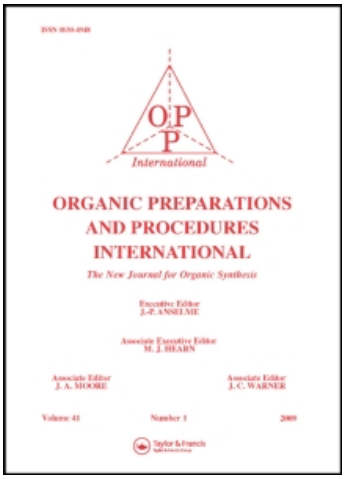

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REDUCTIVE COUPLING OF KETONES WITH IMINES PROMOTED BY THE TITANIUM TETRACHLORIDE/SAMARIUM SYSTEM

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REDUCTIVE COUPLING OF KETONES WITH IMINES PROMOTED BY THE TITANIUM TETRACHLORIDE/SAMARIUM SYSTEM

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(04/18/00)

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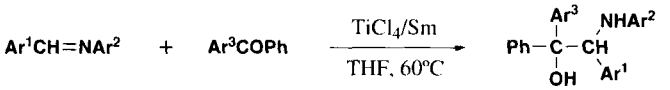
In the early 1970's, three groups discovered that low-valent titanium abstracted oxygen from aldehydes and ketones leading to the formation of olefins.[1] Since then, a large number of coupling reactions induced by low-valent titanium reagent have been reported.[2] Recently, our group reported the intermolecular and intramolecular reductive coupling of ketone-nitrile promoted by $TiCl_4$/Sm system.[3] We now describe our preliminary results on the reductive couplings of aromatic aldimines

(**1**) and aromatic ketones (**2**) promoted by $TiCl_4$/Sm system to give 2-aminoalcohols (**3**).

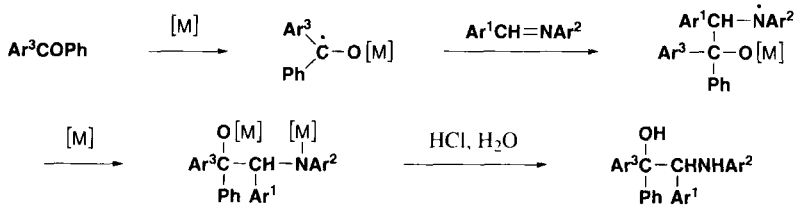


1 2 3

Table. Cross-coupling of Ketones and Imines induced by $TiCl_4$/Sm

Entry	Ar^1	Ar^2	Ar^3	t(h)	Yield(%)
3a	C_6H_5	C_6H_5	C_6H_5	3.0	82
3b	*p*-$CH_3C_6H_4$	C_6H_5	C_6H_5	2.5	77
3c	*p*-ClC_6H_4	C_6H_5	C_6H_5	3.5	88
3d	3,4-$(OCH_2O)C_6H_3$	C_6H_5	C_6H_5	2.5	76
3e	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	C_6H_5	3.5	74
3f	3,4-$(OCH_2O)C_6H_3$	*p*-$CH_3C_6H_4$	C_6H_5	2.5	76
3g	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	C_6H_5	2.5	84
3h	*p*-$CH_3C_6H_4$	3,4-$Cl_2C_6H_3$	C_6H_5	3.0	75
3i	3,4-$(OCH_2O)C_6H_3$	3,4-$Cl_2C_6H_3$	C_6H_5	3.0	70
3j	*p*-$CH_3C_6H_4$	C_6H_5	*p*-$CH_3OC_6H_4$	3.0	84

It was found that rapid addition of the mixture of aldimine and ketone did not give the self-coupling product of the imine. Thus we believe that radical anion intermediates of the imine are not formed in the reaction and the formation of 2-aminoalcohols might be explained by the possible mechanism presented below.



EXPERIMENTAL SECTION

Tetrahydrofuran was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a nitrogen atmosphere. Melting points are uncorrected. TLC analyses were performed on E. Merck silica gel 60 F_{254} plates in EtOAc/hexane solvent systems with UV detection. Infrared spectra were recorded on a Perkin-Elmer 683 spectrometer in KBr with absorptions in cm^{-1}. ^1H-NMR spectra were determined on a Bruker AC 80 spectrometer as $CDCl_3$ solutions. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on HP5989B Mass spectrometer. Elemental analyses were carried out on an EA 1110 instrument.

General Procedure for the Synthesis of 2-Aminoalcohols (3a-j).- Titanium tetrachloride (0.077

mL, 0.7 mmol) was added dropwise using a syringe to a stirred suspension of samarium powder (0.105 g, 0.7 mmol) in freshly distilled dry THF (10 mL) at room temperature under a nitrogen atmosphere. After the completion of the addition, the mixture was refluxed for 2h. The suspension of the low-valent titanium reagent formed was cooled to room temperature and a solution of imine compound **1a-j** (1 mmol) and ketone compound **2a-j** (1 mmol) in anhydrous THF (3 mL) was added quickly in one portion (no noticeable exotherm). The mixture was stirred at 60° under nitrogen atmosphere. Upon completion of the reaction (monitored by TLC), the reaction mixture was quenched with 1N HCl (5 mL) and extracted with diethyl ether (3 x 15 mL). The combined extracts were washed with a saturated solution of $Na_2S_2O_3$ (15 mL) and a saturated solution of NaCl (15 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by preparative TLC on silica gel using ethyl acetate-cyclohexane (1:8) as eluent.

1,1-Diphenyl-2-phenylamino-2-phenylethanol (3a): mp 169-171°, lit.,[4] 171-173°. IR: 3600, 3445, 1615, 1175 cm^{-1}. ^1H NMR: δ 2.60 (1H, s, NH), 4.50 (1H, br s, OH), 5.20 (1H, s, CH), 6.70-7.70 (20H, m, ArH).

1,1-Diphenyl-2-phenylamino-2-(4'-methylphenyl)ethanol (3b): mp 171-173°. IR: 3580, 3405, 1610, 1185 cm^{-1}. ^1H NMR: δ 2.30 (3H, s, CH_3), 2.70 (1H, s, NH), 4.67 (1H, br s, OH), 5.33 (1H, s, CH), 6.60-7.70 (19H, m, ArH). m/z: 380 (M+1 , 1.2), 287 (2.0), 197 (16.9), 196 (100), 105 (7.8), 104 (20.1), 77 (18.3).

Anal. Calcd for $C_{27}H_{25}NO$: C, 85.45; H, 6.64; N, 3.69. Found: C, 85.47; H, 6.69; N, 3.60

1,1-Diphenyl-2-phenylamino-2-(4'-chlorophenyl)ethanol (3c): mp 140-142°. IR: 3580, 3445, 1620, 1175 cm^{-1}. ^1H NMR: δ 2.77 (1H, s, NH), 4.60 (1H, br s, OH), 5.12 (1H, s, CH), 6.63-7.60 (19H, m, ArH). m/z: 400 (M+1, 0.2), 218 (33.4), 217 (17.2), 216 (100), 105 (24.3), 104 (28.1), 77 (39.9).

Anal. Calcd for $C_{26}H_{22}ClNO$: C, 78.09; H, 5.55; N, 3.50. Found: C, 77.91; H, 5.57; N, 3.52

1,1-Diphenyl-2-phenylamino-2-(3',4'-methylenedioxyphenyl)ethanol (3d): mp 166-168°. IR: 3540, 3410, 1615, 1170 cm^{-1}. ^1H NMR: δ 2.60 (1H, s, NH), 4.40 (1H, br s, OH), 5.10 (1H, s, CH), 6.00 (2H, s, CH_2), 6.50-7.60 (18H, m, ArH). m/z: 410 (M+1, 0.40), 317 (1.7), 227 (16.3), 226 (100), 105 (7.0), 104 (26.8), 77 (15.8).

Anal. Calcd for $C_{27}H_{23}NO_3$: C, 79.20; H, 5.66; N, 3.42. Found: C, 79.22; H, 5.61; N, 3.43

1,1-Diphenyl-2-(4'-methylphenylamino)-2-(4'-chlorophenyl)ethanol (3e): mp 190-192°. IR: 3580, 3440, 1640, 1165 cm^{-1}. ^1H NMR: δ 2.12 (3H, s, CH_3), 2.45 (1H, s, NH), 4.30 (1H, br s, OH), 5.12 (1H, s, CH), 6.63-7.50 (18H, m, ArH). m/z: 414 (M+1, 0.4), 232 (34.9), 231 (17.7), 230 (100), 118 (11.4), 105 (7.7), 91 (14.5), 77 (8.4).

Anal. Calcd for $C_{27}H_{24}ClNO$: C, 78.34; H, 5.84; N, 3.38. Found: C, 78.20; H, 5.86; N, 3.34

1,1-Diphenyl-2-(4'-methylphenylamino)-2-(3',4'-methylenedioxyphenyl)ethanol (3f): mp 176-178°. IR: 3585, 3440, 1630, 1195 cm^{-1}. ^1H NMR: δ 2.12 (3H, s, CH_3), 2.55 (1H, s, NH), 4.25 (1H, br s, OH), 5.05 (1H, s, CH), 5.85 (2H, s, CH_2), 6.56-7.50 (17H, m, ArH). m/z: 424 (M+1, 0.2), 317 (0.8), 241 (17.4), 240 (100), 118 (21.0), 105 (4.7), 91 (12.7), 77 (5.1).

Anal. Calcd for $C_{28}H_{25}NO_3$: C, 79.41; H, 5.95; N, 3.31. Found: C, 79.32; H, 5.91; N, 3.34

1,1-Diphenyl-2-(4'-methylphenylamino)-2-(4'-methylphenyl)ethanol (3g): mp 166-168°. IR: 3580, 3420, 1630, 1175 cm^{-1}. ^1H NMR: δ 2.27 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.84 (1H, s, NH), 4.50 (1H, br s, OH), 5.50 (1H, s, CH), 6.53-7.47 (18H, m, ArH). m/z: 394 (M+1, 10.9), 287 (8.7), 211 (17.2), 210 (100), 118 (12.3), 105 (7.6), 91 (12.5), 77 (6.5).

Anal. Calcd for $C_{28}H_{27}NO$: C, 85.46; H, 6.92; N, 3.56. Found: C, 85.33; H, 6.93; N, 3.52

1,1-Diphenyl-2-(3',4'-dichlorophenylamino)-2-(4'-methylphenyl)ethanol (3h): mp 149-151°. IR: 3560, 3410, 1615, 1140 cm^{-1}. ^1H NMR: δ 2.19 (3H, s, CH_3), 2.70 (1H, s, NH), 4.80 (1H, br s, OH), 5.20 (1H, s, CH), 6.50-7.60 (17H, m, ArH). m/z: 448 (M+1, 0.6), 287 (6.2), 268 (10.7), 266 (64.6), 265 (17.9), 264 (100), 174 (9.6), 172 (14.6), 105 (10.9), 77 (8.3).

Anal. Calcd for $C_{27}H_{23}Cl_2NO$: C, 72.32; H, 5.17; N, 3.12. Found: C, 72.05; H, 5.23; N, 3.08

1,1-Diphenyl-2-(3',4'-dichlorophenylamino)-2-(3',4'-methylenedioxyphenyl)ethanol (3i): mp 159-161°. IR: 3560, 3425, 1610, 1140 cm^{-1}. ^1H NMR: δ 2.50 (1H, s, NH), 4.50 (1H, br s, OH), 4.97 (1H, s, CH), 5.80 (2H, s, CH_2), 6.70-7.70 (16H, m, ArH). m/z: 478 (M+1, 0.3), 317 (14.3), 298 (11.3), 296 (65.5), 295 (17.8), 294 (100), 174 (10.5), 172 (16.3), 105 (10.8), 77 (8.8).

Anal. Calcd for $C_{27}H_{21}Cl_2NO_3$: C, 67.79; H, 4.42; N, 2.93. Found: C, 67.89; H, 4.51; N, 2.87

1-Phenyl-1-(4'-methoxyphenyl)-2-phenylamino-2-(4'-methylphenyl)ethanol (3j): mp 122-124°. IR: 3480, 3420, 1610, 1180 cm^{-1}. ^1H NMR: δ 2.23 (3H, s, CH_3), 2.53 (1H, s, NH), 3.77 (3H, s, CH_3), 4.53 (1H, br s, OH), 5.23 (1H, s, CH), 6.40-7.40 (18H, m, ArH). m/z: 410 (M+1, 2.8), 317 (4.9), 197 (18.0), 196 (100), 105 (7.0), 104 (15.9), 77 (13.2).

Anal. Calcd for $C_{28}H_{27}NO_2$: C, 82.12; H, 6.65; N, 3.42. Found: C, 82.23; H, 6.70; N, 3.38

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