SHORT STEP SYNTHESIS OF 4-SUBSTITUTED INDOLES USING PALLADIUM-CATALYZED C-C BOND FORMING REACTION

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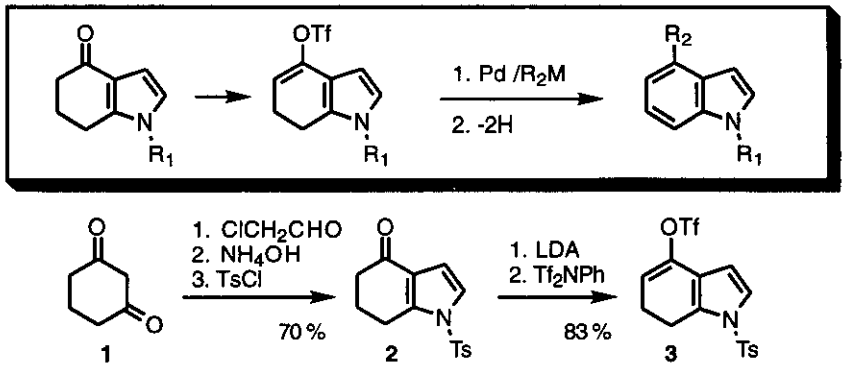
Abstract-----Enol triflate of *N*-tosyl-4-oxo-tetrahydroindole (**2**) was a good precursor for a synthesis of 4-substituted indoles. Various functional groups were introduced to form corresponding indoles using palladium-catalyzed carbonylation and a cross-coupling reaction followed by dehydrogenation by palladium on charcoal.

Indoles bearing substituents at the 4-position have attracted attention as important building blocks for biologically active compounds such as ergot alkaloids.[1] Though a few methods for the preparation of the 4-substituted indoles have been reported, a simple and practical synthetic procedure is needed.[2] Here we report an attempt to synthesize 4-substituted indoles using a palladium-catalyzed carbon-carbon bond forming reaction starting from enol triflate (**3**) as a substrate, which was obtained from readily available *N*-tosyl-4-oxo-tetrahydroindole (**2**).[3]



Initially, we tried to synthesize 4-carbomethoxyindole using palladium-catalyzed carbonylation. When a toluene solution of enol triflate (**3**) (0.12 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), K_2CO_3 (3 eq.) and MeOH (10 eq.) was stirred at 60 °C for 2.5 h under carbon monoxide (1 atm), the desired carbonylative product (**4**) was obtained in 22% yield along with dimeric compound (**6**) (61% yield). The latter product can be obtained by the Heck reaction followed by isomerization of olefin.[4] The reaction was carried out under various conditions

Dedicated to the memory of emeritus professor Dr. Yoshio Ban (Hokkaido University).

(Table I). The carbonylation occurred at room temperature in CH_3CN and DMF (Runs 3 and 4), and a good yield (81%) was attained in DMF. Dehydration of **4** with 10% Pd on charcoal smoothly proceeded in refluxing *p*-xylene for 14 h to give 4-carbomethoxyindole (**5**) in good yield. The result indicates that enol triflate (**3**) is a good precursor for the synthesis of 4-substituted indoles by a Pd-catalyzed carbon-carbon bond formation.[5]

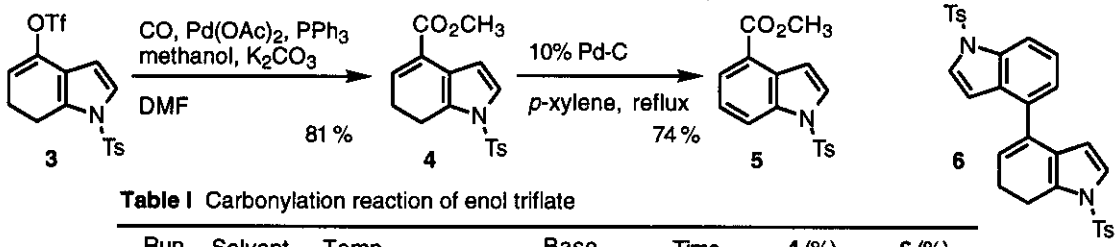


Table I Carbonylation reaction of enol triflate

Run	Solvent	Temp	Base	Time	**4** (%)	**6** (%)
1	toluene	60 °C	*i*Pr_2NEt	2.5 h	22	61
2	CH_3CN	60 °C	*i*Pr_2NEt	1.5 h	42	30
3	CH_3CN	room temperature	K_2CO_3	4.0 h	59	trace
4	DMF	room temperature	K_2CO_3	1.0 h	81	trace

Subsequently, a Pd-catalyzed cross-coupling reaction of **3** with 1-trimethylsilyl-2-tributylstannylacetylene (**7**) was carried out. A DMF solution of **3** (0.12 mmol) and **7** (1.05 eq.) was stirred in the presence of $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %) and LiCl (3 eq.) at room temperature for 16 h to afford **9a** in low yield (5%) (Table II, Run 1). An improved yield (66%) was achieved in refluxing CH_3CN (Run 3) using $PdCl_2(PPh_3)_2$ (5 mol %) as a catalyst. When the reaction of **3** with β-tributylstannylstyrene (**8**) as an organostannyl reagent was carried out in DMF at 100 °C, **9b** was produced in 67% yield (Run 5). The dihydroindoles (**9a** and **9b**) were aromatized by 10% Pd on charcoal in refluxing adequate solvent to give corresponding indoles (**10a** and **10b**).

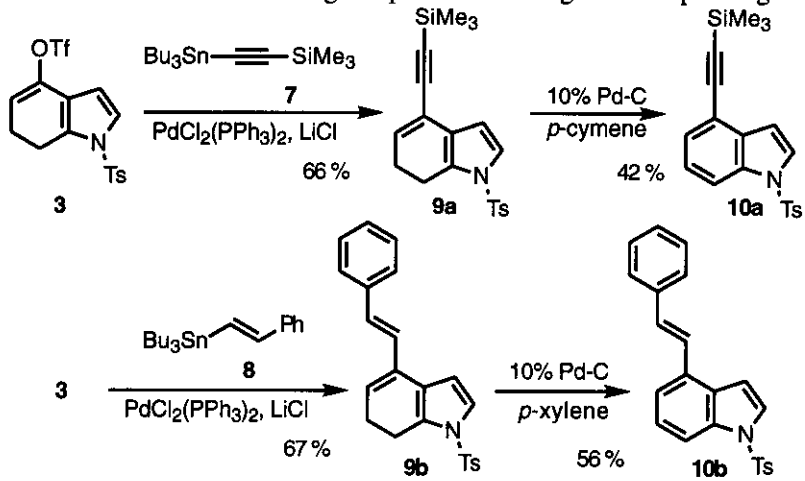


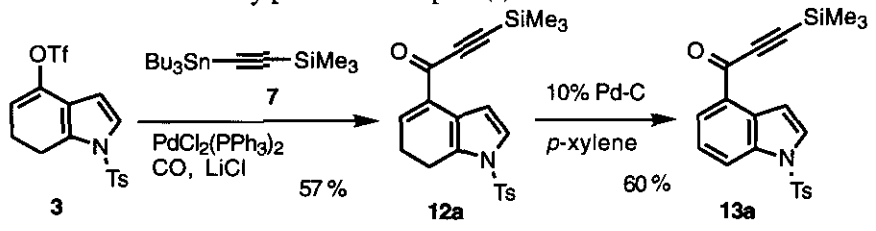
Table II Cross-coupling reaction of enol triflate

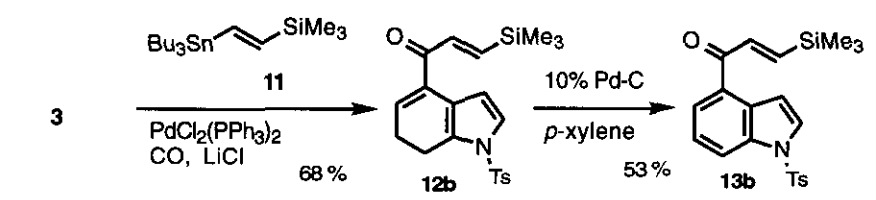
Run	$RSnBu_3$	Solvent	Temp	Time	**9** (%)	**6** (%)	**3** (%)
1 [a]	**7**	DMF	room termperature	16 h	5	14	33
2		DMF	100 °C	10 min	48	trace	–
3		CH_3CN	reflux	20 min	66	trace	–
4	**8**	CH_3CN	60 °C	8 h	trace	22	41
5		DMF	100 °C	7 min	67	trace	–

[a] $Pd(OAc)_2$ (5 mol %) and PPh_3 (10 mol %) was used in the place of $PdCl_2(PPh_3)_2$

A carbonylative cross-coupling reaction is valuable for the introduction of carbonyl moiety. A DMF solution of enol triflate (**3**) (0.12 mmol) and **7** (1.05 eq.) was stirred at 80 °C in the presence of $PdCl_2(PPh_3)_2$ (5 mol %) and LiCl (3 eq.) under carbon monoxide giving desired 4-(trimethylsilyl)propynoyldihydroindole (**12a**) in only 2% yield with the coupling product (**9a**) in 14% yield (Table III, Run 1). In order to obtain the desired **12a** in a higher yield, CH_3CN was used and the solution was stirred at a lower temperature (Runs 2-4). A maximum yield (57%) was achieved at 40 °C for this reaction. In the case of 1-trimethylsilyl-2-trisbutylstannylethylene (**11**) as an organostannyl compound, however, 4-(trimethylsilyl)propenoyldihydroindole (**12b**) was given as a single product in 68% yield (Run 5). The dehydrogenation of the carbonylative coupling products (**12a** and **12b**) by 10% Pd on charcoal in refluxing *p*-xylene gave the corresponding indoles (**13a** and **13b**) in 60% and 53% yields, respectively.

The results indicate that the formation of acylpalladium complex (**II**) can proceed at room temperature. The transmetalation of alkylpalladium complex (**I**) with an organotin compound requires higher temperature. However, the transmetalation of acylpalladium complex (**II**) with an organotin compound proceeds at a lower temperature than that of alkylpalladium complex (**I**).[6]





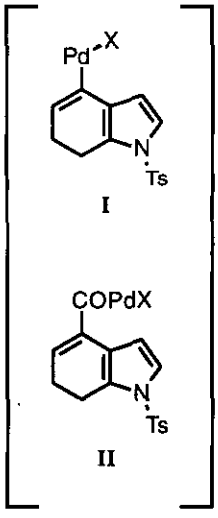
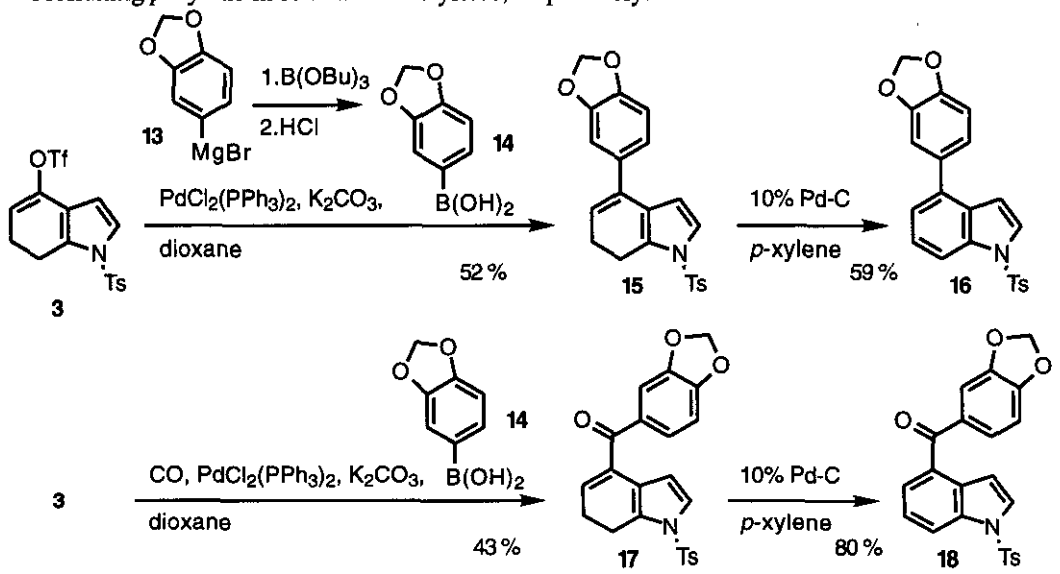


Table III Carbonylative cross-coupling reaction of enol triflate

Run	$RSnBu_3$	Solvent	Temp	Time	**12** (%)	**9** (%)
1	**7**	DMF	80 °C	15 min	2	14
2		CH_3CN	80 °C	55 min	23	42
3		CH_3CN	60 °C	40 min	38	34
4		CH_3CN	40 °C	3.5 h	57	16
5	**11**	CH_3CN	60 °C	7.5 h	68	–

If the Suzuki-coupling[7] of enol triflate (**3**) with organoboron reagents is possible, it will be a strong tool to introduce aryl and vinyl groups to the 4-position of indole. When a dioxane solution of arylboronic acid (**14**) (1.05 eq.), which was prepared from **13** and $B(OBu)_3$ followed by treatment with 10% HCl, enol triflate (**3**) (0.12 mmol), $PdCl_2(PPh_3)_2$ (5 mol %) and K_2CO_3 (3 eq.) was refluxed for 10 min, the desired **15** was obtained in 52% yield. Carbonylative coupling of this boronic acid in refluxing dioxane for 15 min gave **17** in

43% yield. Conversion of **15** and **17** into indole derivatives (**16** and **18**) proceeded smoothly by 10% Pd on charcoal in refluxing *p*-xylene in 59% and 80% yields, respectively.



In summary, enol triflate (**3**) which was easily obtained from **2**, was a good precursor for the synthesis of 4-substituted indoles using Pd-catalyzed carbonylation and Pd-catalyzed cross-coupling with organostannyl and organoboronic compounds. Further studies for the synthesis of 4-substituted indoles are now in progress.

REFERENCES AND NOTES

1. For the review of the synthesis of 4-substituted indoles, see A. P. Kozikowski, *Heterocycles,* 1981, **16**, 267; I. Ninomiya and T. Kiguchi in "The Alkaloids", Ed. A. Brossi, Academic Press, 1990, **38**, 1.
2. For the recent synthetic methods of 4-substituted indoles, see J. H. Tidwell, A. J. Peat, and S. L. Buchwald, *J. Org. Chem.*, 1994, **59**, 7164; H, Ishibashi, S. Akamatsu, H. Iriyama, and M. Ikeda, *Chem. Pharm. Bull.*, 1994, **42**, 2450; M. Fuji, H. Muratake, and M. Natsume, *Chem. Pharm. Bull.*, 1992, **40**, 2338; M. E. Krolski, A. F. Renaldo, D. E. Rudisill, and J. K. Stille, *J. Org. Chem.*, 1988, **53**, 1170.
3. M. Matsumoto and N. Watanabe, *Heterocycles,* 1984, **22**, 2313.
4. An CH_3CN (1.2 ml) solution of **3** (0.12 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %) and K_2CO_3 (2 eq.) was refluxed for 10 min to give dimeric compound (**6**) in 92% yield. The structure of **6** was determined by ^{1}H-nmr and COSY spectra.
5. *N*-Tosyl group could be deprotected by sodium hydroxide in alcoholic solvent if desired.
6. G. T. Crisp, W. J. Scott, and J. K. Stille, *J. Am. Chem. Soc.*, 1984, **106**, 7500.
7. T. Oh-e, N. Miyaura, and A. Suzuki, *Synlett,* **1990**, 221.

Received, 24th March, 1995