Regioselective Palladium-Catalyzed Tandem α-Arylation/Isomerization of Cyclic Enamides

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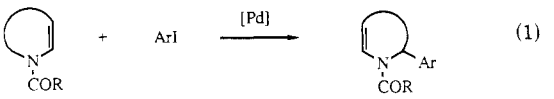
Palladium-catalyzed reactions of aryl iodides with the cyclic enamides 1-(methoxycarbonyl)-1,4,5,6-tetrahydropyridine (**1**), 1-formyl-1,4,5,6-tetrahydropyridine (**2**), and 1-formyl-2-pyrroline (**3**) result in regioselective α-arylation, with concomitant isomerization of the double bond into conjugation with the nitrogen atom. The new enamides 1-(methoxycarbonyl)-2-aryl-1,2,3,4-tetrahydropyridines (**4**), 1-formyl-2-aryl-1,2,3,4-tetrahydropyridines (**5**), and 1-formyl-5-phenyl-2-pyrroline (**6a**) were isolated in various yields. The migration of the double bond is affected (a) by an amino group in the ortho position of the aryl iodide; (b) by the presence of silver salts; and (c) partly by a 4-methyl group in the tetrahydropyridine ring. In these cases the allylic compounds 2-aryl-1,2,5,6-tetrahydropyridines (**10a,b** and **13**) are formed.

Introduction

Numerous natural products contain fragments of nitrogen heterocycles substituted in the 2-position.[1] Five- and six-membered nonaromatic heterocycles, arylated in the 2-position, share partial structures with many interesting alkaloids. Consequently, several methods for their preparation have been developed, including heterocycle formation in the last step by ring-closure reactions,[2] reduction of 2-aryl-substituted pyrroles and pyridines,[3] and the introduction of the aromatic ring in a preformed heterocycle.[4,5] One attractive example of the latter is the use of cyclic *N*-formyl-2-methoxy amines in electrophilic amidoalkylation of aromatic compounds,[5] which takes advantage of the facile electrochemical preparation of the starting materials, the so-called Ross-Eberson-Nyberg reaction.[6] Elimination of methanol from *N*-formyl-[7] or *N*-carbamoyl-2-methoxy amines[6f] furnishes enamides, versatile compounds that allow regiocontrolled functionalizations both in the α-position[8] and the β-position[9] to the nitrogen atom.

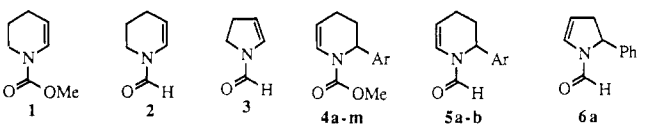
We herein report a palladium-catalyzed tandem α-arylation/isomerization reaction of cyclic enamides, which restores the enamide fragment, thus making it accessible for further structural elaborations (eq 1).



(1)

Results

The reaction of aryl iodides with the enamides **1**, **2**, or **3** under standard Heck reaction conditions,[10] using a catalytic amount of palladium acetate and triethylamine as the base in the absence of solvent, provided 1-(methoxycarbonyl)-2-aryl-1,2,3,4-tetrahydropyridines (**4**), 1-formyl-2-aryl-1,2,3,4-tetrahydropyridines (**5**), and 1-formyl-5-phenyl-2-pyrroline (**6a**).



The reaction was sensitive to the amount of enamide present, and use of a stoichiometric amount of **1** and iodobenzene resulted in biphenyl formation. With a large excess (10 equiv) of the olefin, this undesired reaction was suppressed, but the reaction was very slow. Four equivalents of the enamide were used throughout this study. The reactions were performed in most cases at 80 °C to minimize the amount of double bond isomers which formed at higher temperature (120 °C). The addition of triarylphosphines resulted in lower yields and slower conversion and provided double bond isomers. Reactions in triethylamine as solvent also resulted in a slow reaction rate: the iodobenzene was consumed after 1 week at 115 °C, and a considerable amount of biphenyl was formed. A similar outcome was observed in a nonpolar solvent such as toluene. Reactions under phase-transfer conditions in dimethylformamide or acetonitrile, with sodium carbonate as the base and in the absence of triarylphosphine, a modification of the Heck reaction introduced by Jeffrey,[11]

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(6) (a) Finkelstein, M.; Ross, S. D. *Tetrahedron* **1972**, *28*, 4497. (b) Cedheim, L.; Eberson, L.; Helgée, B.; Nyberg, K.; Servin, R.; Sternerup, H. *Acta Chem. Scand. B* **1975**, *29*, 617. (c) Nyberg, K.; Servin, R. *Ibid.* **1976**, *30*, 640. (d) Mitzlaff, M.; Warning, K.; Jensen, H. *Justus Liebigs Ann. Chem.* **1978**, 1713. (e) Eberson, L.; Hlavaty, J.; Jönsson, L.; Nyberg, K.; Servin, R.; Sternerup, H.; Wistrand, L.-G. *Acta Chem. Scand. B* **1979**, *33*, 113. (f) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.-i.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697. For reviews see: (g) Shono, T. *Tetrahedron* **1984**, *40*, 811. (h) Wistrand, L.-G *Janssen Chim. Acta* **1986**, *4*(2), 34.

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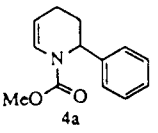
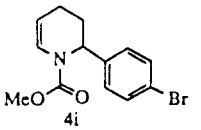
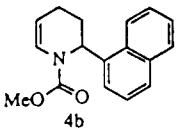
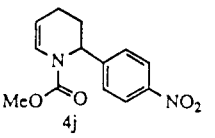
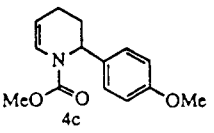
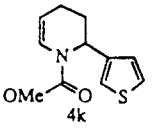
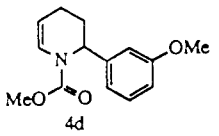
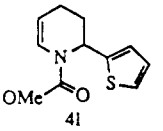
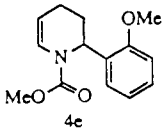
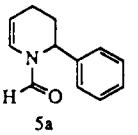
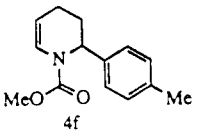
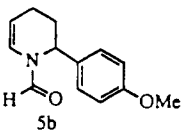
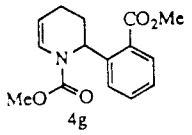
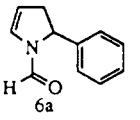
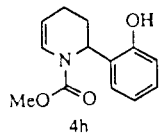
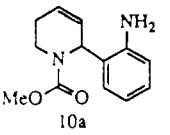
Table I. Palladium-Catalyzed Arylation of Cyclic Enamides (1–3) with Aryl Halides in the Absence of Solvent at 80 °C[a]

entry	product	isolated yield, %	entry	product	isolated yield, %
1	 4a	58[b]	9	 4i	18[c]
2	 4b	70[c]	10[e]	 4j	17[b]
3	 4c	61[c]	11	 4k	20[c]
4	 4d	59[c]	12	 4l	5[c]
5	 4e	62[b]	13	 5a	39[b]
6	 4f	60[b]	14	 5b	48[b]
7	 4g	61[b]	15	 6a	40[c]
8	 4h	26[b,d]	16	 10a	42[b]

[a] The reaction utilized aryl iodide (5 mmol), cyclic enamide (1, 2 or 3) (4 equiv), triethylamine (1.2 equiv), and palladium acetate (3 mol %). [b] Reaction time 2 days. [c] Reaction time 1 day. [d] The tricyclic carbamate 15 (entry 8) was also isolated (15%) from the reaction. [e] 1-Bromo-4-nitrobenzene was used as starting material.

furnished, in a slow reaction, **4a** (20% GC), the isomer **10b** (5% GC), and biphenyl (34% GC) as the only identified products.

The preparative results from a series of aryl iodides are summarized in Table I. Good to moderate yields were obtained with aryl iodides, provided they were not substituted with electron-withdrawing groups. A 3- or 4-nitro substituent affected the product distribution, so that 3,3′- or 4,4′-dinitrobiphenyl, respectively, was formed almost exclusively, and only a trace of coupled product was detected. The nature of the halide was also found to be important, and 1-bromo-4-nitrobenzene gave coupled product, but in low isolated yield (21%). The electron-deficient heterocycle 3-iodopyridine was slowly consumed and furnished 3,3′-bipyridyl, and 23% of coupled product was isolated, consisting of 1-(methoxycarbonyl)-2-(3-pyridyl)-1,2,3,4-tetrahydropyridine (**4m**) and two double bond isomers in the proportions 40/10/1.

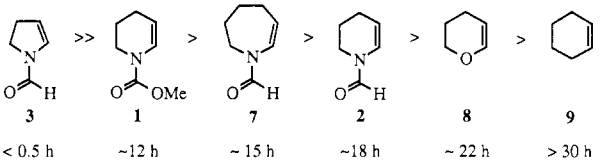


Figure 1.

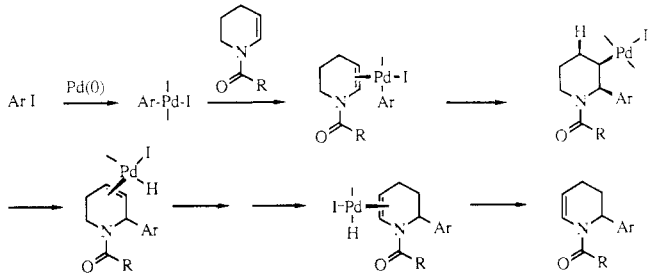
Electron-rich heterocyclic systems such as 2- and 3-iodothiophene and 3-iodofuran exhibited high reactivity, but the reactions were accompanied by bithienyl formation from the thiophene derivatives, and in addition by the formation of tar from 2-iodothiophene and 3-iodofuran. On the contrary, 4-iodo-1-methylpyrazole and 1-iodo-2,4,6-trimethylbenzene[12] were resistant to reaction, and the starting materials were recovered despite increased reaction temperatures (120 °C).

The rate of conversion of iodobenzene is dependent on the ring size of the enamide. Iodobenzene is completely

(11) (a) Jeffrey, T. *Tetrahedron Lett.* **1985**, *26*, 2667. See also (b) Larock, R. C.; Baker, B. E. *Ibid.* **1988**, *29*, 905. (c) Larock, R. C.; Gong, W. H.; Baker, B. E. *Ibid.* **1989**, *30*, 2603.

(12) This substrate reacts smoothly with trimethylvinylsilane. Nilsson, K.; Karabelas, K.; Hallberg, A. *Acta Chem. Scand.*, in press.

Scheme I

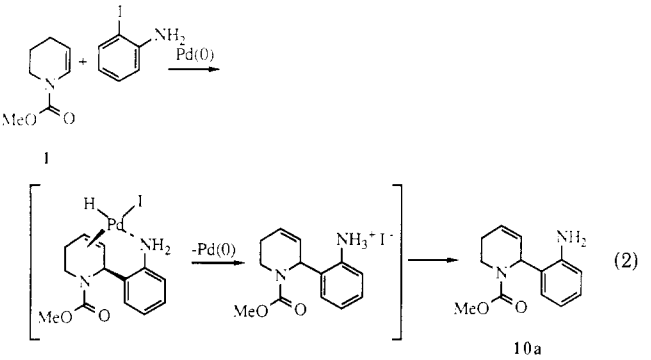


converted after 1 h with **3** as substrate, while longer reaction times are required for the six- and seven-membered rings **1**, **2**, **8**, **9**, and **7**.[13] In the latter case (**7**), a mixture of double bond isomers was formed, making this olefin less attractive as a substrate in preparative reactions. A comparison of the time required for 50% conversion of iodobenzene employing 4 equiv of olefin and 3 mol % of palladium acetate at 80 °C is shown in Figure 1. Note that this order of reactivity was determined in the absence of solvent.

Discussion

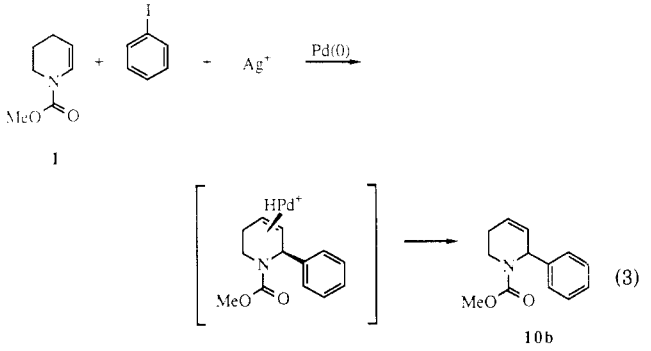
Isomerization. We assume that the α-arylation/isomerization proceeds via the pathway depicted in Scheme I. A syn 1,2-addition of the intermediate organopalladium reagent to the double bond produces an unstable σ-adduct that decomposes by syn elimination of palladium and hydride. Since there is no hydrogen cis to palladium available on the arylated carbon, elimination gives a nonconjugated olefin. By further readdition and reelimination of palladium hydride, the double bond migrates into conjugation with the ring nitrogen π-electrons.[14] The fact that the compound with the double bond in conjugation with the aryl substituent is not formed is good evidence that the PdH species remains bound, and that once dissociation occurs decomposition to Pd(0) precludes readdition. The reaction is analogous to the palladium-catalyzed arylation of dihydropyran extensively studied by Daves Jr.[15] and the related vinylation/isomerization of dihydropyran with a vinyltriflate reported by Stille.[16]

At higher temperatures the dissociation of HPdI and subsequent Pd(0) formation is facilitated, thus furnishing double bond isomers. The dissociation of HPdI from the π-olefin complex also seems to be favored by the presence of ligands.[17] Particularly illustrative is the reaction of 4-iodoanisole with **1**, which gives a **4c**/double bond isomer ratio of 3/2 with P(*o*-tol)$_3$, while a 9/1 ratio is obtained in the absence of ligand. A similar influence on the isomerization, although somewhat less pronounced, was observed with **1**, employing PPh_3, DIOP, or BINAP as ligands.[18] Interestingly, reactions in triethylamine did not promote the formation of nonconjugated olefins.[19] One explanation for the relatively larger amounts of isomers obtained with 3-iodopyridine as substrate could be intermolecular complexation of palladium to the pyridine nitrogen. Intramolecular coordination of palladium to the aniline nitrogen is probably responsible for the formation of the 1,2,5,6-tetrahydropyridine derivative **10a** from 2-iodoaniline (entry 16, eq 2). Readdition of the hydrido-



10a

palladium iodide to the double bond may be intercepted as a result of rapid decomposition of the former by the proximal amino group. Silver ions promote biphenyl formation but are also effective in suppressing the isomerization of the initially formed double bond isomer, and only traces of other isomers were observed (eq 3).[20] We



10b

believe that oxidative addition and subsequent iodide abstraction by silver ions[21] precedes olefin insertion and irreversible syn elimination[22] of a hydridopalladium species, to provide 1-(methoxycarbonyl)-2-phenyl-1,2,5,6-tetrahydropyridine (**10b**). The addition of silver ions exerted only a limited effect on the reaction rate.[23] This is contrary to what we observed in the arylation of cyclo-

(13) (a) The following relative reactivities of cycloalkenes in palladium-catalyzed phenylation have been reported: cyclopentene > cyclooctene > cycloheptene > cyclohexene, see ref 11b. For intermolecular palladium-catalyzed arylation of alicyclic alkenes, see also: (b) Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1977**, 159. (c) Cortese, N. A.; Ziegler, C. B., Jr.; Hrnjez, B. J.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2952. (d) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Ibid.* **1979**, *35*, 329. (e) Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31. (f) Kikukawa, K.; Maemura, K.; Kiseki, Y.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1981**, *46*, 4885. See also ref 11c.

(14) For examples of Pd/C-catalyzed isomerization of *N*-acyl-1,2,5,6-tetrahydropyridines to *N*-acylenamines, see: Wanner, K. Th.; Kärtner, A. *Heterocycles* **1987**, *26*, 917. See also ref 8c.

(15) (a) Arai, I.; Daves, G. D., Jr. *J. Org. Chem.* **1978**, *43*, 4110. (b) Arai, I.; Daves, G. D., Jr. *Ibid.* **1979**, *44*, 21. (c) Lee, T. D.; Daves, G. D., Jr. *Ibid.* **1983**, *48*, 399.

(16) Scott, W. J.; Peña, M. R.; Swärd, K.; Stoessel, S. J.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 2302.

(17) For a discussion of the rate of readdition of the hydridopalladium group in an olefin π-complex intermediate to the double bond relative to its rate of dissociation from the complex, see ref 10b, p 349.

(18) No induction of chirality was observed with (−)-DIOP or (*R*)-(+)-BINAP.

(19) For a discussion of the role of triethylamine in the Heck reaction, see: Benhaddou, R.; Czernecki, S.; Ville, G.; Zegar, A. *Organometallics* **1988**, *7*, 2435.

(20) The suppression of isomerization by silver additives was first reported by Overman's group: (a) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (b) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. See also (c) Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919. (d) Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1989**, *54*, 2047. For palladium-catalyzed arylation of dihydropyran and the use of silver salts, see ref 11c.

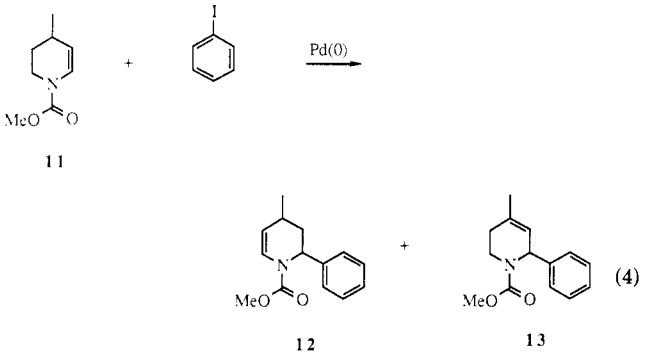
(21) Halide abstraction by silver salts from arylpalladium halides has been reported: (a) Grove, D. M.; van Koten, G.; Louwen, J. N.; Noltes, J. G.; Spek, A. L.; Ubbels, H. J. C. *J. Am. Chem. Soc.* **1982**, *104*, 6609. (b) Rimml, H.; Venanzi, L. M. *J. Organomet. Chem.* **1984**, *260*, C52–54.

(22) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4909.

(23) For examples of rate enhancement induced by the addition of silver ions to palladium-catalyzed Heck reaction medium, see: (a) Karabelas, K.; Hallberg, A. *Tetrahedron Lett.* **1985**, *26*, 3131. (b) Karabelas, K.; Hallberg, A.; Westerlund, C. *J. Org. Chem.* **1985**, *50*, 3896. (c) Karabelas, K.; Hallberg, A. *Ibid.* **1986**, *51*, 5286. See also refs 20a,b and 22.

hexene, where silver additives enhance the reaction rate considerably. In the latter case, the isomer selectivity is low and a 3-phenylcyclohexene/4-phenylcyclohexene ratio of 2.5/1 is obtained. In the absence of silver additives and solvent, and with triethylamine as base, 4-phenylcyclohexene is the main product. This result was unexpected, since 3-phenylcyclohexene has been reported to be formed under Heck reaction conditions.[13c,24]

A methyl group in the 4-position disfavors double bond migration, and a mixture of two olefins as the major products is formed, as depicted in eq 4.



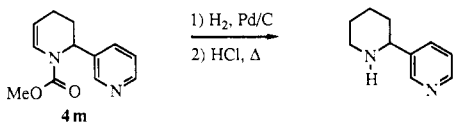
(4)

Regiochemistry. A characteristic feature of the palladium-catalyzed arylation of **1–3** and of cyclic enol ethers[25] is the α-regiospecificity achieved. In intermolecular arylations of acyclic enamides[26] and enol ethers,[27] regioisomeric mixtures are obtained. Arylation of electron-rich acyclic enol ethers in the β-position is strongly favored by an electron-withdrawing group in the para position of the arylating agent.[25b,27d] Reactions of 4-nitro-substituted halobenzenes with 3,4-dihydro-2*H*-pyran[25b] or with the tetrahydropyridine **1** furnish both low yields of α-arylated products and no β-arylated product. This result could be interpreted by suggesting that the β-arylation is reversible, or that in some way the absence of a facile decomposition mode precludes σ-adduct formation.[28] Grigg et al. have performed ring-closure reactions with enamides, in which the regiochemical outcome is governed by access to a syn hydrogen for elimination.[4g] The palladium-catalyzed arylation/reduction method with formic acid, introduced by Cacci,[29] which in principle would allow trapping of the σ-palladium intermediate of both α- and β-arylated *N*-acylpiperidines, was unfortunately unsuccessful and produced biphenyl.

Palladium-catalyzed hydrogenation of the tetrahydropyridine ring to give the saturated heterocycle is facile, as exemplified by the preparation of the tobacco alkaloid anabasine in racemic form (eq 5).

Conclusion

The regioselective palladium-catalyzed reaction of aryl iodides with cyclic enamides offers an alternative route to α-substituted nitrogen heterocycles. The method merits attention due to the easy access of aryl iodides and the simplicity of the experimental procedure. Restoration of the enamide fragment makes the procedure synthetically attractive, since further transformations could, in principle, be performed.



4m

(5)

Experimental Section

General Methods. ^{1}H NMR spectra were recorded on a Varian XL 300 spectrometer. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Infrared spectra were obtained on a Perkin-Elmer 298 spectrophotometer. Mass spectra were recorded on a Finnigan 4021 (Data System Incos 2100) mass spectrometer at an ionizing voltage of 70 eV. Flash chromatography was performed essentially by the procedure of Taber[30] using TLC-silica gel 60 H (15 μm, E. Merck, No. 11695). Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F-254 (E. Merck). Gas chromatographic analyses were carried out on a Varian 3300 instrument, equipped with a 2-m glass column of 5% OV 17 on Chromosorb W. GC yields were determined using 2,3-dimethylnaphthalene as internal standard. HPLC separations were performed with a LDC Consta Metric III system equipped with a RI detector (LKB 2142 refractive index detector). A nucleosil silica gel column (500 × i.d. 10), eluted with heptane/ethyl acetate (90/10) was used for the purification of **12**. The purifications of **13** and **4m** were performed on a RP Polygosil C_{18} column (500 × i.d. 10), 5 μm, using acetonitrile/water (90/10) and acetonitrile, respectively, as eluents. Melting points were determined in capillary tubes and are uncorrected. Elemental analyses were performed by Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim, West Germany, and by the Microanalytical Laboratory at the University of Lund, Sweden. All the reactions were carried out in a 50-mL, heavy-walled, and thin-necked Pyrex tube, sealed with a screw-cap fitted with a Teflon gasket.

Materials. Aryl Halides. Iodobenzene (Janssen), 4-iodotoluene (Janssen), 2-, 3-, and 4-iodoanisole (Fluka), 2-iodoaniline (Fluka), 1-bromo-4-nitrobenzene (Fluka), 1-iodo-3-nitrobenzene (EGA) and 1-iodo-4-nitrobenzene (EGA), 2-iodophenol (Merck, Schuchardt), and 1-bromo-4-iodobenzene (Aldrich) were obtained from commercial sources and used without further purification. 1-Iodonaphthalene (Aldrich) was washed with a saturated sodium thiosulfate solution and distilled before use. 2-(Iodomethyl)-benzoate was prepared from 2-iodobenzoic acid by a published procedure.[31] The iodothiophenes were generously supplied by Professor Salo Gronowitz.

Other Reagents. Palladium acetate, silver carbonate, and triethylamine were obtained from Janssen and used as received. Triphenylphosphine and tri-*o*-tolylphosphine were recrystallized from ethanol. Samples of five-, six-, and seven-membered cyclic enamides[7] were generously supplied by Dr. Mats Malmberg at Synthelec.[32] All solvents were distilled prior to use.

General Procedure for the Arylation of Cyclic Enamides. A mixture of palladium acetate (34 mg, 0.15 mmol), triethylamine (607 mg, 6 mmol), aryl iodide (5 mmol; 1-bromo-4-nitrobenzene was used for the preparation of **4j**), and the cyclic enamide (20 mmol) was stirred under nitrogen until homogeneous and heated in an oil bath at 80 °C. The reaction was analyzed by GC, and after complete consumption of the aryl halide, the reaction was stopped (see Table I for further details). The cooled reaction mixture was diluted with diethyl ether, filtered and washed with water. The aqueous layer was extracted three times with additional diethyl ether. The combined organic phases were once washed with water, dried ($MgSO_4$), and concentrated in vacuo. The excess of enamide **1** was thereupon removed by Kugelrohr distillation (~65 °C/3 mmHg). The excess of **2** and **3** could

(24) A high yield of 3-phenylcyclohexene was also obtained under phase-transfer conditions at room temperature (see ref 11b).

(25) (a) Arai, I.; Daves, G. D., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 287. (b) Andersson, C.-M.; Hallberg, A.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3529. (c) Outten, R. A.; Daves, G. D., Jr. *Ibid.* **1989**, *54*, 29. See also refs 15 and 11c.

(26) Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2949.

(27) (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5535. (b) Danno, S.; Moritani, I.; Fujiwara, Y. *Tetrahedron* **1969**, *25*, 4819. (c) Asano, R.; Moritani, I.; Sonoda, A.; Fujiwara, Y.; Teranishi, S. *J. Chem. Soc. C* **1971**, 3691. (d) Hallberg, A.; Westfelt, L.; Holm, B. *J. Org. Chem.* **1981**, *46*, 5414. See also refs 13b, 15b, and 25b.

(28) For a discussion, see: Daves, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433.

(29) This reaction was successfully applied to α,β-unsaturated carbonyl compounds: Cacchi, S.; Arcadi, A. *J. Org. Chem.* **1983**, *48*, 4236.

(30) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

(31) Brown, H. C.; Okamoto, Y.; Ham, G. *J. Am. Chem. Soc.* **1957**, *79*, 1906.

(32) Synthelec, Ideon, S-223 70 Lund, Sweden.

alternatively be withdrawn by washing the combined organic phases several times with water. The resulting material was subjected to flash chromatography. The crude product (~1.5 g) was dissolved in diethyl ether and evaporated on coarse gel before applicated to the column (ϕ 50-mm, 80 g of silica gel), whereupon 25-mL fractions were collected.

The ^{1}H NMR spectra of the cyclic enamides, with a few exceptions (**4h**, **10a**, **14**, and **15**), show, when recorded in $CDCl_3$ at room temperature (for a recording at 48 °C see preparation of **4i**), the existence of two rotamers in an approximately 1/1 ratio. The vinylic hydrogens and the methine hydrogen appear at different chemical shifts in the two rotamers. In some cases (**4a,b** and **5a**) one of the vinylic hydrogens (NCH=) in one of the rotamers overlaps with the aromatic hydrogens in the spectrum. Selected structures were assigned by decoupling experiments (**4a,g**, **5a**, and **10a**), in which the vinylic hydrogens and the methine hydrogen, and in the case of **10a** also the methylene hydrogens, were irradiated. The structures **10a** and **10b** were further confirmed by COSY experiments. For the structure proof of **13**, see below.

1-(Methoxycarbonyl)-2-phenyl-1,2,3,4-tetrahydropyridine (4a): white crystals, 0.63 g (58%); mp 66–68 °C; eluent, toluene/diethyl ether, 20/1; ^{1}H NMR ($CDCl_3$) δ 1.60–2.10 (m, 4 H), 3.65, 3.77 (s, 3 H, CO_2CH_3), 4.93, 5.01 (m, 1 H, NC=CH), 5.34, 5.45 (br s, 1 H, NCHPh), 7.00 (br d, 0.5 H, NCH=C, J = 7.0 Hz), 7.10–7.37 [m, 5.5 H (5 H, Ph, and 0.5 H, NC=CH)]; IR (KBr) 1710 cm^{-1}; MS m/e (relative intensity) 217 (M$^+$, 41), 158 (20), 142 (53), 115 (11), 104 (100), 91 (32), 82 (13), 78 (26).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96. Found: C, 72.01; H, 7.02.

An additional 0.17 g (16%) was isolated from subsequent fractions, which contained **4a** and a double bond isomer in a ratio of 3/1, as deduced by GC.

According to GC/MS analysis of the reaction mixture before workup, 72% of **4a**, 7% of **10b**, 5% of an unidentified double bond isomer, 5% of three diphenylated **1**, and 5% of biphenyl were formed, and 6% of iodobenzene was recovered.

1-(Methoxycarbonyl)-2-(1-naphthyl)-1,2,3,4-tetrahydropyridine (4b): light yellow crystals, 0.94 g (70%); mp 104–106 °C (from ligroin); eluent, toluene/diethyl ether, 30/1; ^{1}H NMR ($CDCl_3$) δ 1.60–2.26 (m, 4 H), 3.57, 3.76 (s, 3 H, CO_2CH_3), 4.98, 5.06 (m, 1 H, NC=CH), 6.13, 6.25 (br s, 1 H, NCHAr), 7.15 (br d, 0.5 H, NCH=C, J = 8.3 Hz), 7.25–8.15 [m, 7.5 H (7 H, Ar, and 0.5 H, NCH=C)]; IR (KBr) 1685 cm^{-1}; MS m/e (relative intensity) 267 (M$^+$, 34), 208 (10), 192 (53), 179 (20), 165 (26), 153 (100), 139 (26), 89 (11), 82 (12).

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41. Found: C, 76.26; H, 6.46.

1-(Methoxycarbonyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydropyridine (4c): white crystals, 0.75 g (61%); mp 49–51 °C; eluent, pentane/diethyl ether, 4/1; ^{1}H NMR ($CDCl_3$) δ 1.63–2.05 (m, 4 H), 3.66, 3.76 (s, 3 H, CO_2CH_3), 3.78 (s, 3 H, OCH_3), 4.92, 5.00 (m, 1 H, NC=CH), 5.29, 5.39 (br s, 1 H, NCHAr), 6.80–7.17 [m, 5 H (4 H, Ar, and 1 H, NCH=C)]; IR (KBr) 1705 cm^{-1}; MS m/e (relative intensity) 247 (M$^+$, 15), 172 (51), 134 (100), 119 (22), 91 (24), 77 (10).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. Found: C, 67.51; H, 7.03.

According to GC/MS analysis of the reaction mixture before workup, 71% of **4c**, 8% and 7% of two unidentified double bond isomers, 5% of three diphenylated **1**, and 5% of biphenyl were formed, and 4% of iodobenzene was recovered.

1-(Methoxycarbonyl)-2-(3-methoxyphenyl)-1,2,3,4-tetrahydropyridine (4d): light yellow oil, 0.73 g (59%); eluent, pentane/diethyl ether, 3/1; ^{1}H NMR ($CDCl_3$) δ 1.60–2.15 (m, 4 H), 3.65, 3.76 (s, 3 H, CO_2CH_3), 3.78 (s, 3 H, OCH_3), 4.93, 5.01 (m, 1 H, NC=CH), 5.30, 5.41 (br s, 1 H, NCHAr), 6.72–7.26 [m, 5 H (4 H, Ar, and 1 H, NCH=C)]; IR (neat oil) 1710 cm^{-1}; MS m/e (relative intensity) 247 (M$^+$, 46), 188 (17), 172 (100), 159 (33), 140 (11), 134 (82), 121 (18), 104 (21), 91 (48), 78 (21).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. Found: C, 68.00; H, 6.95.

1-(Methoxycarbonyl)-2-(2-methoxyphenyl)-1,2,3,4-tetrahydropyridine (4e): white crystals, 0.77 g (62%); mp 66–68 °C; eluent, toluene/diethyl ether, 20/1; ^{1}H NMR ($CDCl_3$) δ 1.58–2.16 (m, 4 H), 3.63, 3.75 (s, 3 H, CO_2CH_3), 3.86 (s, 3 H, OCH_3), 4.92, 5.02 (m, 1 H, NC=CH), 5.62, 5.75 (br s, 1 H, NCHAr), 6.83–7.25 [m, 5 H (4 H, Ar, and 1 H, NCH=C)]; IR (KBr) 1700 cm^{-1}; MS m/e (relative intensity) 247 (M$^+$, 38), 188 (34), 172 (98), 157 (17), 139 (14), 134 (33), 119 (84), 107 (10), 91 (100), 80 (18), 77 (21).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. Found: C, 68.09; H, 6.94.

According to GC/MS analysis of the reaction mixture before workup, 80% of **4e** and 15% and 5% of two unidentified double bond isomers were formed.

1-(Methoxycarbonyl)-2-(4-tolyl)-1,2,3,4-tetrahydropyridine (4f): white crystals, 0.69 g (60%); mp 77–79 °C (from MeOH–H_2O); eluent, toluene/diethyl ether, 15/1; ^{1}H NMR ($CDCl_3$) δ 1.60–2.08 (m, 4 H), 2.32 (s, 3 H, CH_3), 3.66, 3.76 (s, 3 H, CO_2CH_3), 4.92, 5.00 (m, 1 H, NC=CH), 5.32, 5.41 (br s, 1 H, NCHAr), 6.95–7.17 [m, 5 H (4 H, Ar, and 1 H, NCH=C)]; IR (KBr) 1700 cm^{-1}; MS m/e (relative intensity) 231 (M$^+$, 44), 172 (14), 156 (82), 139 (12), 118 (100), 105 (19), 91 (28), 82 (12), 77 (11).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.96; H, 7.27.

According to GC/MS analysis of the reaction mixture before workup, 79% of **4f**, 9% and 5% of two unidentified double bond isomers, and 7% of three diphenylated **1** were formed.

1-(Methoxycarbonyl)-2-[2-(carboxymethyl)phenyl]-1,2,3,4-tetrahydropyridine (4g): white crystals, 0.84 g (61%); mp 66–67 °C; eluent, pentane/diethyl ether, 2/1; ^{1}H NMR ($CDCl_3$) δ 1.56–2.12 (m, 4 H), 3.60, 3.73 (s, 3 H, NCO_2CH_3), 3.92 (s, 3 H, CO_2CH_3), 4.98, 5.07 (m, 1 H, NC=CH), 6.26 (br s, 1 H, NCHAr), 7.06, 7.20 (br d, 1 H, NCH=C, J = 8.5 Hz), 7.25–7.99 (m, 4 H, Ar); IR (KBr) 1720, 1695 cm^{-1}; MS m/e (relative intensity) 275 (M$^+$, 16), 243 (11), 216 (19), 184 (100), 168 (63), 161 (10), 156 (17), 129 (15), 82 (14), 77 (25).

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22. Found: C, 65.76; H, 6.11.

According to GC/MS analysis of the reaction mixture before workup, 75% of **4g**, 11% and 5% of two unidentified double bond isomers, and 9% of methyl benzoate were formed.

1-(Methoxycarbonyl)-2-(2-hydroxyphenyl)-1,2,3,4-tetrahydropyridine (4h): white crystals, 0.30 g (26%); mp 176–177 °C; eluent, dichloromethane/methanol, 45/1; ^{1}H NMR ($CDCl_3$) δ 1.75–2.23 (m, 4 H), 3.73 (s, 3 H, CO_2CH_3), 5.01 (m, 1 H, NC=CH), 5.65 (br s, 1 H, NCHAr), 6.69 (d, 1 H, NCH=C, J = 8.1 Hz), 6.77–7.15 (m, 4 H, Ar); The hydroxyl proton appears as a singlet with acetone-d_6 as solvent: ^{1}H NMR (acetone-d_6) δ 1.76–2.30 (m, 4 H), 3.58, 3.70 (s, 3 H, CO_2CH_3), 4.92, 4.98 (br s, 1 H, NC=CH), 5.65, 5.72 (br s, 1 H, NCHAr), 6.71–7.18 [m, 5 H (4 H, Ar, and 1 H, NCH=C)], 8.61 (br s, 1 H, OH); IR (KBr) 3300, 1680 cm^{-1}; MS m/e (relative intensity) 233 (M$^+$, 87), 174 (40), 158 (100), 146 (11), 131 (57), 120 (77), 114 (95), 107 (20), 91 (72), 82 (35), 77 (54).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.91. Found: C, 67.00; H, 6.56.

6*H*,10*H*-11,11a-Dihydropyrido[1,2-*c*][1,3]benzoxazin-6-one (15) was also formed in the reaction of 2-iodophenol with **1**: white crystals (0.15 g, 15%); mp 99–102 °C; eluent, pentane/diethyl ether, 3/1; ^{1}H NMR ($CDCl_3$) δ 1.84–2.66 (m, 4 H), 4.71 (dd, 1 H, NC=CH, J = 11.6, 2.4 Hz), 5.28 (m, 1 H, NCHAr), 7.03–7.34 [m, 5 H (4 H, Ar and 1 H, NCH=C)]; IR (KBr) 1710 (br) cm^{-1}; MS m/e (relative intensity) 201 (M$^+$, 53), 157 (13), 147 (10), 131 (14), 119 (12), 91 (28), 82 (100), 77 (24).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51. Found: C, 71.54; H, 5.56.

1-(Methoxycarbonyl)-2-(4-bromophenyl)-1,2,3,4-tetrahydropyridine (4i): white crystals, 0.27 g (18%); mp 61–64 °C; eluent, toluene/diethyl ether, 20/1; ^{1}H NMR ($CDCl_3$) δ 1.62–2.10 (m, 4 H), 3.65, 3.77 (s, 3 H, CO_2CH_3), 4.93, 5.02 (m, 1 H, NC=CH), 5.28, 5.39 (br s, 1 H, NCHAr), 6.93–7.46 [m, 5 H (4 H, Ar, and 1 H, NCH=C)]; ^{1}H NMR ($CDCl_3$) at 48 °C δ 2.10–1.62 (m, 4 H), 3.72 (br s, 3 H, CO_2CH_3), 4.97 (m, 1 H, NC=CH), 5.34 (br s, 1 H, NCHAr), 6.93–7.46 [m, 5 H (4 H, Ar, and 1 H, NCH=C)]; IR (KBr) 1710 cm^{-1}; MS m/e (relative intensity) 297 (M$^+$, 34), 295 (35), 236 (16), 222 (18), 220 (19), 184 (88), 182 (90), 169 (16), 157 (22), 141 (29), 130 (28), 115 (35), 103 (86), 94 (10), 89 (52), 82 (46), 77 (100).

Anal. Calcd for $C_{13}H_{14}BrNO_2$: C, 52.72; H, 4.76. Found: C, 52.70; H, 4.80.

1-(Methoxycarbonyl)-2-(4-nitrophenyl)-1,2,3,4-tetrahydropyridine (4j): yellow crystals, 0.22 g (17%); mp 124–126

°C (from MeOH–H_2O); eluent, pentane/diethyl ether, 2/1; ^1H NMR ($CDCl_3$) δ 1.58–2.17 (m, 4 H), 3.65, 3.78 (s, 3 H, CO_2CH_3), 4.97, 5.06 (m, 1 H, NC=CH), 5.41, 5.52 (br s, 1 H, NCHAr), 7.01, 7.15 (m, 1 H, NCH=C), 7.30–8.21 (m, 4 H, Ar); IR (KBr) 1705 cm^{-1}; MS *m/e* (relative intensity) 262 (M^+, 66), 245 (23), 215 (18), 203 (22), 157 (32), 149 (26), 140 (41), 130 (22), 119 (50), 115 (26), 103 (48), 96 (10), 91 (33), 82 (34), 77 (67).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38. Found: C, 59.73; H, 5.04.

1-(Methoxycarbonyl)-2-(3-thienyl)-1,2,3,4-tetrahydropyridine (4k): yellow oil, 0.22 g (20%); eluent, toluene/diethyl ether, 20/1; ^1H NMR ($CDCl_3$) δ 1.72–2.12 (m, 4 H), 3.70, 3.77 (br s, 3 H, CO_2CH_3), 4.90, 4.98 (m, 1 H, NC=CH), 5.41, 5.53 (br s, 1 H, NCHAr), 6.86–7.28 [m, 4 H (3 H, Ar, and 1 H, NCH=C)]; IR (neat oil) 1710 cm^{-1}; MS *m/e* (relative intensity) 223 (M^+, 17), 148 (82), 135 (11), 110 (100), 97 (23), 89 (14), 82 (18).

Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87. Found: C, 59.34; H, 5.81.

1-(Methoxycarbonyl)-2-(2-thienyl)-1,2,3,4-tetrahydropyridine (4l): yellow oil, 0.056 g (5%); eluent, toluene/diethyl ether, 20/1; ^1H NMR ($CDCl_3$) δ 1.92–2.18 (m, 4 H), 3.74, 3.78 (br s, 3 H, CO_2CH_3), 4.93, 4.98 (m, 1 H, NC=CH), 5.59, 5.71 (m, 1 H, NCHAr), 6.80–7.19 [m, 4 H (3 H, Ar, and 1 H, NCH=C)]; IR (neat oil) 1710 cm^{-1}; MS *m/e* (relative intensity) 223 (M^+, 21), 148 (43), 139 (10), 110 (100), 97 (14).

Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87. Found: C, 59.17; H, 5.83.

1-Formyl-2-phenyl-1,2,3,4-tetrahydropyridine (5a): light yellow oil, 0.37 g (39%); eluent, toluene/ethyl acetate, 3/1; ^1H NMR ($CDCl_3$) δ 1.75–2.21 (m, 4 H), 4.97, 5.59 (dd, 1 H, NCHPh, *J* = 3.8, 3.8 Hz), 5.11, 5.21 (m, 1 H, NC=CH), 6.69 (dd, 0.6 H, NCH=C, *J* = 8.2, 2.6 Hz), 7.15–7.38 [m, 5.4 H (5 H, Ph, and 0.4 H, NCH=C)], 8.03, 8.35 (s, 1 H, CHO); IR (neat oil) 1685 cm^{-1}; MS *m/e* (relative intensity) 187 (M^+, 57), 158 (15), 142 (32), 115 (11), 104 (100), 96 (15), 91 (27), 77 (35).

Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00. Found: C, 76.86; H, 6.83.

1-Formyl-2-(4-methoxyphenyl)-1,2,3,4-tetrahydropyridine (5b): light yellow crystals, 0.52 g (48%); mp 71–73 °C, eluent, toluene/ethyl acetate, 2/1; ^1H NMR ($CDCl_3$) δ 1.73–2.19 (m, 4 H), 3.78, 3.80 (s, 3 H, CO_2CH_3), 4.92, 5.53 (m, 1 H, NCHAr), 5.09, 5.20 (m, 1 H, NC=CH), 6.67, 7.26 (dd, 1 H, NCH=C, *J* = 8.5, 2.1 Hz), 6.80–7.13 (m, 4 H, Ar), 8.02, 8.33 (s, 1 H, CHO); IR (KBr) 1680 cm^{-1}; MS *m/e* (relative intensity) 217 (M^+, 27), 172 (23), 134 (100), 119 (23), 109 (27), 91 (23), 77 (11).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96. Found: C, 72.00; H, 6.94.

1-Formyl-5-phenyl-2-pyrroline (6a): colorless oil, 0.38 g (44%); eluent, toluene/ethyl acetate, 2/3; ^1H NMR ($CDCl_3$) δ 2.61 (m, 1 H, $=CCH_2$), 3.27 (m, 1 H, $=CCH_2$), 5.07–5.35 [m, 2 H (1 H, NCHPh, and 1 H, NC=CH)], 6.62, 7.05 (ddd, 1 H, NCH=C, *J* = 4.4, 2.6, 1.9 Hz), 7.19–7.70 (m, 5 H, Ph), 7.91, 8.43 (s, 1 H, CHO); IR (neat oil) 1665 cm^{-1}; MS *m/e* (relative intensity) 173 (M^+, 100), 144 (91), 128 (33), 115 (39), 104 (67), 91 (28), 77 (31), 68 (56).

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40. Found: C, 76.88; H, 7.09.

An additional 0.15 g (17%) was isolated from subsequent fractions, which contained **6a** and a crystalline double bond isomer in a ratio of 1/2.5, as deduced by GC.

1-(Methoxycarbonyl)-2-(2-aminophenyl)-1,2,5,6-tetrahydropyridine (10a): light yellow crystals, 0.49 g (42%); mp 92–94 °C; eluent, pentane/diethyl ether, 3/1; ^1H NMR ($CDCl_3$) δ 1.35–2.05 (v br s, 2 H, NH_2), 2.05 (m, 1 H, $CH_2C=$), 2.35 (m, 1 H, $CH_2C=$), 2.99 (ddd, 1 H, NCH_2, *J* = 13.5, 13.0, 4.2 Hz), 3.74 (s, 3 H, CO_2CH_3), 3.88 (dd, 1 H, NCH_2, *J* = 13.5, 6.2 Hz), 5.69 (br s, 1 H, NCHAr), 5.77 (m, 1 H, CH=CCAr), 6.07 (m, 1 H, =CHCAr), 6.64–7.23 (m, 4 H, Ar); IR (KBr) 3440, 3360, 1650 cm^{-1}; MS *m/e* (relative intensity) 232 (M^+, 33), 199 (32), 185 (11), 173 (100), 168 (17), 156 (15), 144 (45), 130 (48), 117 (16), 91 (12), 77 (20).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94. Found: C, 67.18; H, 7.06.

Arylation of 1 in the Presence of Silver Carbonate. Palladium acetate (13.5 mg, 0.06 mmol), triphenylphosphine (47.2 mg, 0.18 mmol), iodobenzene (408 mg, 2 mmol), 1 (1.4 g, 10 mmol), silver carbonate (1.1 g, 4 mmol), and 2,3-dimethylnaphthalene (79 mg, 0.51 mmol) were dispersed in acetonitrile (7 mL), and the mixture was then stirred and heated in an oil bath at 80 °C. Additional catalyst was added after 14 h (44.9 mg (0.20 mmol) of palladium acetate and 157.4 mg (0.60 mmol) of triphenylphosphine). The reaction was interrupted after another 28 h. According to GC/MS analysis, 33% 1-(methoxycarbonyl)-2-phenyl-1,2,5,6-tetrahydropyridine (**10b**) and 43% biphenyl were formed, and 11% iodobenzene was recovered. The reaction was worked up according to the general procedure. The crude product was subjected to flash chromatography using toluene/diethyl ether, 20/1, as eluent.

1-(Methoxycarbonyl)-2-phenyl-1,2,5,6-tetrahydropyridine (10b) was obtained as a light yellow oil: ^1H NMR ($CDCl_3$) δ 2.06 (m, 1 H, $CH_2C=$), 2.34 (m, 1 H, $CH_2C=$), 2.95 (ddd, 1 H, NCH_2, *J* = 12.0, 12.0, 4.1 Hz), 3.77, 3.73 (s, 3 H, CO_2CH_3), 4.11 (m, 1 H, NCH_2), 5.62 (m, 1 H, NCHPh), 5.86 (m, 1 H, CH=CCPh), 6.04 (m, 1 H, =CHCPh), 7.23–7.47 (m, 5 H, Ph); IR (neat oil) 1690 cm^{-1}; MS *m/e* (relative intensity) 217 (M^+, 10), 185 (12), 158 (16), 140 (29), 129 (30), 115 (28), 94 (10), 91 (30), 80 (19), 77 (30).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96. Found: C, 71.7; H, 6.81.

Arylation of Cyclohexene in the Presence of Silver Carbonate. Palladium acetate (33.7 mg, 0.15 mmol), triphenylphosphine (118.0 mg, 0.45 mmol), iodobenzene (1.02 g, 5 mmol), cyclohexene (2.05 g, 25 mmol), silver carbonate (2.76 g, 10 mmol), and 2,3-dimethylnaphthalene (380 mg, 2.4 mmol) were dispersed in acetonitrile (10 mL). The mixture was stirred and heated in an oil bath at 80 °C for 8 h. According to GC/MS analysis, the reaction yielded 54% 3-phenylcyclohexene, 34% 4-phenylcyclohexene, 4% biphenyl, and in addition 5% of two diphenylated cyclohexenes (not structure determined). A small amount (3%) of iodobenzene was recovered. The reaction was worked up according to the general procedure, and the crude product was subjected to flash chromatography using pentane as eluent. The two monophenylated products, 3- and 4-phenylcyclohexene, were identified by NMR (in agreement with literature data[33]) and MS.

Arylation of Cyclohexene in the Absence of Silver Carbonate (See General Procedure). A mixture of palladium acetate (13.5 mg, 0.06 mmol), triethylamine (0.24 g, 2.4 mmol), iodobenzene (408 mg, 2 mmol), cyclohexene (0.66 g, 8 mmol), and 2,3-dimethylnaphthalene (180 mg, 1.15 mmol) was stirred under nitrogen until homogeneous and heated in an oil bath at 80 °C. The reaction was interrupted after ~6 days, and according to GC/MS yielded 48% 4-phenylcyclohexene, 10% 3-phenylcyclohexene, and 25% of four diphenylated cyclohexenes (not structure determined). Some iodobenzene (10%) was recovered. The monophenylated products were identified by co-injections (GC/MS).

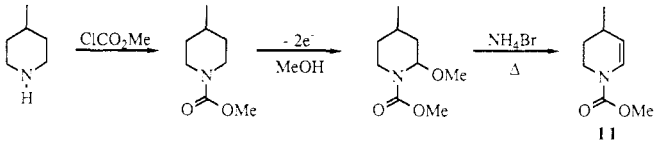
1-(Methoxycarbonyl)-4-methyl-1,4,5,6-tetrahydropyridine (11). To a solution of 4-methylpiperidine (39.7 g, 0.40 mol), triethylamine (112 mL, 0.80 mol), and dichloromethane (400 mL) was added dropwise methyl chloroformate (31.0 mL, 0.40 mol) with stirring. After 3 h, the reaction mixture was evaporated and the resulting material was extracted three times with diethyl ether. The organic portion was concentrated and distilled (bp 93–95 °C/12 mmHg), affording 45.3 g (72%) of a colorless oil. A 600-mL water-cooled cell was charged with the oil (45.3 g, 0.29 mol), methanol (460 mL), and Bu_4NBF_4 (8.9 g, 0.027 mol). The stirred solution was oxidized at a graphite anode (7 × 3.5 cm) using a constant current of 30 mA/cm^2. The reaction was followed by GC and interrupted after 2.2 F/mol. The solvent was evaporated, and the residue was treated with diethyl ether. The precipitated ammonium salt was filtered off. The organic phase was concentrated and purified by distillation (98–103 °C/11 mmHg), yielding 42.1 g (78%) of a colorless oil.

The isolated oil (42.1 g, 0.22 mol) and ammonium bromide (1.1 g, 0.011 mol) were placed in a round-bottomed flask equipped with a distillation head and magnetic stirring. The mixture was heated in an oil bath at 120–130 °C until most of the resulting methanol had distilled off. The crude product was then distilled at reduced pressure, yielding 24.0 g (70%; total yield 39% from 4-methylpiperidine) of the title compound **11** as a colorless oil:

(33) Henry, P. M.; Ward, G. A. *J. Am. Chem. Soc.* **1972**, *94*, 673.

bp 104–106 °C/24 mmHg. For analytical purposes the compound was subjected to flash chromatography, and a mixture of pentane/diethyl ether (4:1) was used as eluent: ^{1}H NMR ($CDCl_3$) δ 1.01 (d, 3 H, CH_3, J = 7.1 Hz), 1.37–2.36 (m, 3 H), 3.43 (m, 1 H, NCH_2), 3.66–3.83 [m, 4 H (1 H, NCH_2, and 3 H, CO_2CH_3)], 4.72, 4.82 (m, 1 H, NC=CH), 6.68, 6.82 (d, 1 H, NCH=C, J = 8.6 Hz); IR (neat oil) 1700 cm^{-1}; MS m/e (relative intensity) 155 (M^+, 26), 140 (100), 94 (16), 81 (19), 68 (27), 59 (26), 53 (17), 41 (65).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.92; H, 8.44. Found: C, 61.78; H, 8.36.



Phenylation of 1-(Methoxycarbonyl)-4-methyl-1,4,5,6-tetrahydropyridine (11). The reaction was performed according to the general procedure, except for the temperature (100 °C). After 5 days the reaction was stopped, and the excess of **11** was removed by Kugelrohr distillation (~72 °C/8 mmHg). The residual oil consisted mainly of two double bond isomers which were separated by flash chromatography, using toluene/diethyl ether, 25/1, as eluent. A yield of 0.34 g (29%) of 1-(methoxycarbonyl)-2-phenyl-4-methyl-1,2,3,4-tetrahydropyridine (**12**) and 0.37 g (32%) of 1-(methoxycarbonyl)-2-phenyl-4-methyl-1,2,5,6-tetrahydropyridine (**13**) was obtained. Analytically pure isomers were obtained by HPLC (see General Methods).

1-(Methoxycarbonyl)-2-phenyl-4-methyl-1,2,3,4-tetrahydropyridine (12): white crystals; mp 46–47 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 3 H, CH_3, J = 6.8 Hz), 1.64–2.12 (m, 3 H), 3.64, 3.77 (s, 3 H, CO_2CH_3), 4.74, 4.84 (br d, 1 H, NC=CH, J = 7.8 Hz), 5.29, 5.40 (br s, 1 H, NCHPh), 6.95, 7.10 (br d, 1 H, NCH=C, J = 7.8 Hz), 7.13–7.36 (m, 5 H, Ph); IR (KBr) 1705 cm^{-1}; MS m/e (relative intensity) 231 (M^+, 70), 216 (70), 184 (10), 172 (22), 156 (38), 141 (26), 128 (13), 115 (20), 104 (100), 96 (17), 91 (60), 77 (36), 68 (37).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.88; H, 7.26.

1-(Methoxycarbonyl)-2-phenyl-4-methyl-1,2,5,6-tetrahydropyridine (13): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 3 H, CH_3), 1.89 (dd, 1 H, CH_2CMe, J = 17.0, 3.9 Hz), 2.32 (m, 1 H, CH_2CMe), 2.94 (ddd, 1 H, NCH_2, J = 12.0, 12.0, 3.9 Hz), 3.72, 3.76 (s, 3 H, CO_2CH_3), 4.11 (m, 1 H, NCH_2), 5.42–5.72 [m, 2 H (1 H, C=CH, and 1 H, NCHPh)], 7.22–7.42 (m, 5 H, Ph); IR (neat oil) 1690 cm^{-1}; MS m/e (relative intensity) 231 (M^+, 67), 216 (74), 199 (25), 172 (28), 154 (100), 141 (12), 129 (41), 115 (17), 91 (32), 77 (34); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 23.38 (CH_3), 29.66 (CH_2), 37.23 (CH_2), 52.58 (CH_3), 54.74 (CH), 120.87 (CH), 127.33 (CH), 128.34 (CH), 134.08 (C), 141.28 (C), 155.91 (C); a DEPT experiment gave the multiplicity of the carbons. Structural assignment of **13** was based on ^{13}C–^{1}H HETCOR and COSY experiments.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.82; H, 7.26.

Racemic Anabasine (14). Arylation of 1 with 3-Iodopyridine. A mixture of palladium acetate (47 mg, 0.21 mmol), triethylamine (1.06 g, 10.5 mmol), 3-iodopyridine (1.43 g, 7 mmol), 1 (3.9 g, 28 mmol), and acetonitrile (2 mL) was flushed with argon, stirred, and heated at 100 °C for 2 days. The cooled reaction was diluted with diethyl ether and hydrolyzed (1 M HCl). The water phase was washed four times with diethyl ether and the combined organic portions were extracted twice with 1 M HCl. The aqueous layer was made alkaline (2 M NaOH) and then extracted four times with diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated. The crude oil was subjected to flash chromatography, using dichloromethane/methanol, 95/5, as eluent, and 0.35 g (23%) of a light yellow oil containing three double bond isomers (40:10:1) was obtained. The major isomer (**4m**) was isolated by HPLC (see General Methods).

1-(Methoxycarbonyl)-2-(3-pyridyl)-1,2,3,4-tetrahydropyridine (4m): light yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.60–2.14 (m, 4 H), 3.66, 3.77 (s, 3 H, CO_2CH_3), 4.95, 5.03 (m, 1 H, NC=CH), 5.37, 5.48 (br s, 1 H, NCHAr), 6.99, 7.13 (m, 1 H, NCH=C), 7.20–8.55 (m, 4 H, Ar); IR (neat oil) 1705 cm^{-1}; MS m/e (relative intensity) 218 (M^+, 34), 189 (18), 159 (34), 140 (19), 130 (18), 117 (25), 105 (100), 93 (27), 80 (40).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47. Found: C, 65.88; H, 6.39.

Hydrogenation/Hydrolysis of the 1-Acyl-2-(3-pyridyl)-tetrahydropyridine Isomer Mixture. The isomeric (40/10/1) mixture (188 mg, 0.86 mmol) was placed in a heavy-walled Pyrex bottle with 5% Pd/C (147 mg) and absolute ethanol (25 mL). The reaction was pressurized with H_2 to 50 psi and stirred vigorously at room temperature for 18 h. The mixture was filtered through silica gel, and the filtrate was evaporated.

The resulting oil was then refluxed in 8 M HCl (30 mL) for 2 days. The reaction was made alkaline (3 M NaOH), and the aqueous layer was extracted three times with dichloromethane. The combined organic portions were washed once with water, dried ($MgSO_4$), and concentrated, yielding 121 mg (87%) of racemic anabasine (**14**), which exhibited spectroscopic data in agreement with literature data.[34]

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Registry No. 1, 56475-87-7; **2**, 61157-70-8; **3**, 61157-69-5; **4a**, 125592-91-8; **4b**, 125592-92-9; **4c**, 125592-93-0; **4d**, 125592-94-1; **4e**, 125592-95-2; **4f**, 125592-96-3; **4g**, 125592-97-4; **4h**, 125592-98-5; **4i**, 125592-99-6; **4j**, 125593-00-2; **4k**, 125593-01-3; **4l**, 125593-02-4; **4m**, 125593-14-8; **5a**, 125593-03-5; **5b**, 125593-04-6; **6a**, 125593-05-7; **9**, 110-83-8; **10a**, 125610-29-9; **10**, 125593-06-8; **11**, 125593-11-5; **12**, 125593-12-6; **13**, 125593-13-7; **14**, 13078-04-1; **15**, 125593-08-0; PhI, 591-50-4; p-$MeOC_6H_4I$, 696-62-8; m-$MeOC_6H_4I$, 766-85-8; o-$MeOC_6H_4I$, 529-28-2; p-MeC_6H_4I, 624-31-7; o-$IC_6H_4CO_2Me$, 610-97-9; o-IC_6H_4OH, 533-58-4; p-BrC_6H_4I, 589-87-7; p-$NO_2C_6H_4Br$, 586-78-7; o-$IC_6H_4NH_2$, 615-43-0; Ph-Ph, 92-52-4; $PhCO_2Me$, 93-58-3; AcOPdOAc, 33571-36-7; 1-Iodonaphthalene, 90-14-2; 3-Iodothiophene, 10486-61-0; 2-Iodothiophene, 3437-95-4; 1-(methoxycarbonyl)-3,3-diphenyl-1,4,5,6-tetrahydropyridine, 125593-07-9; 3-phenylcyclohexene, 15232-96-9; 4-phenylcyclohexene, 4994-16-5; 4-methylpiperidine, 626-58-4; 4-methyl-1-(methoxycarbonyl)piperidine, 125593-09-1; 4-methyl-2-methoxy-1-(methoxycarbonyl)piperidine, 125593-10-4; 3-iodopyridine, 1120-90-7.

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