

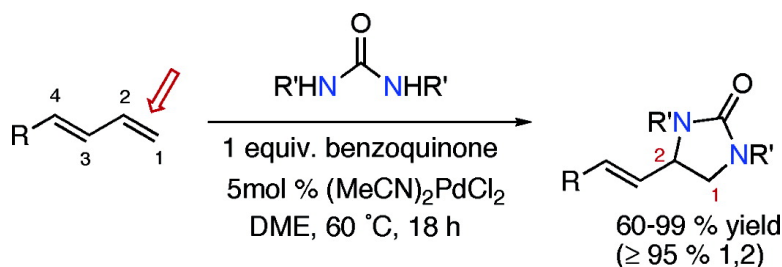
Communication

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Pd(II)-Catalyzed Intermolecular 1,2-Diamination of Conjugated Dienes

Grégory L. J. Bar, Guy C. Lloyd-Jones,* and Kevin I. Booker-Milburn*

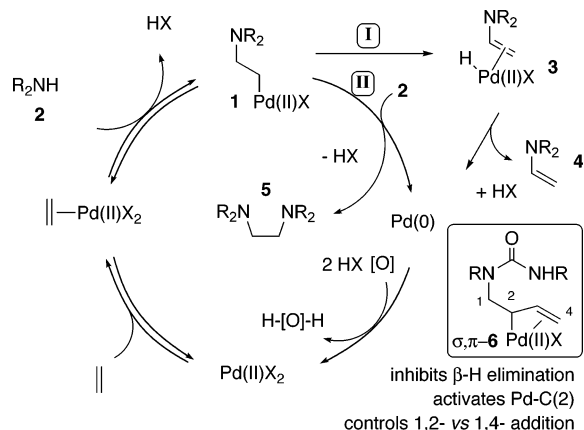
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Considering the extensive utility of 1,2-diamines,¹ for example, as synthetic intermediates, pharmacophores, and scaffolds for chiral ligand design, there are surprisingly few methods for their *direct* generation from alkenes.² Moreover, although transition metal-catalyzed alkene hydroamination and oxidative dehydroamination³ have been extensively developed in recent years, to the best of our knowledge, transition metal-catalyzed alkene 1,2-diamination is unprecedented.⁴ Herein, we report the first Pd-catalyzed intermolecular 1,2-diamination of dienes, proceeding regioselectively and in good to excellent yields based on all components: the diene, the oxidant, and the diamine source.

Our process arose from the concept that σ -alkylpalladium complexes of type **1**, known to be reversibly generated by Pd(II)-catalyzed addition of amines (**2**, Scheme 1) to alkenes,^{3d,5} could

Scheme 1. Schematic Pd(II)-Catalyzed Alkene 1,2-Diamination (pathway II) and Competing Dehydroamination (pathway I)



partition via two pathways: (i) β -hydride elimination to generate hydrido-Pd(II)- π -alkene complex **3** and thus **4** (pathway-I); or (ii) reductive displacement of Pd(II) by a second amine source **2** to yield 1,2-diaminoalkane **5** (pathway-II). Both pathways **I** and **II** formally lead to Pd(0) + 2 H⁺, and a stoichiometric oxidant [O] is thus required to facilitate turnover.

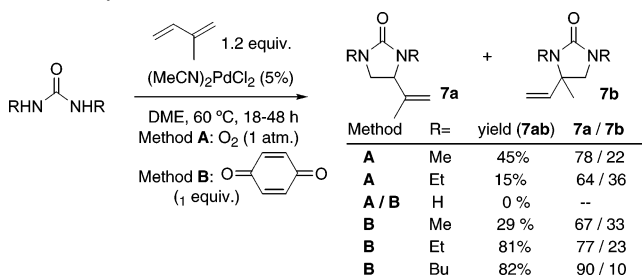
Pathway **II**, viewed as a diverted Wacker-type process, is preceded in the seminal work of Bäckvall on the stoichiometric Pd-mediated 1,2-diamination of alkenes.⁴ It is of note that in the stoichiometric process, oxidation of the intermediate analogous to **1** is required to effect the nucleophilic cleavage of the Pd-C bond. Three major issues present themselves when considering a catalytic route to **5**. First, the amine source (**2**) may coordinate efficiently to Pd(II), sequester HX, or react with [O], all of which may inhibit turnover. Second, in nongeometrically restricted σ -alkylpalladium species **1**,⁶ the process of β -hydride elimination (pathway **I**) is normally rapid, albeit reversible, and is expected to compete very effectively against pathway **II**. Indeed, Stahl has recently reported analogous, high yielding routes to products of type **4**.⁷ Third, the

issue of electrophilic activation of the Pd-C bond in **1** to initiate a second intermolecular nucleophilic attack of amine **2** must be addressed.

Our strategy for facilitating pathway **II**, involves (i) the use of an amide for which the proton affinity, oxidation potential, and propensity for Pd(II) ligation are all substantially attenuated as compared to the parent amine; (ii) the use of 1,3-diene substrates to generate electrophilic π -allyl palladium intermediates, which undergo much less facile β -hydride elimination; and (iii) *tethering* the amide sources, in the form of *N,N'*-substituted ureas, to make pathway **II** intramolecular *and* to control 1,2- versus 1,4-selectivity⁸ (see **6** in inset to Scheme 1).

We began by reacting isoprene with a range of ureas using classic Wacker-type conditions (O₂/cat Cu(I,II)) to regenerate the Pd(II). Although traces of regioisomeric diene-urea adducts **7a/7b** were observed, it became evident that turnover was being inhibited, possibly by complexation of the ureas to Cu(II), thereby inhibiting Pd-Cu redox. Surprisingly, reactions *without* the Cu co-catalyst afforded isolable quantities of the diene-urea adducts **7a/b** (method **A**, Scheme 2). Despite these encouraging results, a major problem

Scheme 2. Pd(II)-Catalyzed 1,2-Diamination of Isoprene with *N,N'*-Dialkyl Ureas



arose from extensive generation of aldehyde side products from both the isoprene and **7a/b**. Switching from O₂ to benzoquinone as reoxidant avoids the generation of water and affords 1,2-adducts **7a/b** in up to 82% yield, using only 1 equiv of oxidant and 1.2 equiv of isoprene (method **B**, Scheme 2). Under these conditions, the 1,2-adducts were generated very cleanly, with good regioselectivity for **7b** (up to 90%), provided that soluble and nucleophilic *N,N'*-dialkyl ureas were employed.⁹

Choosing *N,N'*-diethyl urea, we explored a range of other 1,3-dienes (Table 1). Benzoquinone as oxidant (method **B**) proved to be far superior to O₂ (method **A**), the latter always giving Wacker-type side reaction from the water co-product, even in the presence of molecular sieves. Overall, the palladium-catalyzed 1,2-diamination process works well for aliphatic and aryl-substituted dienes. In most cases, good to excellent yields were obtained, with >95% regioselectivity for diamination at the least-substituted alkene terminus of the diene. Reactions where one of the alkenes is trisubstituted leads to low rates and yields (entries 2, 9, and 10),

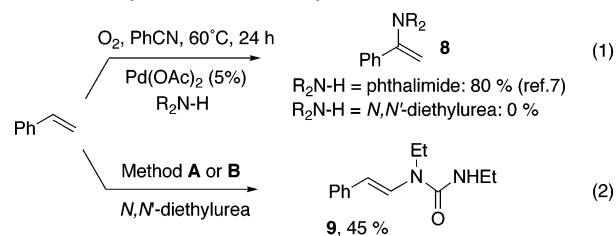
Table 1. Pd(II)-Catalyzed Intermolecular 1,2-Diamination of Dienes (1.2 equiv) Using *N,N'*-Diethyl Urea

entry	diene	product	method ^a	yield(%)
1			R = H (7b)	A 15 B 81 ^b
			R = Me	A 0 ^c B 43 ^{d,e}
3			A 0 ^c B 82 ^f	
4			R = Et	A 17 B 60 ^f
			R = Ph	A 78 B 99 ^f
6			R = C ₆ H ₄ OMe- <i>p</i>	A 45 B 80 ^f
			R = C ₆ H ₄ CF ₃ - <i>p</i>	A 75 B 99 ^f
8			R = 2-naphthyl	A 45 B 73 ^f
9			R = Me, R' = Ph	A 0 ^c B 30 ^d
			R, R' = Ph	A 20 B 6 ^{f,g}
11			n = 0	A 0 ^c B 36 ^h
			n = 1	A 0 ^c B 68 ^d

^a Reaction in DME, 60 °C, 18 h with Pd(MeCN)₂Cl₂ (5 mol %); method A: O₂ (1 atm); method B: benzoquinone (1 equiv). ^b Regioselectivity 77–90%. ^c No product isolated from intractable mixture. ^d For 48 h. ^e Regioselectivity >95%; product: 93% *Z*-isomer. ^f *E/Z* selectivity and/or regioselectivity >95% (¹H NMR). ^g After 2 weeks: 10%. ^h Benzoquinone in DME added over 5 h.

emphasizing the importance of the η³-allyl intermediate (i.e., σ,π-6 or its π-allyl isomer).

For successful reaction, a chloride-bearing Pd(II) precatalyst,¹⁰ a weakly coordinating solvent, a diene, and an alkyl urea are all, currently, essential. It is pertinent to compare this with the oxidative dehydroamination conditions recently reported by Stahl (6 equiv of alkene, cat. Pd(OAc)₂, PhCN, O₂, 60 °C) where, for example, styrene gives the 1,1-isomer **8**, R₂NH = phthalimide (eq 1, Scheme 3).⁷ When R₂NH = *N,N'*-diethyl urea, we obtain no trace of diamination or dehydroamination products (eq 1, Scheme 3). Replacing Pd(OAc)₂ with PdCl₂(MeCN)₂ affords the “conventional” 1,2-regioisomer **9** (no **8** detected) in low yield (ca 23%), which improves to 45% using method A or B. These results are strongly suggestive of differing mechanisms. With the more acidic phthalimide in the presence of a weak base (e.g., acetate or Et₃N), it has

Scheme 3. Contrasting Regioselectivities in the Pd(II)-Catalyzed Oxidative Dehydroamination of Styrene

been shown for norbornene that N–H insertion is followed by syn aminopalladation.⁷ With the more nucleophilic urea and a chloropalladium species, π-alkene or π-diene complexation is followed by anti aminopalladation. This conclusion is supported by the reaction of cyclic dienes (Table 1, entries 11 and 12) where only anti aminopalladation would facilitate the subsequent nucleophilic attack (anti)⁸ on the resulting Pd–π-allyl complex.

In summary, we report a novel method for intermolecular alkene 1,2-diamination, based on Pd(II)-catalyzed addition of ureas to dienes.¹¹ The reaction is notable for the range of dienes tolerated, the mild conditions (60 °C, DME, 5 mol % Pd), and practicality; a large excess of diene is not required. Good yields are obtained based on all three reactants.¹²

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Supporting Information Available: Full experimental details and product characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) Urea itself is of insufficient solubility in DME. Diphenyl urea was not reactive. Dibenzylic urea underwent decomposition by benzylic oxidation.
- (10) Of the following precatalysts, Pd(OAc)₂, Pd(TFA)₂, Pd₂(dba)₃, CHCl₃, Pd(MeCN)₂X₂ (X = Cl, Br, I), and Pd(NH₄)₂Cl₄, only Pd(MeCN)₂Cl₂ gave useful levels of activity with little or no side products.
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- (12) Present work is concerned with elucidation of the mechanism, the development of conditions that will allow the diamination of simple alkenes, and the use of more flexible non-urea diamine sources, with the ultimate goal of developing a general asymmetric catalytic process.

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