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Synthesis of Unexpected Nitrogen Heterocycles via Pd-Catalyzed Cross-Coupling of *o*-Isopropenyl and Methallyl Anilides with Vinylic Halides

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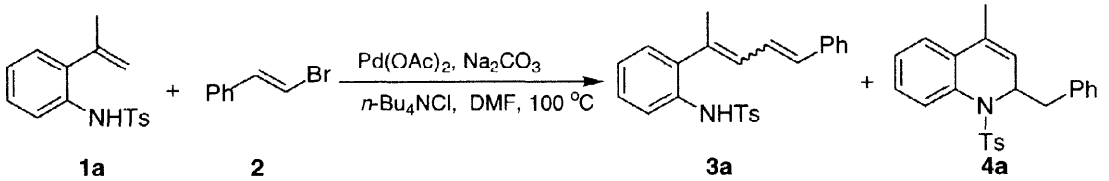
Abstract: The palladium-catalyzed cross-coupling of *o*-isopropenyl and *o*-methallyl-*N*-tosylanilides with vinylic halides affords good yields of unexpected substituted dihydroquinolines and dihydroindoles respectively, apparently via vinylpalladium addition to the olefin and an unusual rearrangement to a π-allylpalladium intermediate.

We have recently been interested in using palladium-catalyzed cross-coupling reactions between vinylic halides or triflates and *ortho*-vinylic or allylic phenols[1] and anilides[2] to prepare oxygen- and nitrogen-containing heterocycles. In our prior work in this area, the key mechanistic step involved the readdition of a palladium hydride to a π-complexed double bond of a diene derived from an initial cross-coupling reaction. During those earlier studies, unusual results were obtained using substrates bearing a terminal disubstituted olefin, which have encouraged us to further investigate the possibility of utilizing this new chemistry to prepare new classes of heterocycles. We now report the success of that project.

Our initial studies have focused on the reaction of *o*-isopropenyl-*N*-tosylaniline (**1a**) and β-bromostyrene (**2**) as our model system (eq. 1). Exposure of tosylanilide **1a** to 1.1 equiv of β-bromostyrene in the presence of 3.5 equiv of Na_2CO_3, 1.2 equiv of *n*-Bu_4NCl and 5 mol % of $Pd(OAc)_2$ in DMF at 100 °C resulted after 1 hour in the formation of diene **3a**,[3] as an 88:12 *Z*:*E* mixture in 40 % yield, **4a** in 7 % yield, and **1a** was recovered in 15 % yield. Extending the reaction time to 24 hours produced **4a** as the major product in 40% yield, together with **3a** in 25% yield, but all attempts to further improve the yield of **4a** by using different bases, salts, solvents and catalysts met with failure.



1a **2** **3a** **4a** (1)

Since TLC and GC analysis of the reaction suggested that tosylamide **4a** was derived from **3a**, we decided to investigate the cyclization step separately. The recovery of **3a** in almost quantitative yield after its treatment with Na_2CO_3 and *n*-Bu_4NCl in DMF at 100 °C for 24 h (see Table 1, entry 1) appeared to rule out processes not involving palladium. Little or no cyclization product was discernible even in the presence of different palladium catalysts (Table 1, entries 2-5). However, in the presence of both 5 mol % $Pd(OAc)_2$ and 1 equiv of β-bromostyrene, diene **3a** was found to undergo a rapid (4 h) conversion into **4a** in 63% yield (Table 1, entry 6).

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Table 1. Cyclization of diene **3a**.

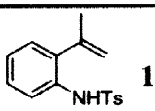
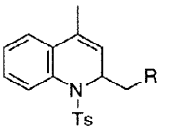
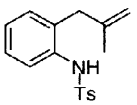
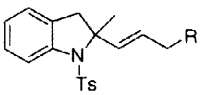
entry	Reaction Conditions [a]	**4a** Yield %[b]
1	Na_2CO_3 (3.5 equiv), *n*-Bu_4NCl (1.2 equiv)	- (84)
2	Na_2CO_3 (3.5 equiv), *n*-Bu_4NCl (1.2 equiv), $Pd(OAc)_2$ (0.05 equiv)	- (88)
3	Na_2CO_3 (3.5 equiv), *n*-Bu_4NCl (1.2 equiv), $Pd(dba)_2$ (0.05 equiv)	20 (76)
4	$PdCl_2$ (0.05 equiv), MeCN (2 mL)	- (98)
5	TsOH (0.05 equiv), $Pd(dba)_2$ (0.05 equiv)	- (90)
6	Na_2CO_3 (3.5 equiv), *n*-Bu_4NCl (1.2 equiv), $Pd(OAc)_2$ (0.05 equiv), *(E)*-PhCH=CHBr (1 equiv), 4 h	63
7	Na_2CO_3 (3.5 equiv), *n*-Bu_4NCl (1.2 equiv), $Pd(OAc)_2$ (0.05 equiv), *(E)*-*n*-BuCH=CHI (1 equiv), 4 h	74
8	Na_2CO_3 (3.5 equiv), *n*-Bu_4NCl (1.2 equiv), $Pd(OAc)_2$ (0.05 equiv), PhI (1 equiv)	-
9	Na_2CO_3 (3.5 equiv), *n*-Bu_4NCl (1.2 equiv), $Pd(OAc)_2$ (0.05 equiv), Me_2C=CHBr (1 equiv)	- (94)

[a] Unless otherwise stated, all reactions were carried out on a 0.25 mmol scale under an argon atmosphere in 2 mL of DMF for 24 h. [b] The number in parentheses refers to the yield of recovered starting material **3a**.

Most interesting, the addition of *(E)*-*n*-BuCH=CHI also facilitated the cyclization of **3a** to **4a**, but no cyclization was observed using PhI or Me_2C=CHBr as the organic halide (entries 7-9). With that information in hand, we were pleased to find that by reacting 1 equiv of **1a** with 2 equiv of β-bromostyrene under our initial reaction conditions (3.5 equiv of Na_2CO_3, 1.2 equiv of *n*-Bu_4NCl, 5 mol % $Pd(OAc)_2$ in DMF at 100 °C), we obtained **4a** in 59 % yield after 6 h. This procedure worked well in the reactions of a variety of other vinylic halides also (see Table 2, entries 1-7).[4] However, no heterocyclic product was observed when PhCBr=CH_2 was employed (entry 7). The reactions of *o*-methallyl-*N*-tosylaniline (**1b**) with various vinylic halides also gave very unusual *N*-tosyl-2,3-dihydro-2-vinylindoles, generally in good yields (Table 2, entries 8-16). However, with this substrate minor amounts of 3-methyl-2-vinyltetrahydroquinolines were sometimes isolated (entries 9-11). These side products are the expected products based on our earlier work, and undoubtedly arise by the mechanism reported by us for the reactions of unsubstituted *o*-allyl and *o*-vinyl anilides with vinylic halides and triflates.[2] With *o*-(α-styryl)-*N*-tosylaniline only low yields and low regioselectivity were observed. Good results were usually observed with both vinylic bromides and iodides, the latter being more reactive; the only vinylic triflate tested resulted in a lower yield (Table 2; compare entries 12, 13 and 14).

The two reaction paths illustrated in Scheme 2 for the formation of these unexpected heterocycles are consistent with the experimental evidence. Contrary to the mechanism previously reported by us for the reactions of *o*-vinylic and allylic phenols and anilides, it appears that the substitution pattern of our olefinic starting materials either alters the regiochemistry of the palladium hydride rearrangement or affects the cyclization by an entirely different route involving prior formation of the vinylic substitution product **3**. The addition of a σ-vinylpalladium complex to the carbon-carbon double bond of **1**, followed by the *syn*-β-elimination of HPdX results in the vinylic substitution intermediate **5**. The central question is how the complexed diene **5** reacts to give the observed products. We propose that the free diene **3** observed in many of these reactions as an intermediate is first formed, but then reacts further with a second equivalent of the σ-vinylpalladium complex to form a π-complex involving the less hindered double bond of the diene **3**. This intermediate **6** then undergoes a palladium hydride elimination and coordination to the less hindered double bond (**7**). Subsequent π-allylpalladium formation (**10**) and intramolecular displacement would afford the products.

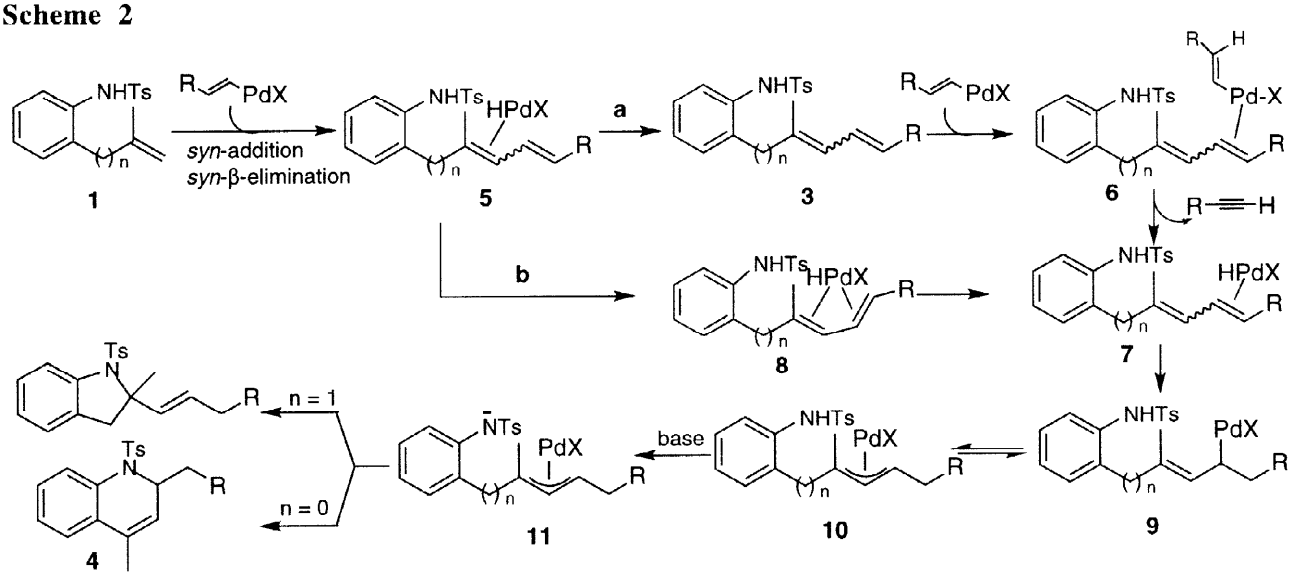
Table 2. Pd-Catalyzed Coupling of *o*-Isopropenyl and *o*-Methallyl Anilides with Vinylic Halides.[a]

entry	Tosylanilide **1**	Vinylic Halide	Product	R	Time (h)	% Yield[b]
1	 **1a**	*(E)*-PhCH=CHBr		Ph	8	59
2		*(E)*-*n*-BuCH=CHI		*n*-Bu	6	75 (72)[c]
3		*(E)*-*t*-BuCH=CHI		*t*-Bu	6	74 (67)[c]
4		*(E)*-*cyclo*-C_6H_{11}CH=CHI		*c*-C_6H_{11}	6	73
5		*(E)*-MeO_2CCH=CHI		MeO_2C	3	37
6		*(E)*-$PhCH_2CH$=CHI		$PhCH_2$	5	70
7		$PhCBr=CH_2$		-	-	-
8	 **1b**	*(E)*-*n*-BuCH=CHI		*n*-Bu	6	59 (31)[c]
9		*(E)*-*n*-BuCH=CHBr			24	53 (13)[d]
10		*(E)*-PhCH=CHBr		Ph	10	62 (21)[d]
11		*(E)*-*t*-BuCHCH-Br		*t*-Bu	24	52 (27)[d]
12		Me_2C=CHX X = I		*i*-Pr	3	61[e]
13		X = Br			5	60[e]
14		X = OTf			2	32[e]
15		*(E)*-*cyclo*-C_6H_{11}CH=CHI		*c*-C_6H_{11}	6	66
16		*(E)*-$PhCH_2CH$=CHI		$PhCH_2$	6	31

[a] Unless otherwise stated, all reactions were carried out under an argon atmosphere on a 0.3-0.5 mmol scale in DMF as the solvent (3 mL) at 100 °C using the following molar ratios: **1**: **2**: Na_2CO_3: *n*-Bu_4NCl: $Pd(OAc)_2$ = 1 : 2 : 3.5 : 1.2 : 0.05. [b] Yields are calculated based on pure, isolated compound, fully characterized by ^1H and ^{13}C NMR, IR and mass spectral analysis. [c] The number in parentheses refers to the yield of heterocycle when only 1 equiv of vinylic halide was used. [d] The number in parentheses refers to the yield of the corresponding 3-methyl-2-vinyltetrahydroquinolines. [e] Only 1 equiv of vinylic halide was used.

Even though we do not have experimental evidence for formation of the alkyne, this pathway is supported by the fact that no cyclization product was observed when **3a** was reacted with 1-bromo-2-methylpropene or phenyl iodide under the usual reaction conditions (Table 1, entries 8 and 9), while *(E)*-1-iodo-1-hexene gave very similar results to β-bromostyrene (Table 1, compare entries 6 and 7).

Scheme 2



The very similar results obtained in the reactions of **1a** with either 1 or 2 equiv of *(E)*-1-iodo-1-hexene or *(E)*-1-iodo-4,4-dimethyl-1-butene (Table 2, entries 2 and 3) clearly show that a different pathway (Scheme 2, path b), not involving the intermediacy of free diene **3**, must be operating as well. The successful cyclization of **1b** by reaction with 1 equiv of 1-halo-2-methylpropene, a vinylic halide unable to generate a Pd-H species in the suggested manner, supports this (Table 2, entries 12-14). It is reasonable to suppose that the η^2-alkene complex

5 is converted into the isomeric complex **7** by an intramolecular shift of the hydridopalladium halide from one double bond to the other by way of the bidentate diene complex **8**, as suggested previously by Heck.[5]

In conclusion, the chemistry herein described provides a new, very attractive route to dihydroindoles and dihydroquinolines. This chemistry apparently proceeds by a totally unanticipated palladium hydride rearrangement. Even though the results reported here are only preliminary, they suggest a novel, new palladium-catalyzed cross-coupling approach to the synthesis of heterocycles.

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References and Notes

1. Larock, R. C.; Yang, H.; Pace, P.; Cacchi, S.; Fabrizi, G. *Tetrahedron Lett.* **1998**, *39*, 237.
2. Larock, R. C.; Yang, H.; Pace, P.; Cacchi, S.; Fabrizi, G. *Tetrahedron Lett.* **1998**, *39*, 1885.
3. Selected spectral data for diene **3a** are: ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 2.64 H), 1.86 (s, 0.36 H), 5.77 (d, J = 11.0 Hz, 0.12 H), 6.07 (dd, J = 15.6, 10.7 Hz, 0.88 H), 6.30 (dd, J = 15.5, 11.0 Hz, 0.12 H), 6.39 (d, J = 10.7 Hz, 0.88 H), 6.45 (d, J = 15.5 Hz, 0.12 H), 6.58 (d, J = 15.6 Hz, 0.88 H), 6.81 (s, 0.88 H), 6.85 (s, 0.12 H), 7.00 - 7.70 (m, 13 H); ^{13}C NMR of the principal stereoisomer ($CDCl_3$) δ 21.4, 25.2, 124.7, 124.5, 126.6, 127.2, 127.7, 128.3, 128.5, 128.7, 129.5, 130.5, 131.5, 133.3, 133.7, 134.8, 136.0, 136.8, 143.7. The stereochemistry of the *E/Z* mixture was assigned by NOE difference studies.
4. A typical procedure follows: to a solution of 0.150 g (0.52 mmol) of 2-isopropenyl-*N*-tosyl-aniline and 1-*(E)*-hexenyl iodide (0.220 g, 1.04 mmol) in DMF (3 mL) were added Na_2CO_3 (0.193 g, 1.82 mmol), *n*-Bu_4NCl (0.173 g, 0.62 mmol) and $Pd(OAc)_2$ (0.006 g, 0.026 mmol). The reaction mixture was stirred under argon at 100 ° C for 6 h and then diluted with ethyl acetate and washed with brine. The organic layer was dried (Na_2SO_4), filtered, concentrated under vacuum, and chromatographed on silica gel, eluting with a 90/10 (v/v) mixture of *n*-hexane/EtOAc to afford 0.145 g (75% yield) of *N*-tosyl-1,2-dihydro-4-methyl-2-pentylquinoline, as a colorless oil: IR (liquid film) 1598, 1167 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 6.6 Hz, 3 H), 1.08-1.49 (m, 8 H), 1.57 (s, 3 H), 2.31 (s, 3 H), 4.63 (m, looks like a quartet, J = 6.3 Hz, 1 H), 5.36 (d, J = 5.7 Hz, 1 H), 7.00 (d, J = 8.1 Hz, 2 H), 7.10 (dd, J = 7.5, 1.5 Hz, 1 H), 7.19-7.24 (m, 3 H), 7.29 (td, J = 7.2, 1.2 Hz, 1 H), 7.70 (dd, J = 7.8, 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 17.8, 21.4, 22.6, 25.1, 31.4, 33.1, 54.9, 123.0, 125.6, 126.5, 127.3, 127.7, 128.3, 128.7, 129.1, 130.8, 132.9, 136.1, 142.9; HRMS (m/z) 369.1767 (calcd. 369.1763 for $C_{22}H_{27}NO_2S$).
5. Kim, J. I.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1981**, *46*, 1067.