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Cerium (III) Chloride Mediated Nitrile Aldol Reactions: Enhanced Diastereoselectivities Using a Chiral Organocerium Complex

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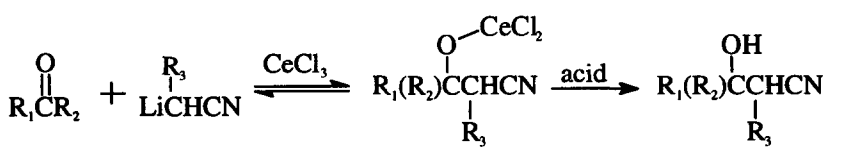
Abstract: The addition of anhydrous cerium chloride to nitrile aldol reactions has been found to provide high yields of β-hydroxynitriles. Also, the aldol reaction of α,β-unsaturated carbonyl compounds with nitrile enolates in the presence of cerium chloride affords 1, 2 addition exclusively in good to excellent yields. The organocerium complexes of R-(+)-1,1'-bi-2-naphthol have successfully mediated the aldol addition of lithio alkyl and arylacetonitriles to aldehydes, and the reaction gives β-hydroxynitriles in good yields with moderate to good diastereoselectivity.

Organocerium reagents have attracted a great deal of attention over the past decade.[1] They have been widely used to facilitate nucleophilic addition to carbonyl compounds,[2] α,β-unsaturated carbonyl compounds,[3] aryl nitriles,[4] and hydrazones.[5] Organocerium reagents have also found use in the synthesis of spiroacetals where addition of anhydrous cerium chloride to the reaction mixture greatly enhances yields .[6] Although the structure and reaction mechanism of organocerium reagents have not been fully clarified, it is certain that their chemical behavior relates to strong coordination of cerium (III) with oxygen and nitrogen.

Condensations of carbonyl compounds with metalated nitriles to form β-hydroxynitriles are reversible. In some cases, the yields with hindered ketones and aryl acetonitriles are very low. It has been reported that magnesium and aluminum cations shift the position of the equilibrium toward products to afford higher yields of β-hydroxynitriles than those of the corresponding lithioacetonitriles.[7] Also, it has been shown that the addition of chlorotrimethylsilane to the reaction mixture of lithioacetonitriles and aldehydes increases the yields of the condensation reactions.[8] We have embarked on a project aimed at improving the yields of this type of condensation by the addition of anhydrous cerium chloride to the reaction mixture (Scheme 1).

Scheme 1



R_1, R_2, R_3 = alkyl, aryl, H

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We chose the condensation reaction of lithioacetonitrile with benzophenone and tested two experimental procedures.

Method A: A mixture of anhydrous cerium chloride and tetrahydrofuran is stirred over two h at r.t. Lithioacetonitrile is added into the above mixture and stirred for 30 min at -78°C. Then, benzophenone is added to the reaction mixture.*

Method B: A mixture of anhydrous cerium chloride and tetrahydrofuran is stirred over two h at r.t. Benzophenone is added to the above mixture and stirred for 1 h at r.t. Then, lithioacetonitrile is added into the reaction mixture at -78°C.*

Table 1: The condensation of lithioacetonitrile with benzophenone in the presence of cerium chloride

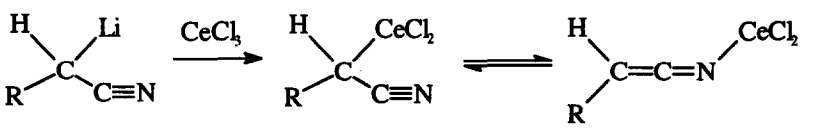
Entry	Reagent	Ratio**	Method	Temp.	Yield (%)
1	$LiCH_2CN/CeCl_3$	1:1:1	A	-78°C	67
2	$LiCH_2CN/CeCl_3$	1:1:1	B	-78°C	75
3	$LiCH_2CN/CeCl_3$	2:1:1	A	-78°C	71
4	$LiCH_2CN/CeCl_3$	2:1:1	B	-78°C	90
5	$LiCH_2CN/CeCl_3$	2:2:1	B	-78°C	77

*All reactions are conducted over 30 min and then quenched with 10% ice-water hydrochloric acid.

**The ratios correspond to $LiCH_2CN/CeCl_3$/benzophenone.

Regardless of the ratio of reactants, method B where benzophenone is in contact with cerium chloride, is superior to method A, where the ketone is added to the equilibrated mixture (Table 1). In cases where the lithioacetonitrile and cerium chloride equivalents are identical, the yields of 3,3-diphenyl-3-hydroxypropionitrile are lower than where the lithio reagent is in excess. Furthermore, more side-reactions occured with the 1:1:1 ratio than 2:1:1. Although the side products have not been indentified, we surmise that lithioacetonitrile undergoes self-condensation in the presence of cerium chloride due to the Lewis acid nature of cerium(III), which produce the stabilized carbanion represented by the tautomeric structure 1 and 2 (Scheme 2).[9] Tautomeric structure 2 is relatively more important than the corresponding lithiated structure. Also, we reason that high yields in the aldol

Scheme 2



R = alkyl, aryl, H 1 2

addition of cerium enolates of nitriles can be attributed to both the more stable, active nitrile carbanion and the

strongly oxophilic nature of cerium, which shifts the equilibrium toward β-hydroxynitriles (Scheme 1). Thus, we chose the optimal condition (Entry 4) for further study.

We have tested this procedure with a variety of aldehydes, ketones and nitriles and all condensation reactions give good to excellent yields (Table 2). In comparison to the corresponding lithiated nitriles, organocerium mediated condensations give rise to much higher yields (Entries 1, 2). It has been well documented that organocerium reagents greatly enhance 1,2 versus 1,4 addition.[3,10] As expected, when α,β-unsaturated aldehydes were employed in the condensation reactions, 1,2 regioselective products were obtained exclusively in good to excellent yields (Entries 9, 10, 13). It is also noteworthy that no side reactions were observed using aryl and alkyl substituted acetonitriles.

Table 2. Organocerium mediated condensations.

Entry	Aldol	Nitrile	Carbonyls	Temperature	Time (h)	Yield(%)
1	1	CH_3CN	1-Pyrenecarboxaldehyde	-95°C	0.5	84 (40)[8]
2	2	CH_3CN	Fluorenone	-95°C	0.5	85 (47)[7]
3	3	$PhCH_2CN$	Benzophenone	-78°C--25°C	3.0	56
4	4	CH_3CH_2CN	Fluorenone	-78°C-rt	3.0	94
5	5	$PhCH_2CN$	Fluorenone	-78°C--25°C	2.0	89
6	6	CH_3CH_2CN	Benzophenone	-78°C--rt°C	3.0	66
7	7	$PhCH_2CN$	Benzaldehyde	-78°C	0.5	99
8	8	$PhCH_2CN$	1-Naphthaldehyde	-78°C	0.5	99
9	9	$PhCH_2CN$	*Trans*-cinnamaldehyde	-78°C	0.5	99
10	10	$PhCH_2CN$	Acrolein	-78°C	1.0	93
11	11	$1\text{-}C_{10}H_7CH_2CN$	Benzaldehyde	-78°C	1.0	97
12	12	CH_3CH_2CN	1-Naphthaldehyde	-78°C--42°C	2.0	76
13	13	CH_3CH_2CN	*Trans*-cinnamaldehyde	-78°C	2.0	71

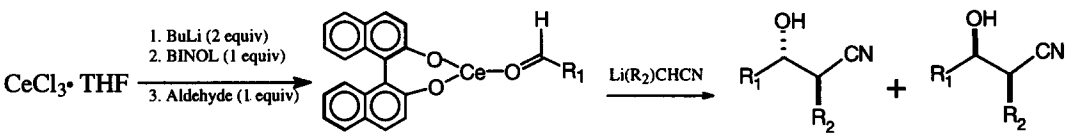
Note: The corresponding diastereomeric ratios are included in the table 3.

In recent years, the stereochemistry of addition of lithiated aryl acetonitriles to aldehydes has been investigated by Carlier.[11] His work showed that more hindered aldehydes generally afforded higher diastereoselectivity in the nitrile aldol reaction. However, for less bulky secondary aldehydes, stereoselectivity was unsatisfactory. Also, transmetalation of lithiated nitriles to the corresponding Fe , Cr, Co, Zn, Al, and Mg derivatives has been studied,[12] and these metals give lower diastereoselectivity than lithium. Furthermore, studies on the ligand modified aldol addition of nitriles to aldehydes have shown little or no diastereoselectivity.[13] We envisioned that the use of chiral organocerium complexes might lead to improved selectivity for less hindered aldehydes and aliphatic nitriles in the aldol reaction.

The chiral 1,1'-bi-2-naphthol metal complexes have become increasingly important in enantio and diastereoselective organic syntheses. Recently, a new synthetic route to enantiomerically enriched homoallylic alcohols has been accomplished by the reaction of aldehydes and allytributyltin with a catalytic amount of an (S)-(-)-BINOL zirconium and titanium complexes.[14] Also, the lanthanum binaphthol complex has been used in the enantioselective synthesis of α-hydroxy phosphonates[15] and the catalytic asymmetric nitroaldol reaction.[16] More recent studies have shown that the R-(+)-BINOL-modified organocerium reagent promoted the enantioselective reaction of aldehydes to produce optically active alcohols.[17]

We have described above the key experimental procedure in the cerium mediated aldol reaction where a suspension of anhydrous $CeCl_3$ in THF was first mixed with the carbonyl compounds, followed by the reaction

Scheme 3



Organocerium Complexes Anti- Syn-

with lithioacetonitriles. Thus, we modified the earlier reported procedure for making a BINOL Cerium (III) complex,[18] and developed the following standard protocol (Scheme 3). After the BINOL is deprotonated by two equivalents of butyllithium, the addition of aldehydes to the BINOL mixture generates the organocerium complexes. Further treatment of this suspension with lithioacetonitriles gives rise to anti-selective β-hydroxynitriles.

Table 3: The Nitrile Aldol Reaction using a R-(+)-BINOL Organocerium Complex

En	Al	Nitrile	Aldehyde	Sol	Temperature	h	Y%[a]	an/sy[b]	an/sy[c]
1	7	$PhCH_2CN$	Benzaldehyde	THF	-78°C	1.0	88	85:15	75:25
2	9	$PhCH_2CN$	*trans*-cinnamaldehyde	THF	-78°C	1.0	93	83:17	70:30
3	11	$1\text{-}C_{10}H_7CH_2CN$	Benzaldehyde	THF	-78°C--42°C	1.5	85	61:39	58:42
4	9	$PhCH_2CN$	*trans*-cinnamaldehyde	THF	-98°C--78°C	2.0	94	88:12	
5	7	$PhCH_2CN$	Benzaldehyde	Et_2O	-78°C-rt	1.0	77	62:38	
6	7	$PhCH_2CN$	Benzaldehyde	THF	-98°C--60°C	2.0	95	87:13	
7	10	$PhCH_2CN$	Acrolein	THF	-78°C	2.0	62	88:12	81:19
8	12	CH_3CH_2CN	1-Naphthaldehyde	THF	-78°C--25°C	2.5	52	78:22	76:24
9	8	$PhCH_2CN$	1-Naphthaldehyde	THF	-78°C	1.5	88	87:13	82:18
10	13	CH_3CH_2CN	*trans*-cinnamaldehyde	THF	-78°C	2.0	50	32:68	47:53

a. Isolated yield; b. Anti/syn diastereomeric ratios were determined by ^1H NMR; c. The organocerium mediated nitrile aldol reaction in the absence of chiral ligands.

A variety of aldehydes and acetonitriles have been used to carry out this sequence (Table 3). The aldol reaction with phenyl acetonitrile in THF generally gives better yields and higher diastereoselectivity than those with 1-naphthyl acetonitrile and propionitrile. Also, starting the aldol reaction at lower temperature affords better diastereoselectivity, while the aldol reaction in ether results in low yield and decreased diastereoselectivity. With conjugated aldehydes, the condensations provide exclusively 1, 2 addition products. In comparison with the aldol reactions in the presence of $CeCl_3$ without the BINOL, while most of the aldol reactions with chiral organocerium complexes offer better diastereoselectivity, some show only slight enhancement of selectivity. Furthermore, the yields of the aldol addition in the presence of the BINOL slightly decrease, and this result is in agreement with the Denmark report that chelating ligands curtailed reactivity of organolanthanide reagents.[5c]

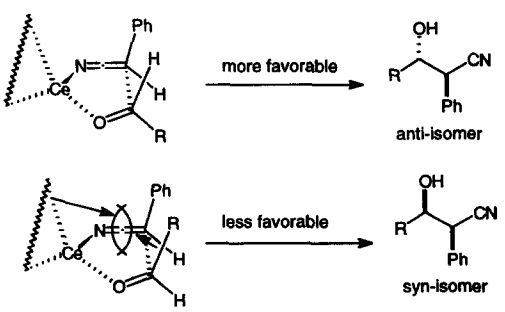
The relative configuration of the major and minor diastereomers can be determined by means of comparing the ^1H chemical shifts and/or the vicinal coupling constants (Table 4). It has been concluded that generally, the

Table 4: ^1H and ^{13}C nmr data

Entry	Aldol	HOCH-*C*HCN						HO*C*H-CHCN			
		^1H		Vicinal J		^{13}C		^1H		^{13}C	
		Maj.	Min.	Maj.	Min.	Maj.	Min.	Maj.	Min.	Maj.	Min.
1	7	4.07	4.11	5.7	6.7	47.34	47.33	5.00	5.04	76.35	76.38
2	8	4.37	4.40	4.5	6.3	46.52	45.00	5.73	5.92	73.17	72.14
3	9	4.01	4.09	5.0	5.7	45.50	45.40	4.61	4.61	74.33	74.74
4	10	3.94	4.01	5.1	6.9	45.13	46.57	4.46	4.46	74.28	74.63
5	11	4.73	4.99	3.9	6.0	44.24	43.32	5.02	5.14	74.40	75.12
6	12	3.23	3.23	4.5	5.7	32.46	34.30	5.77	5.48	70.56	72.37
7	13	2.95	2.83	5.7	5.1	32.84	33.15	4.36	4.36	73.70	73.71

^1H signal for the α-proton appears at lower field for syn-diastereomers than for the corresponding anti-diastereomers, and the vicinal coupling constants for syn isomers are larger than those for anti isomers. This stereochemical assignment of the aldol products is well established and agrees with that from the single-crystal X-ray determination.[19] Thus, the major diastereomers of aldols **8-12** were tentatively assigned as anti-relative configuration, and the major isomer of aldol **13** as the syn configuration on the basis of the chemical shift analogy and/or the vicinal coupling constants. The major isomer of aldol **7** was assigned as anti configuration, and this was

Scheme 4



confirmed by stereospecific synthesis.[20] No conclusive results can be derived from the chemical shifts of β-protons and the ^{13}C chemical shifts of both α and β carbon. It is interesting to note that the aldol reaction of aryl-acetonitriles is uniquely anti-selective, while aldol diastereoselectivity for propionitrile is not consistently anti-selective. The proposed transition model is shown in Scheme 4. As can be seen, the bulky ligand increases steric interaction in the transition state for the syn isomer, and the anti-diastereomer becomes more favorable. Also, It is very likely that both racemic and non-racemic BINOL cerium (III) complexes increase the steric hindrance of transition states for syn isomers to the same extent. Thus, we reason that the selectivity of the aldol reaction in the presence of a racemic BINOL complex would probably be similar to that with a chiral BINOL complex. However, this transition state model does not explain the diastereoselectivity exhibited by propionitrile.

In summary, we have demonstrated that the organocerium mediated nitrile aldol reactions afford high yields of β-hydroxynitriles. We have also developed a new approach for the aldol addition of nitrile enolates in the presence of a chiral organocerium complex, and the enhancement of diastereoselectivity was obtained in most of the aldol reactions. However, more effective ligands are needed to significantly improve the diastereoselectivity of the aldol addition of nitriles to aldehydes.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Varian 300 MHz spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C in $CDCl_3$ with either chloroform (7.26 ppm ^{1}H, 77.00 ppm ^{13}C) or TMS as a reference peak. Coupling constants, J, are reported in Hz. IR spectra were recored on a Magna-IR™ spectrometer 550. Elemental analyses were performed by Atlantic Microlab Corporation.

All commercially available chemicals were purchased from Aldrich. Butyllithium was titrated before use.[21] THF and ether were distilled freshly from sodium/benzophenone. All reactions were carried out under an argon atmosphere in oven-dried (140°C) glassware.

Representive experimental procedure for condensations of lithioacetonitrile with benzophenone in the presence of $CeCl_3$ (Method A):

Mixture A: In a 50 mL two neck round-bottom flask equipped with gas inlet and stopper was placed $CeCl_3.7H_2O$ (745 mg, 2 mmol, 1 equiv), which was dried for 2 h at 140°C in 0.001 torr. The flask was cooled in an ice-bath, vented to argon, and the stopper was changed to a septum. THF(15 mL) was added to the mixture and stirred for 2 h at rt.

Mixture B: To a 50 mL two neck round-bottom flask fitted with septum and gas inlet was added THF (10 mL) and n-butyl lithium (1.49 M in diethyl ether, 2.72 mL, 4 mmol, 2 equiv). The mixture was cooled to -78°C and acetonitrile (0.21 mL, 4 mmol, 2 equiv) was added via syringe during five min. The reaction mixture was

stirred at -78°C over 1 h.

Aldol reactions: Mixture B was transferred to mixture A by cannulation and the resulting mixture was stirred for 30 min at -78°C. Benzophenone (364 mg, 2 mmol, 1 equiv) in THF (2 mL) was added to the flask via syringe and was further stirred for 30 min at -78°C. The reaction mixture was poured into 50 mL of 10% ice-water hydrochloric acid (made by the addition of a small amount of ice to 10% hydrochloric acid solution) and extracted with diethyl ether (3×50 mL). The combined extracts were concentrated under reduced pressure and chromatography afforded 317mg of 3-hydroxyl-3,3diphenyl-propionitrile (**2**, 71%).[7] ^{1}H NMR: δ = 2.85 (br, 1H, -OH), 3.26 (s, 2H, -CH_2-), 7.25-7.45 (m, 10H). ^{13}C NMR: δ = 32.58, 76.44, 117.12, 125.75, 128.15, 128.64, 143.85.

Representive experimental procedure for the organocerium mediated aldol reaction:

Mixture A: A 50 mL two neck round-bottom flask fitted with gas inlet and stopper was charged with $CeCl_3.7H_2O$ (745 mg, 2 mmol, 1 equiv), which was dried for 2 h at 140°C in 0.001 torr. The flask was cooled in an ice-bath, vented to argon, and the stopper was changed to a septum. THF (20 mL) was added to the mixture and stirred for 2 h at rt. Benzaldehyde (0.208 mL, 2 mmol, 1 equiv) was added to the flask via syringe and was further stirred 1 h at rt and then cooled to -78°C.

Mixture B: To a 50 mL two neck round-bottom flask fitted with septum and gas inlet was added THF (10 mL) and n-butyllithium (1.49 M in diethyl ether, 2.72 mL, 4 mmol, 2 equiv). The mixture was cooled to -78°C and phenylacetonitrile (0.48 mL, 4 mmol, 2 equiv) was added via syringe during 5 min. The reaction mixture was stirred at -78°C for 1 h.

Condensation reactions: Mixture B was transferred to mixture A through a syringe and the resulting mixture was stirred for 30 min at -78°C. The reaction mixture was poured into 50 mL of 10% ice-water hydrochloric acid and extracted with diethyl ether (3×50 mL). The combined extracts were concentrated in vacuo and chromatography afforded 442 mg of 3-hydroxy-2,3-diphenylpropionitrile (99%).

3-Pyrenylpropionitrile (1):[8] ^{1}H NMR: δ (ppm) 2.68 (br, 1H, -OH), 2.90-3.15 (m, 2H, -CH_2-), 6.13 (dd, 1H, J = 6.9, 5.1), 8.00-8.30 (m, 9H); ^{13}C NMR: δ (ppm) 27.63, 67.58, 121.37, 122.98, 125.11, 125.68, 125.97, 126.38, 127.49, 128.09, 128.74.

3-Fluorenyl-3-hydroxylpropionitrile (2):[7] ^{1}H NMR: δ (ppm) 2.57 (br, 1H, -OH), 2.74 (s, 2H, -CH_2-), 7.18-7.35 (m, 4H), 7.45-7.55(m, 4H); ^{13}CNMR: δ (ppm) 28.58, 77.53, 116.18, 119.84, 123.06, 127.92, 129.57, 138.42, 145.34.

3,3-Diphenyl-3-hydroxy-2-phenylpropionitrile (3):[7] NMR: δ (ppm) 2.77 (s, 1H, -OH), 4.82 (s, 1H, -CH-), 7.02-7.62 (m, 15H); ^{13}C NMR: δ (ppm) 48.22, 79.72, 119.47, 126.06, 126.30, 127.50, 127.95, 128.13, 128.18,

128.47, 129.93, 131.22, 142.40 143.45.

3-Fluorenyl-3-hydroxy-2-methylpropionitrile (4):The crude product was purified by column chromatography. Semi-solid; Yield: 94%; R_f = 0.2 (hexane:ethyl acetate = 4:1); IR: 735, 755, 770, 1035, 1451, 1607, 2244, 2988, 3062, 3423; ^{1}H NMR: δ 0.82 (d, 3H, J = 7.2, -CH_3), 2.53 (s, 1H, -OH), 3.75 (q, 1H, J = 6.8, -CH-), 7.33-7.51 (m, 5H), 7.64-7.67 (m, 2H), 9.38 (d, 1H, J=8.0); ^{13}C NMR: δ 13.07, 35.46, 81.37, 120.12, 120.17, 120.88, 123.01, 124.31, 128.34, 128.42, 129.91, 130.04. MS/EI: 235.1, 217.1, 181.1, 165.1, 152.1, 126.0, 90.5, 76.0, 63.0; HRMS cacld for $C_{16}H_{13}NO$: 235.09971; found: 235.09989.

3-Fluorenyl-3-hydroxy-2-phenylpropionitrile (5): The crude product was purified by column chromatography. White crystal, mp 135-136^{0}C; Yield: 89%; R_f= 0.2 (hexane/ethyl acetate 4:1); IR: 1045, 1064, 1361, 1491, 1607, 2244, 3029, 3057, 3431, 3510; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.66 (s, 1H, OH), 4.45 (s, 1H, -CH-), 6.88 (td, 2H, J=7.6, 1.6), 7.06 (t, 2H, J=6.9), 7.16 (tt, 2H, J=7.6, 1.2), 7.27-7.55 (m, 9H), 7.67(dt, 1H, J=7.6, 1.2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 47.60, 82.325, 118.96, 119.01, 19.95, 120.3, 123.99, 124.61, 127.61, 127.76, 127.83, 128.11, 129.27, 129.87,130.02, 130.73, 139.61, 139.74, 144.26, 144.86. Anal. Calcd for $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71. Found: C, 84.93; H, 5.17; N, 4.80.

3,3-Diphenyl-3-hydroxy-2-methylpropionitrile (6) : The crude product was purified by column chromatography. White crystal, mp 118-119^{0}C; Yield: 66%; R_f = 0.16 (hexane/ethyl acetate 4:1); IR: 1059, 1188, 1389, 1449, 1491, 2257, 2900, 3087, 3369; ^{1}H NMR: δ (ppm) 1.27 (d, 3H, J=7.2, -CH_3), 2.63 (s, 1H, -OH), 3.74 (q, 1H, J=7.2, -CH-), 7.2-7.6 (m, 10H); ^{13}C NMR: δ (ppm) 13.25, 36.31, 78.40, 121.22, 125.69, 125.84, 127.49, 127.95,128.39, 128.54, 142.53, 144.10. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.84; H, 6.32; N, 5.79.

Representive experimental procedure for the aldol reaction by R-(+)-1,1'-bi-2-naphthol organocerium complexes:

Mixture A: To a 25 mL two neck round-bottom flask fited with gas inlet and stopper was added $CeCl_3.7H_2O$ (187 mg, 0.5 mmol, 1 equiv), which was dried for 2 h at 140^{0}C in 0.001 torr. The flask was cooled in an ice-bath, vented to argon, and the stopper was changed to a septum. THF (6 mL) was added to the mixture and stirred for 2 h at rt. Butyllithium (1.49M, 0.68mL, 1 mmol, 2 equiv) was added via syringe at -78^{0}C, followed by addition of R-(+)1,1'-bi-2-naphthol (143 mg, 0.5 mmol, 1 equiv) in THF (1 mL). The reaction mixture was stirred for 1 h at -78^{0}C. Benzaldehyde (0.52 uL, 0.5 mmol, 1 equiv) was added to the flask via syringe and was further stirred 1 h at rt and then cooled to -78^{0}C.

Mixture B: To a 50 mL two neck round-bottom flask fitted with septum and gas inlet was added THF (4 mL) and n-butyllithium (1.49 M in diethyl ether, 0.68 mL, 1 mmol, 2 equiv). The mixture was cooled to -78^{0}C

and phenylacetonitrile (0.12 mL, 1 mmol, 2 equiv) was added via syringe during 5 min. The reaction mixture was stirred at -78°C for 1 h.

Condensation reactions: Mixture B was transferred to mixture A through a syringe and the resulting mixture was stirred for 30 min at -78°C. The reaction mixture was poured into 50 mL of 10% ice-water hydrochloric acid and extracted with diethyl ether (3×50 mL). The combined extracts were concentrated in vacuo. The biol recrystallized from a solvent of hexane-chloroform and could be reused. The filtrate was concentrated and chromatography afforded 442 mg of 3-hydroxy-2,3-diphenylpropionitrile (99%). Diastereomers were further seperated by preparative TLC.

(2RS,3RS)-3-Hydroxy-2,3-diphenylpropionitrile (*anti*-7):[20] ^{1}H NMR: δ (ppm) 2.42 (d, 1H, J = 3.0, -OH), 4.07 (d, 1H, J = 5.7, -CHCN), 5.00 (dd, 1H, J = 5.4, 3.0, -CHOH); 7.20-7.40 (m, 10H); ^{13}C NMR: δ (ppm) 47.34, 76.35, 118.69, 126.19, 128.39, 128.51, 128.72, 128.87, 132.44, 139.33.

(2RS,3SR)-3-Hydroxy-2,3-diphenylpropionitrile (*syn*-7): [20] ^{1}H NMR: δ (ppm) 2.56 (s, 1H, -OH), 4.11 (d, 1H, J = 6.7, -CHCN), 5.00 (d, 1H, J = 5.4, -CHOH); 7.20-7.40 (m, 10H); ^{13}C NMR: δ (ppm) 47.33 (d), 76.38, 118.67, 126.19, 128.39, 128.52, 128.73, 128.89, 132.45, 139.33.

(2RS,3RS)-3-Hydroxy-3-(1'-naphthyl)-2-phenylpropionitrile (*anti*-8): The analytically pure sample was obtained by preparative TLC. Semi-solid; R_f = 0.31 (hexane/ethyl acetate 4:1); IR: 1083, 1260, 1495, 1597, 2246, 2849, 2947, 3062, 3445; ^{1}H NMR: δ (ppm) 2.54 (d, 1H, J = 3.3, -OH), 4.37 (d, 1H, J = 6.0, -CHCN), 5.73 (t, 1H, J = 3.3, -CHOH); 7.35-7.60 (m, 8H), 7.82-7.97 (m, 4H). ^{13}C NMR: δ (ppm) 46.52, 73.17, 118.22, 121.87, 124.70, 125.63, 125.86, 126.79, 128.21, 128.74, 129.26, 129.44, 129.56, 129.93, 133.64, 133.95, 135.11. MS/EI: 273.1, 235.1, 181.1, 157.1, 128.1 90.0, 77.0, 51.0; HRMS calcd for $C_{19}H_{15}NO$: 273.11536; found: 273.11550.

(2RS,3SR)-3-Hydroxy-2,5-diphenyl-4-pentenenitrile (*anti*-9): The analytically pure sample was obtained by preparative TLC. Yellow oil; R_f = 0.34 (hexane/ethyl acetate 3:1); IR: 1605, 1652, 2245.3030, 3061, 3445; ^{1}H NMR: δ (ppm) 2.40 (br, 1H, -OH), 4.01 (d, 1H, J = 5.0, -CHCN), 4.61 (t, 1H, J = 5.5, -CHOH); 6.20 (dd, 1H, J = 15.9, 6.6), 6.67 (d, 1H, J = 15.9), 7.25-7.47 (m, 10H); ^{13}C NMR: δ (ppm) 45.50, 74.33, 118.73, 126.67, 128.21, 128.35, 128.52, 128.91, 132.16, 133.39, 135.67. MS/EI: 133.1, 117.1, 103.1, 89.0, 77.0, 55.0; HRMS calcd for $C_{17}H_{15}NO$: 249.11536; found: 249.11572.

(2RS,3RS)-3-Hydroxy-2,5-diphenyl-4-pentenenitrile (*syn*-9): The analytically pure sample was obtained by preparative TLC. Yellow oil; R_f = 0.30 (hexane/ethyl acetate 3:1); IR: 1600, 1652, 2246, 2931, 3030, 3061, 3441; ^{1}H NMR: δ (ppm) 2.35 (br, 1H, -OH), 4.09 (d, 1H, J = 5.7, -CHCN), 4.61 (t, 1H, J = 6.4, -CHOH); 6.26 (dd,

1H, J = 15.9, 6.9), 6.65 (d, 1H, J = 15.9), 7.25-7.47 (m, 10H); ^{13}C NMR: δ (ppm) 45.40, 74.74, 118.66, 125.83, 126.77, 128.37, 128.50, 128.64, 129.06, 131.81, 134.25, 135.65. MS/EI: 133.1, 115.1, 103.1, 89.0, 77.0, 65.0, 55.0; HRMS calcd for $C_{17}H_{15}NO$: 249.11536; found: 249.11517.

(2RS,3SR)-3-Hydroxy-2-phenyl-4-pentenenitrile (*anti*-10): The analytically pure sample was obtained by preparative TLC. Yellow oil; R_f = 0.11 (hexane/ethyl acetate 4:1); IR: 1120, 1455, 1495, 1689, 2246, 2918, 3088, 3446; ^{1}H NMR: δ (ppm) 2.04 (d, 1H, J = 4.8, -OH), 3.94 (d, 1H, J = 5.1, -CHCN), 4.46 (dd, 1H, J = 5.1, 4.8, -CHOH); 5.30-5.42 (m, 2H), 5.85-5.96 (m, 1H), 7.35-7.42 (m, 5H). ^{13}C NMR: δ (ppm) 45.13, 74.28, 118.30, 128.40, 128.52, 132.17, 135.83. MS/EI: 173.1, 154.1, 117.1, 90.0, 77.0, 57.0; HRMS calcd for $C_{11}H_{11}NO$: 173.08406; found:173.08406.

(2RS,3RS)-3-Hydroxy-2-(1'-naphthyl)-3-phenylpropionitrile (*anti*-11):[19] ^{1}H NMR: δ (ppm) 2.39 (br, 1H, -OH), 4.99(d, 1H, J = 6.0, -CHCN), 5.14 (d, 1H, J = 6.0, -CHOH); 7.0-8.0 (m, 12H). ^{13}C NMR: δ (ppm)43.32, 75.12, 118.84, 122.13, 125.22, 126.10, 126.66, 127.02,127.48, 128.19, 128.62, 128.83, 129.22, 129.36, 130.64, 133.77, 138.73.

(2RS,3SR)-3-Hydroxy-2-(1'-naphthyl)-3-phenylpropionitrile (*syn*-11): The analytically pure sample was obtained by preparative TLC. Yellow oil; R_f = 0.29 (hexane/ethyl acetate 3:1); IR: 1044, 1598, 2247, 2923, 3063, 3447; ^{1}H NMR: δ (ppm) 2.39 (br, 1H, -OH), 4.99(d, 1H, J = 6.0, -CHCN), 5.14 (d, 1H, J = 6.0, -CHOH); 7.0-8.0 (m, 12H); ^{13}C NMR: δ (ppm)43.32, 75.12, 118.84, 122.13, 125.22, 126.10, 126.66, 127.02,127.48, 128.19, 128.62, 128.83, 129.22, 129.36, 130.64, 133.77, 138.73. MS/EI: 273.1, 228.1, 188.1, 167.1, 139.1, 127.1, 107.0, 77.0, 51.0; HRMS calcd for $C_{19}H_{15}NO$: 273.11536; found:273.11536.

(2RS,3RS)-3-Hydroxy-2-methyl-3-(1'-naphthyl)propionitrile (*anti*-12): The analytically pure sample was obtained by preparative TLC. Yellow oil; R_f = 0.40 (hexane/ethyl acetate 3:1); IR: 2245, 2942, 3053, 3446; ^{1}H NMR: δ (ppm) 1.24 (d, 3H, J = 6.9, -CH_3) 2.58 (br, 1H, -OH), 3.23 (qd, 1H, J = 7.2, 6.0, -CHCN), 5.77 (d, 1H, J = 4.5, -CHOH); 7.48-7.59 (m, 3H); 7.73-8.20 (m, 4H); ^{13}C NMR: δ (ppm) 12.35, 32.36, 70.56, 121.58, 122.35, 124.57, 125.36, 125.97, 126.776, 129.29, 129.41, 130.17, 134.03, 135.25. MS/EI: 211.1, 157.1, 141.1, 129.1, 102.0, 77.0, 51.0; HRMS calcd for $C_{14}H_{13}NO$: 211.09971; found: 211.10006.

(2RS,3SR)-3-Hydroxy-2-methyl-3-(1'-naphthyl)propionitrile (*syn*-12): The analytically pure sample was obtained by preparative TLC. Yellow oil; R_f = 0.30 (hexane/ethyl acetate 3:1); IR: 2246, 2917, 3058, 3445; ^{1}H NMR: δ (ppm) 1.37 (d, 3H, J = 6.9, -CH_3) 2.52 (br, 1H, -OH), 3.23 (qd, 1H, J = 7.2, 6.0, -CHCN), 5.48 (d, 1H, J = 5.7, -CHOH); 7.48-7.59 (m, 3H); 7.73-8.20 (m, 4H). ^{13}C NMR: δ (ppm) 15.64, 34.30, 72.37, 120.78,

122.42, 124.39, 125.56, 126.05, 126.79, 129.46, 129.52, 130.37, 134.12, 135.89.MS/EI: 211.1, 167.1, 157.1, 139.1, 129.1, 102.0, 77.0, 51.0; HRMS calcd for $C_{14}H_{13}NO$: 211.09971; found: 211.10007.

(2RS,3SR)-3-Hydroxy-2-methyl-5-phenyl-4-pentenenitrile (*anti*-13): The analytically pure sample was obtained by preparative TLC. Yellow oil; R_f = 0.38 (hexane/ethyl acetate 1:1); IR: 2243, 2917, 3428; ^{1}H NMR: δ (ppm) 1.34 (d, 3H, J = 7.2, -CH_3) 2.05 (br, 1H, -OH), 2.95 (qd, 1H, J = 7.2, 6.0, -CHCN), 4.36 (br, 1H, -CHOH); 6.27 (dd, 1H, J = 15.9, 7.5), 6.73 (d, 1H, J = 15.9), 7.28-7.44 (m, 5H); ^{13}C NMR: δ (ppm)13.62, 32.84, 73.70, 120.81, 126.67, 126.96, 128.63, 128.86, 134.72. MS/EI: 187.1, 133.1, 115.1, 103.1, 91.1, 77.0, 68.9, 63.0, 55.0; HRMS calcd for $C_{12}H_{13}NO$: 187.09971; found: 187.09989.

(2RS,3RS)-3-Hydroxy-2-methyl-5-phenyl-4-pentenenitrile (*syn*-13): The analytically pure sample was obtained by preparative TLC. Colorless oil; R_f = 0.40 (hexane/ethyl acetate 4:1); IR: 1449, 1653, 1728,2244, 2921, 3445; ^{1}H NMR: δ (ppm) 1.39 (d, 3H, J = 7.2, -CH_3) 2.07 (d, 1H, J = 4.8, -OH), 2.83 (qd, 1H, J = 7.2, 5.7, -CHCN), 4.36 (dd, 1H, J = 12.9, 6.0, -CHOH); 6.22 (dd, 1H, J = 15.6, 6.9), 6.72 (d, 1H, J = 16.2), 7.28-7.44 (m, 5H); ^{13}C NMR: δ (ppm) 14.14, 33.15, 73.71, 126.92, 127.43, 128.62, 128.86, 134.18. MS/EI: 187.1, 133.1, 115.1, 103.1, 77.0, 65.000, 55.0; HRMS calcd for $C_{12}H_{13}NO$: 187.09971; found: 187.09994.

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