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Metallation–Substitution of an α-Oxygenated Chiral Nitrile

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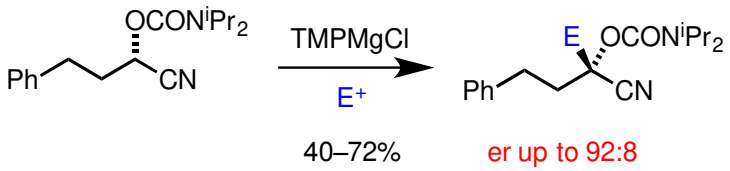
ABSTRACT

Deprotonation of a chiral alpha-oxygenated nitrile with the base TMPMgCl gives rise to a chiral magnesiated nitrile and this anion has sufficient configurationally stability at low temperature to allow for the formation of highly enantiomerically enriched substituted nitrile products after electrophilic quench.

GRAPHICAL ABSTRACT



KEY WORDS

Alkylation; Asymmetric synthesis; Carbanions; Enantioselectivity; Magnesium; Metalation; Synthetic methods

INTRODUCTION

Deprotonation next to carbonyl groups gives rise to enolates that are one of the most extensively used carbon-centred nucleophiles in synthetic chemistry.[1] Enolates are planar species so if the proton to be removed is at a stereogenic centre then this stereochemistry present in the original carbonyl compound will be lost. The same scenario is possible with nitriles **1** if, on deprotonation, they form metallated ketene-imine type structures such as compound **2** (Fig. 1). This is believed to occur in many cases, particularly with lithium as the counterion, where the lithium typically coordinates to the nitrogen atom of the nitrile, although the C–N bond is thought to maintain considerable triple bond character.[2]

Indeed there is X-ray crystallographic evidence for this structure on lithiation of phenylacetonitrile.[3] However, examples of metallated nitriles in which the metal resides on the carbon atom (structure **3**) are known, even for lithium but especially for softer metals such as palladium or ruthenium.[4,5] Therefore there exists the possibility that nitriles could maintain their configuration on metallation, should structures of type **3** be formed directly from the chiral nitrile **1** and if this metallated species does not racemize rapidly.

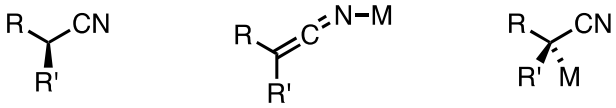


Figure 1. A generic chiral nitrile and possible metallated structures (M = metal).

The first example of such chemistry was reported by Carlier and Zhang.[6,7] They showed that the chiral cyclopropylnitrile **4** (Fig. 2) could be formed by bromine–magnesium exchange with ^{i}PrMgCl and reacts with D_2O to give high enantiomer ratios of the deuterated product. Fleming and co-workers have found very different selectivities between lithiated and magnesiated nitriles and that magnesium counterions favour attachment to the carbon atom of the nitrile.[8] Therefore we were interested in whether it might be possible to take an acyclic chiral nitrile and carry out enantiospecific metallation then substitution, particularly using a base centred on the metal magnesium. We reported our preliminary findings in this area recently in which the chiral nitriles **5** and **6** successfully undergo such chemistry.[9] This work originated from the observation by Takeda and co-workers that low enantiomer ratios were possible by treatment of the nitrile **6** with LDA and in situ benzyl bromide.[10] Since then Takeda and co-workers reported much improved selectivities using more reactive electrophiles (in situ quench with acid chlorides or ethyl cyanoformate) with the nitriles **5** and **6**, with LDA as the base.[11] Herein we describe further results with the nitrile **6** and results with related compounds that demonstrate the importance of the carbamate group. With the base TMPMgCl we show that high enantiomer ratios of new substituted products are possible after quenching with different electrophiles.[12]

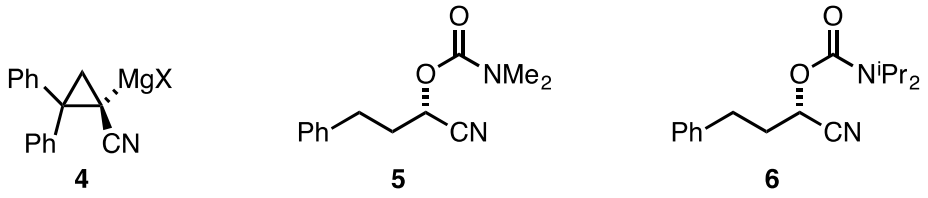
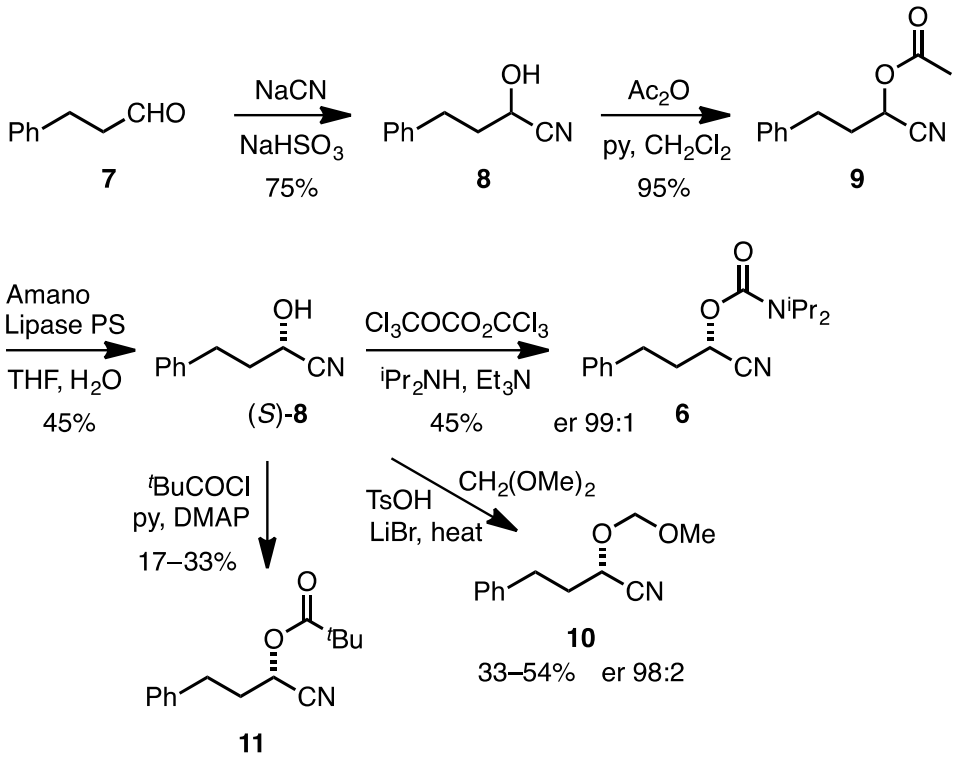


Figure 2. Chiral nitriles **4**–**6**.

RESULTS AND DISCUSSION

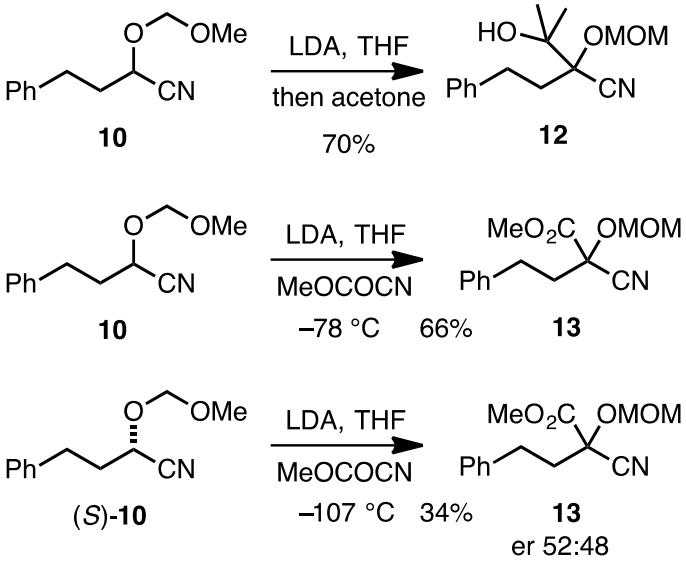
The nitrile **6** was prepared by a method reported by Takeda and co-workers.[10] This involved conversion of the commercially available aldehyde **7** to the cyanohydrin **8** followed by acylation to give the ester **9** (Scheme 1). Treatment of the ester **9** with Amano lipase PS effected a kinetic resolution to give the desired alcohol **8** with high enantiomer ratio.[13] The data matched those reported in the literature for the (*S*) enantiomer.[10] Conversion of the alcohol **8** to the carbamate **6** was carried out with triphosgene and diisopropylamine. The enantiomer ratio (er) of the product **6** was verified by chiral stationary phase (CSP) HPLC (er 99:1). In addition, the alcohol **8** was converted, in unoptimised yields, to the novel compounds **10** and **11** by using dimethoxymethane and pivaloyl chloride respectively. These compounds were used to probe the importance of the carbamate protecting group on the oxygen atom.



Scheme 1. Preparation of chiral nitriles **9**–**11**.

The key chemistry of interest is whether the compounds **6**, **10**, and **11** will undergo metallation then substitution and to what extent, if at all, the enantiopurity will be transferred to the product. We anticipated that the magnesium base TMPMgCl would be better than group 1 bases such as LDA. However initially we confirmed whether metallation was successful or not.

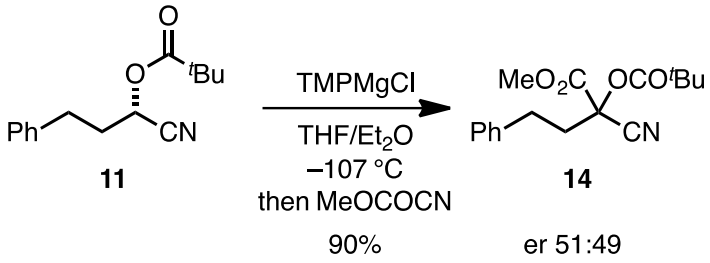
Treatment of the racemic ether **10** with LDA in THF at –78 °C followed by addition of acetone or methyl cyanoformate as the electrophile gave the expected products **12** and **13** in reasonable yields (Scheme 2). The enantiomers of these products could be resolved by CSP-HPLC. The best conditions reported previously for the enantiospecific metallation–quench of **5** or **6** made use of the magnesium base TMPMgCl at –107 °C.[9] However attempts to conduct the metallation of the ether **10** with TMPMgCl were unsuccessful and after addition of the electrophile (or by using in situ MeOCOCN) only starting material **10** was recovered. It was possible to carry out the lithiation–quench of ether (*S*)-**10** with in situ MeOCOCN by using LDA at –107 °C to give the product **13** (34% yield). Unfortunately this product was essentially racemic (er 52:48 by CSP-HPLC).



Scheme 2. Metallation of nitrile **10**.

We then turned to the ester **11**. This compound has a carbonyl group that could help to stabilise the metallated intermediate, although it would not be as good a coordinating group as the carbamate carbonyl in **5** or **6**. Attempted deprotonation adjacent to the nitrile in racemic **11** with LDA followed by addition of MeOCOCl, MeOCOCN or acetone failed to give any of the desired substituted products. However addition of TMPMgCl in THF/Et_2O at –107 °C then MeOCOCN was successful and gave the nitrile product **14** in 90% yield. The enantiomers of this product could be resolved by CSP-HPLC.

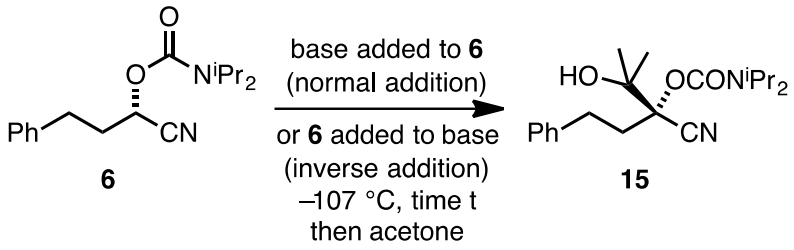
Therefore we screened the enantioenriched nitrile **11** with TMPMgCl at –107 °C followed after 10 min by addition of MeOCOCN (Scheme 3). This gave the desired product **14** in high yield but as a racemic mixture.



Scheme 3. Metallation of nitrile **11**.

We then turned our attention to the carbamate **6**, which is able to undergo the desired transformation with high er by using TMPMgCl and electrophilic quench with acetone, MeOCOCN or BnOCOCN.[9] To extend this study, we screened a variety of bases and some new electrophiles to explore whether TMPMgCl was the base of choice and to increase the scope of this chemistry.

The base screening was carried out with acetone as the electrophile and the nitrile (*S*)-**6** to give the substituted product **15** (Scheme 4). A table of results is given to show the comparison of the different bases in regard to the yield of the isolated product **15** (Table 1). We were concerned about optimising both the yield of the product **15** and its er. In each case the major enantiomer is that shown in Scheme 4, in which the reaction takes place with retention of configuration, as shown by preparation of the *p*-bromophenyl derivative and subsequent X-ray analysis.[9]



Scheme 4. Metallation of nitrile **6** and quench with acetone.

Entry	Base	solvent	Method	t (min)	Yield (%) **15**	er (*S*:*R*)
1	1.2 eq. ^{i}PrMgCl	Et_2O	normal	10	44	82:18
2	1.2 eq. ^{i}PrMgCl	Et_2O	inverse	10	30	87.13
3	4 eq. ^{i}PrMgCl	Et_2O	inverse	10	45	91:9
4	4 eq. ^{i}PrMgCl	Et_2O	inverse	in situ	24	87:13

5	4 eq. ^{i}PrMgCl	^{t}BuOMe/Et_2O	inverse	10	50	71:29
6	4 eq. ^{i}PrMgCl	THF/Et_2O (1:1)	inverse	10	24	89:11
7	4 eq. $^{n}Bu_2Mg$	Et_2O	inverse	10	45	80:20
8	5 eq. TMPMgCl·LiCl	Et_2O	inverse	10	73	70:30
9	4 eq. TMPMgCl	Et_2O	inverse	2	55	85:15
10	3 eq. TMPMgCl	CPME[a]/Et_2O	inverse	in situ	79	60:40
11	4 eq. TMPMgCl	Et_2O	inverse (4 min)	2	50	87:13
12	3 eq. TMPMgCl	Et_2O	inverse (4 min)	0.1	48	86:14

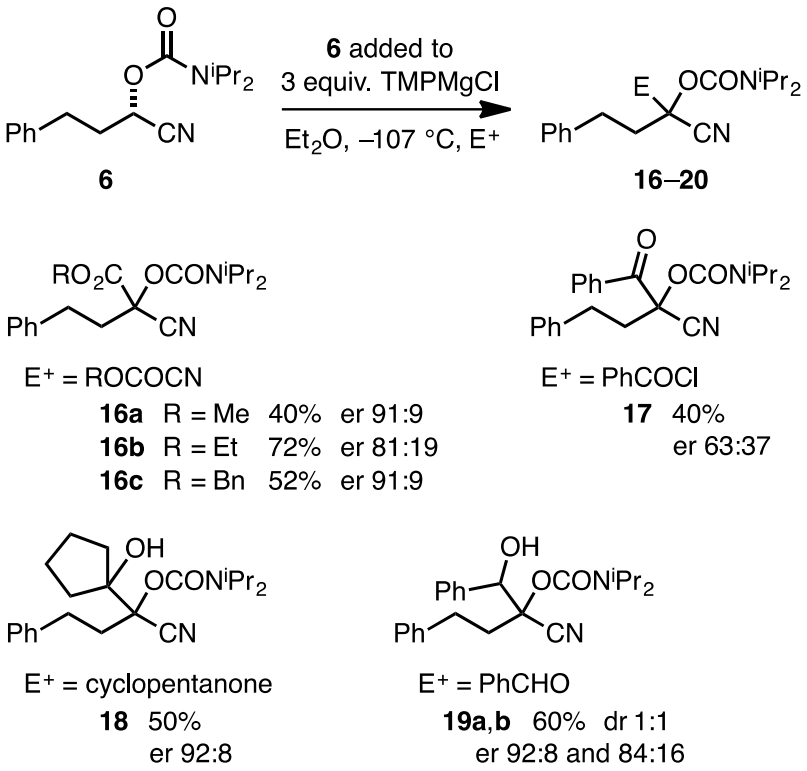
[a]CPME=cyclopentyl methyl ether

Table 1. Effect of different bases and conditions for formation of product **15**.

Initially we investigated the base ^{i}PrMgCl, which was effective for the transformation (Table 1, entries 1–6). Using inverse addition, whereby the nitrile (*S*)-**6** was added to the base gave similar results to normal addition of base to the nitrile, but perhaps with slightly improved enantioselectivity (compare entries 1 and 2). We therefore opted to continue further experiments with inverse addition. The yield was improved with excess base (compare entries 2 and 3). Remarkably, even using in situ acetone that we expected would simply form its enolate, did in fact give some product (entry 4), although disappointingly the er was not improved. It therefore appears that there is a rapid partial loss of enantiopurity on metallation although subsequently the magnesiated intermediate has reasonable configurational stability (for several minutes) at –107 °C. Two other solvents were tested but ^{t}BuOMe gave reduced er (entry 5) and THF/Et_2O mixture gave reduced yield (entry 6). We then tried some other bases and found that Bu_2Mg was effective and gave similar results to ^{i}PrMgCl (entry 7). More promising in terms of the yield was the use of TMPMgCl·LiCl however the er was poorer (entry 8). This may be due to the presence of lithium cations that could coordinate to the nitrogen atom of the nitrile and start to favour a ketene-imine metallated species. The best results were obtained by using TMPMgCl in the absence of LiCl. This base can be prepared readily from TMPH and ^{i}PrMgCl in THF or in Et_2O.[14] Similar results were obtained by using an excess of this base in Et_2O using inverse addition, either by rapid addition of nitrile (*S*)-**6** (entry 9) or addition of (*S*)-**6** more slowly over about 4

minutes (entries 11 and 12). An attempt to use cyclopentyl methyl ether as the main solvent gave a good yield but poor selectivity (entry 10).

As the optimised conditions, we selected to add the nitrile (*S*)-**6** slowly to three equivalents of TMPMgCl in Et_2O at –107 °C, followed by addition of the electrophile. Reasonable yields and er values were obtained on using alkyl cyanoformates as the electrophile to give the products **16a–c** (Scheme 5). We also studied some new electrophiles. Benzoyl chloride gave the product **17** with reduced er. This may be due to slower reaction with the acid chloride that allows partial racemization of the intermediate organomagnesium species, or possible reaction by a mixture of retention and inversion of configuration. However we were pleased to find that the ketone cyclopentanone was successful to give the product **18** with high enantioselectivity (er 92:8). In addition the electrophile benzaldehyde gave, as an inseparable mixture, the enantioenriched diastereomeric products **19a** and **19b**. We have determined that the absolute configuration of the product **15** demonstrated that reaction with acetone occurs with retention of configuration.[9] However we have not determined the stereochemistry of the major enantiomers of the products **16**–**19**. It is possible that these products are formed after reaction with retention of configuration, particularly using cyclopentanone that is similar to acetone. Despite this, reaction of metallated nitrile **5** with ethyl cyanoformate and with benzoyl chloride are known to occur with inversion of configuration.[9,11a] Regardless of the absolute configurations, the reactions occur with high enantioselectivity for a selection of electrophiles, as illustrated in Scheme 5.



Scheme 5. Metallation of nitrile (*S*)-**6** and quench with various electrophiles E^+.

CONCLUSION

The metallation of chiral nitriles with magnesium bases such as TMPMgCl at low temperature occurs with significant retention of enantiopurity. The magnesiated intermediates can be quenched with a variety of electrophiles. Better results were found with the carbamate **6** than the ether **10** or ester **11**. This is likely due to the better coordinating ability of a carbamate that can stabilise the magnesiated intermediate through chelation of the carbonyl oxygen atom with the magnesium. This will then reduce the extent of loss of the metal from the stereocentre and help to retain high levels of enantiopurity in the substituted product after electrophilic quench.

EXPERIMENTAL

Procedures and data for compounds **6**–**9** have been reported.[9,11a]

2-(Methoxymethoxy)-4-phenylbutanenitrile 10

To a solution of alcohol (±)-**8** (1.0 g, 6.2 mmol) in dimethoxymethane (12 mL) was added LiBr (285 mg, 3.3 mmol) and *p*-TsOH monohydrate (118 mg, 0.62 mmol) and the mixture was heated under

reflux. After 3 d, the mixture was cooled to room temp. and the solvent was evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), gave the nitrile **10** (686 mg, 54%) as an oil; R_f 0.2 [petrol–Et_2O (9:1)]; ν_{max} (neat)/cm^{-1} 2955, 2900, 1455, 1150, 1105, 1090, 1020; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.20 (5H, m, Ph), 4.87 (1H, d, *J* 7, CH), 4.69 (1H, d, *J* 7, CH), 4.35 (1H, t, *J* 7.5, CH), 3.45 (3H, s, CH_3), 2.87 (2H, t, *J* 7.5, CH_2), 2.30–2.19 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.7, 128.7, 128.4, 126.5, 118.3, 95.8, 64.2, 56.3, 35.1, 30.9; HRMS (ES) Found: M^+, 205.1112. $C_{12}H_{15}NO_2$ requires M^+ 205.1103.

The enantiomers were resolved by chiral stationary phase HPLC using a Cellulose-2 column at 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g L^{-1} solution of 0.5% ^{i}PrOH in hexanes. Retention times 14.5 and 15.4 min.

In the same way as above, the alcohol (*S*)-**8** (4.1 g, 25.5 mmol), dimethoxymethane (50 mL), LiBr (1.22 g, 14.1 mmol), and *p*-TsOH monohydrate (507 mg, 2.67 mmol) gave, after purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), the nitrile (*S*)-**10** (1.8 g, 33%) as an oil; $[\alpha]_D^{21}$ −57 (1.0, $CHCl_3$); other data as above; er 98:2 (major peak at 14.5 min).

1-Cyano-3-phenylpropyl 2,2-Dimethylpropanoate 11

To a solution of alcohol (±)-**8** (2.0 g, 12.4 mmol) and DMAP (25 mg, 2 mmol) in pyridine (126 mL) was added pivaloyl chloride (1.67 mL, 13.7 mmol) at room temp. After 12 h, the solvent was evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), gave the nitrile **11** (1.0 g, 33%) as an oil; R_f 0.8 [petrol–Et_2O (9:1)]; ν_{max} (neat)/cm^{-1} 2975, 1740, 1500, 1480, 1455, 1275, 1130, 1035; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.17 (5H, m, Ph), 5.28 (1H, t, *J* 7, CH), 2.85 (2H, t, *J* 8, CH_2), 2.32–2.20 (2H, m, CH_2), 1.27 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.5, 139.1, 128.8, 128.4, 126.7, 116.9, 60.5, 38.8, 33.9, 30.8, 26.9; HRMS (ES) Found: M^+, 245.1408. $C_{15}H_{19}NO_2$ requires M^+ 245.1416.

In the same way as above, the alcohol (*S*)-**8** (1.0 g, 6.2 mmol), DMAP (13 mg, 1.0 mmol), pyridine (64 mL), and pivaloyl chloride (0.83 mL, 6.8 mmol) gave, after purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), the nitrile (*S*)-**11** (0.26 g, 17%) as an oil; $[\alpha]_D^{21}$ −40 (1.0, $CHCl_3$); other data as above.

3-Hydroxy-2-(methoxymethoxy)-3-methyl-2-(2-phenylethyl)butanenitrile 12

^{n}BuLi (254 μL, 0.63 mmol, 2.5 M in hexanes) was added to $^{i}Pr_2NH$ (83 μL, 0.63 mmol) in THF (2 mL) at –78 °C. After 10 min, nitrile (±)-**10** (92 mg, 0.45 mmol) in THF (1 mL) was added. After 10 min, acetone (72 μL, 0.97 mmol) was added. After 30 min, the mixture was warmed to room temp. and sat. $NH_4Cl_{(aq)}$ (4 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL). The combined organics layers were dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (95:5), gave the nitrile **12** (90 mg, 70%) as an oil; R_f 0.2 [petrol–Et_2O (95:5)]; ν_{max} (neat)/cm^{-1} 3055, 2985, 1420, 1265, 1015; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37–7.15 (5H, m, Ph), 5.18 (1H, d, *J* 7.5, CH), 4.94 (1H, d, *J* 7.5, CH), 3.79 (1H, br s, OH), 3.55 (3H, s, CH_3), 2.99–2.82 (2H, m, CH_2), 2.10–1.96 (2H, m, CH_2), 1.37 (3H, s, CH_3), 1.29 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.8, 128.6, 128.5, 126.3, 117.3, 95.7, 86.6, 74.4, 56.7, 37.7, 31.3, 25.7, 23.8; HRMS (ES) Found: MH^+, 264.1589. $C_{15}H_{22}NO_3$ requires MH^+ 264.1600.

The enantiomers were resolved by chiral stationary phase HPLC using a Cellulose-1 column at 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g L^{-1} solution of 2% ^{i}PrOH in hexanes. Retention times 19.6 and 22.2 min.

Methyl 2-Cyano-2-(methoxymethoxy)-4-phenylbutanoate 13

In the same way as nitrile **12**, ^{n}BuLi (254 μL, 0.63 mmol, 2.5 M in hexanes), $^{i}Pr_2NH$ (83 μL, 0.63 mmol), nitrile **10** (100 mg, 0.49 mmol) and MeOCOCN (77 μL, 0.97 mmol) gave, after purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), the nitrile **13** (84 mg, 66%) as an oil; R_f 0.1 [petrol–Et_2O (9:1)]; ν_{max} (neat)/cm^{-1} 3055, 2985, 1760, 1420, 1265, 1160, 1105, 1050; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37–7.18 (5H, m, Ph), 5.10 (1H, d, *J* 7, CH), 4.83 (1H, d, *J* 7, CH), 3.81 (3H, s, CH_3), 3.43 (3H, s, CH_3), 3.08–2.72 (2H, m, CH_2), 2.46–2.28 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.1, 139.4, 128.7, 128.6, 128.5, 126.7, 126.5, 115.6, 95.5, 76.4, 57.2, 53.8, 39.9, 30.0; HRMS (ES) Found: M^+, 263.1170. $C_{14}H_{17}NO_4$ requires M^+ 263.1158.

The enantiomers were resolved by chiral stationary phase HPLC using a Cellulose-1 column at 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g L^{-1} solution of 0.2% ^{i}PrOH in hexanes. Retention times 35.0 and 40.3 min.

The same reaction was conducted at –107 °C with nitrile **10** (100 mg, 0.49 mmol) to give the nitrile **13** (41 mg, 34%) as an oil; data as above; er 52:48.

1-Cyano-3-phenylpropyl 2,2-Dimethylpropanoate 14

The nitrile (±)-**10** (42 mg, 0.17 mmol) in Et_2O–THF (0.5 mL, 1:1) was added to TMPMgCl (1.56 mL, 0.51 mmol, 0.33 M in THF) in Et_2O–THF (2.5 mL, 1:1) at −107 °C. After 10 min, MeOCOCN (41 μL, 0.51 mmol) was added. After 10 min, the mixture was allowed to warm to room temp. and then sat. $NH_4Cl_{(aq)}$ (4 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL). The combined organics layers were dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (95:5), gave the nitrile **14** (45 mg, 90%) as an oil; R_f 0.1 [petrol–Et_2O (9:1)]; ν_{max} (neat)/cm^{-1} 2975, 2935, 1750, 1455, 1280, 1255, 1125, 1105, 1085, 1055, 1030; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.19 (5H, m, Ph), 3.87 (3H, s, CH_3), 3.00–2.87 (2H, m, CH_2), 2.50–2.39 (2H, m, CH_2), 1.32 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.5, 165.4, 138.9, 128.7, 128.4, 126.7, 115.1, 72.5, 54.0, 39.2, 38.3, 30.0, 26.7; HRMS (ES) Found: MH^+, 304.1536. $C_{17}H_{22}NO_4$ requires MH^+ 304.1549.

The enantiomers were resolved by chiral stationary phase HPLC using a Cellulose-1 column at 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g L^{-1} solution of 1% ^{i}PrOH in hexanes. Retention times 11.8 and 13.8 min.

In the same way as above, the nitrile (*S*)-**10** (50 mg, 0.2 mmol), TMPMgCl (2.6 mL, 0.44 mmol, 0.17 M in THF), and MeOCOCN (38 μL, 0.48 mmol) gave, after purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), the nitrile **14** (57 mg, 92%) as an oil; data as above; er 51:49.

[1-Cyano-2-hydroxy-2-methyl-1-(2-phenylethyl)]propyl *N,N-bis*(Propan-2-yl)carbamate 15[9]

Method for Table 1, entry 10:

A solution of nitrile (*S*)-**6** (100 mg, 0.35 mmol) in dry Et_2O (2 mL) was added dropwise over 4 min using a syringe pump to a solution of TMPMgCl (3.5 mL, 1.4 mmol, 0.4 M solution in Et_2O) in dry Et_2O (1 mL) at −107 °C. After 2 min, dry acetone (0.12 mL, 1.75 mmol) was added. After 30 min, sat. $NH_4Cl_{(aq)}$ (2 mL) was added and the mixture was allowed to warm to room temp. The mixture was extracted with Et_2O (3 × 5 mL). The combined organics layers were dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), gave the nitrile **15** (60 mg, 50%) as an oil; $[\alpha]_D^{21}$ −8.0 (1.0, $CHCl_3$); other data as reported;[9] er 87:13 (major peak at 15 min) determined by chiral stationary phase HPLC using a Cellulose-1 column at 1 mL/min,

ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g L^{-1} solution of 1% ^{i}PrOH in hexanes. Retention times 15 and 17 min.

Methyl 2-{*[bis*(Propan-2-yl)carbamoyl]oxy}-2-cyano-4-phenylbutanoate 16a[9]

A solution of nitrile (*S*)-**6** (50 mg, 0.17 mmol) and methyl cyanoformate (0.05 mL, 0.52 mmol) in dry Et_2O–THF (1:1) (0.5 mL) was added dropwise over 4 min using a syringe pump to a solution of TMPMgCl (1.3 mL, 0.52 mmol, 0.4 M solution in Et_2O–THF) in dry Et_2O–THF (1:1) (2.5 mL) at –107 °C. After 30 min, sat. $NH_4Cl_{(aq)}$ (2 mL) was added and the mixture was allowed to warm to room temp. The mixture was extracted with Et_2O (3 × 5 mL). The combined organics layers were dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), gave the ester **16a** (25 mg, 40%) as needles; m.p. 70−73 °C; other data as reported;[9] $[\alpha]^{23}_{D}$ +3.0 (*c* 1.0, $CHCl_3$); er 91:9 (major peak at 16.8 min) determined by chiral stationary phase HPLC using a Cellulose-1 column at 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g L^{-1} solution of 1% ^{i}PrOH in hexanes. Retention times 16.8 and 20.9 min.

Ethyl 2-{[*bis*(Propan-2-yl)carbamoyl]oxy}-2-cyano-4-phenylbutanoate 16b[11a]

From racemic nitrile **6**:

n-Butyllithium (0.4 mL, 0.95 mmol, 2.5 M solution in hexanes) was added to diisopropylamine (0.15 mL, 1.02 mmol) in Et_2O (2.5 mL) at –78 °C. After 10 min, nitrile (±)-**6** (50 mg, 0.17 mmol) in Et_2O (0.5 mL) was added. After 10 min, ethyl cyanoformate (0.10 mL, 1.02 mmol) was added. After 30 min, the mixture was allowed to warm to room temperature and sat. $NH_4Cl_{(aq)}$ (2 mL) was added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organics layers were dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), gave the ester **16b** (50 mg, 82%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.32 (2H, m, Ph), 7.28–7.23 (3H, m, Ph), 4.39–4.26 (2H, m, CH_2), 4.09–4.00 (1H, m, CH), 3.80–3.73 (1H, m, CH), 3.03–2.90 (2H, m, CH_2), 2.48–2.36 (2H, m, CH_2), 1.35 (3H, t, *J* 7, CH_3), 1.32–1.25 (12H, m, 4 × Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.6, 152.7, 139.2, 128.7, 128.3, 126.6, 116.0, 73.5, 62.9, 47.4, 46.1, 38.6, 30.4, 21.6, 21.3, 20.3, 20.2, 13.9; HRMS (ES) found: MH^+, 361.2132. $C_{20}H_{29}N_2O_4$ requires MH^+, 361.2127; data as reported.[11a]

The enantiomers were resolved by chiral stationary phase HPLC using a CHIRALPAK AD column at 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g L^{-1} solution of 1% ^{i}PrOH in hexanes. Retention times 8.1 and 9.1 min.

From nitrile (*S*)-**6**:

The nitrile (*S*)-**6** (100 mg, 0.35 mmol) and dry ethyl cyanoformate (0.10 mL, 1.02 mmol) in dry Et_2O–THF (1:1) (0.5 mL) was added dropwise over 4 min to TMPMgCl (3.3 mL, 1.04 mmol, 0.4 M in THF) in dry Et_2O–THF (1:1) (2.5 mL) at –107 °C. After 30 min, sat. $NH_4Cl_{(aq)}$ (2 mL) was added and the mixture was allowed to warm to room temp. The mixture was extracted with Et_2O (3 × 5 mL). The combined organics layers were dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), gave the ester **16b** (90 mg, 72%) as an oil; $[\alpha]^{23}_{D}$ +27.0 (c 1.0, $CHCl_3$); er 80:10 (major peak at 9.1 min) determined by CSP-HPLC; other data as above or as reported (no specific rotation data given in the literature).[11a]

Benzyl 2-{[*bis*(Propan-2-yl)carbamoyl]oxy}-2-cyano-4-phenylbutanoate 16c[9]

A solution of nitrile (*S*)-**6** (50 mg, 0.17 mmol) and benzyl cyanoformate (0.08 mL, 0.52 mmol) in dry Et_2O–THF (1:1) (0.5 mL) was added dropwise over 4 min using a syringe pump to a solution of TMPMgCl (1.3 mL, 0.52 mmol, 0.4 M solution in Et_2O–THF) in dry Et_2O–THF (1:1) (2.5 mL) at –107 °C. After 30 min, sat. $NH_4Cl_{(aq)}$ (2 mL) was added and the mixture was allowed to warm to room temp. The mixture was extracted with Et_2O (3 × 5 mL). The combined organics layers were dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (19:1), gave the ester **16a** (40 mg, 52%) as an oil; data as reported;[9] $[\alpha]^{23}_{D}$ +12.0 (*c* 1.0, $CHCl_3$); er 91:9 (major peak at 21.4 min) determined by chiral stationary phase HPLC using a Cellulose-1 column at 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g L^{-1} solution of 1% ^{i}PrOH in hexanes. Retention times 21.4 and 26.9 min.

1-Benzoyl-1-cyano-3-phenylpropyl *N,N-bis*(Propan-2-yl)carbamate 17

From racemic nitrile **6**:

n-Butyllithium (0.79 mL, 1.9 mmol, 2.5 M solution in hexanes) was added to diisopropylamine (0.29 mL, 2.08 mmol) in Et_2O (2.5 mL) at –78 °C. After 10 min, nitrile (±)-**6** (100 mg, 0.35 mmol) in Et_2O

(0.5 mL) was added. After 10 min, benzoyl chloride (0.25 mL, 2.0 mmol) was added. After 30 min, the mixture was allowed to warm to room temperature and sat. $NH_4Cl_{(aq)}$ (2 mL) was added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organics layers were dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), gave the ketone **17** (100 mg, 72%) as plates; m.p. 127–130 °C; R_f 0.65 [petrol–Et_2O (4:1)]; ν_{max} (neat)/cm^{-1} 2970, 2940, 1735, 1705, 1690, 1430; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03 (2H, d, *J* 7.5, Ph), 7.58 (1H, t, *J* 7.5, Ph), 7.46 (2H, t, *J* 7.5, Ph), 7.36–7.31 (2H, m, Ph), 7.26–7.24 (3H, m, Ph), 3.92–3.85 (1H, m, CH), 3.75–3.69 (1H, m, CH), 3.14–3.01 (2H, m, CH_2), 2.71–2.64 (1H, m, CH), 2.59–2.51 (1H, m, CH), 1.31–1.15 (12H, m, 4 × Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.4 , 151.9, 139.4, 133.3, 128.8, 128.7, 128.5, 128.3, 128.2, 126.6, 116.8, 79.6, 46.8, 46.7, 38.5, 30.8, 21.4, 21.3, 20.3, 19.7; HRMS (ES) found: MH^+, 393.2161. $C_{24}H_{29}N_2O_3$ requires MH^+, 393.2178.

The enantiomers were resolved by chiral stationary phase HPLC using a Cellulose 1 column at 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g L^{-1} solution of 1% ^{i}PrOH in hexanes. Retention times 15.0 and 18.7 min.

From nitrile (*S*)-**6**:

The nitrile (*S*)-**6** (100 mg, 0.35 mmol) and dry benzoyl chloride (0.12 mL, 1.04 mmol) in dry Et_2O–THF (1:1) (0.5 mL) was added dropwise over 4 min to TMPMgCl (3.1 mL, 1.0 mmol, 0.4 M in THF) in dry Et_2O–THF (1:1) (2.5 mL) at –107 °C. After 30 min, sat. $NH_4Cl_{(aq)}$ (2 mL) was added and the mixture was allowed to warm to room temp. The mixture was extracted with Et_2O (3 × 5 mL). The combined organics layers were dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), gave the ester **17** (40 mg, 40%) as plates; $[\alpha]^{23}_D$ +2.0 (c 1.0, $CHCl_3$); er 63:37 (major peak at 14.9 min) determined by CSP-HPLC; other data as above.

1-Cyano-1-(1-hydroxycyclopentyl)-3-phenylpropyl *N,N-bis*(Propan-2-yl)carbamate 18

From racemic nitrile **6**:

TMPMgCl (3.80 mL, 1.4 mmol, 0.4 M solution in Et_2O) was added to the nitrile (±)-**6** (100 mg, 0.35 mmol) in Et_2O (3 mL) at –78 °C. After 10 min, dry cyclopentanone (0.15 mL, 1.75 mmol) was added. After 30 min, the mixture was allowed to warm to room temperature and sat. $NH_4Cl_{(aq)}$ (2 mL) was added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organics layers were dried

($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), gave the alcohol **18** (70 mg, 54%) as needles; m.p. 135−137 °C; R_f 0.75 [petrol–Et_2O (4:1)]; ν_{max} (neat)/cm^{-1} 3465, 2970, 2940, 1700; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.30 (2H, m, Ph), 7.25–7.22 (3H, m, Ph), 4.47 (1H, s, OH), 4.09–3.97 (1H, m, CH), 3.91–3.79 (1H, m, CH), 3.02–2.95 (1H, m, CH), 2.88–2.79 (2H, m, CH_2), 2.31–2.23 (1H, m, CH), 2.12–1.99 (2H, m, 2 × CH), 1.97–1.87 (2H, m, 2 × CH), 1.79–1.71 (4H, m, 2 × CH_2), 1.28 (12H, d, *J* 7, 4 × Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.3, 140.3, 128.6, 128.3, 126.3, 118.3, 85.8, 85.7, 47.1, 46.5, 38.0, 37.9, 35.3, 31.3, 24.7, 24.0, 21.4, 20.3; HRMS (ES) found: MH^+, 373.2475. $C_{22}H_{33}N_2O_3$ requires MH^+, 373.2491.

The enantiomers were resolved by chiral stationary phase HPLC using a Cellulose 1 column at 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g L^{-1} solution of 1% ^{i}PrOH in hexanes. Retention times 14.4 and 20.3 min.

From nitrile (*S*)-**6**:

The nitrile (*S*)-**6** (100 mg, 0.35 mmol) in dry Et_2O (2 mL) was added dropwise over 4 min to TMPMgCl (3.8 mL, 1.4 mmol, 0.4 M in Et_2O) in dry Et_2O (1 mL) at –107 °C. After 2 min, dry cyclopentanone (0.15 mL, 1.75 mmol) was added. After 30 min, sat. $NH_4Cl_{(aq)}$ (2 mL) was added and the mixture was allowed to warm to room temp. The mixture was extracted with Et_2O (3 × 5 mL). The combined organics layers were dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), gave the alcohol **18** (65 mg, 50%) as needles; $[\alpha]^{23}_D$ –2.0 (c 1.0, $CHCl_3$); er 92:8 (major peak at 14.4 min) determined by CSP-HPLC; other data as above.

1-Cyano-1-(1-hydroxybenzyl)-3-phenylpropyl *N,N-bis*(Propan-2-yl)carbamate 19a and 19b

From racemic nitrile **6**:

Isopropyl magnesium chloride (1.20 mol, 1.4 mmol, 1.15 M solution in Et_2O) was added to nitrile (±)-**6** (100 mg, 0.35 mmol) in Et_2O (3 mL) at –78 °C. After 10 min, dry benzaldehyde (0.20 mL, 1.75 mmol) was added. After 30 min, the mixture was allowed to warm to room temperature and sat. $NH_4Cl_{(aq)}$ (2 mL) was added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organics layers were dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (9:1), gave an inseparable mixture of diastereomers **19a** and **19b** (dr 1:1) (100 mg, 77%) as a solid; R_f 0.3 [petrol–Et_2O (4:1)]; ν_{max} (neat)/cm^{-1} 3445, 2965, 2940, 2255, 1685, 1455;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47–7.17 (10H, m, Ph), 5.50 (0.5H, d, *J* 5, CH), 5.24 (0.5H, d, *J* 6.5, CH), 4.83 (0.5H, d, *J* 6.5, OH), 4.38 (0.5H, d, *J* 5, OH), 4.02–3.92 (1H, m, CH), 3.75–3.63 (1H, m, CH), 3.02–2.77 (2H, m, CH_2), 2.59–2.23 (2H, m, CH_2), 1.32–1.27 (6H, m, 2 × Me), 1.13–0.97 (6H, m, 2 × Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.7, 153.6, 140.1, 140.0, 137.5, 137.2, 128.7, 128.6, 128.4, 128.35, 128.3, 127.4, 126.5, 126.4, 126.35, 126.3, 117.9, 117.1, 80.7, 76.5, 75.5, 46.9, 46.5, 37.2, 35.2, 30.8, 30.7, 21.1, 21.0, 20.8, 20.3; HRMS (ES) found: MH^+, 395.2334. $C_{24}H_{31}N_2O_3$ requires MH^+, 395.2335.

The diastereomers and enantiomers were resolved by chiral stationary phase HPLC using a Cellulose 1 column at 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g L^{-1} solution of 1% ^{i}PrOH in hexanes. Retention times 30.3, 38.2, 51.4 and 60.0 min.

From nitrile (*S*)-**6**:

The nitrile (*S*)-**6** (100 mg, 0.35 mmol) in dry Et_2O (2 mL) was added dropwise over 4 min to TMPMgCl (3.8 mL, 1.4 mmol, 0.4 M in Et_2O) in dry Et_2O (1 mL) at –107 °C. After 2 min, dry benzaldehyde (0.20 mL, 1.75 mmol) was added. After 30 min, sat. $NH_4Cl_{(aq)}$ (2 mL) was added and the mixture was allowed to warm to room temp. The mixture was extracted with Et_2O (3 × 5 mL). The combined organics layers were dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica, eluting with petrol–Et_2O (19:1), gave an inseparable mixture of diastereomers **19a** and **19b** (dr 1:1) (75 mg, 60%) as a solid; $[\alpha]^{23}_{D}$ 6.0 (c 1.0, $CHCl_3$); er 92:8 and 84:16 (major peaks at 30.3 and 38.2 min) determined by CSP-HPLC; other data as above.

SUPPORTING INFORMATION

Copies of NMR spectra for all novel compounds are provided in the Supporting Information.

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