reactions. Keinan, E.; Roth, Z. *Israel J. Chem.* **1990**, *30*, 305.
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8. All compounds were fully characterized by ^1H, ^{13}C, and IR spectroscopy. Product ratios were determined by ^1H NMR (400 MHz).
9. For mechanistic evidence of the general base-promoted elimination of π-allyl palladium intermediates, see: (a) Andersson, P. G.; Schab, S. *Organometallics* **1995**, *14*, 1. (b) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **1997**, *119*, 5956.
10. In Tsuji's original report of the Pd-catalyzed elimination of allylic acetates and phenyl ethers, it is noted that $PdCl_2(Ph_3P)_2$ was not an active catalyst, while $Pd(OAc)_2$ was. See ref 2a.