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Distinct Reactivity of Pd(OTs)₂: The Intermolecular Pd(II)-Catalyzed 1,2-Carboamination of Dienes

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As a consequence of the key roles of 1,2-diamines¹ and 1,2-amino-alcohols² as pharmacophores and as ligands for catalysis, new routes for their synthesis are important goals. In this context, there has been much recent activity in the area of metal-catalyzed 1,2-difunctionalization of alkenes. In particular, a number of groups have reported synthetically useful 1,2-diamination protocols using a variety of diamine sources under Cu or Pd catalysis.^{3,4} Our prior contribution to this area involved a Pd(II)-catalyzed 1,2-diamination of dienes with *N,N'*-dialkyl ureas, using either benzoquinone (BQ) or molecular oxygen as reoxidant.⁵ Herein we report an efficient Pd(II)-catalyzed 1,2-carboamination of dienes that proceeds under mild conditions and facilitates the synthesis of indolines from *N*-aryl ureas, via aryl C–H activation.⁶ We demonstrate that (MeCN)₂Pd(OTs)₂ offers distinct reactivity, as compared to the ubiquitous Pd(OAc)₂, and that the presence of a urea moiety, rather than a simple amide, is pivotal in attaining efficient C–H insertion.

During an ongoing study to extend our earlier work on (MeCN)₂PdCl₂-catalyzed diamination⁵ we observed the low-yielding (ca. 10%) formation of indoline **2**, from α -methylstyrene and *N*-ethyl-*N'*-phenyl urea (**1**), Scheme 1. Attempts to optimize this reaction failed and the *N,N*-dimethyl-*N'*-phenyl urea **3a** gave none of the corresponding indoline whatsoever. Generation of the indoline **2** can be envisaged to proceed via an *interrupted* Heck-type process that evolves from a urea-directed ortho C–H insertion by Pd(II) (\rightarrow **4**). The latter step is analogous to the first part of the ortho-vinylation of acetanilides with acrylate esters reported by de Vries and van Leeuwen,⁸ which requires rather acidic solvent conditions (66% AcOH) as well as TsOH (50 mol%) as an additive.

To exploit the stability and electrophilicity of an η^3 -allyl Pd(II) intermediate (cf. **5**) we switched from α -methylstyrene to the electron deficient diene **6a**. Applying the de Vries-van Leeuwen conditions,⁸ (A, Scheme 2) afforded indoline **7a** in 37% yield from **3a**. In view of the possible sensitivity of the urea and diene to the acidic reaction medium, we explored a variety of conditions, with the aim of eliminating acid altogether. Significantly, in the absence of TsOH (with or without AcOH) there was no reaction, while the AcOH could be eliminated without any significant effect on yield (~35%). Eventually it became apparent that water was detrimental to the reaction and by employing molecular sieves with THF as solvent, **7a** was obtained in 80% yield after 4 h at 50 °C (B, Scheme 2). As a further refinement, use of Ac₂O

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

(1 equiv) as a drying agent⁹ consistently afforded high yields of **7a** (82%, C, Scheme 2). It is important to note that the reaction is tolerant of a range of solvents, including anisole, DCE, 1,4-dioxane, EtOAc, PhMe, *t*BuOMe, and *t*BuOH (78.5% average yield for **3a**→**7a**).

The reaction of the parent aryl urea **3a** under conditions C was successfully applied to a variety of electron-deficient dienes (Table 1, entries 1–6). Substitution of the *N*-phenyl ring (entries 7–13) proved informative. Electron donating groups in the meta and para position of the aryl ring led to single regioisomers of the corresponding indoline rings in moderate to excellent yields. In contrast, CF₃ substitution in the meta position inhibited the reaction completely, while substitution in the para position reduced both the rate and the yield, indicative of strong electronic deactivation of the ortho C–H position.

Perhaps the most surprising observation, in addition to the lack of oxidation, or double-bond migration, of **7a–n** to form indoles, was that *o*-methyl substitution inhibited the reaction completely (entry 13). It is possible that in this position the methyl substituent prevents the urea moiety from adopting a conformation suitable for Pd-complexation and/or ortho C–H insertion. Substitution of the nonaryl nitrogen also proved possible (entries 14 and 15) and in the case of *N*-ethyl-*N'*-phenyl urea **3i** further in situ cyclization of the initial indoline effected a one-pot carbodiamination sequence to yield **7n** as a single diastereoisomer (entry 15). The activating effect of the urea moiety is highlighted by the poor yield of indoline product **8** obtained from acetanilide (entry 16), even after prolonged reaction times (24 h).

The requirement for TsOH in the reaction medium suggested the in situ formation of a reactive palladium mono- or bistosylate species from the Pd(OAc)₂ precatalyst. Indeed, reaction of **3b** with **6a** catalyzed by (MeCN)₂Pd(OTs)₂¹⁰ (10%) in the *absence* of added TsOH yielded **7g** in 85% yield (Scheme 3). Even in the absence of Ac₂O, this precatalyst system afforded **7g** (65%) and was essentially unaffected by the addition of AcOH, indicative that Ac₂O acts solely as drying agent rather than a source of AcOH. Accordingly, addition of 3 Å MS (dried) instead, gave **7g** in 72% yield (Scheme 3).

In summary, we have developed a new Pd(II)-catalyzed diene 1,2-carboamination reaction, involving an ortho C–H insertion/carbopalladation/cyclization sequence. It enables the high-yielding generation of functionalized indolines from readily available *N*-aryl ureas, in a single operation.

A key observation is that the reaction involves in situ generation of a reactive palladium tosylate species from the Pd(OAc)₂ precatalyst. These results clearly demonstrate that, in contrast to previous reports,¹¹ highly electrophilic Pd(II) species, capable of aryl C–H activation, can be generated under mild reaction conditions (relatively nonacidic media, 50 °C, 2–4 h, Scheme 3).

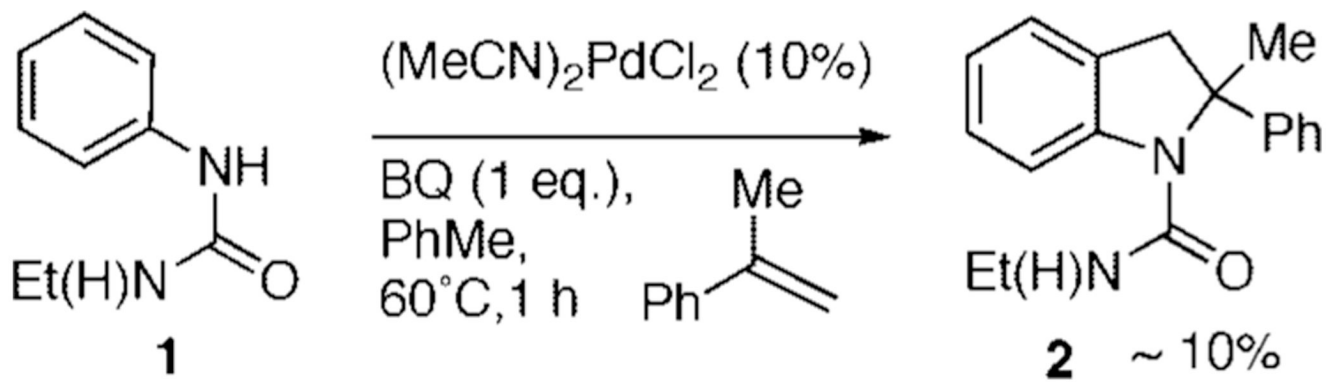
Acknowledgment

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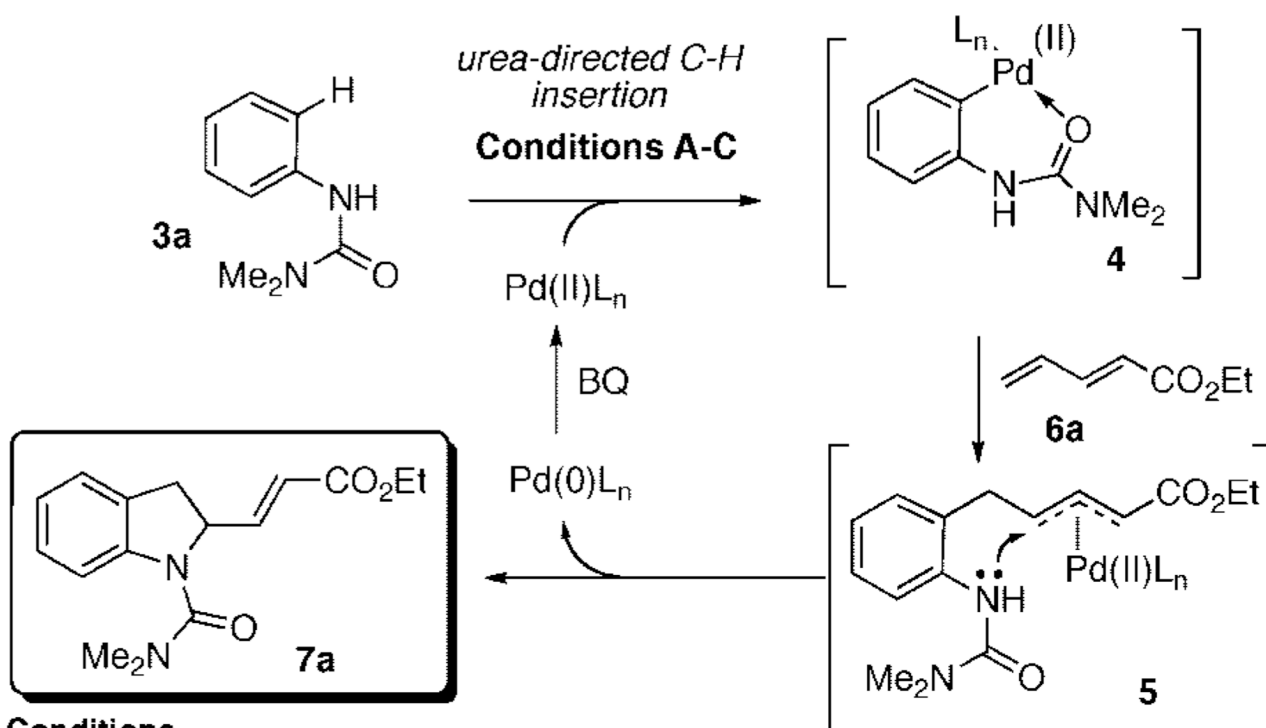
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Scheme 1.
Formation of **2** via *o*-C-H Insertion/Interrupted Heck

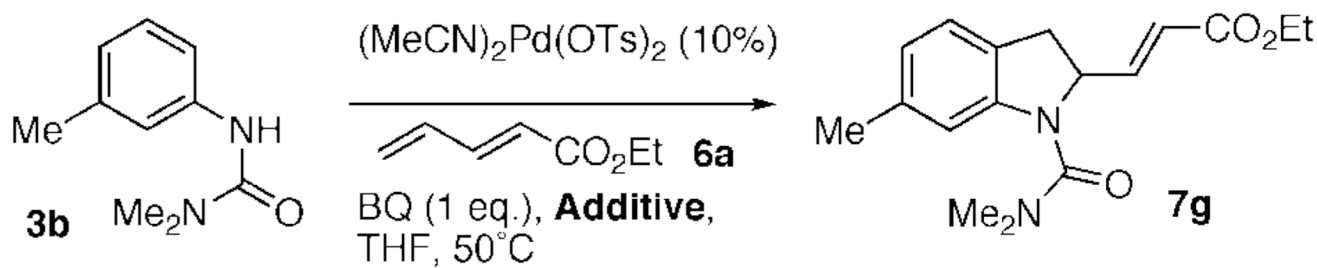
**Conditions**

A: Pd(OAc)₂ (10%), BQ (1 eq.), TsOH·H₂O (0.5 eq.), AcOH/PhMe (2:1 v/v), 50°C; 24 h; 37%

B: Pd(OAc)₂ (10%), BQ (1 eq.), TsOH·H₂O (0.5 eq.), 3Å mol. sieves, THF, 50°C; 4 h; 80%

C: Pd(OAc)₂ (10%), BQ (1 eq.), TsOH·H₂O (0.5 eq.), Ac₂O (1 eq.), THF, 50°C; 4 h; 82%


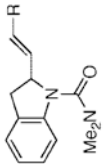
Scheme 2.
Pd(II) Carboamination of Dienes with Aryl Ureas



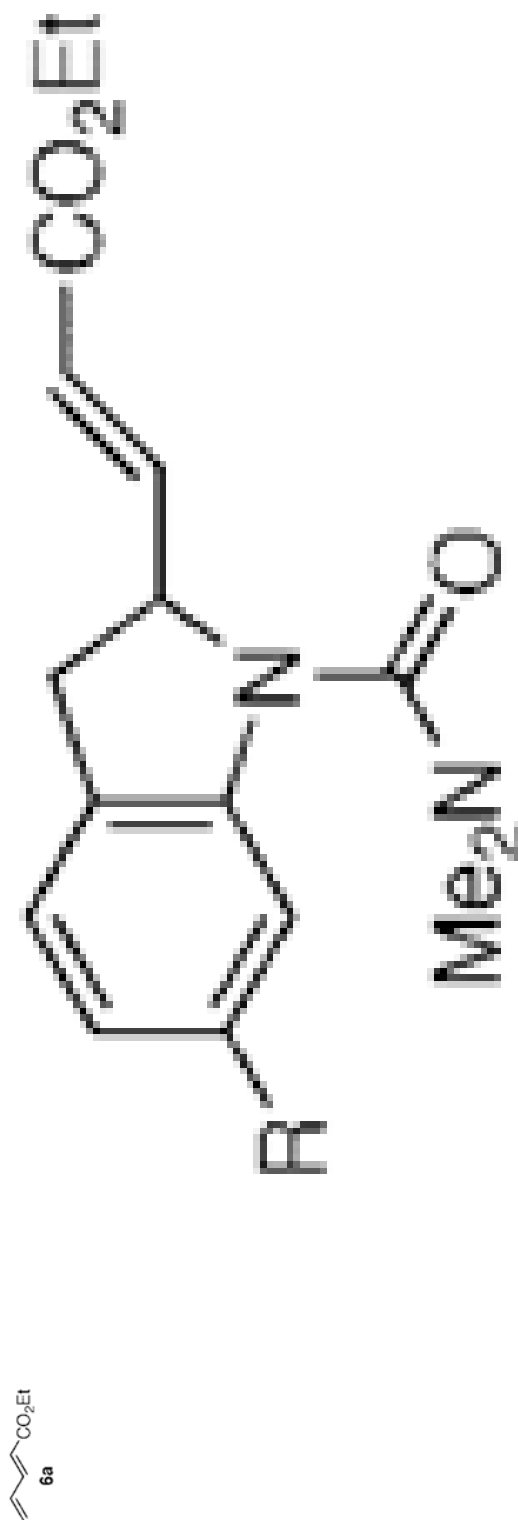
Additive: Ac_2O (1 eq.) 85%; 3Å MS 72%; AcOH (1 eq.) 66%; no additive 62%

Scheme 3.
Use of $(\text{MeCN})_2\text{Pd}(\text{OTs})_2$ as a Precatalyst

Table 1

diene 6	R	product 7	yield (%)
			

diene 6	R	product 7	yield (%)
6a	CO ₂ Et	7a	82
6b	SO ₂ Ph	7b	45
6c	CN	7c	70
6d	NO ₂	7d	70
6e	COMe	7e	48
6f	Ph	7f	45



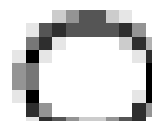
diene 6	R	product 7	yield (%)
6a	Me	7g	90
6a	OMe	7h	53
6a	CF ₃	7i	0

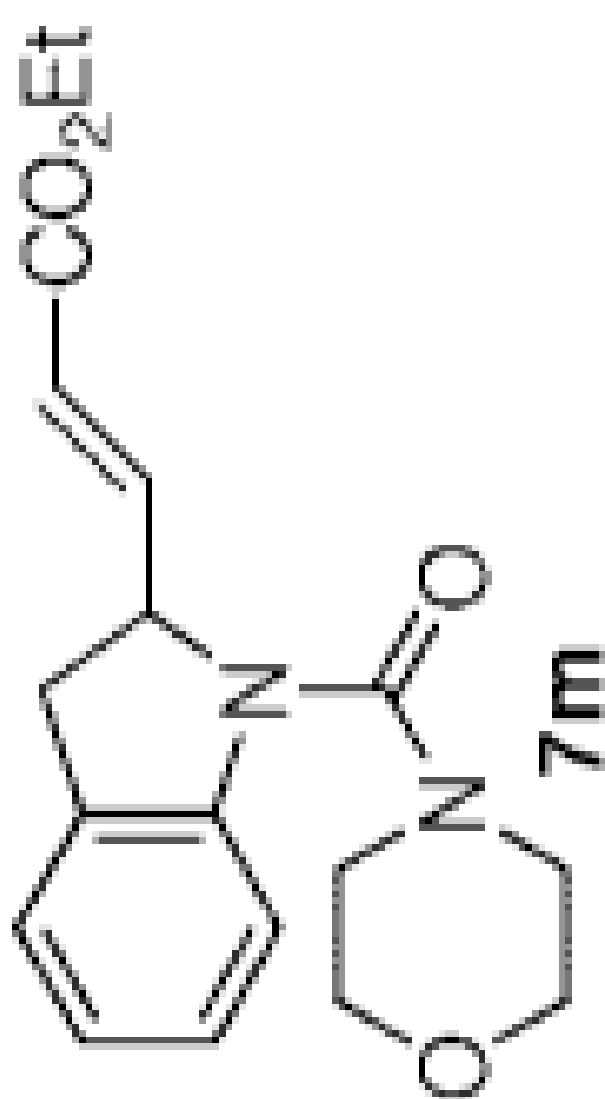
6a	Me	7j	62
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Chemical structure of product 7: A benzimidazole ring system with a methylcarbamoyl group (-NHMe) at the 2-position and a (E)-alkene at the 3-position. The alkene is substituted with a CO₂Et group and an R group.

diene 6	R	product 7	yield (%)
6a	OMe	7k	52
6a	CF ₃	7l	25

diene 6	R	product 7	yield (%)
6a			no reaction

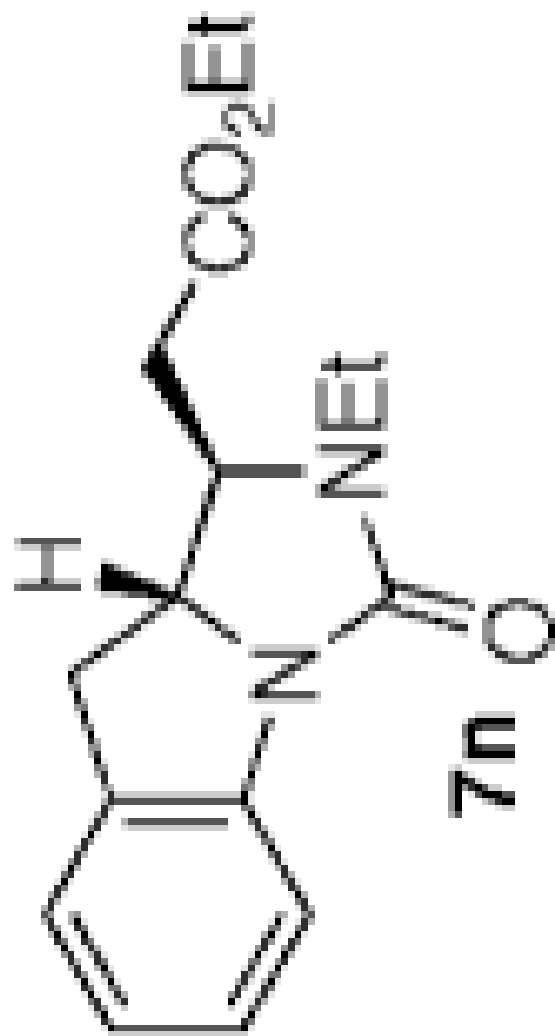


diene 6	R	product 7	yield (%)
6a			72

yield (%)

43

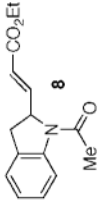
product 7



R

diene 6

6a

diene 6	R	product 7	yield (%)
6a			15

