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# Palladium(II)-Catalyzed Enantio- and Diastereoselective Synthesis of Pyrrolidine Derivatives

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## **Abstract**

A palladium-catalyzed enantio- and diastereoselective synthesis of pyrrolidine derivatives is described. Initial intramolecular nucleopalladation of the tethered protected amine forms the pyrrolidine moiety and a quinone methide intermediate. A second nucleophile adds intermolecularly to afford diverse products in high enantio- and diastereoselectivity.

The strategic generation and interception of Pd(II)-alkyl species is an attractive approach for the development of alkene difunctionalization reactions.  $^1$  A major challenge in this pursuit is to suppress  $\pi$ -hydride elimination of the Pd(II)-alkyl species, which would result in Heck  $^2$  or Wacker-type products  $^3$ . To avoid  $\pi$ -hydride elimination, Pd(II)-alkyl intermediates derived from initial addition of a nucleophile may be stabilized via  $\pi$ -allyl and  $\pi$ -benzyl formation, or the Pd(II)-alkyl may be further oxidized prior to functionalization.  $^6$ 

In addition to these strategies, our group has accomplished alkene difunctionalization reactions of a specific alkene class, namely *ortho*-vinyl phenols (e.g., 1, Scheme 1), wherein the Pd(II)-alkyl intermediate derived from nucleopalladation of  $\bf A$  is proposed to undergo a redox reaction, forming Pd(0) and an *ortho*-quinone methide intermediate ( $\bf B \rightarrow \bf C$ ). This intermediate can be trapped by various exogenous nucleophiles. Our group has developed highly diastereoselective and enantioselective variants of this reaction using a pendant alcohol nucleophile to form an oxygen-containing heterocycle. Pe, A broad scope of exogenous alcohol- and indole-based nucleophiles may be added to the quinone methide. Of particular importance, certain products accessible using this route, particularly those featuring an indole, have been identified to have not only differential activity toward breast cancer cell lines but also unique cellular targets based on initial biological investigations (Figure 1). Therefore, we became interested in expanding this reaction manifold to nitrogen-based intramolecular nucleophiles, a substrate class that had previously performed poorly. A successful variant employing a tethered amine as the intramolecular 8 nucleophile would allow facile access to pyrrolidines 10 9 and catalysis which are privileged structures

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in biology Phenol bearing pyrrolidines are also important analogs in ongoing biological investigations in our labs. Herein, we report the successful identification of a suitable intramolecular nitrogen nucleophile that expands the substrate scope to enable the enantioselective construction of complex pyrrolidine small molecules bearing a diverse array of heterocycles.

In our early attempts to form pyrrolidine derivatives with nitrogen-based intramolecular nucleophiles, tosyl carbamate 2 (Figure 1) was prepared and submitted to our previous reaction conditions, but unfortunately, no desired product formation was observed. In contrast, methyl carbamate-protected substrate 3 did afford the desired product 4, albeit in low yield and moderate enantioselectivity. The realtively low observed enantioselectivity may be the result of the Lewis basic carbamate displacing the chiral quinox ligand during the reaction. Therefore, lowering the Lewis basicity and simultaneously the  $pK_a$  of the nucleophile was thought to be a prudent approach to faciliating this reaction. As such, tosylamide 5a was prepared and, after exporsure to the optimal conditions, the desired product 6a was observed in modest yield (43%) and high enantioselectivity, albiet in low diastereoselectivity.

Considering our standing interest in the products derived from indole additions to the generated quinone methindes and the improved diastereoselectivity typically observed when using these nucleophiles, we evaluated N-methyl indole with substrate  $\mathbf{5a}$  (Table 1).  $^{7g}$ Initially, we found considerable variation in reaction yield. A possible origin for this result is the stereoisomeric purity of 5a, which was found to be dependent on how long the Wittig reaction used to prepare 5a was allowed to stir (see supporting information). To probe this hypothesis, a sample of 5a with >95 % E geometry was submitted to the reaction. A low yield of 7a was observed with excellent enantio- and diasteroselectivity. However, significant remaining starting material was isolated. In contrast, an evaluation of ~80% Zsample of 5a resulted in significantly improved yields and the same high levels of selectivity (entry 2). Of particular importance, only the E-isomer of 5a (25%) was isolated (entry2, the starting material only contained 20%), indicating that the Z-isomer isomerizes to the thermodynamically more stable E-isomer under the reaction conditions. Additionally, the results suggest that the E-isomer reacts faster than the Z-isomer, which is consistent with previous mechanistic studies on this reaction type in that the Z-alkene is proposed to undergo trans-nucleopalladation to achieve the observed stereochemical outcome as depicted in Scheme 1.7f Therefore, modest heating of the reaction to faciliate alkene isomerization modestly improved the yield when using the enriched E-alkene (37%, entry 3) as compared to the use of room temperature (entry 1). Under these conditions, the use of the predominantly Z-alkene resulted in synthetically useful yields of the desired product with only a slight reduction in enantioselectivity (entry 4). Of note, poor mass balance is believed to arise from oligomerization of the proposed quinone methide intermediate.

Under these conditions, the substrate scope for this reaction was explored. Several *N*-protected indoles underwent the reaction to yield the desired products in high enantioselectivity and diastereoselectivity (**7a-7g**). Modest changes to the electronic nature of the phenol did not affect the reaction outcome (**7g**). However, highly electron rich phenols (X = OMe) do not undergo the reaction due to rapid decomposition (not depicted). In addition to indoles, substituted furans (**7h**, **7i**) and indolizines (**7j-7o**) are highly effective reaction partners; these reactants have not been evaluated previously in this reaction class and lead to new pharmacophores in the products. <sup>11</sup> Although an excess (15 equiv) of the external nucleophile is required, it can be effectively recovered after the reaction.

To further explore the scope of the intramolecular nucleophile, substrate  $\bf 8$  with a pendant carboxylic acid was prepared and evaluated. An excellent yield of the desired lactone

product was observed (Figure 2A). Surprisingly, the product of this reaction is racemic, albeit isolated as a single diastereomer. One mechanistic hypothesis to account for this observation is a reversible nucleopalladation step, as a carboxylate is a better leaving group than an alkoxide, which could lead to an erosion of enantioselectivity (Figure 2B). Alternatively, the significant change in nucleophile  $pK_a$  may lead to a change in mechanism (Figure 2C). The nucleopalladation step of this reaction has been proposed to proceed through a *trans*-nucleopalladation of the bidentate Z-alkene and phenol to account for the stereoinduction (Scheme 1). However, the nature of the nucleophile has been reported to strongly influence the stereochemical course of nucleopalladation. In this case, an alkene-Pd-carboxylate complex likely forms preferentially due to the higher acidity of the acid (as compare to the realtively high  $pK_a$ 's of both alcohol and sulfonamide nucleophiles) resulting in *cis*-nucleopalladation (Figure 2C, II). To acount for the loss of enantioselectivity, either the chiral ligand is displaced due to the presumed change in mechanism or the enantioselectivity is lost if the phenol is not engaged in this key step.

In conclusion, we have expanded the scope of enantioselective alkene difunctionalization reactions to include amine nucleophiles through modest, but mechanistically guided, changes to the reaction conditions. The diverse products incorporate vetted pharmacophores in unique structures. Current efforts are focused on exploring the biological properties of these compounds and will be reported in due course.

## **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

## **Acknowledgments**

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**Figure 1.** Substrate Optimization. Reaction conditions: a) 4 mol %  $Pd(CH_3CN)_2Cl_2$ , 8 mol % CuCl, 14 mol % Pquinox, 40 mol % Pquinox, 50 equiv MeOH, Pquinox, 40 mol % Pquinox, 50 equiv MeOH, Pquinox, 41, 24 h.

**Figure 2.** Evaluation of lactone formation.

#### Scheme 1.

Proposed mechanism for Pd(II)-catalyzed alkene difunctionalization via a putative quinone methide intermediate

Table 1

Conditions optimization

2	₹-	\ \_	ZNST Z	73	•
4 mol % Pd(CH <sub>3</sub> CN) <sub>2</sub> Cl <sub>2</sub>	14 mol % 'Prquinox	1 equiv KHCO <sub>3</sub>	15 equiv NuH	O <sub>2</sub> balloon, rt	toluene:THF (4:1), 24 h
		NHTS	$\neg$		
	-등			,	3

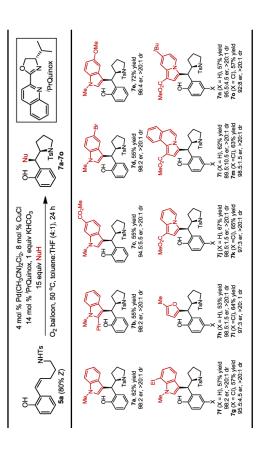
entry	entry temp	5a	% yield (7a)	remaining 5a	er (dr)
1	ц	>95% E	15%	50%, only $E$	>99:1 (>20:1)
2	Ħ	Z %08<	45%	25%, only $E$	>99:1 (>20:1)
3	20 °C	>95% E	37%	none	98:2 (>20:1)
4	20 °C	Z %08<	62%	none	98:2 (>20:1)

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Table 2

Substrate scope<sup>a</sup>



 $^{a}$ All reactions were carried out on 0.50 mmol scale. Yields refer to the average of at least two reactions.

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