TiCl(O^{i}Pr)$_3$-mediated One-pot Reductive Amination of 1,1'-Diacetylferrocene with Aryl Amines

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1,1'-Disubstituted-ferrocenes, especially bearing chelating nitrogen atoms, are an important class of ligands in organic synthesis.[1,2] These nitrogen-containing ferrocenes served as [N,N] bidentate ligands to directly coordinate with transition metals for studying structures and mechanisms.[3] 1,1'-Diaminoferrocenes undergo cycloplatination to produce cycloplatinated complexes,[4] which exhibit potential medical and biological activities.[4d]

To introduce the nitrogen atom in 1,1'-diacetylferrocene, reductive amination is an important method to target the 1,1'-bis(*N*-aryl-1-aminoethyl)ferrocene. A successful reductive amination procedure relying on the two-step transformation proceeds *via* the formation of an imine that is reduced to the corresponding amine by various reducing agents.[5-8] In addition, the reduction of the ketone or the aldehyde must be slower than imine formation to avoid alcohol as a by-product. When the iminium adduct is difficult to form, activators are employed to facilitate the reaction. There are now known several activators such as CH$_3$CO$_2$H,[9] H$_3$BO$_3$,[10] TiCl$_4$,[2] Ti(O^{i}Pr)$_4$,[11] and TiCl(O^{i}Pr)$_3$[12] for the reductive amination of aryl ketones.

Among others, Ti(O^{i}Pr)$_4$ and TiCl(O^{i}Pr)$_3$ are expected to be more useful for a direct reductive amination reaction. Replacement of an isopropoxide from Ti(O^{i}Pr)$_4$ with a chlorine atom would increase the Lewis acidity of the reagent facilitating condensation of ketone with amine. The reductive amination of aryl ketone with aryl amine is not an easy transformation, and normally requires two steps; isolation of imine followed by reduction to amine. A two-step reductive amination of acetophenone with various aryl amines has recently been achieved; initial formation of solvent-free acetophenone with anilines at room temperature

in the presence of an activator such as boric acid and/or benzoic acid, and the subsequent reduction of the latter with NaBH$_4$.[10] The method for the reductive amination of 1,1'-diacetylferrocene with aryl amine is also known, which requires stepwise reactions and higher reaction temperature (110 °C).[2] In this regard, there still remains a need for a mild and one-pot method for the synthesis of a new class of aryl amines.

Herein, we report a TiCl(O^{i}Pr)$_3$-mediated one-pot reductive amination of 1,1'-diacetylferrocene with aryl amine under mild conditions. The advantage of the present method makes it unnecessary for the isolation of the intermediate imine. As imine formation is usually the rate-determining step for in situ reductive amination, a series of activators such as CH$_3$CO$_2$H, Ti(O^{i}Pr)$_4$, and TiCl(O^{i}Pr)$_3$ were employed in the reductive amination of acetophenone by NaBH(OAc)$_3$ at room temperature (Table 1, entries 1-3). Dichloromethane among others is the choice of preference as solvent in the formation of **1a** in an excellent yield (entries 3-5) (Figure 1). When the comparison is made between TiCl(O^{i}Pr)$_3$ and Ti(O^{i}Pr)$_4$, the former exhibits better reactivity by giving a much higher yield of **1a** in a shorter period of time under milder conditions. For instance, under the same reaction conditions, TiCl(O^{i}Pr)$_3$ provided the product in 92% in 2.5 h while Ti(O^{i}Pr)$_4$ exhibited a very poor yield (35%) in an extended period of reaction time (~25 h) (entries 2 and 3). Reductive amination of acetophenone with 4-methoxyaniline gave **1b** in 98% yield under the same reaction conditions (entry 6).[7c] Here it is interesting to note that 4-nitroaniline, a hard case for reductive amination, yields the product (**1c**) in as high as 40% (entry 7).[13]

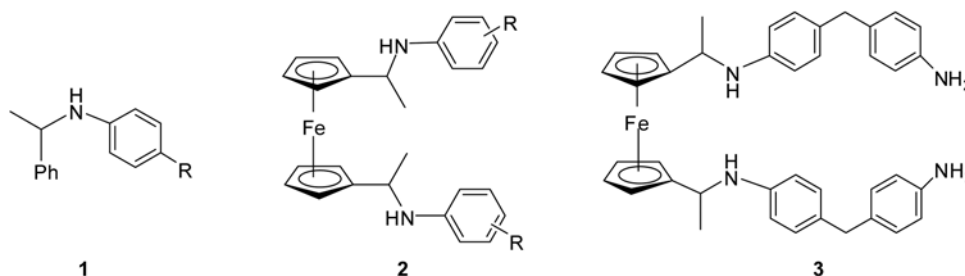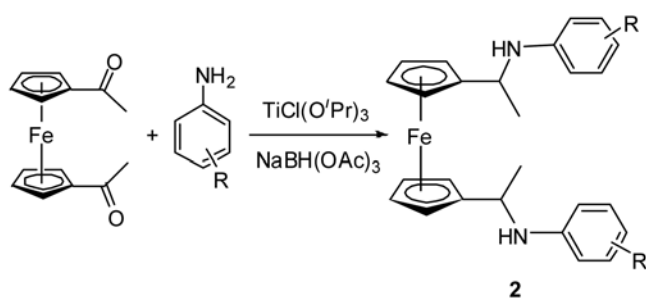The efficacy of the present protocol was extended to 1,1'-

Figure 1. Structures of **1**, **2**, and **3**.

Table 1. The reductive amination of acetophenone with anilines[a]

Entry	R	Solvent	Activator[d]	Product	Yield (%)[e]
1[b]	H	CH_2Cl_2	CH_3CO_2H	**1a**	-
2[b]	H	CH_2Cl_2	$Ti(O^iPr)_4$	**1a**	35
3[c]	H	CH_2Cl_2	$TiCl(O^iPr)_3$	**1a**	92
4[c]	H	THF	$TiCl(O^iPr)_3$	**1a**	75
5[c]	H	MeOH	$TiCl(O^iPr)_3$	**1a**	70
6[c]	OCH_3	CH_2Cl_2	$TiCl(O^iPr)_3$	**1b**	98
7[b]	NO_2	CH_2Cl_2	$TiCl(O^iPr)_3$	**1c**	40

[a]All reactions were carried out at room temperature. [b]Reaction was carried out for 25 h. [c]Reaction was carried out for 2.5 h. [d]CH_3CO_2H (5 drops), $Ti(O^iPr)_4$ (1.2 equiv), $TiCl(O^iPr)_3$ (1.2 equiv). [e]Isolated yields.

Scheme 1. $TiCl(O^iPr)_3$-mediated one-pot reductive amination of 1,1'-diacetylferrocene with anilines.

Table 2. The reductive amination of 1,1'-diacetylferrocene with aniline derivatives[a]

Entry	R	Activator[b]	Product	Yield (%)[c]
1	H	CH_3CO_2H	**2a**	-
2	H	$Ti(O^iPr)_4$	**2a**	30
3	H	$TiCl(O^iPr)_3$	**2a**	76
4	4-OCH_3	$TiCl(O^iPr)_3$	**2b**	82
5	4-CH_3	$TiCl(O^iPr)_3$	**2c**	78
6	4-$BocNHC_6H_4$	$TiCl(O^iPr)_3$	**2d**	59
7	4-Br	$TiCl(O^iPr)_3$	**2e**	55
8	3-Br	$TiCl(O^iPr)_3$	**2f**	48
9	2-Br	$TiCl(O^iPr)_3$	**2g**	40
10	4-NO_2	$TiCl(O^iPr)_3$	**2h**	40

[a]All reactions were carried out in CH_2Cl_2 at room temperature for 25 h. [b]CH_3CO_2H (10 drops), $Ti(O^iPr)_4$ (4 equiv), $TiCl(O^iPr)_3$ (4 equiv). [c]Isolated yields.

In summary, we disclosed a protocol for the $TiCl(O^iPr)_3$-mediated one-pot reductive amination of acetophenone with anilines in good yield. Moreover, the successful one-pot synthesis of new 1,1'-bis(*N*-aryl-1-aminoethyl)ferrocene derivatives in good yield has been achieved. This protocol is currently being applied for the reductive amination of 3,7-diketosteroid with aryl amines.

Experimental Section

The NMR spectra were recorded on a Bruker AM-400 spectrometer in $CDCl_3$ using Me_4Si as the internal standard. The high-resolution mass spectral data were obtained from the Korean Basic Science Institute (at Daegu branch) on a Jeol JMS 700 high resolution mass spectrometer. Flash column chromatography was performed with Merck silica gel 60 (70-230 mesh). Reactions were carried out under an argon atmosphere, and the solutions were washed with brine and dried over anhydrous sodium sulfate. 1,1'-Diacetylferrocene and other reagents were purchased from Aldrich Chemical Co.

***N*-Phenyl-[1-(phenyl)-ethyl]amine (1a):**[7c] A mixture of acetophenone (1 equiv), aniline (1.5 equiv), and 1.2 M $TiCl(O^iPr)_3$ in hexane (1.2 equiv) in CH_2Cl_2 (10 mL) was stirred for 2 h at room temperature, and then treated with $NaBH(OAc)_3$ for 30 min. After the reaction was completed, the solvent was removed. The residue was neutralized with $NaHCO_3$ solution, and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness. The residue was purified by column chromatography (SiO_2, elution with 10% EtOAc in hexane) to give **1a**. Yield: 92%; ^{1}H NMR δ 1.47 (d, *J* = 6.8 Hz, 3H, CHC*H₃*), 3.95 (bs, 1H, N*H*), 4.45 (q, *J* = 6.5 Hz, 1H, C*H₂*CH3), 6.48 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 6.61 (t, *J* = 7.3 Hz, 1H, Ar*H*), 7.06 (dd, *J* = 8.3, 7.3 Hz, 2H, Ar*H*), 7.16-7.34 (m, 5H, Ar*H*).

***N*-(4-Methoxyphenyl)-[1-(phenyl)-ethyl]amine (1b):**[7c] Yield 98%; ^{1}H NMR δ 1.38 (d, *J* = 6.8 Hz, 3H, CHC*H₃*), 3.56 (s, 3H, OC*H₃*), 3.64 (bs, 1H, N*H*), 4.30 (q, *J* = 6.8 Hz, 1H, C*H₂*CH3), 6.36 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.58 (d, *J* =

diacetylferrocene as an aryl ketone. The one-pot reductive amination with aryl amines under $NaBH(OAc)_3$ gave **2** as shown in Scheme 1.

The yield of **2** mainly depends on the nature and the position of the substituent on aniline. When acetic acid was used as an activator, no amine product **2** was produced. The best result was obtained from the reaction of 1,1'-diacetylferrocene with 4-methoxyaniline under $TiCl(O^iPr)_3$ as shown in Table 2. A typical procedure is described as follows: A mixture of 1,1'-diacetylferrocene (1 equiv), 4-methoxyaniline (6 equiv), and $TiCl(O^iPr)_3$ (4 equiv) in CH_2Cl_2 was reacted for 24 h and the resulting mixture was treated with $NaBH(OAc)_3$ (4 equiv) for 1 h at room temperature to give **2b** in 82% yield. Similarly, 4-methylaniline and 4-*N*-(*Boc*)aminoaniline afforded **2c** and **2d** in 78% and 59% yields, respectively. Reaction of 1,1'-diacetylferrocene with 4-bromo- and 3-bromoanilines gave the corresponding amines **2e** and **2f** in 55% and 48% yields, respectively. In the case of 2-bromoaniline, due to the steric hindrance, **2g** was provided with a low yield of 40%. The same reaction with 4-nitroaniline gave **2h** with a 40% yield. As a consequence of substitution by electron-withdrawing substituents on the aniline ring, these anilines are both poor nucleophiles and weak bases. This retards the initial nucleophilic attack on the carbonyl carbon and leads to a slower overall reaction rate and lower yield. Finally, we examined the reaction of 4,4'-diaminodiphenylmethane with 1,1'-diacetylferrocene to provide [2+2]-cyclized product, but we obtained only [1+2] adduct **3** in 55% yield, as shown in Figure 1.

Notes

Bull. Korean Chem. Soc. **2011**, Vol. 32, No. 11   4081

8.8 Hz, 2 H, Ar*H*), 7.10 (t, *J* = 7.0 Hz, 1H, Ar*H*), 7.18-7.26 (m, 4H, Ar*H*).

N-(4-Nitrophenyl)-[1-(phenyl)-ethyl]amine (1c):[13] Yield 40%; ^{1}H NMR δ 1.61 (d, *J* = 6.5 Hz, 3H, CHC*H₃*), 4.61 (q, *J* = 6.5 Hz, 1H, C*H₂*CH₃), 5.30 (bs, 1H, N*H*), 6.51 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.61 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.33-7.36 (m, 4H, Ar*H*), 8.01 (d, *J* = 8.3 Hz, 2 H, Ar*H*).

Fe{(η⁵-C₅H₄)-CH(CH₃)NHC₆H₅}₂ (2a): A mixture of 1,1'-diacetylferrocene (75 mg, 0.27 mmol), 1.2 M TiCl(O*ⁱ*Pr)₃ in hexane (1.2 mL, 1.11 mmol) and aniline (128 mg, 1.66 mmol) in CH₂Cl₂ (5 mL) was stirred at room temperature for 24 h. NaBH(OAc)₃ (235 mg, 1.11 mmol) was then added and the resulting mixture was stirred for an additional 1 h. After work-up, compound **2a** was purified by column chromatography (SiO₂, elution with 2% EtOAc in hexane). Yield: 76%; Liquid; TLC R*f* 0.72 (20% EtOAc in hexane); ^{1}H NMR δ 1.52 (d, *J* = 6.3 Hz, 6H), 2.18 (s, 2H, NH), 4.17 (s, 4H, Fc), 4.24 (m, 4H, Fc), 4.37 (m, 2H, CH), 6.66 (d, *J* = 8.0 Hz, 4H), 6.74 (t, *J* = 7.3 Hz, 2H), 7.20 (dd, *J* = 7.8, 7.8 Hz, 4H); ^{13}C NMR δ 20.9, 21.0, 29.8, 31.0, 47.8, 47.9, 66.7, 67.0, 67.5, 67.7, 68.2, 68.5, 93.3, 114.0, 118.0, 129.4, 129.5, 146.3, 146.7; HR-FAB MS Calcd. for C₂₆H₂₈FeN₂ (M)⁺: 424.1602, found: *m/z* 424.1603.

Fe{(η⁵-C₅H₄)-CH(CH₃)NHC₆H₄OCH₃-4}₂ (2b): Yield 82%; Liquid; TLC R*f* 0.55 (33% EtOAc in hexane); ^{1}H NMR δ 1.50 (d, *J* = 6.3 Hz, 6H), 3.75 (s, 2H, NH), 3.77 (s, 6H, OCH₃), 4.16 (m, 4H, Fc), 4.22 (m, 4H, Fc), 4.27 (m, 2H, CH), 6.63 (d, *J* = 8.8 Hz, 4H), 6.80 (d, *J* = 6.8 Hz, 4H); ^{13}C NMR δ 21.1, 21.3, 48.6, 48.8, 55.7, 55.8, 66.6, 66.8, 67.3, 67.6, 68.0, 68.2, 93.7, 93.8, 114.9, 114.9, 115.3, 115.4, 141.2, 141.3, 152.3, 152.4; HR-FAB MS Calcd. for C₂₈H₃₂FeN₂O₂ (M)⁺: 484.1814, found: *m/z* 484.1811.

Fe{(η⁵-C₅H₄)-CH(CH₃)NHC₆H₄CH₃-4}₂ (2c): Yield 78%; Liquid; TLC R*f* 0.63 (20% EtOAc in hexane); ^{1}H NMR δ 1.50 (d, *J* = 6.3 Hz, 6H), 2.26 (s, 6H, CH₃), 4.10 (s, 4H, Fc), 4.15 (m, 4H, Fc), 4.25 (s, 2H, NH), 4.31 (m, 2H, CH), 6.59 (d, *J* = 8.8 Hz, 4H), 7.00 (d, *J* = 7.8 Hz, 4H); ^{13}C NMR δ 20.5, 20.9, 21.0, 29.8, 48.3, 66.8, 67.0, 67.5, 67.8, 68.2, 68.4, 68.4, 93.3, 114.4, 129.9, 129.9, 130.0; HR-FAB MS Calcd. for C₂₈H₃₂FeN₂ (M)⁺: 452.1915, found: *m/z* 452.1918.

Fe{(η⁵-C₅H₄)-CH(CH₃)NHC₆H₄NHBoc-4}₂ (2d): Yield 59%; Liquid; TLC R*f* 0.33 (33% EtOAc in hexane); ^{1}H NMR δ 1.49 (d, *J* = 3.5 Hz, 6H), 1.48 (s, 18H, NH*Boc*), 3.83 (s, 4H, Fc), 4.14 (m, 4H, Fc), 4.27 (m, 1H, CH), 6.42 (s, 2H, NH), 6.55 (s, 1H, NH), 6.60 (d, *J* = 7.6 Hz, 4H), 7.11 (d, *J* = 7.8 Hz, 4H); ^{13}C NMR δ 21.1, 21.2, 28.4, 28.5, 29.7, 48.2, 48.4, 66.6, 66.9, 67.3, 67.6, 68.0, 68.0, 68.3, 80.0, 93.5, 93.6, 114.4, 115.7, 121.0, 121.3, 129.0, 129.8, 142.3, 143.4, 153.4.

Fe{(η⁵-C₅H₄)-CH(CH₃)NHC₆H₄Br-4}₂ (2e): Yield 55%; Liquid; TLC R*f* 0.61 (20% EtOAc in hexane); ^{1}H NMR δ 1.52 (d, *J* = 6.0 Hz, 6H), 2.18 (s, 1H, NH), 4.17 (s, 4H, Fc), 4.20 (m, 4H, Fc), 4.29 (m, 2H, CH), 6.50 (d, *J* = 8.3 Hz, 4H), 7.25 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 21.0, 21.1, 29.8, 31.1, 47.6, 47.7, 66.7, 67.0, 67.4, 67.7, 68.3, 68.6, 93.4, 93.5, 109.1, 115.1, 115.2, 132.2, 132.2, 146.3; HR-FAB MS Calcd. for C₂₆H₂₆Br₂FeN₂ (M)⁺, (M+2)⁺ and (M+4)⁺: 579.9814,

581.9795 and 583.9779, found: *m/z* 579.9815, 581.9770 and 583.9742.

Fe{(η⁵-C₅H₄)-CH(CH₃)NHC₆H₄Br-3}₂ (2f): Yield 48%; Liquid; TLC R*f* 0.69 (20% EtOAc in hexane); ^{1}H NMR δ 1.49 (d, *J* = 6.3 Hz, 6H), 3.63 (s, 2H, NH), 4.18 (s, 4H, Fc), 4.21 (m, 4H, Fc), 4.31 (m, 2H, CH), 6.58 (d, *J* = 7.6 Hz, 2H), 6.82 (s, 2H), 6.86 (d, *J* = 7.8 Hz, 2H), 7.01 (t *J* = 7.8 Hz, 2H); ^{13}C NMR δ 21.0, 21.1, 29.8, 47.3, 47.4, 66.7, 66.9, 67.4, 67.7, 68.4, 68.6, 93.3, 93.4, 112.1, 112.2, 113.8, 115.8, 115.8, 117.9, 121.5, 123.1, 130.7, 130.8, 147.9; HR-FAB MS Calcd. for C₂₆H₂₆Br₂FeN₂ (M)⁺, (M+2)⁺ and (M+4)⁺: 579.9815, 581.9795 and 583.9779, found: *m/z* 579.9816, 581.9818 and 583.9850.

Fe{(η⁵-C₅H₄)-CH(CH₃)NHC₆H₄Br-2}₂ (2g): Yield 40%; Liquid; TLC R*f* 0.83 (20% EtOAc in hexane); ^{1}H NMR δ 1.53 (d, *J* = 5.8 Hz, 6H), 4.09 (s, 2H, NH), 4.32 (s, 4H, Fc), 4.37 (m, 4H, Fc), 4.44 (m, 2H, CH), 6.60-6.66 (m, 2H), 6.75-6.78 (m, 2H), 7.13 (t, *J* = 7.0 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 20.7, 20.9, 29.7, 46.5, 46.5, 66.8, 67.0, 67.3, 67.5, 68.7, 68.8, 93.7, 109.0, 109.8, 111.8, 115.9, 117.5, 119.4, 128.4, 129.1, 132.5, 132.9, 143.7, 143.9; HR-FAB MS Calcd. for C₂₆H₂₆Br₂FeN₂ (M)⁺, (M+2)⁺ and (M+4)⁺: 579.9815, 581.9795 and 583.9779, found: *m/z* 579.9808, 581.9764 and 583.9751.

Fe{(η⁵-C₅H₄)-CH(CH₃)NHC₆H₄NO₂-4}₂ (2h): Yield 40%; Yellow liquid; TLC R*f* 0.63 (33% EtOAc in hexane); ^{1}H NMR δ 1.57 (d, *J* = 6.3 Hz, 6H), 2.16 (s, 2H, NH), 4.07 (s, 4H, Fc), 4.16 (m, 4H, Fc), 4.42 (m, 2H, CH), 6.62 (d, *J* = 7.8 Hz, 4H), 6.74 (d, *J* = 12.6 Hz, 4H); ^{13}C NMR δ 19.7, 20.3, 29.9, 30.3, 46.2, 46.3, 49.0, 66.2, 66.3, 66.9, 67.1, 67.6, 67.6, 67.9, 68.1, 91.4, 91.4, 110.3, 112.1, 125.6, 125.8, 135.8, 136.4, 152.4, 152.5, 154.1; HR-FAB MS Calcd. for C₂₆H₂₆FeN₄O₄ (M)⁺: 514.1304, found: *m/z* 514.1306.

Fe{(η⁵-C₅H₄-CH(CH₃)NH(C₆H₄CH₂C₆H₄NH₂-4)}₂ (3): Yield 55%; Liquid; TLC R*f* 0.25 (66% EtOAc in hexane); ^{1}H NMR δ 3.20 (d, *J* = 7.0 Hz, 3H), 3.43 (d, *J* = 6.3 Hz, 3H), 4.06 (s, 4H, NHPy*CH₂*PyNH₂), 5.70 (s, 2H, NH), 5.77 (s, 4H, Fc), 6.09 (m, 4H, Fc), 6.26 (m, 2H, CH), 8.53 (dd, *J* = 8.3, 7.0 Hz, 8H Py), 8.90 (dd, *J* = 7.8, 6.5 Hz, 8H Py) 9.06 (d, *J* = 8.0 Hz, 2H, NH₂), 9.34 (d, *J* = 8.0 Hz, 2H, NH₂); ^{13}C NMR δ 20.8, 21.0, 24.3, 29.6, 47.3, 47.4, 60.2, 66.4, 66.7, 67.1, 67.6, 67.4, 67.9, 68.1, 93.7, 113.3, 115.0, 115.0, 119.9, 128.3, 129.0, 129.3, 130.9, 131.9, 135.8, 137.9, 144.4, 144.6, 168.2; HR-FAB MS Calcd. for C₄₀H₄₂FeN₄ (M)⁺: 634.2761, found: *m/z* 634.2760.

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