New C–N–C Bond Formation Reaction using the Nitrogenation-transmetallation Process

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Ketones and aryl or vinyl halides couple to give divinyl or arylvinyl amines 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 **6** with aryl or vinyl palladium bromide (THF tetrahydrofuran).

Over the past two decades molecular nitrogen fixation has intrigued many research groups.[1] The nitrogenation method using a titanium–nitrogen complex[2] developed by us[3] is one of the earliest indications of the applicability of transition metal nitrogen complexes in organic synthesis as an N_1 unit reagent **1**.[2c] During our investigations, we have found a new C–N–C bond formation reaction and we now describe the novel ring construction of the heterocycles by use of this reaction.

When the diketone **2** and bromobenzene **3a** were treated with **1** in the presence of $Pd(PPh_3)_4$ (5 mol %) in *N*-methyl-2-pyrrolidone (NMP) at 100 °C for 12 h, the enaminone **4a**† was obtained in 39% yield along with **5** (30% yield). Similar treatment of *p*-bromotoluene **3b** afforded compound **4b** 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: (*i*) imine formation by nitrogenation with the titanium isocyanate complex **1** and (*ii*) unprecedented transmetallation of the imine–titanium complex and the palladium complex.

In order to confirm the imine formation from the diketone and complex **1**, a solution of the diketone **2** and 3 equiv. of **1** was heated at 100 °C in NMP for 12 h, and the enaminone **5** was obtained in 80% yield (based on **2**). Moreover, when a butan-2-one solution of **1** was refluxed for 24 h and then the solvent evaporated *in vacuo*, a grey-green residue was obtained. $LiAlH_4$ reduction of the residue in THF followed by treatment with benzoyl chloride afforded **6-H** in 26% yield (based on **1**). $LiAlD_4$ reduction followed by benzoylation afford the α-deuteriated product **6-D** in 24% yield. These experiments suggested that the *N*-titano-imine complex **7** was formed as an intermediate in the reaction of **1** with butan-2-one.

The effectiveness of the 1,3-diketone for imine formation compared with the monoketone is considered to arise as

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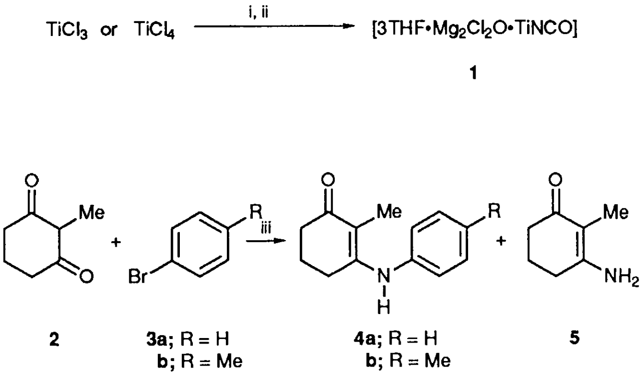
† All new compounds exhibited ^1H NMR, IR, mass and high resolution mass spectra consistent with the assigned structure.

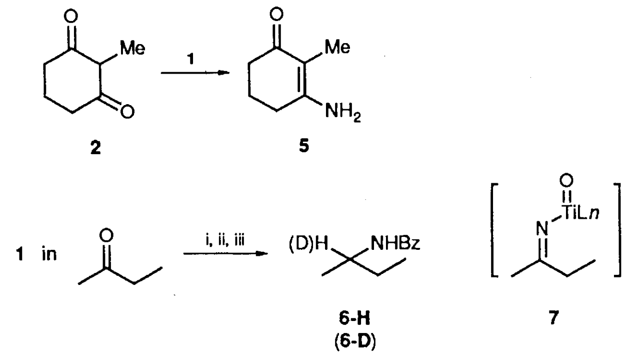
follows. (*i*) The initial stage of the reaction would be electron transfer from the low-valent titanium complex to the carbonyl group. The electron transfer to the 1,3-diketone is more effective than that to the monoketone[4] because of its lower reducing electron potential. The generated radical species **8** is stabilized by the contribution of its resonance structures in the 1,3-diketone system. The monoketone affords the unstabilized radical which can revert to the starting material. (*ii*) The *N*-titano-imine complex **4** produced from **2** is stabilized by the contribution of its enol and/or enamine forms **4′**, **4″**.

The transmetallation process of the *N*-titano-imine complex **9** and aryl palladium bromide **10** was confirmed as follows (Table 1). Though the reaction of **2** with **1** afforded enaminone **5** (run 1), *p*-bromotoluene **3b** did not react with **1** even in the presence of palladium(0) catalyst (run 2). The desired product **4b** could not be obtained without palladium(0) catalyst under the same conditions (run 3). However, the reaction of **2** with **3b** proceeded in the presence of **1** and Pd^0 catalyst to give **4b** (run 4). Based on these results, this process must take place by the transmetallation of the *N*-titano-imine complex **9** with **10** generated from aryl halide **3** and palladium(0).

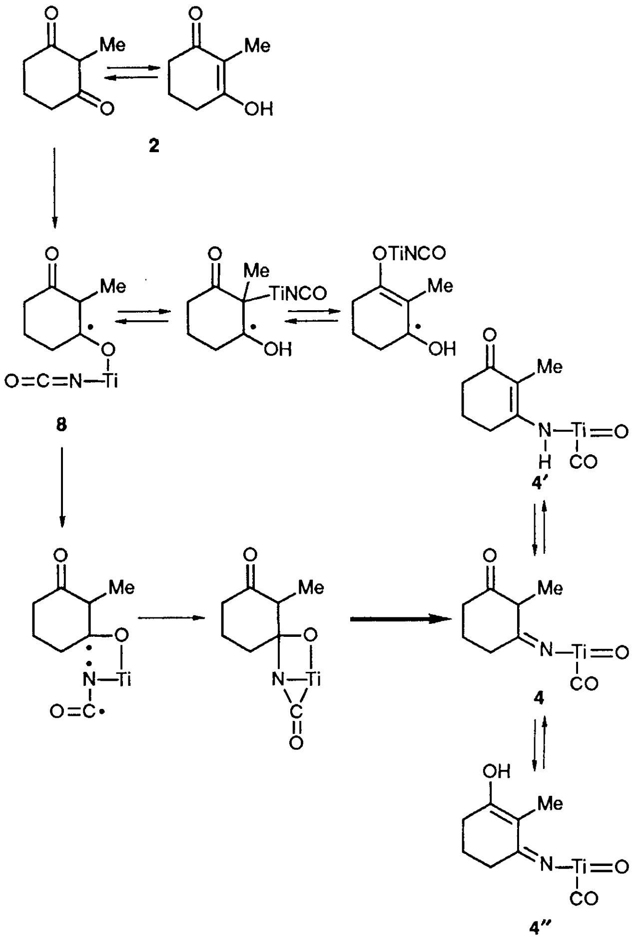
To demonstrate the applicability of this nitrogenation-transmetallation process, an intramolecular cyclization was examined as shown in Scheme 5. The diketo-vinyl bromide **11a** was treated with **1** in the presence of a catalytic amount of Pd(PPh$_3$)$_4$ in NMP at 100 °C for 12 h to afford the indole



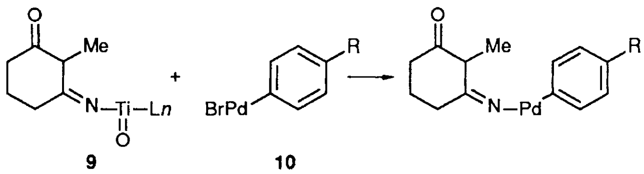
Scheme 1 *Reagents and conditions*: i, Mg, N_2 (1 atm), THF, room temp., ii, CO_2 (1 atm), THF, room temp., iii, **1**, Pd^0



Scheme 2 *Reagents and conditions*: i, Reflux 24 h, ii, $LiAlH_4$ (or $LiAlD_4$), iii, BzCl



Scheme 3



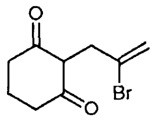
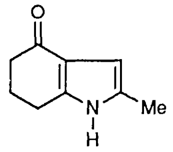
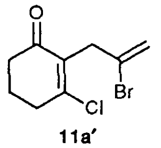
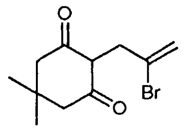
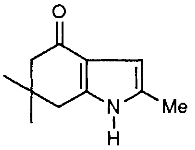
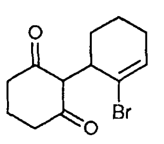
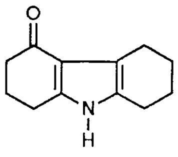
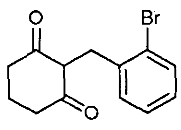
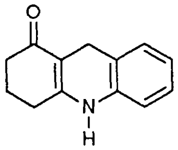
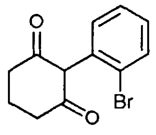
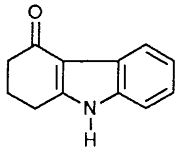
Scheme 4

Table 1 Reaction of **2** with **3b** under various conditions[a]

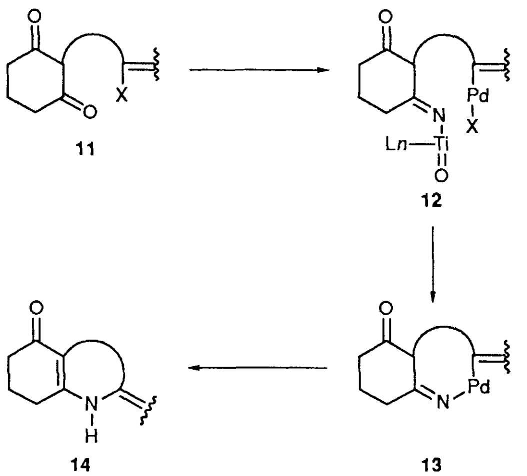
Run	Diketone	Aryl halide[b]	Additive	Yield (%) **5**	**3b** (recovery)	**4b**
1	2	—	—	80	—	—
2	—	**3b**	Pd(PPh$_3$)$_4$ (5 mol%)	—	79%	—
3	2	**3b**	—	72	70	—
4	2	**3b**	Pd(PPh$_3$)$_4$ (5 mol%)	32	—	37

[a] All reactions were run with 3 equiv. of **1** in NMP at 100 °C for 12 h under argon. [b] 1 equiv.

Table 2 Ring construction of heterocycles *via* nitrogenation-transmetallation process[a]

Run	Starting materials	Products	Yield (%)
1	 **11a**	 **14a**	87
2	 **11a′**	**14a**	50
3	 **11b**	 **14b**	73
4	 **11c**	 **14c**	82
5	 **11d**	 **14d**	75
6	 **11e**	 **14e**	85

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



Scheme 5

derivative **14a** in 87% yield (Table 2, Run 1).‡ Representative results for this process are shown in Table 2. Chroenone **11a′** and the dimethyl derivative **11b** afforded **14a** and **14b** (50% and 73% yields respectively) under the same reaction conditions (runs 2,3). Likewise, the tricyclic compound **14c** was obtained in 82% yield from **11c**. The *N*-titano-imine complex could also be transmetallated with arylpalladium bromide. Thus, the ring constructions 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–transmetallation process is effective for alkaloid synthesis, especially for the syntheses of biologically important 4-substituted indole derivatives.[5,6] Further studies along these lines are under investigation.

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‡ *General procedure*: A solution of diketo-vinyl(aryl) halide **11**, **1** (3 equiv.) and $Pd(PPh_3)_4$ (5 mol %) in NMP (0.1 mol dm^{-3}) was degassed through a freeze–pump–thaw cycle. The solution was heated at 100 °C under argon atmospher for 12 h. After cooling, the reaction mixture was diluted with AcOEt and a small amount of water was added to decompose the titanium complex. The mixture was filtered through a short Celite column and the filtrate was washed with HCl (dil.), $NaHCO_3$ (sat.) and brine (dried over Na_2SO_4). After removal of the solvent, the residue was purified to give the desired product (usually silica gel chromatography was used).

The indole derivative **14a** could not be obtained in the absence of palladium(0) catalyst.

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