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Synthesis of (*E*)-3-styryl-2,5-dihydro-1*H*-pyrrole derivatives *via* Pd-catalyzed addition of indoles to hydroxy 1,6-enynes†

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A mild Pd-catalyzed addition of indoles to hydroxy 1,6-enynes has been developed. In this reaction, hydroxy 1,6-enynes were selectively transformed into (*E*)-3-styryl-2,5-dihydro-1*H*-pyrrole derivatives.

Pd-catalyzed cycloisomerization of 1,6-enynes has emerged as a powerful method for the construction of five- and six- membered heterocycles and carboncycles in recent years.[1] These compounds are important intermediates for the synthesis of pharmaceutically and biologically active molecules, such as (−)-domoic acid,[2a] isodomoic acid H,[2b] kainic acid,[2c] conessine[2d,e] and (+)-intricarene.[2f–h] Lately, attack of a nucleophile toward 1,6-enynes has expanded the diversity of these products. However, most of the Pd-catalyzed reactions were restricted to water,[3a] halogen[3b–e] and OAc[3f–j] as nucleophiles. Several years ago, Echavarren group reported gold(I)-catalyzed addition reactions of electron-rich arenes and indoles to the 1,6-enynes.[4a,b] Veronique Michelet also developed asymmetric gold-catalyzed hydroarylation/cyclization reactions.[4c] To our knowledge, Pd-catalyzed intermolecular reaction of 1,6-enynes and indoles has not yet been reported. In the context of our ongoing efforts on Pd-catalyzed cyclization of enynols to construct hetero- and carbo-cyclic structures,[1i,5a,b] we wish to report the Pd-catalyzed addition of indoles to the hydroxyl 1,6-enynes.

Our initial investigations were focused on 1,6-enynol **1a** due to its stability and reactivity. After some optimization, we were pleased to find that treatment of **1a** with 3 equiv. of *N*-methyl indole, 1 equiv. of TBHP, 10 mol% of $Pd(acac)_2$ in AcOH at 70 °C gave the product **3aa** (*E*)-1-methyl-3-(phenyl(4-styryl-1-tosyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl)-1*H*-indole in 47% yield after 1.5 h (Table 1, entry 1). The structure of **3aa** was unambiguously confirmed by X-ray crystallographic analysis (see ESI†). A screen of various phosphine ligands revealed that electron-withdrawing groups on the ligand were beneficial for this reaction, $(C_6F_5)_3P$ improved the yield to 59% (entries 2–5). Although other Pd catalysts were also tested, no better result was obtained (entries 6–8). To our surprise, solvent investigations revealed that AcOH was essential for this reaction and no reaction occurred in other solvents (entries 9–11). With this result in mind, we tested cosolvents. Using $MeNO_2$ as a cosolvent with AcOH improved the yield of **3aa**. After certain optimization of the $MeNO_2$/AcOH, the yield improved to 66% under $MeNO_2$–AcOH (1 : 1) (entries 12–14). When the temperature reduced to 60 °C, we could get a higher yield to 71%, lower temperature gave a negative result (entries 14–16). Other cosolvents showed to be less effective (entries 17–18). As expected, no reaction occurred in the absence of Pd catalyst (entry 19).

The amounts of the additive and *N*-methyl indole were also important, 3 equiv. of *N*-methyl indole and 1 equiv. of TBHP was optimum (Table 2, entries 4–9). It is worth mentioning that the reaction could proceed in the absence of oxidant (entry 4). The result indicates that TBHP only plays a supporting role in the reaction. Thus, the optimized reaction conditions were affirmed as follows: 3 equiv. of indole as nucleophile, 10 mol% $Pd(acac)_2$ as catalyst, 20 mol% $(C_6F_5)_3P$ as ligand and 1 equiv. of TBHP as the additive under Ar in $MeNO_2$/AcOH (1 : 1) at 60 °C for 1.5 h.

Having identified the optimal conditions, we next examined the scope and limitations of the Pd-catalyzed cyclization reaction. As can be seen in Table 3, the reaction tolerated both electron-withdrawing and -donating groups on the aromatic R^2, the corresponding products **3ba**–**3ea** were obtained in moderate yields (Table 3, entries 2–5). Compound **1e**, containing a naphthalene moiety, was a good substrate for this reaction, and **3ea** was obtained in 74% yield (entry 5). The substrates with an aliphatic or a heterocyclic R^2 group can also smoothly converted into the corresponding products in moderate yields (entries 6–7). Substrate 1 h, with aliphatic R^1 and R^2 groups, affords the desired product in 50% yield (entry 8). The reaction efficiency was somewhat affected by the substituents on the C–C double bond. Terminal olefin **1i** only provides **3ia** in 27% yield (entry 9).

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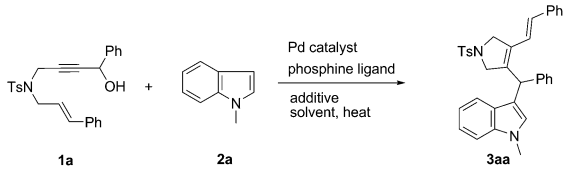
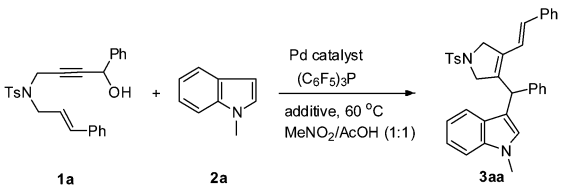
Table 1 Pd-catalyzed reactions of **1a** with indole under various conditions[a]



Entry	Catalyst	Ligand	Solvent	T/°C	*t*/h	Yield[b]/%
1	$Pd(acac)_2$	—	AcOH	70	1.5	47
2	$Pd(acac)_2$	P(2-furyl)$_3$	AcOH	70	1	47
3	$Pd(acac)_2$	X-Phos	AcOH	70	2	54
4	$Pd(acac)_2$	P[O(*o*-tol)]$_3$	AcOH	70	2.5	52
5	$Pd(acac)_2$	$(C_6F_5)_3P$	AcOH	50	5	59
6	$Pd(OAc)_2$	$(C_6F_5)_3P$	AcOH	70	3.5	44
7	$Pd(CF_3CO_2)_2$	$(C_6F_5)_3P$	AcOH	70	3.5	51
8	$PdCl_2$	$(C_6F_5)_3P$	AcOH	70	1	—[c]
9	$Pd(acac)_2$	$(C_6F_5)_3P$	MeCN	70	1	—
10	$Pd(acac)_2$	$(C_6F_5)_3P$	DCE	70	1	—
11	$Pd(acac)_2$	$(C_6F_5)_3P$	THF	70	1	—
12	$Pd(acac)_2$	$(C_6F_5)_3P$	$MeNO_2$–AcOH (10 : 1)	70	2	63
13	$Pd(acac)_2$	$(C_6F_5)_3P$	$MeNO_2$–AcOH (1 : 10)	70	1.5	64
14	$Pd(acac)_2$	$(C_6F_5)_3P$	$MeNO_2$–AcOH (1 : 1)	70	1.5	66
15	$Pd(acac)_2$	$(C_6F_5)_3P$	$MeNO_2$–AcOH (1 : 1)	60	1.5	71
16	$Pd(acac)_2$	$(C_6F_5)_3P$	$MeNO_2$–AcOH (1 : 1)	50	5	30
17	$Pd(acac)_2$	$(C_6F_5)_3P$	DCE–AcOH (1 : 1)	70	2.5	56
18	$Pd(acac)_2$	$(C_6F_5)_3P$	DCM–AcOH (1 : 1)	60	1	59
19	—	$(C_6F_5)_3P$	$MeNO_2$–AcOH (1 : 1)	60	1	—

[a] Unless otherwise noted, all of the reaction were carried out using 0.1 mmol of **1a**, 3 equiv. of **2a**, 10 mol% catalyst, 20 mol% ligand and 1 equiv. of TBHP (*t*-butyl hydroperoxide) under Ar in 1 mL solvent. [b] Isolated yields. [c] No reaction.

Table 2 Optimization studies for the amounts of reagents[a]



Entry	Oxidant (equiv.)	$Pd(acac)_2$ (mol%)	$(C_6F_5)_3P$ (mol%)	Equiv. of **2a**	*t*/h	Yield[b]/%
1	$K_2S_2O_8$ (1)	10	20	3	4.5	65
2	O_2 (1 atm)	10	20	3	4.5	66
3	BQ (1)	10	20	3	1	—[c]
4	—	10	20	3	4	64
5	TBHP (0.2)	10	20	3	3	68
6	TBHP (2)	10	20	3	5	55
7	TBHP (1)	10	20	1.1	3	64
8	TBHP (1)	10	20	2	3	69
9	TBHP (1)	10	20	5	3	70
10	TBHP (1)	5	10	3	6	63
11	TBHP (1)	10	10	3	2	65
12	TBHP (1)	10	30	3	2	57

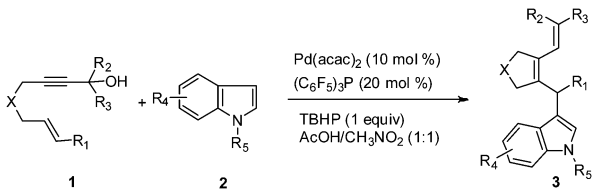
[a] Unless otherwise noted, all of the reaction were carried out using 0.1 mmol of **1**, *N*-methyl indole, $Pd(acac)_2$, $(C_6F_5)_3P$ and TBHP under Ar in 1 mL $MeNO_2$–AcOH (1 : 1) at 60 °C. [b] Isolated yields. [c] No reaction.

Notably, carbon-tethered 1,6-enynol were also applicable to this reaction, giving **3ja** in 63% yield (entry 10).

To further expand the scope of this reaction, unprotected indole was tested. To our delight, the reaction proceeds smoothly under the standard condition (entry 11). Therefore, we investigated a range of indoles and *N*-methyl indoles. A weak electron-donating or electron-withdrawing group is most favorable for this reaction (entries 14, 16 and 17), but a strong electron-donating or electron-withdrawing group is less effective (entries 12, 13 and 15). *N*-benzyl-substituted indole lead to a good result in 70% yield (entry 18). We also attempted other nucleophiles, such as furan and 2,6-dimethylphenol. To our disappointment, no desired product was observed.

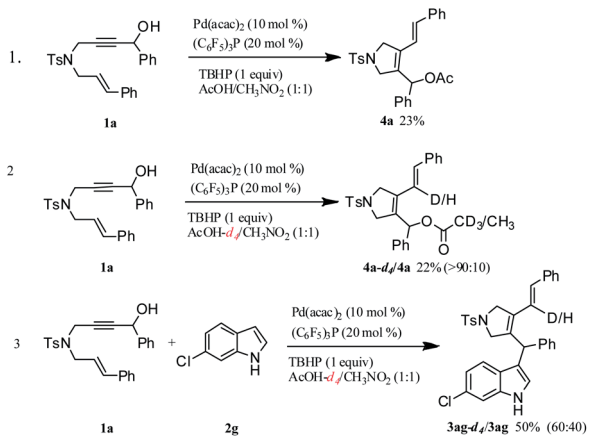
To gain more insight into the mechanism of the present reaction, we applied the optimal condition on **1a** without nucleophiles, AcOH react with the 1,6 enyne **1a** and gave the product **4a** (Scheme 1, eqn (1)). Meanwhile, we investigated the origin of the proton incorporated into the cyclic product by using deuterium labeled AcOH. Deuterium labeled product **4a-*d*$_4$** was obtained when AcOH-d_4 was used in the absence of nucleophiles (Scheme 1, eqn (2)). However, when treating **1a** and indole **2g** with AcOH-d_4, a 60 : 40 mixture of **3ag-*d*$_4$** and **3ag** was obtained in 50% yield (Scheme 1, eqn (3)). The low deuterium incorporation observed in the reaction with indole and AcOH-d_4 could be due to H/D exchange between the acidic proton of the acid and the proton in C-3 of the indole. So protonolysis of a C–Pd bond was involved in the mechanism.

Table 3 Pd-catalyzed reactions of hydroxy 1,6-enynes with nucleophiles[a]

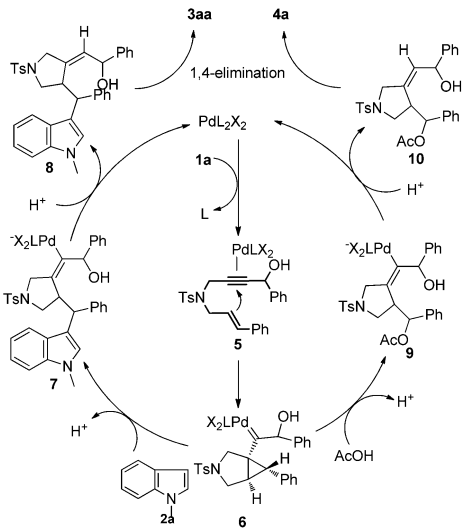


Entry	Enyne	X	R^1	R^2	R^3	Indole	R^4	R^5	Product	*t*/h	Yield[b]/%
1	**1a**	NTs	Ph	Ph	H	**2a**	H	Me	**3aa**	1.5	71
2	**1b**	NTs	Ph	4-Me Ph	H	**2a**	H	Me	**3ba**	3	65
3	**1c**	NTs	Ph	4-Br Ph	H	**2a**	H	Me	**3ca**	3	64
4	**1d**	NTs	Ph	4-OMe Ph	H	**2a**	H	Me	**3da**	3	60
5	**1e**	NTs	Ph	1-Naphthyl	H	**2a**	H	Me	**3ea**	3	74
6	**1f**	NTs	Ph	1-Furyl	H	**2a**	H	Me	**3fa**	1.5	64
7	**1g**	NTs	Ph	*n*-C_6H_{13}	H	**2a**	H	Me	**3ga**	5	62
8	**1h**	NTs	Ph	Me	Me	**2a**	H	Me	**3ha**	12	50
9	**1i**	NTs	H	Ph	H	**2a**	H	Me	**3ia**	2	27
10	**1j**	$C(CO_2Me)_2$	Ph	Ph	H	**2a**	H	Me	**3ja**	4	63
11	**1a**	NTs	Ph	Ph	H	**2b**	H	H	**3ab**	2.5	66
12	**1a**	NTs	Ph	Ph	H	**2c**	5-OMe	Me	**3ac**	4	50
13	**1a**	NTs	Ph	Ph	H	**2d**	5-CN	Me	**3ad**	12	44
14	**1a**	NTs	Ph	Ph	H	**2e**	7-Me	Me	**3ae**	2.5	63
15	**1a**	NTs	Ph	Ph	H	**2f**	4-OMe	H	**3af**	4	53
16	**1a**	NTs	Ph	Ph	H	**2g**	6-Cl	H	**3ag**	4	63
17	**1a**	NTs	Ph	Ph	H	**2h**	7-Me	H	**3ah**	4	70
18	**1a**	NTs	Ph	Ph	H	**2i**	H	Bn	**3ai**	2	70

[a] Unless otherwise noted, all of the reaction were carried out using 0.1 mmol of **1**, 3 equiv. of **2**, 10 mol% $Pd(acac)_2$, 20 mol% $(C_6F_5)_3P$ and 1 equiv. of TBHP under Ar in 1 mL $MeNO_2$–AcOH (1 : 1) at 60 °C. [b] Isolated yields.



Scheme 1 Mechanism investigation.



Scheme 2 Reaction mechanism of $Pd(acac)_2$-catalyzed reaction of 1,6-enyne with *N*-methyl indole.

Based on the above observations together with previous literature reports,[6] a plausible mechanism for this reaction is proposed (Scheme 2). Coordination of catalyst with ligand affords active PdL_2X_2 species. The PdL_2X_2 would coordinate to the enyne to form complex **5.** Cyclization of **5** would give cyclopropylpalladium carbene complex **6.** The attack of indole at the cyclopropyl carbon give the intermediate **7** and a proton is released at the same time. **8** would formed from the protonolysis of **7**, which undergoes 1,4-elimination to give the final product **3aa**.[7] It is worth to notice that H/D exchange between the acidic proton of the acid and the proton in C-3 of the indole leads to the low deuterium incorporation observed in the reaction with indole and AcOH-d_4. However, when the reaction carried out in the absence of indole, AcOH attack the intermediate **6** to form **9**, which undergoes 1,4-elimination to give **10.** In

this case, AcOH is the sole origin of proton and deuterium labeled product would obtained in the solvent AcOH-d_4.

Conclusions

In summary, we have developed a mild Pd-catalyzed addition of indoles to hydroxyl 1,6-enynes. In this reaction, 1,6-enynes were selectively transformed into (*E*)-3-styryl-2,5-dihydro-1*H*-pyrrole derivatives. A variety of substituted enynes and indoles can proceed this reaction in moderate yields. We are currently investigating Pd-catalyzed addition of other nucleophiles to 1,6-enynes.

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