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Pd-CATALYZED ALLYLIC ALKYLATION OF PYRROLES WITH ALLYL ALCOHOLS PROMOTED BY TRIETHYLBORANE†

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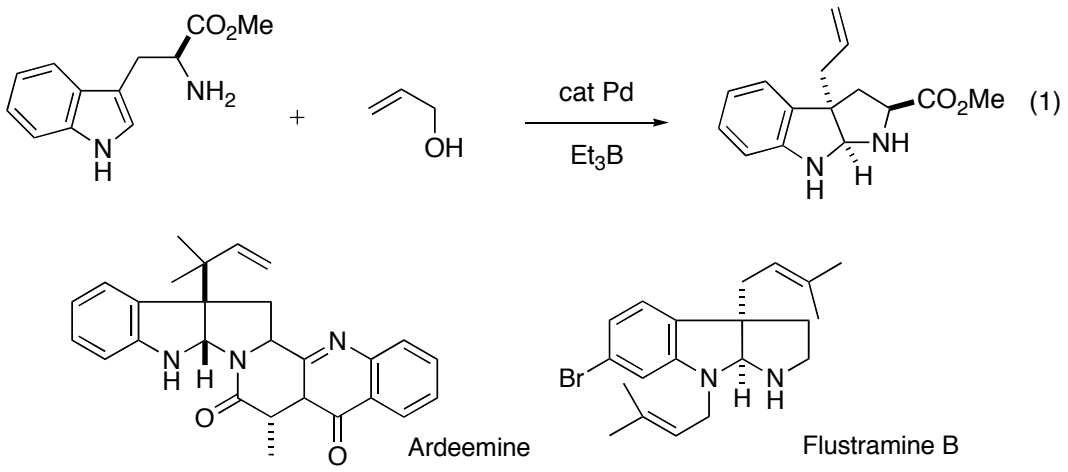
Abstract – Triethylborane promotes the Pd-catalyzed allylic alkylation of pyrroles with a variety of allylic alcohols to provide either C2 allylation products (α,α-, γ,γ-dimethylallyl alcohol and geraniol) or C2,C5 diallylation products (allyl alcohol, α-, β-, γ-methyl-, and α-, γ-phenylallyl alcohols) in good to excellent yields under mild conditions.

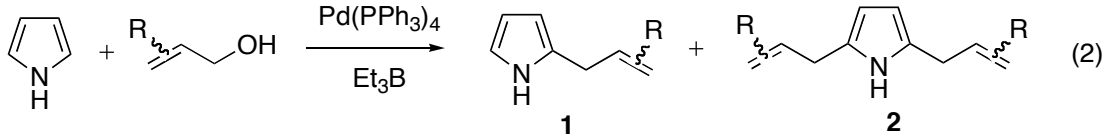
Pyrroles is among the most important fundamental constituents of the biologically and physiologically active molecules, such as chlorophyll, porphyrin, hemoglobin and their related compounds,[1] and of electron conducting polymers with excessive π-electron systems.[2] The synthesis and reactions of pyrroles have attracted much interest for over a century. To date, however, pyrrole reactions remain a challenge for synthetic chemists because some pyrroles are extremely sensitive to acids and air.[3] Alkylation of pyrroles by the Friedel–Crafts approach, for example, frequently meets difficulties because the Brønsted acid and Lewis acid catalysts induce polyalkylation, ring opening, and polymerization reactions.[4] Alkylation (at C2,[5] C3,[6] and/or N[7]) with aliphatic halides or allyl halides has proved to be most successful under strongly basic conditions (alkaline metal hydroxides or carbonates or organomagnesium or -zinc reagents), which may be sometimes incompatible with functional groups of pyrrole substituents.

Recently, we demonstrated that a Pd(0) species in the presence of Et_3B catalytically promoted allylic alcohols to undergo the electrophilic C-allylation of active methylene compounds[8] and *N*-allylation of

primary and secondary aromatic and aliphatic amines.[9] Furthermore, the Pd/Et_3B catalytic system worked nicely for the C3 selective allylation of indoles by direct use of allyl alcohols and provided 3-allylindoles in excellent yields.[10] The same procedure was applied to the diastereofacial selective alkylative cyclic amination upon the C2-C3 double bond of tryptophan methyl ester and furnished pyrroloindole skeletons, widely seen in many alkaloids, such as ardeemine and flustramine families (eq. 1).

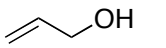
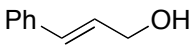
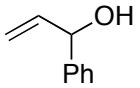
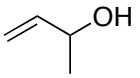
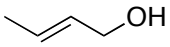
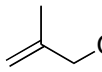
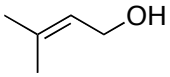
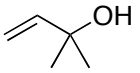


Herein, we disclose that the combination of Et_3B and $Pd(PPh_3)_4$ nicely promotes a variety of allyl alcohols to undergo either selective monoallylic alkylation of pyrroles at the C2 position (with disubstituted allyl alcohols) or diallylic alkylation at C2 and C5 positions (with the parent and monosubstituted allyl alcohols) in good to excellent yields under neutral and weakly basic conditions (eqs. 2–4). For the latter case, it is possible to shift the selectivity in favor of the C2 monoallylation under the conditions employing an excess amount of pyrrole and Et_3N as a promoter.



The allylation could be performed very easily just by mixing a homogeneous mixture of pyrrole, $Pd(PPh_3)_4$ (5 mol%), an allyl alcohol (100–200 mol%), and triethylborane (30–240 mol%) in dry toluene at room temperature under nitrogen atmosphere.[11] Both catalysts, $Pd(PPh_3)_4$ and Et_3B, are indispensable; in the absence of either of them, no reaction takes place.

Table 1. Pd-Et_3B Catalyzed Allylation of Pyrrole with Allylic Alcohols[a]

run	allylic alcohol (mmol)		Et_3B (mmol)	reaction time (hour)	% isolated yield [ratio][b]	
					1	**2**
1		(1)	0.3	28	**1a**: 0	**2a**: 30
2		(2)	0.3	7	**1a**: 0	**2a**: 91
3		(1)	0.3	28	**1b**: 19[c]	**2b**: 17[c]
4		(2)	0.3	24	**1b** :20[c]	**2b**: 57[c]
5		(2)	0.3	25	**1b**: 0	**2b**: 69
6		(2)	0.3	24	**1c**: 60 [1.4:1]	**2c**: 32[d]
7		(2)	0.3	23	**1c**: 36 [1:1]	**2c**: 45[d]
8		(2)	0.3	24	**1d**: 7	**2d**: 22
9		(2)	2.4	24	**1d**: 11	**2d**: 56
10		(2)	2.4	24	0	0
11		(2)	2.4	24	0	0

[a] Reaction conditions: pyrrole (1 mmol), $Pd(PPh_3)_4$ (5 mol%), an allyl alcohol (an indicated amount in parenthses), and Et_3B in toluene (2.5 mL) at rt under N_2.
[b] The ratio is meant to refer to the ratio of regioisomeric mixture of linear isomer (*l*) to branched isomer (*b*).
[c] *trans*-Isomer is formed exclusively.
[d] Mixture of isomers of *l,l*, *l,b* and a pair of diastereomeric isomers *b,b*.

The results for the reactions of pyrrole with the parent allyl alcohol and mono- and disubstituted allyl alcohols are summarized in Table 1. Even in the reactions of pyrrole and alcohols in a 1:1 molar ratio, the parent allyl alcohol and cinnamyl alcohol provided C2,C5 diallylation products (**2**) exclusively (or in a considerable amount), which indicates the second C5 allylation proceeds much faster than the first C2 allylation (runs 1 and 3, Table 1). Indeed, the reaction of cinnamyl alcohol with 10 equivalents of pyrrole provided the diallylation product (**2b**) in as much as 30% yield along with the monoallylation product (**1b**) in 40% yield (room temperature for 8 h). As expected, use of 2 equivalents of allyl alcohols with respect to pyrrole produced the C2,C5 diallylation products (**2**) in good yields (runs 2 and 4). α-Phenylallyl alcohol showed similar reactivity and selectivity to those of cinnamyl alcohol and furnished **2b** exclusively (run 5). A pair of α-methyl- and γ-methylallyl alcohols showed complicated

results, furnishing **1c** and **2c** in comparable amounts. In both cases, **1c** was obtained as mixtures of linear (*l*) and branched (*b*) isomers in a ratio of *ca*. 1:1. C2,C5 diallylation products (**2c**) were also obtained as mixtures of four stereoisomers (*l*,*l*-, *l*,*b*-, and a diastereoisomeric pair of *b*,*b*-isomers). In sharp contrast to these, both α-phenylallyl alcohol and cinnamyl alcohol selectively provided **1b** and **2b** as linear *trans*-isomers. β-Methylallyl alcohol was apparently less reactive as compared with the above-mentioned alcohols and provided a mixture of **1d** and **2d** in low combined isolated yield (run 8). Loading a large amount of Et_3B effected the reaction and increased the yield to a synthetically useful level (run 9).

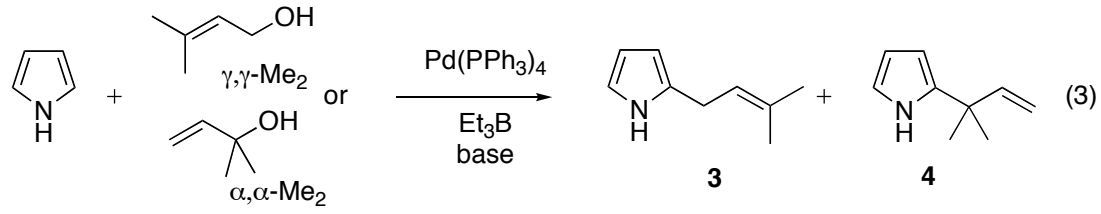


Table 2. Pd-Et_3B Promoted Allylation of Pyrrole with Prenyl Alcohol (γ,γ-Me_2) and α,α-Dimethylallyl Alcohol (α,α-Me_2): Effect of Bases[a]

run		base	temperature (°C)/ time (hour)	% isolated yield		
				3	**4**	**3 + 4**
1	γ,γ-Me_2	Cs_2CO_3	25 °C, 24 h	trace	trace	trace
2	γ,γ-Me_2	K_2CO_3	25 °C, 24 h	18	22	40
3	γ,γ-Me_2	pyridine	25 °C, 24 h	34	37	71
4	γ,γ-Me_2	*i*-Pr_2EtN	25 °C, 24 h	23	50	73
5	γ,γ-Me_2	Et_3N	25 °C, 24 h	53	41	94
6	α,α-Me_2	Et_3N	25 °C, 24 h	18	27	45
7	α,α-Me_2	Et_3N	50 ˚C, 24 h	50	37	87

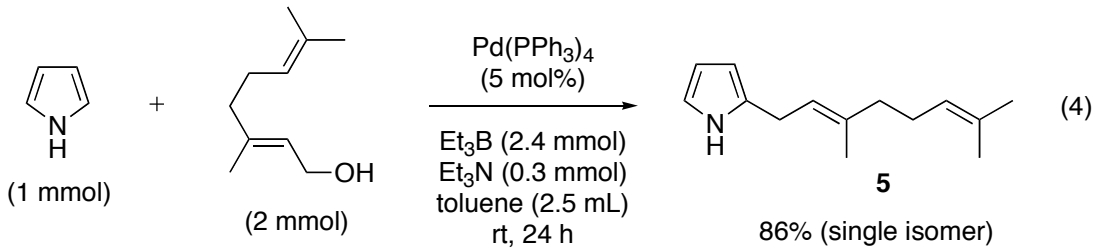
[a] Reaction conditions: pyrrole (1 mmol), $Pd(PPh_3)_4$ (5 mol%), an allyl alcohol (200 mol%), Et_3B (240 mol%), and a base (30 mol%) in toluene (2.5 mL) under N_2.

Neither γ,γ-dimethyl- nor α,α-dimethylallyl alcohol was willing to react under the above conditions (runs 10 and 11, Table 1), and no reaction progress was observed at all even when the reactions were undertaken at 50 °C. Suggested by the precedents using alkali metal hydroxides or carbonates or Grignard or organozinc reagents as promoters, we examined several bases (30 mol%) and found alkali metal carbonates showed a limited success (runs 1 and 2, Table 2) and amine bases greatly effected the

allylation (runs 3–7, Table 2). Triethylamine was the best choice of amines examined; 1,8-diazabicyclo[5.4.0]undecene and 1,4-diazabicyclo[2.2.2]octane were ineffective and provided **3** in 7% and 2% and **4** in 20% and 9% yields, respectively. Interestingly, in sharp contrast to the results in Table 1, the reactions of pyrrole with γ,γ-dimethyl- and α,α-dimethylallyl alcohols selectively provided C2 monoallylation products and no C2,C5 diallylation products were produced at all, even though all the reactions were performed in the presence of 2 equivalents of alcohols with respect to pyrrole. Here again, the C2 allylation products were obtained as mixtures of a linear isomer (**3**) and a branched isomer (**4**). The ratios of **3**/**4** are affected by many factors: alcohol structures (runs 5 and 6), the kinds of bases, and the reaction temperatures. The formation of a thermodynamically less stable branched isomer to such a great extent is unusual for the π-allylpalladium mediated reactions, suggesting some special mechanistic features behind the present allylation reaction (*vide infra*, Scheme 1).

Triethylamine also accelerated the allylation of pyrrole with monosubstituted allyl alcohols and contributed toward increasing the selectivity in favor of the C2 monoallylation. For example, the reaction of pyrrole (10 mmol) with cinnamyl alcohol (1 mmol) in the presence of $Pd(PPh_3)_4$ (0.05 mmol), Et_3B (0.3 mmol), and Et_3N (1 mmol) in toluene (2.5 mL) at room temperature for 3 h, furnished **1b** in 65% isolated yield together with **2b** in 13% yield (*vide infra*).

Under the identical conditions to those applied for the allylation with γ,γ-dimethylallyl alcohol, geraniol smoothly underwent allylation and provided C2-allylation pyrrole (**5**) in excellent yield (eq. 4). Surprisingly, geraniol provided **5** as a linear isomer exclusively and no branched isomer was detected.



(4)

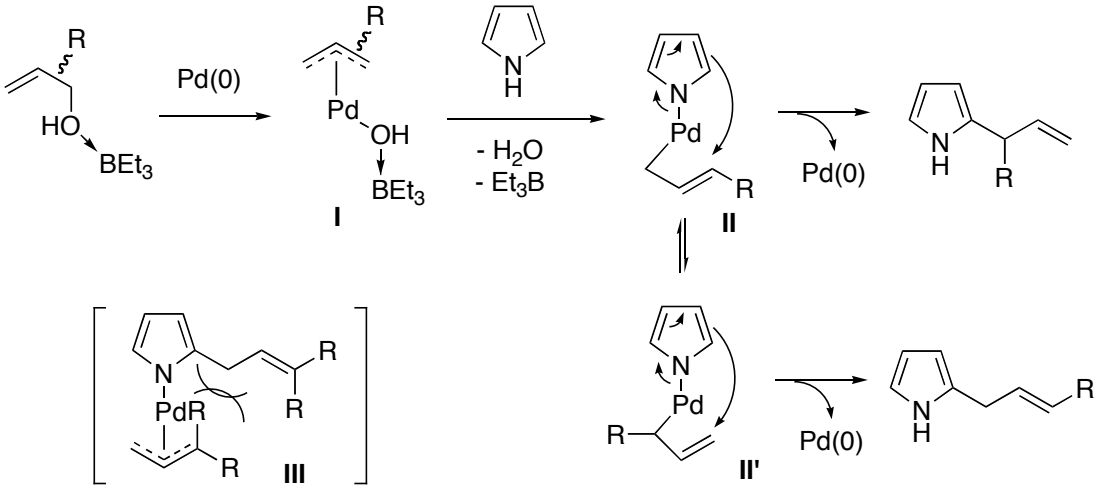
The contrasting reactivities that typically the parent allyl alcohol, providing the C2,C5-diallylation products, and disubstituted allyl alcohols, selectively furnishing C2 monoallylation products (eqs. 3 and 4), display may be rationalized supposing π-allylpalladium pyrrylamides (**II**) and (**II'**) as reactive intermediates (Scheme 1). Once **II** and **II'** were formed, they would smoothly undergo an intramolecular substitution reaction as indicated by curved arrows to furnish regioisomeric C2 allylation products. Pyrrole is such a weakly Lewis basic nitrogen heterocycle that the ease of formation of **II/II'** from an intermediate (**I**) might be subject of many factors, especially the Lewis acidity of Pd^{2+} metal and

the steric environment around the metal of **I**. When R = H, Ph, or Me, **I** might be reactive enough toward pyrrole irrespective of the presence or absence of bases, and **II/II'** thus formed would lead to C2 monoallylation products. An intermediate (**I**) (typically, R = Me_2), on the other hand, is sterically congested and the metal is a relatively poor Lewis acid because of electron-donation by the two Me groups, and hence in order to generate **II/II'** (R = Me_2) some bases, such as Et_3N, might be essential, which would activate pyrrole by abstraction of a proton from the NH group.[12]

The second allylation would proceed similarly via an intermediate **III**, when typically R = H. However, when typically R = Me, the steric repulsion between the two allyl groups on C2 and Pd^{2+} is such that **III** (R = Me) would be hardly formed resulting in the selective C2 monoallylation.

It may be worth noting that the present allylation is most successful with allyl alcohols; other allylating agents, having been most widely utilized, turned out to give mixtures of 2-allylpyrroles (**1**) and 2,5-diallylpyrroles (**2**), albeit in poor yields. For example, under the identical conditions to those of run 2 in Table 1 (20 h at room temperature), both allyl methyl carbonate and allyl acetate provided **1a** and **2a** in 10–13% and 15–20% yields, respectively.

In summary, this communication demonstrates that Et_3B nicely promotes a variety of allyl alcohols to undergo the C allylation of pyrrole in the presence of $Pd(PPh_3)_4$. The parent allyl alcohol and monosubstituted allyl alcohols with methyl and phenyl groups tend to furnish the C2,C5 diallylation products, while prenyl alcohol and geraniol provide the C2 monoallylation products selectively, the latter reactions being promoted most effectively in the presence of Et_3N.



Scheme 1. A plausible reaction mechanism for the allylation of pyrrole.

ACKNOWLEDGEMENTS

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†This paper is dedicated to Professor Barry M. Trost for his 65th birthday.

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10. M. Kimura, M. Futamata, R. Mukai, and Y. Tamaru, *J. Am. Chem. Soc*., 2005, **127**, 4592.
11. Typical reaction procedure (run 4, Table 1): Into a N_2 purged flask containing $Pd(PPh_3)_4$ (55.6 mg, 0.05 mmol), cinnamyl alcohol (268 mg, 2.0 mmol), toluene (2.5 mL), pyrrole (67 mg, 1.0 mmol), and triethylborane (0.3 mL, 1 M hexane) were introduced successively *via* a syringe. The reaction mixture was stirred at rt for 24 h, during which the reaction was monitored by means of TLC. After dilution with ethyl acetate (30 mL), the mixture was washed with sat. NaCl (30 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was

subjected to the column chromatography over silica gel (Fujisirisia NH; eluent: hexane/ethyl acetate = 32:1) and 2-cinnamylpyrrole (**1b**) and 2,5-dicinnamylpyrrole (**2b**) were obtained in 20 and 57% yields, respectively. 2-Cinnamylpyrrole **(1b)**: IR (neat) 3379 (s), 1651 (m), 1088 (m), 964 (s), 710 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.55 (d, J = 6.6 Hz, 2 H), 6.01 (br s, 1 H), 6.17 (br d, J = 1.4 Hz, 1 H), 6.33 (dt, J = 15.8, 6.6 Hz, 1 H), 6.50 (d, J = 15.8 Hz, 1 H), 6.71 (d, J = 1.4 Hz, 1 H), 7.19 – 7.40 (m, 5 H), 7.98 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 105.8, 108.5, 116.7, 126.0, 127.2, 128.4, 129.6, 131.4, 137.0; HRMS, calcd for $C_{13}H_{13}N$: 183.1048, found m/z (relative intensity) 183.1033 (M^+, 100), 182 (61), 168 (10). 2,5-Dicinnamylpyrrole **(2b)**: IR (neat) 3423 (s), 1651 (m), 966 (m), 754 (s), 692 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.50 (d, J = 6.6 Hz, 4 H), 5.91 (br s, 2 H), 6.32 (dt, J = 15.8, 6.5 Hz, 2 H), 6.45 (d, J = 15.8 Hz, 2 H), 7.18 – 7.38 (m, 10 H), 7.73 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 106.1, 126.2, 125.7, 127.2, 127.6, 128.6, 131.4; HRMS, calcd for $C_{22}H_{21}N$: 299.1674, found m/z (relative intensity) 299.1669 (M^+, 100), 273 (3), 272 (15).

12. Pyrrole NH group is indispensable for the allylic alkylation to proceed; *N*-substituted pyrroles, such as *N*-methylpyrrole and *N*-allylpyrrole did not undergo the allylation at all.