1a was 2. On the other hand, formation of the pyrrole **16** in 40% yield was detected by NMR when 2.33 g (12 mmol) of **2j** and 415 mg (5.7 mmol) of *N-tert*-butylamine was reacted at 200 °C for 9 h.

The Reaction of the Imine 1a with 1-Pyrrolidinocyclohexene (2o). A solution of **1a** (5.0 g, 59 mmol) and **2o** (7.1 g, 47 mmol) in benzene (50 mL) was heated at 150 °C for 15 h in a sealed tube. Distillation of the reaction mixture gave 6.2 g (81%) of 6-methylene-1-pyrrolidino-1-cyclohexene (**18**) as a colorless liquid: bp 70–72 °C (3 mmHg); IR (neat) 1635 and 1600 cm^{-1}; NMR δ 1.6–2.0 (m, 6 H, 2 CH_2CH_2N and $CH_2CH_2CH_2$), 2.1–2.5 (m, 4 H, 2 $=CCH_2$), 2.7–3.2 (t, 4 H, 2 NCH_2), 4.6–5.0 (m, 1 H, NC=CH), 4.84 (br s, 1 H, =CHH), 5.10 (s, 1 H, =CHH); MS, *m/e* 163 (M^+).

The Reaction of 2-Phenyl-1-pyrroline (1g) with the Enamine 2b. A solution of **1g** (4.24 g, 29 mmol), **2b** (8.23 g, 59 mmol), and PTS (0.53 g, 3.1 mmol) in benzene (30 mL) was heated at 150 °C for 7 h in a sealed tube. Worked as above yielded 2.3 g (39%) of a colorless liquid, which was proved to be 3-butylidene-2-phenyl-1-pyrroline (**22**): bp 95–100 °C (2 mmHg); IR (neat) 1650 and 1580 cm^{-1}; NMR δ 0.93 (t, 3 H, Me), 1.16–1.83 (m, 2 H, $MeCH_2$), 1.83–2.50 (m, 2 H, $=CCH_2$), 2.50–2.90 (m, 2 H, $=CCH_2$), 3.81–4.26 (m, 2 H, NCH_2), 5.70–6.10 (m, 1 H, CH=), 7.26–7.76 (m, 5 H, Ph); MS, *m/e* 199 (M^+).

Acknowledgment. The present work was partially supported by a Grant-in-Aid for special project research from the Ministry of Education, Science and Culture, to which our thanks are due.

Registry No. **1a**, 13987-61-6; **1b**, 77037-04-8; **1c**, 4393-14-0; **1d**, 100-62-9; **1e**, 7020-80-6; **1f**, 6852-58-0; **1g**, 700-91-4; **1h**, 2045-74-1; **1i**, 90554-27-1; **1j**, 90554-28-2; **2a**, 7182-09-4; **2b**, 7182-10-7; **2c**, 51840-50-7; **2d**, 90554-29-3; **2e**, 81816-90-2; **2f**, 36838-59-2; **2g**, 332-15-0; **2h**, 77084-89-0; **2i**, 19524-67-5; **2j**, 882-34-8; **2k**, 90554-30-6; **2l**, 81816-91-3; **2m**, 90554-31-7; **2n**, 67948-52-1; **3a**, 90554-32-8; **3b**, 80716-46-7; **3c**, 90554-33-9; **3d**, 90554-34-0; **3e**, 90554-35-1; **3f**, 62134-70-7; **3g**, 62134-72-9; **3h**, 90331-06-9; **3i**, 90554-36-2; **3j**, 90554-42-0; **3k**, 62135-03-9; **4a**, 591-22-0; **4b**, 699-25-2; **4b**·picrate, 15367-34-7; **4c**, 79169-70-3; **4d**, 90554-37-3; **4e**, 81816-89-9; **4e**·picrate, 90554-43-1; **4f**, 92-07-9; **4g**, 85665-54-9; **4g**·picrate, 90554-44-2; **4h**, 2973-87-7; **4i**, 73669-44-0; **4i**·picrate, 73669-48-4; **4j**, 3999-78-8; **4j**·picrate, 90554-45-3; **4k**, 90554-38-4; **4l**, 79116-22-6; **4l**·picrate, 90554-46-4; **4m**, 81816-92-4; **4m**·picrate, 90554-47-5; **4n**, 68686-59-9; **4n**·picrate, 90554-48-6; **4o**, 90554-39-5; **4o**·picrate, 90554-49-7; **4p**, 90554-40-8; **4q**, 82437-95-4; **4q**·picrate, 82437-96-5; **4r**, 90554-41-9; **4s**, 90554-50-0; **4s**·picrate, 90554-51-1; **4t**, 90554-53-3; **4u**, 90554-54-4; **5**, 4604-65-3; **7**, 867-89-0; **8**, 90554-52-2; **9**, 64244-33-3; **14a**, 90554-55-5; **15a**, 10321-86-5; **16**, 90554-56-6; **18**, 90554-58-8; **22**, 90554-57-7; *N-tert*-butylamine, 75-64-9; α-ethylcinnamaldehyde, 28467-92-7; benzaldehyde, 100-52-7; butyraldehyde, 123-72-8.

Pictet–Spengler Reactions in Aprotic Media

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The reaction of tryptophan methyl ester (**1**) with aldehydes such as benzaldehyde (**2a**) and cyclohexanecarboxaldehyde (**2b**) in refluxing benzene provides the corresponding tetrahydro-β-carbolines **5a** and **5b**, respectively, as earlier reported,[1] in contrast to the report of Grigg.[4]

In 1976 we reported that reaction of tryptophan methyl ester (**1**) with aldehydes such as benzaldehyde (**2a**), cyclohexanecarboxaldehyde (**2b**), or α-keto acids in refluxing benzene (Dean–Stark trap to remove water)[1] provided much improved yields of the Pictet–Spengler reaction with respect to the traditional method performed in aqueous acidic media. The reasons for this were simple for acid-labile substrates were much less prone to decomposition in a nonacidic, nonaqueous medium. Since our original reports,[1,2] a number of 3-methoxycarbonyl tetrahydro-β-carbolines have been successfully prepared by this procedure.[3,5–7,11] In view of these reports it was surprising to find that Grigg et al. reported that "A repeat of Cook's original work (tryptophan methyl ester, benzaldehyde, benzene, 80 °C, 48 h), i.e., generating the Schiffs base in situ gave only Schiffs base (**1a**) and no β-carboline (**2a,b**)."[4] To examine the conflicting experiences regarding this reaction, we have carried out several further experiments.

An important feature of the procedure that was successful in our hands is use of a Dean–Stark trap below the reflux condenser to remove water formed in the reaction.[1,2] In the Grigg report, most of the experiments were carried out in sealed NMR tubes, and no mention is made of the use of a water separator.[4] We have compared the course of the reactions of **1** and benzaldehyde (**2a**, purified by K_2CO_3 wash, drying, and distillation) in benzene with an open system and a water separator and in refluxing benzene in a closed system. Under the former conditions, after 12 h TLC indicated the presence of about 50% imine **4a**, the remainder of the material was a mixture of cis and trans carbolines **5a**. After 48 h the reaction had proceeded almost completely to **5a**. In a closed system without removal of water, the formation of **5a** was negligible, and the Schiff base **4a** was recovered quantitatively (Scheme I). To definitely determine the significance of the use of a Dean–Stark trap in the sequence, identical reactions between **1** and **2a** were performed both open to the air; however, in one case a Dean–Stark trap was used, while in the second experiment none was employed. Afte 24 h at reflux, aliquots of each reaction were analyzed by ^{13}C

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(9) DBU has been employed to deprotonate malonic esters for alkylation reactions and therefore should serve as a good proton scavenger in this case (Oedigerod, H.; Moeller, F. *Liebigs Ann. Chem.* **1976**, 348). It also is a strong enough base to deprotonate trinitrotoluene [Sugimoto, N.; Sasaki, M.; Osusi, J. *J. Phys. Chem.* **1982**, *86*, 3418; Ebel, H., F. C–H Acidity of Organic Compounds In "Methods der Organischen Chemie", Houben-Weyl; 1970, 13 (Part I), 27, 57].
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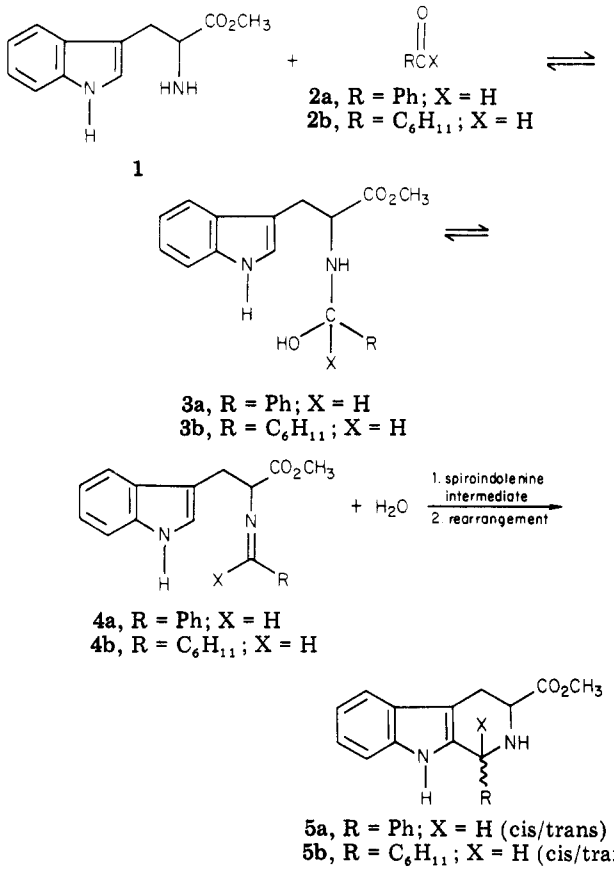
Scheme I



NMR. The condensation performed in the usual manner (DST) gave almost exclusively tetrahydro-β-carboline **5a** at this point, whereas the reaction carried out in the absence of the trap gave exclusively the noncyclized **4a**. Nevertheless the cyclization in the absence of a DST did eventually take place for after 84 h of heating this gave the cyclized product **5a**, but the reaction was extremely slow in comparison to the previously reported conditions (DST).[1,2]

A second point concerning reaction conditions concerns the presence of acid. Grigg et al. demonstrated the role of acid catalysis in the reaction and suggest that acidic impurities are responsible for the successful cyclization. To test the possibility that air oxidation of aldehyde occurred under the conditions originally used, the reaction of **1** and **2a** was carried out in a nitrogen stream, and cyclization to **5a** was found to be much slower. Moreover, addition of the proton scavenger DBU[9] completely suppressed the cyclization. The weaker base imidazole retarded the reaction significantly. Similar results were observed in reactions of **1** with the more reactive cyclohexanecarboxaldehyde (**2b**). These data support the hypothesis that a small amount of benzoic acid formed by air oxidation facilitates the cyclization.

In regard to the report by Grigg et al.[4] that the ratio of cis and trans isomers of the 1-phenyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines (**5a**) in their series was different from that reported in our earlier work,[8] this is entirely correct. The yields in ref 8 (60% trans) were based on isolated materials, while examination of the crude product by NMR (see Experimental Section) indicates the reaction mixture is composed of **5a** (58% cis, 42% trans). Hamaguchi reported isolation of a 1:1 mixture of cis to trans isomers of **5a**.[10] Grigg found the ratio to be 1:33:1 (NMR), while Bhaduri et al.[11] reported that the trans isomer predominated. In the present study a similar ratio (cis > trans) was observed in the 1-cyclohexyl series **5b** as well, although on the basis of isolated yields the trans isomer predominated.[2]

In conclusion, we emphasize that our experience and that of several other groups[3,5-7,11] establishes, contrary to the implication of Grigg et al.,[4] that the simple condensation of tryptophan methyl ester and aldehydes in refluxing benzene in an open system with a water separator provides a simple and very practical method for preparing 3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines.

Experimental Section

Tryptophan methyl ester·HCl was obtained from *dl*-tryptophan by esterification in methanolic HCl and converted into the free base (K_2CO_3).[12] This material **1** was recrystallized from ether–hexane (mp 70.5–72 °C (lit.[13] mp 71–73 °C)). Nuclear magnetic resonance spectra were recorded on Varian T-60 MHz, Varian CFT-20 ^{13}C NMR, and Brucker WH-250 (250-MHz Fourier transform instrument with multinuclear capability) spectrometers. Precoated TLC sheets used were silica gel 60F-254 (E. Merck). TLC plates were developed with the spray reagent ceric ammonium sulfate in 50% sulfuric acid.

Reactions of Tryptophan Methyl Ester (1) with Benzaldehyde (2a). Preparation of N_b-Benzylidenetryptophan Methyl Ester (4a). Tryptophan methyl ester (**1**, 4.4 g, 0.02 mol) and benzaldehyde (**2a**, 2.5 g, 0.025 mol) were dissolved in benzene (70 mL) and the solution was refluxed for 1 h in a flask equipped with a Dean–Stark trap and a reflux condenser open to the air. The solvent was evaporated and the residue was recrystallized from methanol to afford 5.87 g of material **4a** which melted at 123–126 °C (95.7% yield). An analytical sample melted at 130 °C (lit. mp 120 °C,[1] 128–129 °C[4]); ^{13}C NMR ($CDCl_3$, Me_4Si) 29.7, 52.1, 73.8, 111.2, 118.8, 119.4, 122.0, 123.6, 127.4, 128.5, 131.0, 135.8, 136.3, 163.6, 172.7.

Direct Preparation of 3-(Methoxycarbonyl)-1-phenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (5a) from 1 and 2a. 1. Tryptophan methyl ester (**1**, 2.2 g, 0.01 mol) and benzaldehyde (**2a**, 1.1 g, 0.0105 mol) from a newly purchased bottle were dissolved in distilled benzene (50 mL). The solution was held at reflux under a reflux condenser (open to the air) equipped with a Dean–Stark trap. The reaction progress was monitored by TLC after 12, 24, 48, and 70 h by comparison of R_f values with those of authentic samples.[2] After 12 h about 50% of the Schiff base was converted into a cis/trans mixture of **5a**. After 24 h the conversion increased to about 70–85% (estimated by TLC). After 48 h the reaction mixture showed only a small amount of unreacted **4a** (TLC) and after 70 h the reaction was essentially completed. Evaporation of benzene to dryness gave 3.19 g of crude **5a**. TLC of this material showed only two spots corresponding to the cis and trans isomers of **5a**. The chemical shifts of the carbon atoms in the ^{13}C NMR spectrum of the material were consistent with those reported in the literature.[8] The crude product was dissolved in $CDCl_3$ and the ^1H and ^{13}C NMR spectra were taken. The integration of the C(1) protons in the cis and trans **5a** isomers (250-MHz NMR spectrometer) was consistent with a ratio of cis to trans of 58:42 while integration of the ^{13}C NMR spectrum with suppressed NOE for several nonsuperimposable resonance lines also gave the value of 58:42. These values are consistent with values reported in the literature (54:46) measured by mass spectroscopy[3] and (54.5:45.5)[4] measured by 90-MHz ^1H NMR.

2. The reaction described above (see 1) was carried out in an open system exactly analogous to the above experiment but in the absence of a Dean–Stark trap (water separator). After 24 h an aliquot of the reaction mixture was analyzed by ^{13}C NMR and was shown to essentially contain only the imine **4a**. On heating the mixture for 36 h the tetrahydro-β-carbolines began to appear (TLC, ~30% **5a**) and after 84 h **4a** had cyclized completely to **5a**. The control experiment (experiment 1, DST) after 24 h at reflux contained essentially only **5a** (^{13}C NMR analysis).

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3. The same quantities of 1 and **2a** and benzene were used as in the two previous cases; however, **2a** was washed with a 50% solution of K_2CO_3, and then dried ($MgSO_4$) and distilled under reduced pressure at 38 °C (1 torr). The reaction mixture was held at reflux for 84 h in a closed system with a reflux condenser in the absence of a Dean–Stark trap. The condenser was closed with an oil bubbler. After 84 h TLC did not show any appreciable amount of the cyclized product **5a**. Evaporation of benzene to dryness gave a quantitative recovery of **4a**.

4. The reaction sequence termed 3 above was repeated by employing a Dean–Stark trap but under a nitrogen (Ameri-Gas, 99%) atmosphere. After the reaction was held for 12 h in refluxing benzene, no trace of **5a** was observed (compare 50% in experiment 1), and after 48 h only 10% of **5a** had been formed.

5. The reaction sequence termed 1 above was carried out in the presence of 1.5 g (0.01 mol) of DBU (1,8-diazabicyclo-[5.4.0]undec-5-ene) although **2a** was pretreated as indicated under 3. After 70 h no **5a** was detected. Although DBU is a strong enough base[9] to act as a proton scavenger and also abstract the proton from the α position of the ester, the Schiff base was observed in this sequence by TLC. The same reaction was repeated (reagents the same as above) with the addition of 0.7 g (0.01 mol) of imidazole. After the mixture was held for 50 h in refluxing benzene, the amount of the cyclized product **5a** was estimated to be 10–15%.

Registry No. 1, 7303-49-3; **2a**, 100-52-7; **2b**, 2043-61-0; **3a**, 90414-29-2; **3b**, 90414-30-5; **4a**, 19779-75-0; **4b**, 90414-31-6; *cis*-**5a**, 50302-60-8; *trans*-**5a**, 50302-61-9; *cis*-**5b**, 75140-08-8; *trans*-**5b**, 73327-06-7.

Supplementary Material Available: Experimental details for the work with 1 and cyclohexanecarboxaldehyde (**2b**) and additional experiments with **2a** (2 pages). Ordering information is given on any current masthead page.

Mercury in Organic Chemistry. 28. Synthesis of (π-Allyl)palladium Compounds by Remote Palladium Migration

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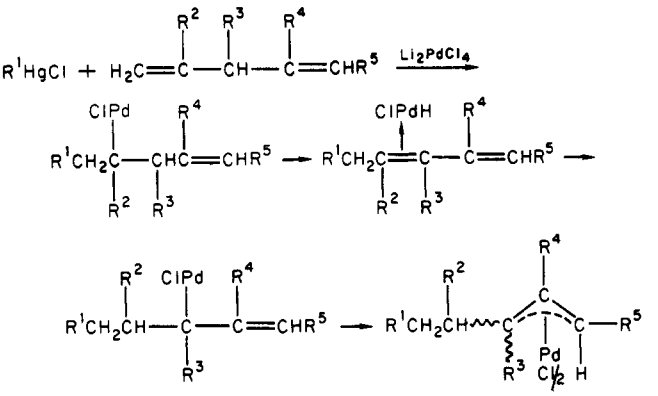
A variety of organomercurials react regioselectively with 1,4-, 1,5-, 1,6-, and 1,7-dienes and Li_2PdCl_4 to form good yields of (π-allyl)palladium compounds. These reactions apparently proceed by organopalladium addition to one of the diene double bonds and subsequent palladium migration.

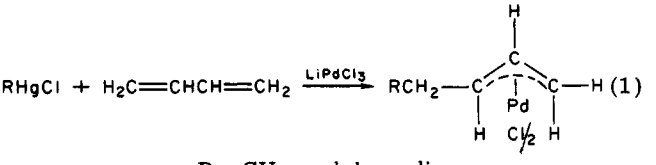
(π-Allyl)palladium compounds were first prepared 25 years ago.[2] In the meantime, a number of procedures have been reported for their preparation,[3-6] the most important of which are the insertion of palladium(0) reagents into the carbon–halogen bond of allylic halides[7-11] and the direct allylic hydrogen substitution of alkenes by palladium salts.[12-17] The former method requires substrates difficult to prepare and handle, while the latter suffers from an inability to predict or control the regioselectivity of palladation.

The palladium-promoted addition of organomercurials to 1,3-dienes and alkenes has recently provided new routes

Scheme I



to (π-allyl)palladium compounds. Thus, certain organomercurials react with $LiPdCl_3$ and 1,3-dienes to afford (π-allyl)palladium compounds (eq 1).[18,19] We have found



R = CH_3, aryl, benzylic

that vinylmercurials readily react with Li_2PdCl_4 and simple

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