Dehalogenation of Monohalopyridines Catalyzed by Group 4 Metallocene Reagent

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The Cp'_2MCl_2/hydride (Cp' = Cp or Cp^*: Cp = η^5-C_5H_5, Cp^* = η^5-C_5Me_5; M = Ti, Zr, Hf) reagent catalyzes the dehalogenation of monohalopyridines at room temperature to give pyridine. The catalytic activity decreases in the order of M = Ti > Zr > Hf: M-F ≈ M-Cl ≈ M-Br ≈ M-I; Cp_2M > $CpCp^*M$ > Cp^*_2M; Red-Al > N-Selectride > K-Selectride > L-Selectride >> DIBAL-H, MeLi, *n*-BuLi; 2-fluoropyridine > 3-fluoropyridine; C-F > C-Cl > C-Br. The rate of dehalogenation is boosted by adding 4 Å molecular sieve. The catalyst combinations are all ineffective on the defluorination of fluorobenzenes and perfluorodecalin at the reaction condition. The possible mechanisms are suggested.

Introduction

Halogenated organic compounds are important constituents of modern industries, but they are globally implicated as major environmental pollutants.[1] Therefore, their conversion to less dangerous or harmless organics after end use is very essential to our life. 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).[2] Dissociation energy of aromatic C-F bond (*e.g.*, 155 kcal/mol for C_6F_6) is notoriously high due to p_π-p_π interaction in the C-F bond.[3] Heterogeneous defluorination was destructively performed under harsh reaction conditions by using activated transition metals, transition metal oxides or organic salts at 200-700 °C.[4,5] Since transition metal-halogen bonds are very strong, dehalogenation of halogenated organic compounds by using transition metal complexes under mild homogeneous conditions seems feasible.[6] Global research efforts have been focused upon the catalytic/stoichiometric activation of the strong C-F bonds of saturated perfluoroalkanes or fluorinated aromatics with transition metal complexes.[7-9] Metallocenes are generally known to mediate the dehalogenation of halo complounds.[7-9] In particular, Schwartz *et al*. described the dechlorination of chlorobenzenes by using the Cp_2TiCl_2/$NaBH_4$ reagent in N,N-dimethylacetamide at 85 °C.[10] Richmond *et al*. reported the reductive defluorination of perfluorodecalin by using the Cp_2TiF_2/Al/$HgCl_2$ reagent in THF at 25 °C and the hydrogenolysis of octafluoronaphthalene by using the Cp_2ZrCl_2/Mg/$HgCl_2$ reagent in THF at 25 °C, where THF solvent is the hydrogen donor.[11,12] 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.[13] We have reported the dehydropolymerization of hydrosilanes to polysilanes catalyzed by group 4 metallocene complexes generated *in situ* from Cp_2MCl_2/Red-Al.[14] During the dehydrocoupling study we found the group 4 metallocene-mediated dehalogenation of halopyridines in the presence of inorganic hydrides at room temperature. We communicated our preliminary findings on the catalytic dehalogenation of monohalopyridines with Cp_2TiCl_2/Red-Al reagent.[15] The Cp_2TiCl_2/Red-Al reagent was practically ineffective to the halobenzenes and halothiophenes, but it was selectively effective to the haopyridines under the mild reaction condition. In this article we report our results of the dehalogenation of monohalopyridines catalyzed by various Cp'_2MCl_2/hydride (Cp' = Cp or Cp^*: Cp = η^5-C_5H_5, Cp^* = η^5-C_5Me_5; M = Ti, Zr, Hf) combinations.

Experimental Section

Materials and Instrumentation. All reactions and manipulations were performed under prepurified nitrogen atmosphere using Schlenk techniques. Dry, oxygen-free solvents were employed throughout. Glassware was flame-dried or oven-dried before use. Approximate distances between ring-nitrogen and halogen substituent of monohalopyridines were obtained by using CS Chem 3D Pro™ Program (version 3.0) developed by the Cambridge Soft Corporation operating on a Power Macintosh personal computer. Proton NMR spectra were recorded on a Bruker ASX 32 (300 MHz) spectrometer using $CDCl_3$/$CHCl_3$ as a reference at 7.24 ppm downfield from TMS. Carbon MNR spectra were recorded on a Bruker ASX 32 (75.5 MHz) spectrometer using $CDCl_3$ as a reference at 77.0 ppm. Cp_2MCl_2 (M = Ti, Zr, Hf), Red-Al, A-Selectride (A = L, N, K), DIBAL-H, *n*-BuLi, and MeLi were purchased from Aldrich Chemical Co. and used as received. Molecular sieve 4 Å (MS4A, powder; purchased from Aldrich Chemical Co.) was dried at reduced pressure in 180 °C for 6 h before use. Cp_2ZrX_2 (X = F, Br, I),[16] $CpCp^*ZrCl_2$,[17] and $Cp^*_2ZrCl_2$[18] were prepared according to the literature procedures.

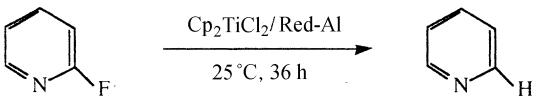
Catalytic Dehalogenation of Monohalopyridines with

the Group 4 Metallocene Combinations. The following procedure is the representative of catalytic dehalogenations. 2-Fluoropyridine (0.29 g, 3.0 mmol) was added to a Schlenk flask containing 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). The reaction started immediately, as monitored by the immediate color change from deep blue into deep green. The progress of reaction was monitored by GC and NMR techniques. After stirring at 25 °C for 36 h, the analyses showed that 2-fluoropyridine was quantitatively converted to pyridine. The ^{1}H MNR data of 2-fluoropyridine and pyridine are as follows.: 2-fluoropyridine [^{1}H NMR (δ, $CDCl_3$, 300 MHz): 6.50, 6.65 (m, 1H, *m*-C_5H_4FN), 7.19 (m, 1H, *p*-C_5H_4FN), 7.93 (br d, 1H, *o*-C_5H_4FN); ^{13}C{^{1}H} NMR (δ, $CDCl_3$, 75.5 MHz): 109.11, 109.85, 121.28, 121.35, 140.94, 141.09, 147.72, 148.02, 161.65, 166.36 ($^1J_{C\text{-}F}$ = 237 Hz)]; pyridine [^{1}H NMR (δ, $CDCl_3$, 300 MHz): 6.82 (m, 2H, *m*-C_5H_5N), 7.19 (m, 1H, *p*-C_5H_5N), 8.48 (m, 2H, *o*-C_5H_5N); ^{13}C{^{1}H} NMR (δ, $CDCl_3$, 75.5 MHz): 123.71, 135.59, 150.13 (C_5H_5N)].

Results and Discussion

2-Fluoropyridine was quantitatively converted to pyridine by Red-Al in the presence of catalytic amount of Cp_2TiCl_2. Fluoride ion may be removed in the form of NaF and AlF_3 during the reaction. The reaction started immediately and its progress was monitored by GC and NMR techniques.

Similarily, Cp_2ZrCl_2/Red-Al and Cp_2HfCl_2/Red-Al combinations transformed 2-fluoropyridine into pyridine under the same reaction condition in 73% and 65% yield, respectively. Other various combinations were also tested for the dehalogenation of monohalopyridines. The results were summarized in Table 1.

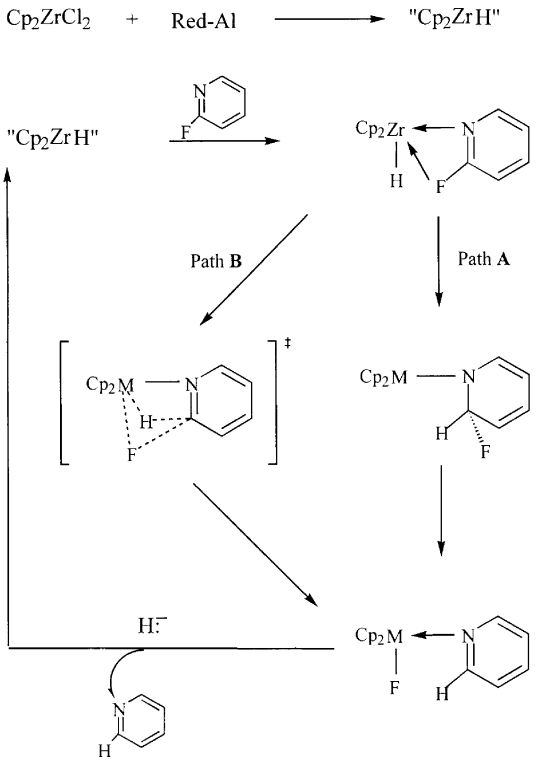


As shown in Table 1, the catalytic activity decreases in the order of M = Ti > Zr > Hf; M-F ≈ M-Cl ≈ M-Br ≈ M-I; Cp_2M > $CpCp^*M$ > Cp^*_2M; hydride = Red-Al > N-Selectride > K-Selectride > L-Selectride; 2-fluoropyridine > 3-fluoropyridine; C-F > C-Cl > C-Br. The higher catalytic activity of titanocene relative to the zirconocene and hafnocene is due probably to the higher intrinsic kinetic instability of Ti-X bonds.[19] The noticeable difference of catalytic activity with the strength of group 4 metal-halogen bond was not observed, contrary to expectation from the bond strength (in kcal/mol) order of Zr-F (155) > Zr-Cl (114) > Zr-Br (97).[6] The lower catalytic activity with higher substitution of Cp^* instead of Cp is probably due to steric effect. The Cp_2MCl_2/DIBAL-H and Cp_2MCl_2/RLi (R = Me, *n*-Bu) combinations were ineffective to the defluorination of 2-fluoropyridine. Anionic hydride (*i.e.*, Red-Al, Selectrides) is proved to be by far more effective than neutral hydride (*i.e.*, DIBAL-H) and alkyl anion. However, the inorganic hydrides in the absence of the group 4 metallocenes were found to be ineffective to this reaction. At the moment, we cannot rationalize properly the activity order of Red-Al > N-Selectride > K-Selectride > L-Selectride. It appears that Al-H is more reactive than B-H and that the presence of counter cation is also important. The inorganic hydride 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.[15] The catalyst combinations listed in Table 1 were all ineffective in the defluorination of fluorobenzenes and perfluorodecalin under the reaction condition. We sometimes used fluorobenzenes and perfluorodecalin even as an inert solvent for the dehalogenation of halopyridines. Interestingly, the rate of dehalogenation was accelerated by adding 4 Å molecular sieve (MS4A). Molecular sieve is well-known to mediate many useful reactions in industry *via* synergistic shape-selectivity and super-acidity.[20a] The MS4A often significantly affects some metal complex-mediated reactions *via* some unknown process.[20b,20c] We cannot rationalize the observation at present, but a study to clarify it is in progress. The defluorination of 3-fluoropyridine occurred at a slower rate than that of 2-fluoropyridine with Cp_2ZrCl_2/Red-Al combination (yield: 33% *vs* 73%) without formation of bipyridines, the expected coupling products of their respective pyridyl radicals. 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. Surprisingly, the reactivity of 2-halopyridines was in the order of C-F > C-Cl > C-Br,

Table 1. Catalytic Dehalogenation of Monohalopyridines with Group 4 Metallocene Combination[a]

Catalyst	Monohalopyridine	%Yield[b]
Cp_2TiCl_2/Red-Al	2-F	100
Cp_2TiCl_2/N-Selectride	2-F	91
Cp_2TiCl_2/DIBAL-H	2-F	0
Cp_2ZrCl_2/Red-Al	2-F	73
Cp_2ZrX_2/Red-Al (X = F, Br, I)	2-F	74
$CpCp^*ZrCl_2$/Red-Al	2-F	59
$Cp^*_2ZrCl_2$/Red-Al	2-F	32
Cp_2ZrCl_2/Red-Al/MS4A[c]	2-F	100
Cp_2ZrCl_2/Red-Al	3-F	33
Cp_2ZrCl_2/Red-Al	2-Cl	50
Cp_2ZrCl_2/Red-Al	2-Br	44
Cp_2ZrCl_2/L-Selectride	2-F	45
Cp_2ZrCl_2/N-Selectride	2-F	66
Cp_2ZrCl_2/K-Selectride	2-F	60
Cp_2ZrCl_2/DIBAL-H	2-F	0
Cp_2ZrCl_2/*n*-BuLi	2-F	0
Cp_2ZrCl_2/MeLi	2-F	0
Cp_2HfCl_2/Red-Al	2-F	65
Cp_2HfCl_2/Red-Al/MS4A[d]	2-F	100

[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 integation of ^{1}H NMR spectrum. [c][MS4A] = 10 wt% of Cp_2ZrCl_2; reaction time 24 h. [d][MS4A] = 10 wt% of Cp_2HfCl_2; reaction time 36 h.



Scheme 1. Possible Mechanisms for the Defluorination of 2-Fluoropyridine by Cp_2ZrCl_2/Red-Al.

which is opposite to the order of their bond strength (in kcal/mol): C-F (106) > C-Cl (81) > C-Br (69) > C-I (53). The observed C-X reactivity order should not be related to the M-X bond strength, as described above. Approximate distances between ring-nitrogen and halogen substituent of 2-fluoropyridine, 3-fluoropyridine, 2-chloropyridine, and 2-bromopyridine are 2.479, 3.720, 2.716, and 2.851 Å, respectively. The size and position of halogen atoms in halopyridines have a significant influence on their reactivity and basicity. The gas-phase basicity of monohalopyridine increases in the order of 2-fluoropyridine < 3-fluoropyridine ≈ 2-chloropyridine < 2-bromopyridine < 4-fluoropyridine.[21]

The possible mechanisms for the dehalogenation/hydrogenation processes between C-X and M-H bonds are (**A**) stepwise nucleophilic, (**B**) concerted sigma-bond metathesis,[22] (**C**) oxidative addition/reductive elimination.[13] and (**D**) free radical.[7] Although a radical-based hydrogen fluorine exchange using divalent lanthanoid reagents has been reported, a free radical mechanism **D** can be here ruled out on the basis of the present 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. In addition, the mechanism C is less likely because the oxidation state of +4 is more stable than +2 for Zr and Hf.

We have been unsuccessful to isolate a good quality of single crystal of stable intermediate directly from the stoichiometric reaction of group 4 metallocene dihydrides with halopyridines to clarify the dehalogenation mechanism of halopyridines. We currently prefer the mechanism **A** to the mechanisms **B** for our catalytic dehalogenation system because the nucleophilic reaction of group 4 metal hydride or silyl on pyridine is well documented and the analogous intermediate is known.[23-25] The observed reactivity orders of C-F > C-Cl > C-Br and 2-fluoropyridine > 3-fluoropyridine can be explained by the steric and electronic effect of halogen atom as you see in the mechanism **A** of Scheme 1.

In summary, this work describes the catalytic dehalogenation of monohalopyridines at room temperature to give pyridine with Cp'_2MCl_2/hydride (Cp' = Cp or Cp^*: Cp = η^5-C_5H_5, Cp^* = η^5-C_5Me_5; M = Ti, Zr, Hf) combination. The catalytic activity was found to decrease in the order of M = Ti > Zr > Hf; M-F ≈ M-Cl ≈ M-Br ≈ M-I; Cp_2M > $CpCp^*M$ > Cp^*_2M; Red-Al > N-Selectride > K-Selectride > L-Selectride >> DIBAL-H, MeLi, *n*-BuLi; 2-fluoropyridine > 3-fluoropyridine; C-F > C-Cl > C-Br. The rate of dehalogenation increased in the presence of 4 Å molecular sieve. The defluorination of fluorobenzenes and perfluorodecalin at the reaction condition with all the metallocene combinations used here did not occur. The possible mechanisms are suggested.

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