($MgSO_4$), and concentrated. Kugelrohr distillation (bp 90 °C, ~25 mm) of the residue gave 1.68 g (58%) of vinyl iodide **23** as a clear, pale yellow liquid (~90% pure by ^1H NMR).

(3*R*,1′*S*)-4,4-Dimethyl-6-hepten-1-yn-3-yl *N*-[1′-(1-Naphthyl)ethyl]-carbamate (25b). Racemic propargyl alcohol (±)-**22** (1.16 g, 8.40 mmol), (*S*)-(+)-1-(naphthyl)ethyl isocyanate **24b** (1.74 g, 8.83 mmol), *N*,*N*-dimethylethanolamine (3 drops, distilled from NaOH), and benzene (18.7 mL, distilled from sodium/benzophenone ketyl) were placed in a 50-mL flask equipped with a West condenser, and the resulting mixture was then refluxed under N_2 for 48 h. The reaction mixture was cooled to room temperature, the solvent was removed, and the residue was purified by flash chromatography (10% EtOAc/hexanes, 8.0 × 23 cm silica gel) to afford the expected diastereomers in the following order of elution: (3*S*,1′*S*)-isomer **26b** followed by the desired (3*R*,1′*S*)-isomer **25b** (1.14 g, 40%). For analytical purposes, a mixture of the diastereomers was separated by HPLC (Rainin Dynamax 2.24 × 25 cm, 5 μm silica gel column, 10% EtOAc/hexanes, 9 mL/min flow rate) to afford (3*S*,1′*S*)-isomer **26b** (retention time = 26 min) and (3*R*,1′*S*)-isomer **25b** (retention time = 38 min). A sample of the (3*R*,1′*S*)-isomer **25b** obtained by flash column purification was analyzed by HPLC: integration (cut and weigh method) of the RI trace indicated a ratio of **25b**/**26b** of 119:1 (de > 99%).

(6*R,8*R**)- and (6*S*,8*S*)-2,6,10,10-Tetramethyltricyclo[6.3.0.0^{3,6}]-undeca-1(11),2-diene (33).** To a solution of sulfoxide (±)-**5** (diastereomeric mixture, 56 mg, 0.18 mmol) in THF (4.9 mL, distilled from sodium/benzophenone ketyl) under N_2 was introduced [1,3-bis(diphenylphosphino)propane]nickel(II) dichloride (Ni(dppp)Cl_2, 12 mg, 0.018 mmol) followed by methylmagnesium bromide (2.73 M in ether, 0.49 mL, 1.35 mmol). The reaction mixture was refluxed for 14.5 h, cooled to room temperature, and quenched with saturated aqueous NH_4Cl (~2 mL). Ether was added, and then the organic extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatographic purification (hexanes, 1.5 × 20 cm silica gel) gave 24 mg (66%) of pure (±)-**33**.

Optically active sulfoxide (−)-**5** (distereomeric mixture; 74 mg, 0.24 mmol) was treated in the same manner described above [16 mg (0.024 mmol) Ni(dppp)Cl_2, 0.65 mL (1.78 mmol) MeMgBr (2.73 M in ether), 6.4 mL THF] to afford 30 mg (62%) of pure (6*S*,8*S*)-diene (−)-**33** ($[\alpha]_D$ −49.2 (*c* 1.3, $CHCl_3$)).

Acknowledgment. This study was supported by NSF Grant CHE-8518801 and in part by the UC Riverside Intramural Research Fund. K.B. acknowledges receipt of a postdoctoral fellowship from the Deutsche Forschungsgemeinschaft, Federal Republic of Germany; and R.G. acknowledges receipt of a Chancellor's Patent Fund grant from UC Riverside for partial support. We are very grateful to Professor W. A. Ayer for providing the optical rotation of sterpurene and Dr. C. Abell for informing us of his results prior to publication. We also thank Professor R. D. Little and Professor E.-I. Negishi for providing us with additional experimental details. Purchase of the GE GN 500 was made possible in parts by grants from the NSF (DMB 8604091), the Department of Energy (FG03-86FR13535), and the NIH (PHS BRSG 2 507).

Registry No. (±)-**4** (isomer 1), 119904-10-8; (±)-**4** (isomer 2), 119904-11-9; (−)-**5** (isomer 1), 114636-41-8; (−)-**5** (isomer 2), 114715-41-2; (±)-**5** (isomer 1), 119904-14-2; (±)-**5** (isomer 2), 119904-15-3; (−)-**6**, 114636-39-4; (±)-**6**, 119904-12-0; (±)-**6** benzoate, 119795-88-9; (±)-**7**, 119795-76-5; (+)-**8**, 79579-56-9; (±)-**8**, 81370-74-3; **9**, 79367-59-2; **11**, 1610-13-5; **12a**, 5497-67-6; (±)-**13a**, 119795-77-6; (±)-**13b**, 119795-90-3; (±)-**14a**, 119795-78-7; (±)-**14b**, 119795-91-4; (±)-**15a**, 119795-79-8; (±)-**15b**, 119795-89-0; (±)-**16**, 119795-80-1; (±)-**17**, 119795-81-2; (±)-**18a**, 119795-82-3; (±)-**18b**, 119795-93-6; **19**, 119795-83-4; (±)-**20** (isomer 1), 119795-84-5; (±)-**20** (isomer 2), 119905-58-7; (±)-**21**, 119795-85-6; (−)-**22**, 114715-40-1; (±)-**22**, 114636-42-9; **23**, 92144-00-8; **24a**, 42340-98-7; **24b**, 73671-79-1; **25a**, 119818-77-8; **25b**, 114636-44-1; **26a**, 119795-86-7; **26b**, 119795-92-5; **27**, 87413-09-0; **28**, 119795-87-8; (−)-**33**, 114636-43-0; (±)-**33**, 119904-13-1; $HC{\equiv}C(CH_2)_2Br$, 38771-21-0.

Supplementary Material Available: Spectral data for all new compounds, discussion of resonance assignments for diene **33** and sterpurene, procedures for the preparation of (−)-**22** (via Chirald reduction of **28**), **25a**, **28**, and detailed procedures for the 2D NMR experiments (31 pages). Ordering information is given on any current masthead page.

Novel Lactam Synthesis by Use of a Combination System of Carbonylation and Nitrogenation[1]

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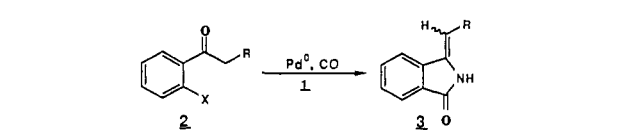
Contribution from the Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan. *Received September 6, 1988. Revised Manuscript Received December 16, 1988*

Abstract: An amide unit was constructed from aryl halide and titanium–isocyanate complex prepared from $TiCl_4$ under atmospheric pressure of molecular nitrogen and carbon monoxide in the presence of a palladium catalyst. With this combination system of carbonylation and nitrogenation, isoindolinone and quinazolinone derivatives were synthesized from *o*-halophenyl alkyl ketone in one step. The reaction proceeds through the oxidative addition of enol lactone, generated by palladium-catalyzed carbonylation to *o*-halophenyl alkyl ketone, to titanium–isocyanate complex.

Compared to the impressive development of molecular nitrogen fixation by a variety of transition metal,[2] incorporation of nitrogen into organic compounds using these nitrogen–metal complexes has received only scant attention. Therefore, the use of dinitrogen gas in organic synthesis is still a major challenge. Recently, we have reported[3] a new nitrogenation method for amide and imide

Scheme I

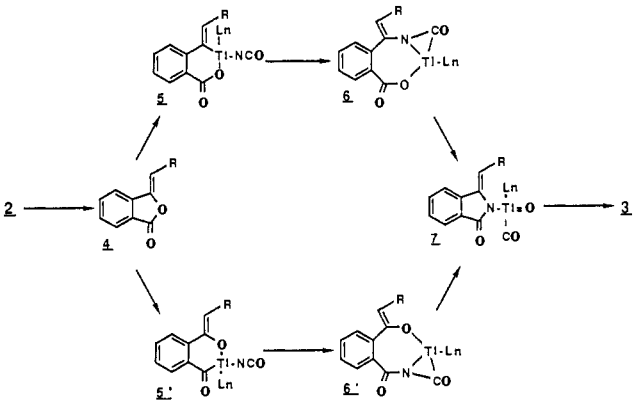


(1) This is paper 2 of the series "Incorporation of Molecular Nitrogen into Organic Compounds".

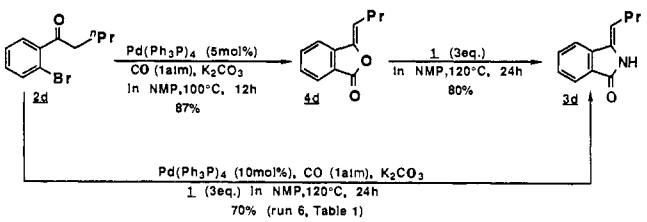
(2) For reviews: (a) Dilworth, J. R.; Richards, R. L. In *Comprehensive Organometallic Chemistry*; Pergamon Press: New York, 1982; Vol. 8, 1073. (b) George, T. A. In *Homogeneous Catalysis with Metal Phosphine Complexes*; Pinolet, L. H., Ed.; Plenum Press: New York, 1983; p 405. (c) Hidai, M. In *Molybdenum Enzyme*; Spiro, T. G., Ed.; Wiley: New York, 1985; p 285.

0002-7863/89/1511-3725$01.50/0

Scheme II



Scheme III



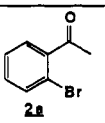
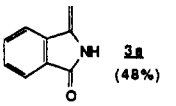
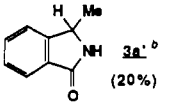
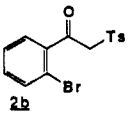
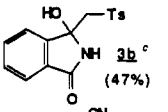
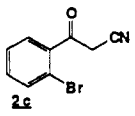
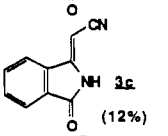
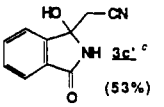
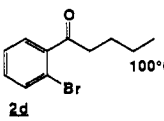
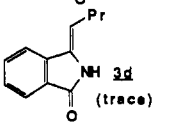
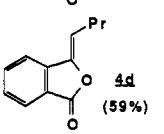
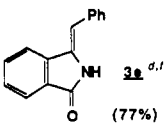
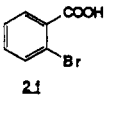
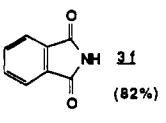
syntheses by titanium–nitrogen complexes.[4] The results made us think that the combination of nitrogenation by titanium–isocyanate complex (**1**)[4c,5] and palladium-catalyzed carbonylation[6] would be an effective process for the synthesis of lactams.[7] We now report herein the first successful result of the novel lactam synthesis using a metal–nitrogen complex prepared from atmospheric pressure of nitrogen gas and carbon monoxide (Scheme I).

A solution of *o*-bromoacetophenone (**2a**), titanium–isocyanate complex (**1**) (3 equiv), $Pd(Ph_3P)_4$ (10 mol %), and K_2CO_3 (2 equiv) in *N*-methylpyrrolidone (NMP) was heated at 100 °C under CO (1 atm) for 24 h, and we were pleased to find that methyleneisoindolinone (**3a**) was obtained in 48% yield. The mechanism of this reaction system was envisaged as in Scheme II. First, an enol lactone intermediate (**4**) is generated in situ via palladium-catalyzed carbonylation followed by intramolecular cyclization.[8] Second, the intermediate should oxidatively add to **1** to provide a metalacycle (**5** or **5'**). An insertion of an isocyanate moiety into a metal–carbon bond might provide a seven-membered metalacycle (**6** or **6'**), which should be followed by intramolecular five-membered ring formation to afford **7** convertible into **3**. Several representative results are summarized in Table I (Scheme II).

As can be seen from the table, reaction of **2a** with **1** at a higher temperature (120 °C) provided a high yield of the cyclized products (**3a** and **3a'**) (55% and 20%, respectively) (run 2). The reaction rate was accelerated by electron-withdrawing substituents such as tosyl and nitrile. The results shown in runs 5 and 6 were mechanistically significant. Only a small amount of the desired lactam was obtained from *o*-bromophenyl butyl ketone (**2d**) at 100 °C under the usual reaction conditions, and a main product was butylidene lactone **4d** (run 5). However, the desired lactam **3d** was obtained at 120 °C in a similar manner (run 6). On the other hand, enol lactone **4d** was obtained from **2d** by palladium-catalyzed carbonylation in good yield and was converted to lactam **3d** by treatment with **1** under argon atmosphere at 120 °C for 24 h. These results indicated that the enol lactone **4** should be an intermediate of this reaction (Scheme III).

One-step formation of **3e** from *o*-bromophenyl benzyl ketone (**2e**) (run 7)[9] indicated the effectiveness of this reaction for the synthesis of some natural products such as those of the fumaridine family[10] and the aristololactam family.[11] *o*-Bromobenzoic acid

Table I. Construction of Nitrogen Heterocycles Using a Combination System of Carbonylation and Nitrogenation[a]

run	substrate	condition	product (yield,%)		
1	 **2a**	100°C, 16h	 **3a** (48%)		
2	**2a**	120°C, 24h	**3a** (55%)	 **3a'**[b] (20%)	
3	 **2b**	70°C, 40min.	 **3b**[c] (47%)		
4	 **2c**	80°C, 1h	 **3c** (12%)	 **3c'**[c] (53%)	
5	 **2d**	100°C, 16h	 **3d** (trace)	 **4d** (59%)	
6	**2d**	120°C, 24h	**3d**[d,e] (70%)		
7	 **2e**	120°C, 24h	 **3e**[d,f] (77%)		
8	 **2f**	100°C, 24h	 **3f** (82%)		
9[g]	**2f**	100°C, 24h	**3f** (13.6%)	SM (51%)	
10[g]	**2e**	100°C, 24h	**3e** (14%)	SM (67%)	

[a] All reactions were run with **1** (3 equiv), K_2CO_3 (2 mol equiv), and CO (1 atm) in NMP. [b] An enamine moiety was reduced in situ under reaction condition. [c] Products were isolated as the hydrate form after aquous workup. [d] Geometry and the ratio of the products were determined by ^1H NMR analysis and NOE experiment. [e] E/Z = 1/12. [f] Sole product (*Z* form). [g] Ammonia (excess) was used instead of **1**.

(3) Paper 1 of the series "Incorporation of Molecular Nitrogen Into Organic Compounds" is Mori, M.; Uozumi, Y.; Shibasaki, M. *Tetrahedron Lett.* **1987**, *28*, 6187.

(4) (a) Yamamoto, A.; Ookawa, M.; Ikeda, S. *J. Chem. Soc., Chem. Commun.* **1968**, 841. (b) Yamamoto, A.; Go, S.; Ookawa, M.; Takahashi, M.; Ikeda, S.; Keii, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3110. (c) Sobota, P.; J-Trzebiatowska, B.; Janas, Z. *J. Organomet. Chem.* **1976**, *118*, 253.

(5) Complex **1** is easily prepared from dinitrogen gas at atmospheric pressure and room temperature; it is a storable powder at room temperature for several months.

(6) For review; Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985; Chapter 8.

(7) Reaction of aryl halides with **1** in the presence of zero-valent palladium catalyst under carbon monoxide afforded the corresponding aryl amides and/or imides in moderate yield.

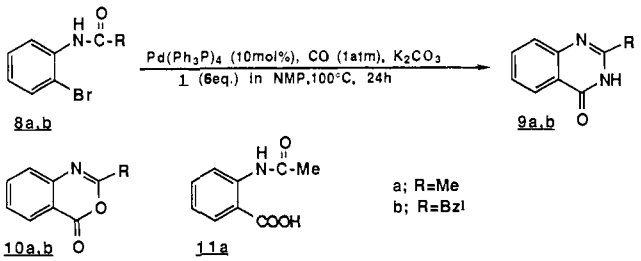
(8) Negishi, E.; Tour, J. M. *Tetrahedron Lett.* **1986**, *27*, 4869.

(9) The intermediate **4e** was detectable on TLC.

(10) Shamma, M.; Moniot, J. L. *J. Chem. Soc., Chem. Commun.* **1975**, 89.

(11) (a) Tomita, M.; Sasagawa, S. *J. Pharm. Soc. Jpn.* **1959**, *79*, 973; *Chem. Abstr.* **1959**, *53*, 21841. (b) Tomita, M.; Sasagawa, S. *J. Pharm. Soc. Jpn.* **1959**, *79*, 1470; *Chem. Abstr.* **1960**, *54*, 6688. (c) Sasagawa, S. *J. Pharm. Soc. Jpn.* **1962**, *82*, 921. (d) Kupchan, S. M.; Merianos, J. J. *J. Org. Chem.* **1968**, *10*, 3735. (e) Crohare, R.; Priestap, H. A.; Farina, M.; Cedola, M.; Ruveda, E. A. *Phytochemistry* **1974**, *13*, 1957. (f) Akasu, M.; Itokawa, H.; Fujita, M. *Tetrahedron Lett.* **1974**, 3609. (g) Sun, J.-J.; Antoun, M.; Change, C.-J.; Cassady, J. M. *J. Nat. Prod.* **1987**, *50*, 843.

Scheme IV



provided phthalimide in 82% yield in a similar manner via phthalic anhydride (run 8).[12] Use of ammonia[13] instead of **1** inevitably led to a decrease in the yield of the desired compounds (runs 9 and 10), suggesting that **1** can be used as nonsubstituted N1 unit reagent.

In order to expand the scope of this reaction, an attempt to construct the quinazolinone skeletons was made.[14] *o*-Bromoacetoanilide (**7a**) was treated with $Pd(Ph_3P)_4$ (10 mol %), K_2CO_3 (2 equiv), and 6 equiv of **1** in NMP at 100 °C under CO (1 atm) for 24 h to give 2-methylquinazolinone (**9a**) in 54% yield along with the anthranilic acid derivative (**11a**)[15] (29%). The possible intermediate of this reaction should be benzoxazone **10**, which should be formed from *o*-haloanilide derivative **8** through palladium-catalyzed carbonylation. It was quite interesting that glycosminine (**9b**),[16] a naturally occurring alkaloid, was synthesized from (*o*-bromophenyl)acetoanilide under the same reaction conditions in one step in 40% yield (Scheme IV).

This combination system of palladium-catalyzed carbonylation and nitrogenation with titanium–isocyanate complex is of great value because of the following feature. (1) Dinitrogen can be incorporated into nitrogen heterocycles via a metal–nitrogen complex. These results make the first proof of the applicability of transition-metal nitrogen complex prepared from an atmospheric pressure of nitrogen gas for organic synthesis, especially in alkaloid synthesis. (2) A synthetically useful N1 unit reagent has been discovered. Namely, titanium–isocyanate complex (**1**) is a neutral, nonsubstituted N1 reagent and is intact to the palladium-catalyzed reaction. (3) By use of this combination system, the conceptually new method for the lactam ring construction has been developed without isolation of an unstable intermediate such as enol lactone or benzoxazone.

Work to further expand the scope of this reaction system and the mechanistic study is currently in progress.

Experimental Section

Preparation of [3THF·Mg_2Cl_2O·Ti–NCO] (1). To a mixture of Mg (1 g) in freshly distilled THF (50 mL) was added 1.90 g of $TiCl_4$ at −78 °C under Ar. The solution was degassed through a freeze–pump–thaw cycle and then stirred at room temperature under N_2 gas for 16 h. The color of the solution changed slowly from yellow through blue and green to black with evolution of heat and absorption of N_2 gas. After separation of unreacted Mg by filtration under nitrogen, an atmosphere of reaction vessel containing the filtrate was replaced by carbon dioxide. After the solution was stirred for 1 h at room temperature, the black precipitate was formed. To the reaction mixture was added 1 mL of *n*-hexane under cooling with an ice–water bath. The black precipitate was separated from the solution and washed with freshly distilled ether (20 mL, three times) and dried under vacuum.

General Procedure for Conversion of 2 to 3. To a mixture of **2** (0.2 mmol), K_2CO_3 (0.4 mmol), $Pd(Ph_3P)_4$ (0.01 mmol), and **1** (0.6 mmol) was added 1.2–2.0 mL of *N*-methylpyrrolidone (NMP). The solution was degassed through a freeze–pump–thaw cycle and then heated (70–120 °C) under carbon monoxide (1 atm) (the reaction was monitored by TLC). After cooling, the reaction mixture was diluted with AcOEt and quenched with small amount of water. The whole solution was stirred for several hours to decompose the complex. The mixture was filtered through Celite, and the solid was washed with AcOEt. The combined filtrates were washed with 5% HCl, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel to give **3**.

3-Methyleneisoindolinone (3a): ^1H NMR ($CDCl_3$) δ 4.98 (d, J = 2.2 Hz, 1 H), 5.21 (d, J = 2.0 Hz, 1 H) 7.49–7.93 (m, 4 H), 8.25 (br s, 1 H); IR ($CHCl_3$) 3450, 1710, 1655 cm^{-1}; MS (m/z) 145 (M^+, base peak), 130, 117, 103, 90, 76, 63; HR-MS, calcd fro C_9H_7ON 145.0527, found 145.0540.

3-Methylisoindolinone (3a′): ^1H NMR ($CDCl_3$) δ 1.51 (d, J = 6.83 Hz, 3 H), 4.70 (q, J = 6.83 Hz, 1 H), 6.96 (br s, 1 H), 7.40–7.90 (m, 4 H); IR ($CHCl_3$) 3460, 1695, 1620 cm^{-1}; MS (m/z) 147 (M^+), 132 (base peak), 119, 104, 91, 77; HR-MS, calcd for C_9H_9ON 147.0684, found 147.0671.

3-[(*p*-Tolylsulfonyl)methylene]isoindolinone (3b): ^1H NMR ($CDCl_3$) δ 2.44 (s, 3 H), 3.35 (d, J = 14.5 Hz, 1 H), 4.08 (d, J = 14.5 Hz, 1 H), 4.35 (br s, 1 H), 7.33–7.91 (m, 9 H); IR ($CHCl_3$) 3420, 1718 cm^{-1}; MS (m/z) 317 (M^+), 299, 235, 170, 148, 130, 91; HR-Ms, calcd for $C_{16}H_{15}O_4NS$ 317.0726, found 317.0727.

3-(Cyanomethylene)isoindolinone (3c): ^1H NMR ($CDCl_3$) δ 5.24 (s, 1 H), 7.62–7.97 (m, 4 H), 8.20 (br s, 1 H); IR ($CHCl_3$) 3440, 2210, 1740, 1650 cm^{-1}; MS (m/z) 170 (M^+, base peak), 130, 103, 76; HR-MS, calcd for $C_{10}H_6ON_2$ 170.0480, found 170.0483.

3-Butylideneisoindolinone (3d): ^1H NMR ($CDCl_3$) δ 0.944 (t, J = 7.3 Hz, 3 H), 1.45–1.64 (m, 2 H), 2.292 (dt, J = 7.3 and 7.9 Hz, 2 H), 5.565 (t, J = 7.9 Hz, 1 H), 7.35–7.82 (m, 4 H), 8.70 (br s, 1 H); IR ($CHCl_3$) 3450, 1700 cm^{-1}; MS (m/z) 187 (M^+), 158 (base peak), 130, 103, 89; HR-MS, calcd for $C_{12}H_{13}ON$ 187.0998, found 187.0999.

3-Benzylideneisoindolinone (3e): ^1H NMR ($CDCl_3$) δ 6.56 (s, 1 H), 7.29–7.93 (m, 9 H), 8.17 (br s, 1 H); IR ($CHCl_3$) 3450, 1700 cm^{-1}; MS (m/z) 221 (M^+, base peak), 193, 165, 130; HR-MS, calcd for $C_{15}H_{10}ON$ 221.0841, found 221.0825.

3-Butylidenephthalide (4d): ^1H NMR ($CDCl_3$) δ 0.99 (t, J = 7.2 Hz, 3 H), 1.45–1.67 (m, 2 H), 2.46 (dt, J = 7.6 and 8.0 Hz, 2 H), 5.64 (t, J = 8.0 Hz, 1 H), 7.30–7.96 (m, 4 H); IR ($CHCl_3$) 1780 cm^{-1}; MS (m/z) 188 (M^+), 159 (base peak), 146, 131, 103, 76; HR-MS, calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0847.

Glycosimine (9b): ^1H NMR ($CDCl_3$) δ 4.08 (s, 2 H), 7.33–8.26 (m, 9 H), 9.18 (br s, 1 H); IR (Nujole) 3400, 1690, 1620 cm^{-1}; MS (m/z) 236 (M^+), 235 (base peak), 119; HR-MS, calcd for $C_{15}H_{12}ON_2$ 236.0950, found 236.0937; mp 244–246 °C.

Conversion of 2a to 3a by NH_3 and Carbon Monoxide. To a mixture of **2a** (20 mg, 0.1 mM) and $Pd(PPh_3)_4$ (11.6 mg, 0.01 mM) was added 1.5 mL of NMP containing 3% dry ammonia in a sealed tube purged with dry ammonia. Then an atmosphere of reaction vessel was replaced by carbon monoxide (1 kg/cm^2), and the mixture was heated at 100 °C for 24 h. After cooling, the reaction mixture was diluted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography to give **3a** (2 mg, 14%) and unreacted **2a** (13.4 mg, 67%).

(12) The reaction of phthalic anhydride with **1** afforded phthalimide (**3f**) in high yield.

(13) There are some severe disadvantages to using ammonia: (a) It is technically difficult to replace the dry NH_3 atmosphere of the reaction vessel with carbon monoxide. (b) Since a fair amount of starting material was recovered (runs 9 and 10, Table I), it is likely that the palladium catalyst is deactivated by ammonia.

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