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## Communication

### Catalytic Dehalogenation of Monohalopyridines with Titanocene Complexes


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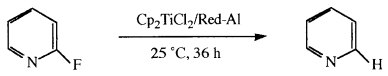
Since halogenated organics are chief constituents of various modern industries, their conversion to less dangerous or harmless organics after and use is very important. Bond dissociation energy (kcal/mol) of carbon-halogen bond decreases in the order of C-F (106) > C-Cl (81) > C-Br (69) > C-I (53).[1] Bond dissociation energy of aromatic carbon-fluorine bond is known to be pronouncedly high: for example, 155 kcal/mol for $C_6F_6$.[2] Typical destructive defluorination was performed under harsh heterogeneous conditions by using activated transition metals, transition metals, transition metal oxides or organic salts at 200-700 °C.[3,4] Worldwide research efforts have been devoted to the catalytic or stoichiometric activation of the strong C-F bonds of saturated perfluoroalkanes or fluorinated aromatics with transition metal complexes.[5-7] The dechlorination of chlorobenzenes by using $Cp_2TiCl_2/NaBH_4$ combination reagent in dimethylacetamide at 85 °C was reported.[8] Richmond *et al.* described the reductive defluorination of perfluorodecalin by using $Cp_2TiF_2/Al/HgCl_2$ combination reagent in THF at 25 °C.[9] Takahashi *et al.* recently reported the zirconocene-catalyzed dehalogenation of aromatic halides (such as Cl, Br, I-substituted benzenes, naphthalenes, and thiophenes) by alkyl Grignard reagents: *i.e.*, $0.1Cp_2ZrCl_2/3RMgX$, where RMgX is the hydrogen donor.[10] The dehalogenation of halogenated pyridines at mild homogeneous condition by using group 4 metallocene catalysts has not been reported to our knowledge. We recently reported the dehydropolymerization of hydrosilanes to polysilanes catalyzed by group 4 metallocene complexes generated *in situ* from $Cp_2MCl_2$/Red-Al combination.[11] During the dehydrocoupling study we found the group 4 metallocene-mediated dehalogenation of halopyridines in the presence of inorganic hydrides at room temperature.

In a typical experiment, toluene was completely removed under vacuum from a deep blue mixture of $Cp_2TiCl_2$ (37.4 mg, 0.15 mmol) and Red-Al (1.32 mL, 4.5 mmol; 3.4 M solution in toluene) in a Schlenk flask. 2-Fluoropyridine (0.29 g, 3.0 mmol) was added to the dried mixture. The reaction started immediately, as evidenced by the immediate color change from deep blue into deep green. The progress of reaction was monitored by GC and $^1$H NMR analytical techniques. After stirring at 25 °C for 36 h, the reaction mixture was exposed to air to oxidize the active organometallic moieties. Benzenes-$d_6$ (1.0 mL) was added to the mixture. The supernatant liquid (0.2 mL) in a NMR tube was diluted with benzene-$d_6$ (0.2 mL) and cyclohexane (0.1 mL). The $^1$H MNR was taken immediately. The analyses showed that 2-fluoropyridine was quantitatively converted to pyridine.




The other agents were also tested in combination with several titanocenes for the dehalogenation of monohalopyridine. The results were summarized in Table 1.

As shown in Table 1, the catalytic activity decreases in the order of $Cp_2Ti > Cp(C_5Me_5)Ti > (C_5Me_5)_2Ti$ due probably to steric effect. The $Cp_2TiCl_2$/*n*-BuLi combination was ineffective to the defluorination of 2-fluoropyridine. Red-Al in the absence of the group 4 metallocenes was found to be ineffective in this reaction. Red-Al in the presence of the group 4 metallocenes should be the source of hydrogen because appreciable deuterium scrambling by deuterium-substituted solvents such as THF-$d_8$ and toluene-$d_8$ was not observed.[12] The catalyst combinations listed in Table 1 were all ineffective in the defluorination of fluorobenzenes and perfluorodecalin under the reaction condition. We sometimes used

**Table 1**. Catalytic Dehalogenation of Monohalopyridines with Titanocene Complexes[a]

| Catalyst | Halopyridine | % Yield[b] |
|---|---|---|
| $Cp_2TiCl_2$/Red-Al | 2-F | 100 |
| $Cp(C_5Me_5)TiCl_2$/Red-Al | 2-F | 81 |
| $(C_5Me_5)_2TiCl_2$/Red-Al | 2-F | 43 |
| $Cp_2TiCl_2$/Red-Al/MS4A[c] | 2-F | 100 |
| $Cp_2TiCl_2$/Red-Al | 3-F | 45 |
| $Cp_2TiCl_2$/Red-Al | 2-Cl | 68 |
| $Cp_2TiCl_2$/Red-Al | 2-Br | 60 |
| $Cp_2TiCl_2$/*n*-BuLi | 2-F | 0 |

[a]Reaction conditions: [M] = 0.10, [$H^-$] = 1.5, [X-Py] = 1.0; stirring at 25 °C for 36 h, except where stated otherwise. [b]Estimated by integration of $^1$H NMR spectrum. [c][MS4A] = 10wt% of $Cp_2TiCl_2$; reaction time 18 h.

fluorobenzenes and perfluorodecalin even as an inert solvent for the dehalogenation of halopyridines. Interestingly, the defluorination of 3-fluoropyridine occurred at a slower rate than that of 2-fluoropyridine with $Cp_2TiCl_2$/Red-Al combination (yield: 45% *vs* 100%) without formation of bipyridines, the expected coupling products of their respective pyridyl radicals. Interestingly, the rate of dehalogenation was accelerated by adding 4 Å molecular sieve (MS4A). The presence of halogen in the 2-position of halopyridines is apparently essential to the effective dehalogenation, suggesting that the nitrogen moiety of halopyridine should first coordinate to the metal center and then undergo the dehalogenation/hydrogenation presumably *via* orthometalation. Surprisingly, the reactivity of 2-halopyridines was in the order of C-F > C-Cl > C-Br, which is opposite to the order of their bond strength. The observed C-X reactivity order may be related to the Ti-X bond strength.

The possible mechanisms for the dehalogenation/hydrogenation processes between C-F and M-H bonds are (**A**) concerted sigma-bond metathesis,[13] (**B**) oxidative addition/reductive elimination,[10] and (**C**) free radical.[5] The free radical mechanism **C** can be here ruled out on the basis of the experimental facts: (1) reactivity order of C-F > C-Cl > C-Br and 2-fluoropyridine > 3-fluoropyridine, (2) no formation of bipyridine, and (3) no appreciable deuterium scrambling by deuterium-substituted solvents such as THF-$d_8$ and toluene-$d_8$. Since enough experimental data are not currently available, it is not clear yet which mechanism between the possible mechanisms **A-B** should solely operate for the dehalogenation of monohalopyridines.

We have failed to isolate a stable intermediate from the stoichiometric reaction of the titanocene dihydrides with halopyridines. The detailed studies on the dehalogenation mechanism of halopyridines, on the role of MS4A, and on the other possible combination catalysts, which are supported or unsupported over inorganic materials such as silica and alumina for the industrial application, are in progress and will be reported as a separate full paper in the future.

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12. In these experiment, the toluene-$H_8$ solvent was completely removed *in vacuo* from the deep blue mixture of $Cp_2TiCl_2$ (37.4 mg, 0.15 mmol) and Red-Al (1.32 mL, 4.5 mmol; 3.4 M solution in toluene-$H_8$). THF-$d_8$ (or toluene-$d_8$; 2.0 mL) and 2-fluoropyridine (0.29 g, 3.0 mmol) were added to the mixture and stirred for 36 h at 25 °C. The reaction mixture was then exposed to air for 10 min to kill the organometallic moieties. The supernatant liquid (0.2 mL) in a NMR tube was diluted with the same deutero solvent (0.2 mL) and cyclohexane (0.1 mL). The $^1$H NMR was taken immediately.
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