NEW C-N-C BOND FORMATION REACTION USING NITROGENATION-TRANSMETALLATION PROCESS. NOVEL RING CONSTRUCTION OF INDOLE AND QUINOLINE DERIVATIVES

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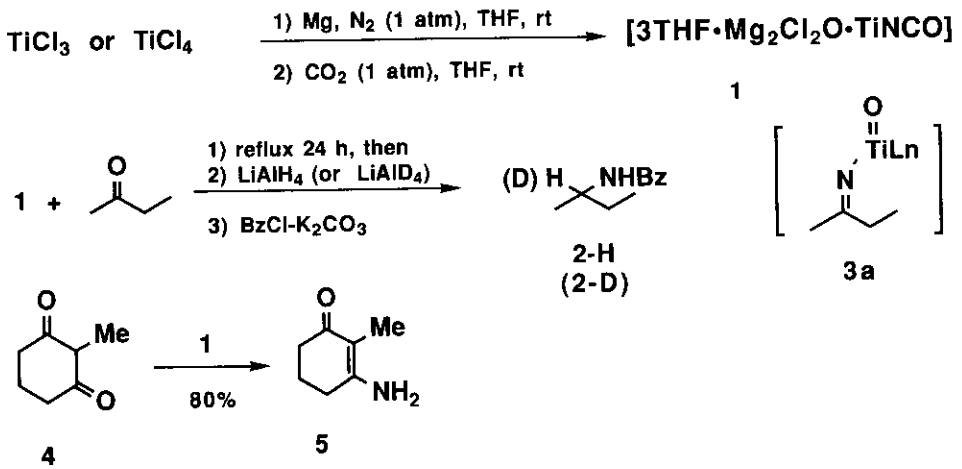
Abstract----Ketones and aryl or vinyl halides couple to give divinyl- or arylvinylamines in the presence of the titanium-isocyanate complex [3THF•Mg_2Cl_2O•TiNCO] (**1**) and a palladium catalyst, *via* transmetallation of the titano imine complex (**3**) with aryl- or vinylpalladium bromide.

Over the past two decades molecular nitrogen fixation has intrigued many research group.[1] The nitrogenation method by use of titanium-nitrogen complex[2] developed by us[3] is one of the earliest indication of the applicability of transition metal nitrogen complexes in organic synthesis as an N1 unit reagent(**1**).[3b]

Dedicated to Professor Emeritus Masatomo Hamana of Kyushu University on the occasion of his 75th birthday.

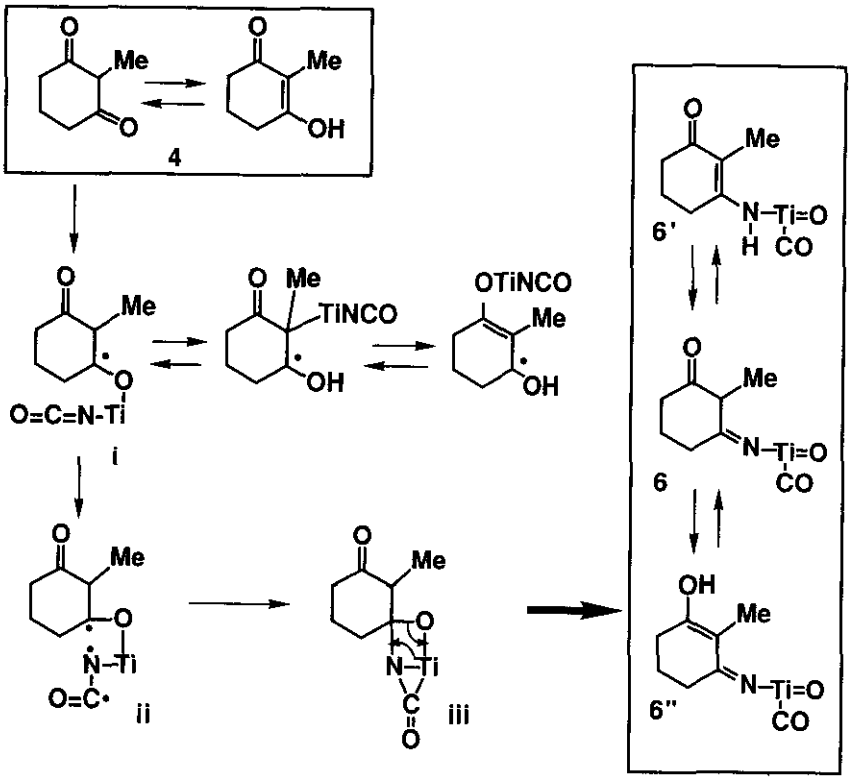
During the course of our investigation, we found a new C-N-C bond formation reaction and we describe the novel ring construction of the heterocycles by use of this reaction.[4] In order to examine the reactivity of titanium isocyanate complex (**1**) to carbonyl compounds,. the reaction of butan-2-one with **1** was tried.



When a butan-2-one solution of **1** was refluxed for 24 h and then the solvent was removed *in vacuo*, the gray-green residue was obtained. LiAlH4 reduction of the residue in THF followed by treatment with benzoyl chloride afforded **2-H** in 26% yield(based on **1**). LiAlD4 reduction and then benzoylation afforded the α-deuterated product (**2-D**) in 24% yield. These experiments suggested that titanium isocyanate complex (**1**) can react with carbonyl compounds and *N*-titano-imine complex (**3a**) was formed as an intermediate in the reaction of **1** with ketone. Thus, we tried to react titanium isocyanate complex (**1**) with various ketones. When a solution of diketone (**4**) and 3 eq. of **1** was heated at 100 °C in *N*-methyl-2-pyrrolidone(NMP) for 12 h, and we can obtain the enaminone (**5**) in 80% yield(based on **4**).

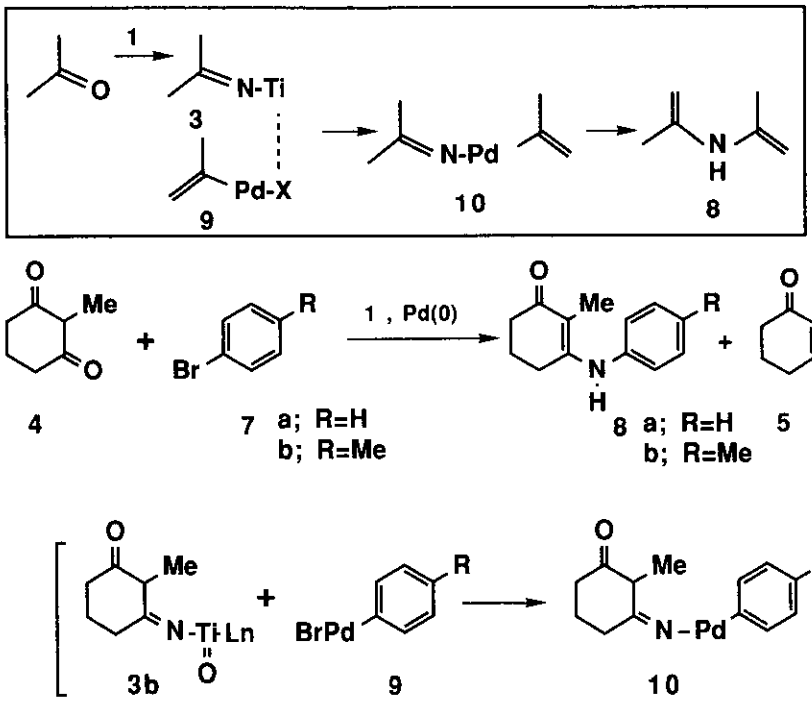
The effectiveness of 1,3-diketone for imine formation compared with monoketone is considered to arise as follows: (1) The initial stage of this reaction would be electron transfer from the low-valent titanium complex to the carbonyl group. The

electron transfer to 1,3-diketone is more effective than that to monoketone[5] because of its lower reducing electron potential. The generated radical species (**i**) is stabilized by the contribution of its resonance structures in the 1,3-dicarbonyl system. The monoketone affords the unstabilized radical, which can revert to the starting material. (2) The *N*-titanoimine complex (**6**) produced from 1,3-diketone (**4**) is stabilized by the contribution of its enol and/or enamine forms (**6'**) and (**6"**).



If titanoimine complex (**3**) can be transmetallated with arylpalladium complex, aniline derivative (**8**) should be formed from imino-palladium complex (**10**) followed by reductive elimination. When a NMP solution of diketone (**4**) and bromobenzene (**7**) were heated with **1** in the presence of Pd(PPh3)4(5 mol%) at 100 °C for 12 h, enaminone (**8a**) was obtained in 39% yield along with **5**(30% yield). Similar treatment of *p*-bromotoluene(**7b**) afforded compound (**8b**) in 37%

yield. The results indicate that aryl halides are converted directly into aniline derivatives by use of complex (**1**) and Pd(0) catalyst. The above reaction involved two processes: (1) imine-formation by nitrogenation with the titanium-isocyanate complex (**1**) and (2) unprecedented transmetallation of imine-titanium complex (**3**) with the palladium complex (**9**).



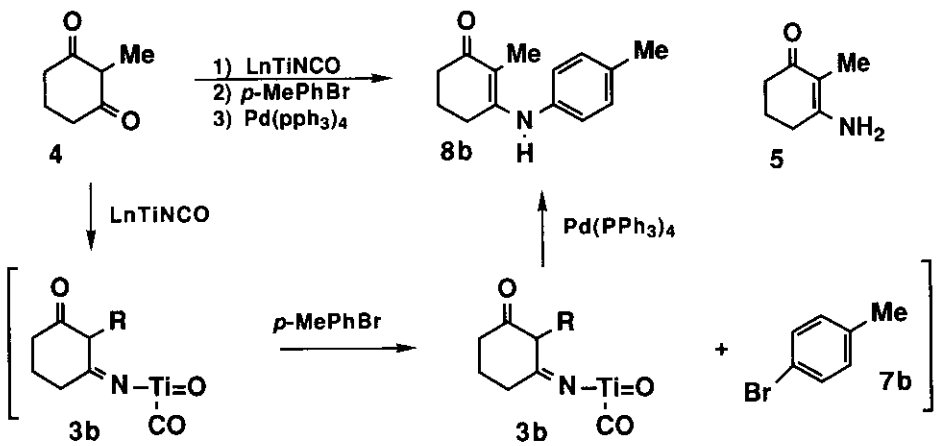
The transmetallation process of the *N*-titanoimine complex (**3b**) and an arylpalladium bromide (**9b**) was confirmed as follows(Table 1): Though the reaction of **4** with **1** afforded enaminone (**5**) (run 1), *p*-bromotoluene (**7b**) did not react with **1** even in the presence of palladium(0) catalyst(run 2). The desired product (**8b**) could not be obtained without palladium(0) catalyst under the same reaction conditions(run 3). However, the reaction of **4** with **7b** proceeded in the presence of **1** and Pd(0) catalyst to give **8b** (run 4). Moreover, the reaction course was monitored by TLC. When a NMP solution of the diketone (**4**) and the titanium isocyanate complex (**1**) was heated at 100 °C, the spot of the enaminone (**5**) was

shown on TLC. To the solution was added *p*-bromotoluene (**7b**) and the solution was heated at 100 °C. At this stage, no change was observed on tlc except the spot of *p*-bromotoluene. Then a catalytic amount of Pd(PPh3)4(10 mol %) was added to the solution and the whole mixture was continued to heat at 100 °C. Apparently, the spot of the desired product (**8b**) was shown on tlc along with the spots of **7b** and **5** and we could obtain compound (**8b**) in 32% yield. Based on these results, this process must take place by the transmetallation of *N*-titano-imine complex (**3**) with aryl-palladium bromide (**9**) generated from aryl halide (**7**) and palladium(0).

Table 1 Reaction of 4 with 7b under various conditions

run	diketone	aryl halide	additive	5	7b (recovery)	8b
1	4	-	-	80%	-	-
2	-	7b (1 eq.)	$Pd(PPh_3)_4$ (5 mol %)	-	79%	-
3	4	7b (1 eq.)	-	72%	70%	-
4	4	7b(1 eq.)	$Pd(PPh_3)_4$ (5 mol %)	32%	-	37%

* All reactions were run with 3 eq. of 1 in NMP at 100°C for 12 h under argon.



To demonstrate the applicability of this nitrogenation-transmetallation process, an intramolecular cyclization was examined. The diketo-vinyl bromide (**11a**) was treated with **1** in the presence of a catalytic amount of Pd(PPh3)4 in NMP at 100 °C for 12 h to afford indole derivative (**14a**) in 87% yield(Table 2, Run 1).[6]

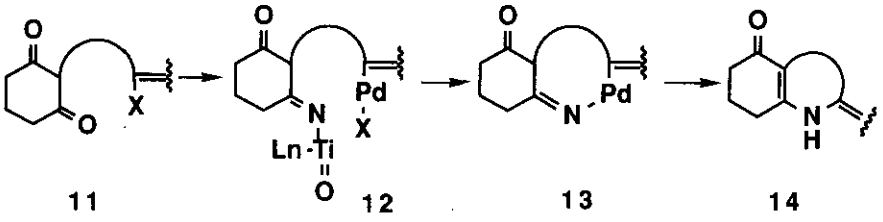
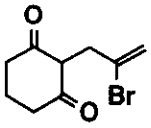
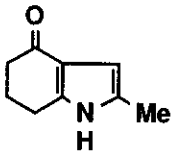
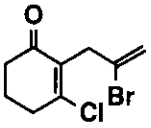
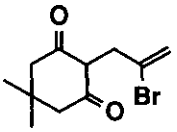
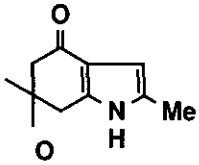
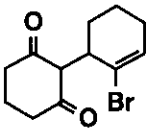
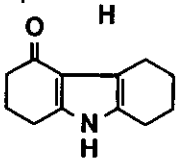
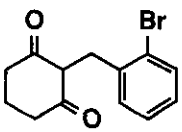
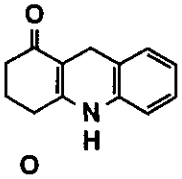
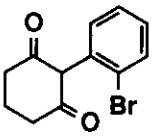
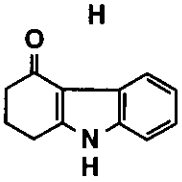


Table 2 Ring construction of Heterocycles *via* Nitrogenation-Transmetallation Process

run	starting materials	products
1	 11a	 14a (87%)
2	 11a'	14a (50%)
3	 11b	 14b (73%)
4	 11c	 14c (82%)
5	 11d	 14d (75%)
6	 11e	 14e (85%)

* All reactions were run with 3 eq. of **1** and $Pd(PPh_3)_4$ (5 mol %) in NMP at 100°C for 12 h.

Representative results for this process are shown in Table 2. Chroenone (**11a'**) and dimethyl derivatives (**11b**) afforded **14a** and **14b** (50% and 73% yields, respectively) under the same reaction conditions(run 2,3). Likewise, tricyclic compound (**14c**) was obtained in 82% yield from **11c**. The *N*-titanoimine complex could also be transmetallated with arylpalladium bromide. Thus, the ring construction of quinoline (**14d**) and carbazole (**14e**) were achieved from **11d** and **11e** in 75% and 85% yields, respectively.

Since the starting material can be easily prepared from the corresponding diketone and allylic or benzylic halide, this nitrogenation-transmetalltion process is effective for alkaloid synthesis, especially for the syntheses of biologically important 4-substituted indole derivatives.[7,8]

EXPERIMENTAL SECTION

General Experimental Procedure. All reactions were run under argon atmosphere. Melting points were determined on a Yanagimoto No. 815 melting point apparatus or Ishii melting point apparatus and are uncorrected. Ir spectra were recorded on a Jasco A-300 spectrophotometer. ^{1}H Nmr spectra were measured on a JEOL FX-90Q at 90 MHz or JEOL FX-100 at 100MHz. EI-mass and high resolution mass spectra were recorded on a JEOL JMS DX-303 instrument.

N-Benzoyl-2-methylpropylamine (2-H). Titanium isocyanate complex (**1**) (441 mg, 1 mmol) was added in 3 ml of butan-2-one and the solution was refluxed for 16 h. The reaction mixture was concentrated under reduced pressure and the residual green-gray solids were suspended in THF(5 ml). To a solution was added $LiAlH_4$ (100 mg) at 0 °C and the mixture was stirred for 2 h. After quenching with $Na_2SO_4 \cdot 10H_2O$, a large amount of benzoyl chloride and saturated $NaHCO_3$ solution were added and the solution was stirred at room temperature for 12 h. The reaction mixture was diluted with AcOEt and the organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced

pressure and the residue was purified by column chromatography on silica gel using AcOEt/Hexane (1:2) as eluent to give 46 mg (26%) of **2-H**. ^{1}H-Nmr ($CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3H), 1.23 (d, J = 6.6 Hz, 3H), 1.54 (dq, J = 7.4 Hz and 8.1 Hz, 2H), 4.13 (tq, J = 6.6 Hz and 8.1 Hz, 1H), 5.90 (br s, 1H), 7.31-7.80 (m, 5H); ir (neat) ν max 3450, 1680 cm^{-1}; ms (m/z) 177 (M^+), 105 (base peak); HR-ms calcd for $C_{11}H_{15}NO$: 177.1154. Found: 177.1150.

N-Benzoyl-2-deutro-2-methylpropylamine (2-D). **2-D** was prepared by the same procedure as **2-H** using $LiAlD_4$ to afford 43 mg of **2-D** (24%). ^{1}H-Nmr ($CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3H), 1.22 (s, 3H), 1.54 (q, J = 7.4 Hz, 2H), 5.84 (br s, 1H), 7.31~7.80 (m, 5H); ir (neat) ν max 3450, 1680 cm^{-1}; ms (m/z) 178 (M^+), 105 (base peak); HR-ms calcd for $C_{11}H_{14}DNO$: 178.12165. Found: 178.12175.

3-Amino-2-methyl-2-cyclohexene (5). A solution of 2-methyl-1,3-cyclohexadione (**4**) (63 mg, 0.5 mmol) and **1** (662 mg, 1.5 mmol) in 5 ml of N-methyl-2-pyrrolidinone (NMP) was degassed through a freeze-pump-thaw cycle and then the solution was heated upon 100 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with AcOEt and a small amount of water was added. The whole reaction mixture was filtered through a Celite and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel using AcOEt as eluent to give 50 mg of **5** (80%). ^{1}H-Nmr ($CDCl_3$) δ 1.89-2.08 (m, 2H), 2.32-2.48 (m, 4H), 4.44 (brs, 2H); ir (neat) ν max 3450, 1615 cm^{-1}; ms (m/z) 125 (M^+, base peak), 97.

***N*-(*p*-Tolyl)-2-amino-1-methyl-2-cyclohexenone (8b).** A solution of **2** (63 mg, 0.5 mmol), **7b** (85.5 mg, 0.5 mmol), **1** (662 mg, 1.5 mmol) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) in 5 ml of NMP was degassed through freeze-pump-thaw cycle, and then the solution was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with AcOEt and a small amount of water was added. The whole mixture was stirred for several hours. The solution was filtered through Celite and the solids were washed with AcOEt. The combined filtrates were washed with brine and dried over Na_2SO_4. The solvent was

evaporated and the residue was purified by column chromatography on silica gel using AcOEt/Hexane (1:1) as eluent to give 40 mg of **8b** (37%) and 20 mg of **5** (32 %). ^{1}H-Nmr ($CDCl_3$) δ 1.83 (s, 3H), 1.8-2.08 (m, 2H), 2.36 (s, 3H), 2.33-2.39 (m, 4H), 6.20 (brs, 1H), 7.03 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H); ir ($CHCl_3$) ν max 3440, 1680, 1520 cm^{-1}; ms (m/z) 215 (M^+, base peak), 106; HR-ms calcd for $C_{14}H_{17}NO$: 215.1320. Found: 215.1285.

1-(*o*-Bromophenyl)-5-carbomethoxy-2-pentanone. To a suspension of Zn (327 mg, 5 mmol) in THF (2 ml) was added *o*-bromobenzylbromide (1g, 4 mmol) and the reaction mixture was stirred at room temperature for 3 h. After Zn was filtered off under an argon atmosphere and the filtrate was added to a THF (3 ml) solution containing LiCl (340 mg, 4 mmol) and CuCN(358 mmg, 8 mmol) at -78 °C and the whole solution was stirred at -0 °C for 2 h. To the solution was added 4-carbomethoxybutyryl chloride(493 mg, 3 mmol) at -78°C and the solution was stirred at 0 °C for 2 h. The reaction mixture was diluted with ether and the ether layer was washed with sat.$NaHCO_3$, and brine and dried over Na_2SO_4. Solvent was removed and the residue was purified by column chromatography on silica gel using AcOEt/hexane (1/3) as eluent to give colorless oil of 1-(*o*-bromophenyl)5-carbomethoxy-2-pentanone (787 mg, 87%). ^{1}H-Nmr ($CDCl_3$) δ 1.80-2.05 (m, 2 H), 2.36 (t, J=3.6 Hz, 2 H), 2.59 (t, J=3.7 Hz, 2 H), 3.69 (s, 3 H), 3.85 (s, 2 H), 7.01-7.60 (m, 4H); ir ($CHCl_3$) ν max 1730, 1705 cm^{-1}; ms (m/z) 269, 267 (M^+-OMe), 241, 239 (M^+-COOMe), 171, 169 (*o*-$BrPhCH_2$, base peak).

2-(o-Bromophenyl)cyclohexane-1,3-dione. To a solution of 1-(*o*-bromophenyl)-5-carbomethoxy-2-pentanone (299 mg, 1.0 mmol) in ether (2 ml) was added NaOMe (54 mg, 1 mmol) and the solution was stirred at room temperature for 3 h. The solution was diluted with ethyl acetate and the organic layer was washed with HCl and brine, dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel using EtOAc/hexane (1/2) to give colorless oil of **11e** (195 mg, 73%). ^{1}H-Nmr ($CDCl_3$) δ 1.84-2.22 (m, 2 H), 2.32-2.68 (m, 4 H), 3.83 (s, 0.38 H), 5.60 (br s, 0.63),

7.06-7.66 (m, 4H); ir ($CHCl_3$) ν max 3000, 1720, 1620 cm^{-1}; ms (m/z) 269, 267 (M^++1-OMe), 187 (M^+-Br, base peak).

General Procedure for the Synthesis of Indole and Quinoline Derivatives(14)

A solution of **11** (0.2 mmol), $Pd(PPh_3)_4$ (0.01 mmol) and **1** (0.6 mmol) in 2 ml of NMP was degassed through freeze-pump-thaw cycle and then the solution was heated (100 °C) for 12 h. After cooling to room temperature, the reaction mixture was diluted with AcOEt and a small amount of water was added. The whole mixture was filtered through Celite and the solids were washed with AcOEt. The combined filtrates were washed with H_2O, 5% aq. HCl, saturated $NaHCO_3$ and brine, and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to give **14**.

2-Methyl-4-oxo-4,5,6,7-tetrahydroindole (14a). A crude product which was prepared from **11a** (46 mg, 0.2 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01mmol) and **1** (265 mg, 0.6 mmol) in 2 ml of NMP was purified by column chromatography on silica gel using AcOEt/Hexane (1/1) as eluent to give 26 mg (87%) of **14a**. ^{1}H-Nmr ($CDCl_3$) δ 2.06-2.20 (m, 2H), 2.24 (s, 3H), 2.39-2.51 (m, 2H), 2.71-2.83 (m, 2H), 6.19 (brs, 1H), 8.52 (brs, 1H); ir ($CHCl_3$) ν max 3490, 1655 cm^{-1}; ms (m/z) 149 (M^+), 121, 93 (base peak); mp 208 °C.

2,6,6-Trimethyl-4-oxo-4,5,6,7-tetrahydroindole (14b). A crude product which was prepared from **11b** (52 mg, 0.2 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01mmol) and **1** (265 mg, 0.6 mmol) in 2 ml of NMP was purified by column chromatography on silica gel using AcOEt/Hexane (1/1) as eluent to give 26 mg (73 %) of **14b**. ^{1}H-Nmr ($CDCl_3$) δ 1.11 (s, 6H), 2.24 (d, J = 1.2 Hz, 3H), 2.32 (s, 2H), 2.62 (s, 2H), 6.16 (m, 1H), 7.40 (brs, 1H); ir ($CHCl_3$) ν max 3490, 1650 cm^{-1}; ms (m/z) 177 (M^+), 121 (base peak), 93; HR-ms calcd for $C_{11}H_{15}NO$: 177.1154. Found: 177.1146.

4-Oxo-1,2,3,4,5,6,7,8-octahydro-carbazole (14c). A crude product which was prepared from **11c** (54 mg, 0.2 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01mmol) and **1** (265 mg, 0.6 mmol) in 2 ml of NMP was purified by column chromatography on

silica gel using AcOEt/Hexane (1/1) as eluent to give 31 mg (82%) of **14c**. ^{1}H-Nmr ($CDCl_3$) δ 1.64-1.91 (m, 4H), 1.98-2.24 (m, 2H), 2.19-2.51 (m, 4H), 2.71-2.83 (m, 4H), 7.90 (br s, 1H); ir ($CHCl_3$) ν max 3470, 1645 cm^{-1}; ms (m/z) 189 (M^+), 161 (base peak), 133; mp 228-229 °C.

1-Oxo-1,2,3,4-tetrahydro-acridine (14d). A crude product which was prepared from **11d** (56 mg, 0.2 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01mmol) and **1** (265 mg, 0.6 mmol) in 2 ml of NMP was purified by column chromatography on silica gel using AcOEt/Hexane (1/1) as eluent to give 30 mg (75%) of **14a**. ^{1}H-Nmr ($CDCl_3$) δ 2.21-2.40 (m, 2H), 2.75-2.87 (m, 2H), 2.82-3.40 (m, 2H), 3.65 (s, 2H), 6.56-7.52 (m, 4H); ir ($CHCl_3$) ν max 3450, 3000, 1610, 1590 cm^{-1}; ms (m/z) 199 (M^+), 198 (base peak); HR-ms Calcd for $C_{13}H_{11}NO$ ($M-H_2$): 197.0840. Found: 197.0817.

4-Oxo-4,5,6,7-tetrahydrocarbazole (14e). A crude product which was prepared from **11e** (80 mg, 0.3 mmol), $Pd(PPh_3)_4$ (18 mg, 0.015mmol) and **1** (398 mg, 0.9 mmol) in 3 ml of NMP was purified by column chromatography on silica gel using AcOEt/Hexane (1/1) as eluent to give 47 mg (85%) of **14d**. ^{1}H-Nmr ($CDCl_3$) δ 2.18-2.38 (m, 2H), 2.54-2.66 (m, 2H), 2.95-3.04 (m, 2H), 7.13-7.36 (m, 3H), 7.17 (dd, J = 3.0 Hz and 8.2 Hz, 1H), 7.44 (brs, 1H); ir ($CHCl_3$) ν max 3450, 3050, 1605 cm^{-1}; ms (m/z) 185 (M^+), 157 (base peak), 129; mp 218-220 °C.

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