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Stereoselective synthesis of α,α-disubstituted amines by a sequential nucleophilic addition to *O*-protected cyanohydrins

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Abstract

The first enantioselective double nucleophilic addition reaction to *O*-protected cyanohydrin was achieved in 71% yield and 82:18 enantiomeric ratio by using a bis(BINOL)titanium Lewis acid complex. New (4*S*,5*S*)-2,2-dialkyl-4,5-bis(hydroxymethyl)-1,3-dioxolane titanium complexes were synthesized and they displayed good levels of enantioselection in the nucleophilic addition reaction.

1. Introduction

Chiral 1,2-aminoalcohols are an important class of compounds. This subunit is found in numerous biologically important compounds, in chiral ligands and catalysts, and they have been extensively used as chiral building blocks.[1] Among these building blocks, the α,α-disubstituted α-amino acids[2] and amines[3] have attracted some attention in recent years because they can affect the conformation, metabolic stability and biological activity of peptides and other biologically relevant compounds.[4] For example, dramatic effects were observed by simply replacing the α-proton of an α-amino acid with a methyl group.[5] In a previous paper,[6] we demonstrated that racemic α,α-disubstituted α-amino acids could be readily obtained from the corresponding 1,2-aminoalcohols generated by a titanium-promoted double nucleophilic addition to cyanohydrins.[7,8] In this paper, we would like to present our preliminary results on the first chiral titanium-promoted enantioselective double nucleophilic addition to cyanohydrins **1** and **2** (Eq. 1).

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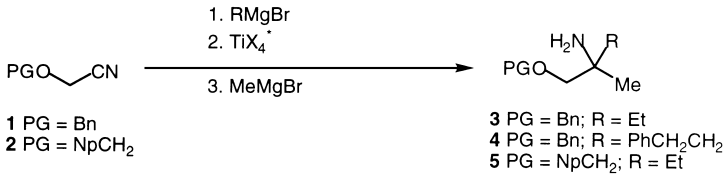


(1)

2. Results and discussion

We initially investigated the enantioselective version of the double nucleophilic addition on cyanohydrins by using (4*R*,5*R*)-2,2-dimethyl-4,5-bis(hydroxydiphenylmethyl)-1,3-dioxolane (TADDOL)[9] titanium complex **6** (Fig. 1) which was synthesized according to Seebach's procedure.[10]

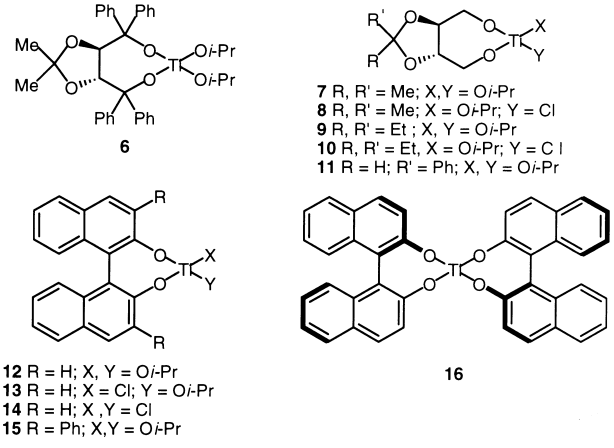


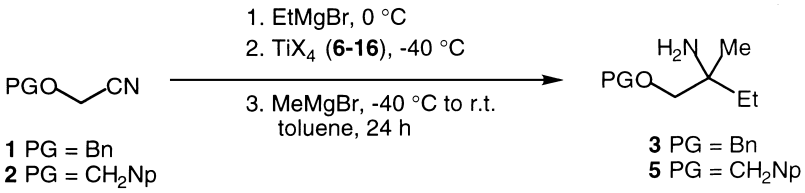
Figure 1. Chiral Lewis acids tested in the double nucleophilic addition reaction

When EtMgBr was added to benzyloxyacetonitrile **1** followed by the addition of **6** and MeMgBr, none of the amine **3** could be isolated (entry 1, Table 1). Since steric hindrance was previously found to have an impact on the efficiency of the double addition,[6] a less hindered chiral ligand was tested. When we removed the phenyl groups of the TADDOL ligand, we found that titanium complex **7** produced the amine **3** in 45% yield and 81:19 enantiomeric ratio (er) (entry 2, Table 1).[11] This result encouraged us to further investigate the scope of several structurally different chiral ligands for this sequential nucleophilic addition process. Several chiral diols were synthesized and converted into their titanium Lewis acidic derivatives (Fig. 1). These results are summarized in Table 1.

We first tried the more Lewis acidic complex **8** and found that the yield of the double addition product slightly improved but a similar er was observed (entry 4, Table 1). It is interesting to note that the use of the slightly more hindered diethyl complexes **9** and **10** (entries 6 and 7, Table 1) led to comparable levels of enantioselection but with lower yields. The replacement of the acetonide on the diol by a benzylidene acetal (complex **11**) gave us the carbinamine **3** in similar yield to that observed with complex **7** but with considerably lower er (entry 8, Table 1). Several other combinations of chloride, isopropoxide and diols were tested but they all gave lower conversions and/or ers. We then turned our attention to the well known binaphthol titanium complexes[12] (*R*)-**12**, (*R*)-**13,** (*R*)-**14** and (*S*)-**15** (entries 9–14, Table 1)[11] and found that complex (*R*)-**14** gave the highest er, albeit at low yield (entry 12, Table 1).

Interestingly, the (*S*)-3,3′-diphenylbinaphthol titanium complex **15** gave us the same major enantiomer of the amine **3** as the nonsubstituted binaphthol complex (*R*)-**12**. The use of the bis(binaphthol)titanium complex **16** led to the amine in high yield and satisfactory er (entry 14, Table 1). The replacement of the

Table 1
Enantioselective double nucleophilic addition to cyanohydrins **1** and **2** promoted by the chiral titanium Lewis acid



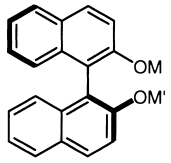
Entry	PG	TiX_4	Yield (%)[a]	er (*R*:*S*)[b]
1	Bn	**6**	0	N.D.[c]
2	Bn	**7**	45	81:19
3	$NpCH_2$	**7**	27	77:23
4	Bn	**8**	58	82:18
5	$NpCH_2$	**8**	13	78:22
6	Bn	**9**	35	77:23
7	Bn	**10**	37	82:18
8	Bn	**11**	41	73:27
9	Bn	**(*R*)-12**	73	76:24
10	$NpCH_2$	**(*R*)-12**	69	80:20
11	Bn	**(*R*)-13**	58	75:25
12	Bn	**(*R*)-14**	21	86:14
13	Bn	**(*S*)-15**	58	71:29
14	Bn	**(*R*)-16**	71	82:18
15	$NpCH_2$	**(*R,R*)-16**	49	80:20

[a] Isolated yields. [b] Evaluated by ^{13}C NMR of the corresponding (1*S*)-(+)-10-camphor sulfonylchloride derivative. [c] Not Determined

benzyl protecting group by a naphthylmethyl group did not improve either the yield or the enantiomeric ratio (entries 3, 5, 10 and 15, Table 1). Several other binaphthol and tartaric acid-derived ligands, as well as some chiral diamines were synthesized and tested, but low conversions and enantioselectivities were observed.

We then tested a different system in which the binaphthol unit possibly binds to two metal centers (Fig. 2).[13] Different combinations of titanium, magnesium and lithium were tried (Table 2). When no titanium was present in the complex (entries 1 and 2, Table 2), 1-benzyloxybutan-2-one was obtained in quantitative yield by hydrolysis of the corresponding ketiminate. However, by using complex **19**, the amine **3** was isolated in 58% yield with an er of 83:17 favoring the *S*-isomer (entry 1, Table 2). The replacement of one titanium by magnesium (complex **20**) or lithium (complex **21**) resulted in lower yield and er (entries 4 and 5, Table 2).

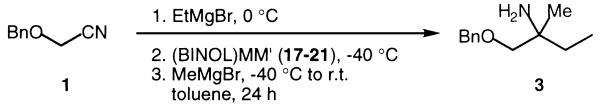
To test the scope of the enantioselective version, we used phenethylmagnesium bromide as the first nucleophile and obtained the corresponding amine **4** in 38% yield and with 73:27 er (Eq. 2), suggesting that the method could be used with other primary alkyl nucleophiles.



17 M, M' = MgBr
18 M, M' = Li
19 M, M' = Ti(O*i*-Pr)$_3$
20 M = Ti(O*i*-Pr)$_3$; M' = MgBr
21 M = Ti(O*i*-Pr)$_3$; M' = Li

Figure 2.

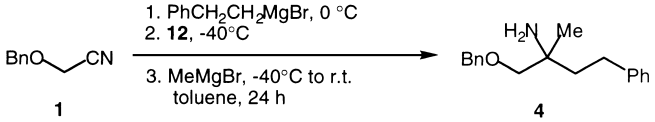
Table 2
Enantioselective double nucleophilic addition to cyanohydrin **1** promoted by BINOL-derived bimetallic species



1 **3**

entry	(binol)MM'	yield (%)	er (*R*:*S*)
1	(*S*)-**17**	0	N.D.[a]
2	(*S*)-**18**	0	N.D.[a]
3	(*S*)-**19**	58	17:83
4	(*S*)-**20**	49	25:75
5	(*S*)-**21**	36	21:79

[a] Not Determined



1 **4**
41%, 81 : 19 er

(2)

3. Conclusion

In conclusion, we have developed the first titanium-promoted enantioselective double nucleophilic addition to protected cyanohydrins. Binaphthol titanium complexes and new (4*S*,5*S*)-2,2-dialkyl-4,5-bis(hydroxymethyl)-1,3-dioxolane titanium complexes were used to generate 1,2-amino alcohols containing a quaternary center in satisfactory yields and modest ers. Although the yields are sometimes quite modest, the amine could easily be isolated in analytically pure form by simple acid–base extractions. We also demonstrated that a bimetallic–binaphthol system can generate these carbinamines in modest er and satisfactory yields. Further studies are underway in our laboratory to increase the efficiency of the reaction and results will be reported in due course.

4. Experimental

4.1. General

All non-aqueous reactions were carried out under argon with careful exclusion of moisture and air from reagents and glassware. Analytical thin-layer chromatography (TLC) was performed using EM Reagent 0.25 mm silica gel 60-F plates. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicyle silica gel (230–400 mesh). Unless otherwise

noted, NMR spectra were recorded at 300 MHz or 400 MHz for ^{1}H and at 75 MHz or 100 MHz for ^{13}C in $CDCl_3$. Combustion analyses were performed by the Laboratoire d'analyse élémentaire of the Université de Montréal. High resolution mass spectra were obtained from the Centre régional de Spectrométrie de Masse of the Université de Montréal. Toluene was distilled over sodium, ether was distilled over sodium ketyl, dichloromethane and triethylamine were distilled over calcium hydride. Methylmagnesium bromide (3.0 M), 2-(bromomethyl)naphthalene, and (1*S*)-(+)-10-camphorsulfonyl chloride were purchased from Aldrich Chemical Co., Inc. Ethylmagnesium bromide and phenethylmagnesium bromide were synthesized from the corresponding alkylbromide in ether as a 2 M or 3 M solution. Benzyloxyacetonitrile was synthesized according to Roth and McLymont.[14] All titanium complexes were synthesized according to Seebach,[10] except for complexes **17** and **18** which were synthesized by mixing one equivalent of binaphthol with two equivalents of MeMgBr bromide or *n*-BuLi, respectively. (4*S*,5*S*)-2,2-Dimethyl-4,5-bis(hydroxymethyl)-1,3-dioxolane was synthesized according to Mash.[15] (4*S*,5*S*)-2,2-Diethyl-4,5-bis(hydroxymethyl)-1,3-dioxolane was synthesized according to Zheng.[16] Benzylidene L-threitol was synthesized according to Wenger.[17] Racemic binaphthol was resolved according to Cai's procedure and was found to be of 98% ee by HPLC analysis on Pirkle covalent D-phenylglycine Rexchrom (5 micron) column.[18] (*S*)-3,3′-Diphenyl-2,2′-dihydroxy-1,1′-dinaphthyl was synthesized according to Jørgensen.[19]

*4.2. 2-Naphthylmethyloxyacetonitrile (**2**)*

Sodium iodide (410 mg, 2.71 mmol) was dissolved in water (2 mL). To this solution was added DMF (20 mL), 2-(bromomethyl)naphthalene (3.0 g, 13 mmol) and 37% aqueous formaldehyde (1.2 mL, 16 mmol) to give a yellow mixture. Sodium cyanide (690 mg, 14.1 mmol) was crushed to a fine powder and dissolved in water (3.6 mL). CAUTION: This operation should be done while wearing gloves and in a well-ventilated fumehood. The cyanide solution was slowly added to the reaction flask at room temperature over a 30 min period. When TLC analysis of the reaction mixture showed the complete disappearance of the 2-(bromomethyl)naphthalene (1 h), as indicated by TLC (20% EtOAc/hexanes), the reaction mixture was diluted with ether:hexanes (1:1, 300 mL). The layers were separated and the organic extract was washed three times with water (20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The yellow residue was purified on silica gel (gradient of 3–10% EtOAc–hexanes) to afford the desired cyanohydrin **2** (1.50 g, 56%) as a white solid: R_f 0.32 (20% EtOAc/toluene); IR (neat) 3035, 2944, 1600, 1508, 1433, 1404, 1102, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.75 (m, 4H, $C_{10}H_7$), 7.56–7.47 (m, 3H, $C_{10}H_7$), 4.81 (s, 2H, $C_{10}H_7CH_2$), 4.24 (s, 2H, OCH_2CN); ^{13}C NMR (100 MHz, $CDCl_3$): 133.24, 133.07, 132.82, 128.60, 127.93, 127.71, 127.52, 126.41, 125.65, 115.93, 73.03, 54.74; HRMS (FAB) calcd for $C_{13}H_{11}NO$ (M): 197.0841. Found: 197.0840. Anal. calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 78.86; H, 5.66; N, 7.08.

4.3. General procedure for derivatization and analysis of er

To a solution of the amines **3**, **4** or **5** in anhydrous dichloromethane (0.1 M) at 0°C was added triethylamine (4.0 equiv.) and (1*S*)-(+)-10-camphorsulfonylchloride (2.0 equiv.). The ice bath was removed and the reaction mixture was stirred until complete consumption of the starting compound as indicated by TLC (80% EtOAc, 5% Et_3N/hexanes) (1–2 h). The reaction mixture was diluted with ether and saturated aqueous $NaHCO_3$. The phases were separated and the organic extract was washed twice with saturated aqueous $NaHCO_3$ and once with brine. Drying over sodium sulfate and concentration under reduced pressure gave the crude derivatized amine which was analyzed by ^{13}C NMR.

4.4. General procedure for the sequential nucleophilic additions

To a solution of cyanohydrin **1** or **2** in toluene (0.1 M) at 0°C was slowly added the first Grignard reagent (EtMgBr or $PhCH_2CH_2MgBr$, 1.05 equiv.). The ice bath was removed and the solution was stirred at room temperature until TLC analysis (20% EtOAc/toluene) showed complete consumption of the starting cyanohydrin (5–10 min). The reaction was cooled to −40°C and a 0.1 M solution of the chiral Lewis acid (1.05 equiv.) in toluene was slowly added via cannula. The reaction mixture was stirred at −40°C for 15 min and MeMgBr (3.05 equiv.) was added over a 5 min period. The reaction mixture was allowed to slowly warm up to room temperature during 24 h and poured into NH_4OH/Et_2O and stirred for 12 h. The layers were separated and the aqueous layer was extracted three times with ether. The organic extracts were combined and washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude residue was dissolved in ether and extracted three times with 10% HCl. The aqueous phases were combined, washed twice with a small volume of ether and basified with NaOH 2 M. This aqueous layer was extracted three times with chloroform to give the pure amine as a slightly yellow oil. The compound was pure enough for derivatization and determination of the er. A small portion was purified over silica gel (80% EtOAc, 5% Et_3N/hexanes) for characterization.

4.5. 1-Benzyloxy-2-methyl-2-butylamine (**3**)

Following the general procedure on a 0.4484 mmol scale, the title compound was obtained as a colorless oil in 71% yield using complex **16**: R_f 0.15 gel (90% EtOAc, 5% Et_3N/hexanes); IR (neat) 3366, 3298, 3087, 3063, 3030, 2964, 2923, 2877, 2859, 1453, 1097, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H, C_6H_5), 4.54 (s, 2H, $C_6H_5CH_2O$), 3.25 (d, J=8.7 Hz, 1H, $C_6H_5CH_2OCH_2$), 3.21 (d, J=8.7 Hz, 1H, $C_6H_5CH_2OCH_2$), 1.48–1.39 (m, 4H, CH_2CH_3 and NH_2), 1.04 (s, 3H, CCH_3), 0.87 (t, J=7.5 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.54, 128.19, 127.35, 127.33, 78.60, 73.16, 52.11, 32.35, 24.39, 8.07. HRMS (FAB) calcd for $C_{12}H_{20}NO$ (M+H): 194.1546. Found: 194.1551. Anal. calcd for $C_{19}H_{20}NO$: C, 74.18; H, 10.19; N, 7.07. Found: C, 74.57; H, 9.91; N, 7.25. The enantiomeric ratio was evaluated by ^{13}C NMR of the (1*S*)-(+)-10-camphorsulfonyl derivative by relative height of the peaks at 7.93, 25.84, 30.95 ppm (major) and 8.01, 25.75, 31.17 ppm (minor) and was found to be 82:18.

4.6. 1-Benzyloxy-2-methyl-4-phenyl-2-butylamine (**4**)

Following the general procedure on a 0.2483 mmol scale, the title compound was obtained with complex **16** in 38% yield as a colorless oil: R_f 0.67 (10% MeOH, 5% Et_3N/CH_2Cl_2); IR (neat) 3333, 3288, 3197, 3091, 3061, 3023, 2934, 2930, 1606, 1500, 1455, 1410, 1106, 744, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.19 (m, 10H, $OCH_2C_6H_5$ and $CH_2CH_2C_6H_5$), 4.56 (s, 2H, OCH_2Ph), 3.32 (d, 1H, J=8.7 Hz, OCH_2C), 3.27 (d, 1H, J=8.7 Hz, OCH_2C), 2.68–2.60 (m, 2H, CH_2CH_2Ph), 1.78–1.72 (td, 2H, J=9.3, 1.3 Hz, CH_2CH_2Ph), 1.44 (br, 2H, NH_2), 1.16 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.67, 138.49, 128.32, 127.50, 125.64, 78.90, 73.30, 52.23, 42.06, 30.39, 25.04. HRMS (FAB) calcd for $C_{18}H_{24}NO$ (M+H): 270.1859. Found: 270.1857. The enantiomeric ratio was evaluated by ^{13}C NMR by relative height of the peaks at 25.97, 42.62, 75.15 ppm (major) and 25.80, 42.69, 75.19 ppm (minor) and was found to be 71:29.

4.7. 1-(Naphthylmethyl)oxy-2-methyl-2-butylamine (**5**)

Following the general procedure on a 0.5244 mmol scale, the title compound was obtained in 49% yield as a colorless oil with complex **16**: R_f 0.12 (85% EtOAc, 5% Et_3N/hexanes); IR (neat) 3367, 3287, 3181, 3054, 2970, 2931, 2876, 1602, 1510, 1461, 1374, 1100, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85–7.78 (m, 4H, $C_{10}H_7$), 7.50–7.47 (m, 3H, $C_{10}H_7$), 4.71 (s, 2H, $C_{10}H_7CH_2O$), 3.30 (d, *J*=8.7 Hz, 2H, OCH_2C), 3.25 (d, *J*=8.7 Hz, 2H, OCH_2C), 1.52–1.42 (m, 4H, CH_2CH_3 and NH_2), 1.07 (s, 3H, CH_3), 0.88 (t, *J*=7.5 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.01, 133.12, 132.83, 128.00, 127.73, 127.59, 126.09, 125.97, 125.69, 125.56, 73.34, 52.19, 32.37, 24.40, 8.09. HRMS (FAB) calcd for $C_{16}H_{22}NO$ (M+H): 244.1702. Found: 244.1701. Anal. calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.60; H, 9.12; N, 5.81. The enantiomeric ratio was evaluated by ^{13}C NMR by relative height of the peaks at 7.97, 25.86, 53.45, 59.05, 60.15 ppm (major) and 8.06, 25.77, 53.35, 59.00, 60.13 ppm (minor) and was found to be 80:20.

Acknowledgements

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