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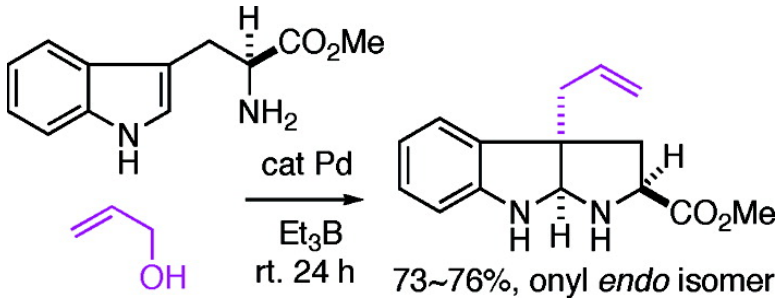

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Pd-Catalyzed C3-Selective Allylation of Indoles with Allyl Alcohols Promoted by Triethylborane

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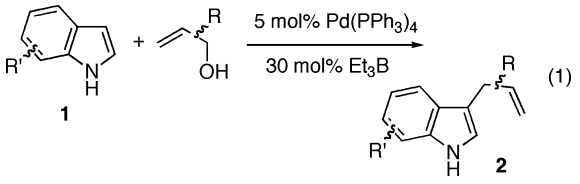
Indole is a versatile and useful heterocycle for the synthesis of a wide range of physiologically important molecules.[1] Indole serves as an ambient nucleophile, and some sophisticated conditions are required to achieve selective alkylation either at the 1-(*N*-) or 3-position.[1] Regioselective allylic alkylation at the 3-position of indoles[2] lends itself to an efficient and straightforward method for the synthesis of many naturally occurring indole alkaloids,[3] e.g., the plant growth-promoting acidic materials, auxins,[4] and of unnatural potent HIV inhibitors, BMS-378806.[5]

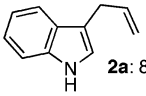
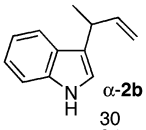
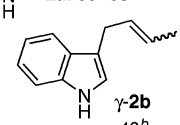
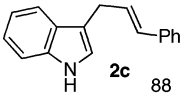
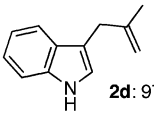
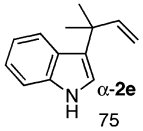
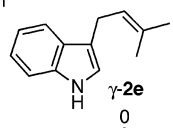
Taking into consideration versatile reactivities of indoles as a nucleophile and π-allylpalladiums as an electrophile, it is rather surprising that only a few articles have appeared on the palladium-based allylation of indoles, which describe formation of either a mixture of *N*- and 3-allylindoles together with *N*,3-diallylindole, albeit in poor yields,[6] or *N*-allylindoles selectively in modest yield.[7] Nickel chemistry, on the other hand, seems to be more promising in view of selectivity; 3-allylindole forms selectively in 59% yield by the reaction of indole, allyl alcohol in an excess, and a Grignard reagent in a stoichiometric quantity to indole and allyl alcohol.[8] Regrettably, however, the scope has not been clarified yet.

Recently, we have disclosed that a Pd(0) species in the presence of Et_3B catalytically promotes allyl alcohols to undergo both N-allylation of amines[9] and C-allylation of active methylene compounds.[10] Herein, we report for the first time that the Pd−Et_3B system works nicely for the C3 selective allylation of indoles and provides 3-allylindoles **2** in excellent yields (eq 1). The reaction can be performed very easily as exemplified by the following procedure (Table 1, run 1): a homogeneous mixture of **1a** (R′ = H, 1.0 mmol), allyl alcohol (1.0 mmol), $Pd(PPh_3)_4$ (5 mol %), and Et_3B (30 mol %) in THF (2.5 mL) was stirred at 50 °C for 12 h under N_2. The product **2a** was isolated in 80−85% yields after usual extractive workup and purification by column chromatography.[11]



The reaction shows a wide scope for the structural variation of both allyl alcohols and indoles. Table 1 summarizes the allylation of **1a** with a variety of allyl alcohols. As one can see in runs 1−5 (cf., footnote *a*), the parent allyl alcohol, α-, γ-methyl, and α-, γ-phenyl-substituted allyl alcohols are all reactive; reactions are complete within 20 h at 50 °C in the presence of 30 mol % of Et_3B and 100 mol % of an allyl alcohol and provide **2** in almost quantitative yields. β-Methyl, α,α-, and γ,γ-dimethylallyl alcohols

Table 1. Allylation of Indole (**1a**, R′ = H) with Allyl Alcohols[a]

run	alcohols	time (h)	products **2**: % yield
1		12	 **2a**: 80~85
			 α-**2b**  γ-**2b**
2	γ-Me	20	30
3	α-Me	20	34
			γ-**2b**: 48[b] 46[b]
			 **2c**
4	γ-Ph	20	88
5	α-Ph	20	83
6		25	 **2d**: 97
			 α-**2e**  γ-**2e**
7	γ,γ-Me_2	24	75
8	α,α-Me_2	24	86
			γ-**2e**: 0 9

[a] Reaction conditions: **1a** (1.0 mmol), an allyl alcohol (1.0 mmol in runs 1−5, 3.0 mmol in runs 6−8), $Pd(PPh_3)_4$ (5 mol %), and Et_3B (1 M solution in hexane; 0.3 mmol in runs 1−5, 2.4 mmol in runs 6−8) in THF (2.5 mL) at 50 °C under N_2. [b] cis/trans = 1:10.

are reluctant (runs 6−8), and the use of excess amounts of both alcohols (300 mol %) and Et_3B (240 mol %) is required to obtain **2** in reasonable yields. Remarkably, no N-allylation products were detected at all.[12]

Each of the three pairs of unsymmetrical allyl alcohols (runs 2 and 3, 4 and 5, and 7 and 8) showed almost the same regioselectivities, suggesting that reactions proceed via common intermediates, most likely π-allylpalladium species. At this moment, however, it is premature to give a rationale for the contrasting regioselectivities providing either a straight-chain isomer **2c** or a branched-chain isomer α-**2e** almost exclusively.

Table 2 compiles the allylation of a variety of indoles **1b**−**h** with allyl alcohol. As compared with others, 2- (**1c**) and 3-methylindoles (**1d**) showed a marked difference in reactivity (runs 2 and 3). The former was unreactive and required 3 equiv of allyl alcohol and long heating, while the latter was so reactive that the reaction was even complete at room temperature within 2 h. Interestingly, *N*-methylindole did not undergo allylation under the conditions and was recovered quantitatively. It should be noted that the reaction tolerates both the electron-rich and electron-deficient

† Graduate School of Science and Technology.

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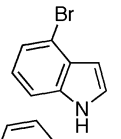
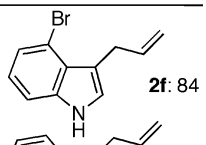
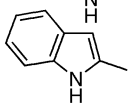
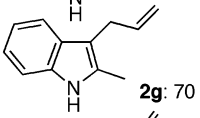
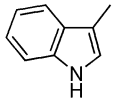
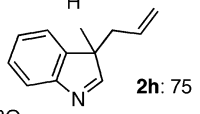
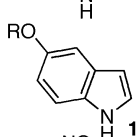
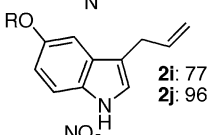
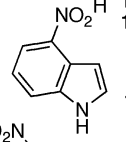
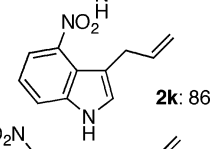
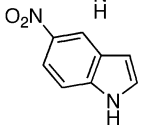
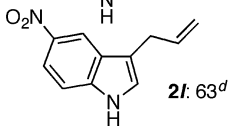
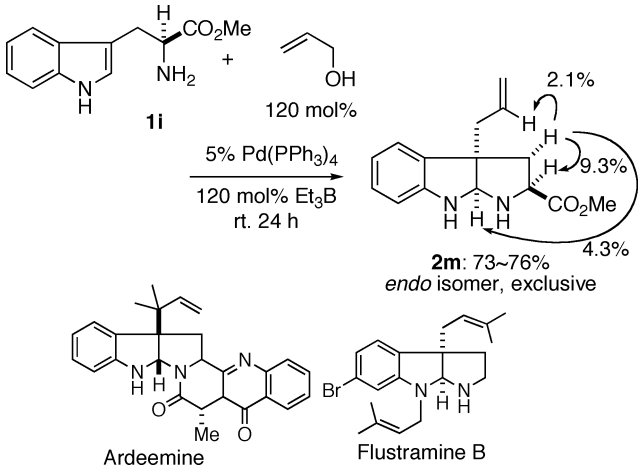
Table 2. Pd-Catalyzed Allylation of Indoles **1** with Allyl Alcohol[a]

run	indole **1**	time (h)	% isolated yield
1	 **1b**	24	 **2f**: 84
2[b]	 **1c**	70	 **2g**: 70
3[c]	 **1d**	2	 **2h**: 75
4 5	 **1e** (R = Me) **1f** (R = H)	23 24	 **2i**: 77 **2j**: 96
6	 **1g**	3	 **2k**: 86
7	 **1h**	24	 **2l**: 63[d]

[a] Reaction conditions: **1** (1.0 mmol), $Pd(PPh_3)_4$ (5 mol %), allyl alcohol (1.0 mmol), and Et_3B (0.3 mmol) at 50 °C under N_2. [b] Allyl alcohol (3 mmol) and Et_3B (2.4 mmol). [c] At room temperature. [d] 63% conversion.

Scheme 1. Stereoselective Synthesis of Pyrroloindole Frameworks (Figures Refer to the NOE Increments)



indoles and the otherwise reactive indolic N−H and phenolic OH groups (run 5).

Encouraged by a facile reaction of **1d**, we examined allylation of L-tryptophan methyl ester (**1i**). Selective alkylative amination upon the indole C2−C3 bond took place and provided **2m** as a single diastereomer in ~73−76% isolated yield without protecting two kinds of amino groups (Scheme 1).[13,14] The mode of stereoselectivity is opposite to that reported for the sulfenylation−amination of the Boc derivative of **1i**, which selectively provides an *exo*-pyrroloindole product.[15] The present stereoselective alkylative amination may be utilized for the synthesis of, for example, ardeemine and flustramine family alkaloids.[14−16]

In conclusion, this communication demonstrates that under palladium catalysis, Et_3B nicely promotes the C3-selective allylation of indoles and tryptophans using a wide structural variety of allyl alcohols as allylation agents. The yields of allylation are excellent and in most cases exceed 80%. Mechanistic details that account for the contrasting regioselectivity (providing either straight-chain isomer **2c** or branched-chain isomer α-**2e**) and diastereoselectivity (providing an endo-isomer of **2m**) are a subject to be addressed, and the results together with synthetic applications will be reported soon.

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Supporting Information Available: Experimental procedure, characterization data of **2a**−**m**, and complete ref 5. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Both $Pd(PPh_3)_4$ and Et_3B are indispensable for the allylation. In the absence of either of them, no reactions take place. The simple Friedel−Crafts allylation promoted by Et_3B as a Lewis acid catalyst is improbable.
(12) Use of allyl chloride, in place of allyl alcohol, under the conditions resulted in no reaction.
(13) The structure of **2m** was deduced on the basis of NOE experiments. Some typical data are given in Scheme 1.
(14) Phosphoric acid promoted hydroamination across the C2−C3 bond provides *exo*- and *endo*-pyrroloindole in a 9:1 ratio: Bruncko, M.; Crich, D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543.
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