An Efficient Diastereoselective Reduction of α-Alkyl-β-keto Carbonitriles with $TiCl_4/BH_3$ or $LiBH_4/CeCl_3$ to *syn*- or *anti*-α-Alkyl-β-hydroxy Carbonitriles

Renato Dalpozzo,*[a] Giuseppe Bartoli,[a] Marcella Bosco,[b] Antonio De Nino,[a] Antonio Procopio,[a] Letizia Sambri,[b] and Antonio Tagarelli[a]

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α-Alkyl-β-keto carbonitriles can be reduced stereoselectively to *syn*- and *anti*-α-alkyl-β-hydroxy carbonitriles. The stereoselectivity can be explained in terms of properties of the Lewis acid employed. $TiCl_4$ in noncoordinating solvents such as dichloromethane, followed by reduction with the borane/pyridine complex, predominantly led to the *syn*-α-alkyl-β-hydroxy carbonitriles, according to a chelate transition state, whereas $CeCl_3$ in coordinating solvents such as THF, followed by reduction with $LiBH_4$, predominantly led to the *anti*-isomers, in agreement with an open-chain transition state. The reduction to *syn*-α-alkyl-β-hydroxy carbonitriles is the first general preparation of these compounds.

Introduction

The achievement of new protocols for the diastereoselective synthesis of β-hydroxy carbonitriles undoubtedly represents an important goal in organic chemistry,[1] since the cyano group is a versatile precursor of both amino and carbonyl groups, although general and efficient methodologies are not widely available.

One of the most direct approaches to these compounds is the generally *anti*-selective aldol reaction between lithium nitriles and aldehydes. Nevertheless, good *anti*-selectivities are obtained only with sterically hindered aldehydes, while a dramatic selectivity decrease is observed with straight chain aldehydes.[2−4] Addition of dry cerium(III) chloride has been found to enhance diastereoselectivity, but the reaction is restricted to aromatic and unsaturated aldehydes.[5] In both these methodologies, however, unexpected reversed diastereoselectivity is observed with some alkyl nitriles. Other kinds of approaches such as Reformatsky-type reactions are limited in scope and are poorly selective.[6−10]

An HMPA-promoted retro-aldol reaction between lithiated 1-naphthylacetonitrile and aromatic aldehydes mostly leads, in turn, to *syn*-selective β-hydroxy carbonitrile formation; however, this method cannot be considered to be widely applicable, since thermodynamic control governs the stereochemical outcome of the reaction.[11]

Another easy access to β-hydroxy carbonitriles seems to be the direct reduction of β-keto carbonitriles. In recent years, a great deal of work has been devoted to the diastereoselective reduction of functionalized ketones that have a stereogenic center near to the prochiral carbonyl group.[12] In particular we found that in the reduction of α-alkyl-β-hydroxy ketones,[13] β-diketones,[14] α-alkyl-β-keto sulfones,[15] -phosphane oxides[16] and -esters,[17] a pivotal role is played by the Lewis acid; *syn* selectivity was observed when $TiCl_4$ was employed: titanium chelation power increase with decreasing ability of the solvent to coordinate so allowing the reduction with boranes to occur from the less-hindered face of this chelate. On the contrary, *anti*-selectivity was observed in reductions with boron hydrides and anhydrous $CeCl_3$ in coordinating solvents which avoid chelation of cerium, by an open-chain Felkin−Ahn model pathway.

We thought to extend these widely applicable methodologies to α-alkyl-β-keto carbonitriles, to set up two protocols for a new highly diastereoselective entry to *syn*- and *anti*-α-alkyl-β-hydroxy carbonitriles. Until now, this reaction has been studied only by employing KBH_4 as the reducing agent. The reaction proceeds with poor to moderate *syn*-selectivity depending on the bulkiness of the α-alkyl group.[18] On the other hand, bakers' yeast reduction has high *syn*-selectivity only with an aromatic substituent in the α-position, while the *syn*/*anti* ratio is about 1:1 in all other cases.[19]

Results and Discussion

Synthesis of *syn*-α-Alkyl-β-hydroxy Carbonitriles

As mentioned above, the protocol for *syn*-selective reduction of functionalized ketones is now well-documented,[13−17] therefore we examined the reduction of 2-phenyl-3-oxobutanenitrile (**1a**) under those experimental conditions. A borane/pyridine complex was dropped into a mixture of α-alkyl-β-keto carbonitrile and titanium(IV) chloride at −78 °C in a noncoordinating solvent. The reaction was carried out in the presence of an excess of reducing agent ranging from 1.1 to 3 equivalents with respect to **1a**

[a] Dipartimento di Chimica, Università della Calabria, Ponte Bucci, 87030 Arcavacata di Rende (Cs), Italy
Fax: (internat.) +39-098/449-2044
E-mail dalpozzo@unical.it
[b] Dipartimento di Chimica Organica 'A. Mangini', Università di Bologna, viale Risorgimento 4, 40136 Bologna, Italy

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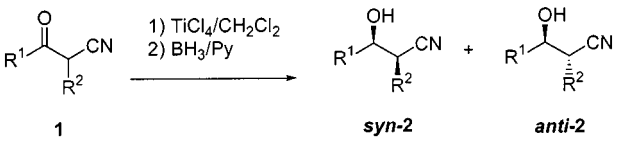
Table 1. Reduction of α-alkyl-β-keto carbonitriles in the presence of titanium(IV) chloride (1.5:1 molar ratio) in dichloromethane at −78 °C for 2 h



Entry	β-Keto carbonitrile	R^1	R^2	Reductant[a]	Product	Yield [%]	*syn*/*anti* ratio[b]
1	**1a**	Me	Ph	BH_3/py[c]	**2a**	15[d]	50:50
2	**1a**	Me	Ph	$LiBH_4$[c]	**2a**	43[e]	55:45
3	**1a**	Me	Ph	$LiBH_4$	**2a**	37 [e]	54:46
4	**1a**	Me	Ph	$LiB(Et)_3H$	**2a**	0[f]	
5	**1a**	Me	Ph	BH_3/py	**2a**	69	94:6
6	**1b**	Et	Ph	BH_3/py	**2b**	65	> 98:2
7	**1c**	iPr	Ph	BH_3/py	**2c**	67	>98:2
8	**1d**	*t*Bu	Ph	BH_3/py	**2d**	61	92:8
9	**1e**	Ph	Me	BH_3/py	**2e**	62	77:23
10	**1f**	Ph	Pr	BH_3/py	**2f**	77	80:20
11	**1g**	Ph	iPr	BH_3/py	**2g**	70	89:11

[a] 1.5:1 molar ratio with respect to nitrile. − [b] The *syn*/*anti* ratio was determined by NMR analysis of the crude mixture and re-determined after chromatography, without modifications. The diastereoisomers can be separated by preparative TLC provided at least 10% of the minor isomer is present. − [c] Carried out without Lewis acid. − [d] 74% starting material was also recovered. − [e] After 5 h. − [f] After 2 h, only starting material was recovered. Overnight at room temperature, only phenylacetonitrile was recovered.

and monitored at various times by GC/MS analysis. We found that under the above conditions the cyano group can also be reduced. However, this process is much slower than the reduction of the carbonyl function.

A two-hour reaction time and a 1:1.5 **1a:**BH_3-py ratio were found to be the best compromise to have complete reduction of the starting ketone moiety and very negligible reduction of the nitrile function. In fact, under these conditions, 3-hydroxy-2-phenylbutanenitrile (**2a**) was obtained in 69% yields and with excellent diastereoselectivity (*syn*/*anti* ratio = 94:6) (Table 1).[20,21]

This procedure was found to be efficient for the reduction of a large variety of keto carbonitriles. In fact, compounds with aromatic, primary, secondary or tertiary carbon chains undergo reduction to the corresponding *syn*-hydroxy carbonitrile in satisfactory yields with good to excellent selectivity (Table 1).

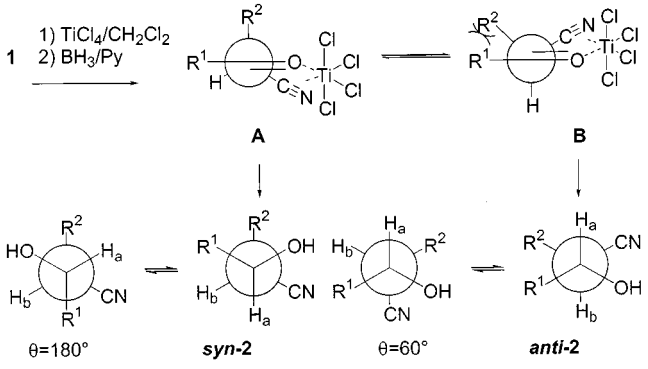
However, this methodology is not efficient for the preparation of *syn*-amino alcohols, since too long reaction times are required and decomposition phenomena can occur in the presence of a large excess of BH_3-py. Furthermore, after quenching the large amounts of pyridine present do not allow the amino alcohols to be purified.

$TiCl_4$ allows the reaction to be carried out in a shorter time and with better stereoselectivity. In fact, from the reduction of **1a** under the same conditions, but without $TiCl_4$, starting material in 74% yield and alcohols **2a** in 15% yield (diastereoisomeric ratio 1:1) were recovered (Table 1, entry 1).

When the classical BH_3-py-$TiCl_4$ procedure failed, we tested other reducing agents that had already been used previously under various reaction conditions, in order to improve yields and selectivity. The $LiBH_4$-$TiCl_4$ reducing system in THF, for example, was found to be efficient for the selective reduction of β-keto phosphane oxides.[16] However, in the case of keto carbonitrile **1a**, the use of $LiBH_4$ alone or with $TiCl_4$ requires longer reaction times with a dramatic decrease in selectivity (Table 1, entry 2, 3). In addition, more reactive and sterically hindered reagents, such as Super-Hydride®, do not work at −78 °C. It is probable that this basic reagent prefers proton abstraction rather than reduction processes.

The observed stereochemical course suggests a prevalent $TiCl_4$-induced chelation-controlled mechanism in good agreement with the previously observed outcome of closely related systems (Scheme 1).[13−17,22]

In the chelation model the steric interactions between R^1 and R^2 groups favor conformation **A** (Scheme 1). The diastereoselective trend observed when R^2 = alkyl is in good



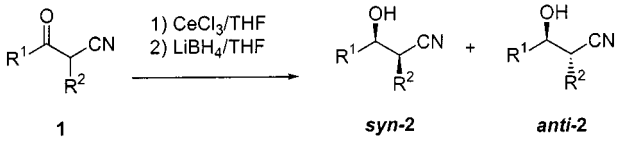
Scheme 1

agreement with this model. In fact, increasing the steric hindrance of R^2 means that the steric interactions destabilize conformation **B** and, as a consequence, the diastereoselectivity must increase (Table 1, entries 9−11). However, it should be noted that in the present system the chelation power of titanium is obviously lowered because of the linear shape of the nitrile function; in other words, conformer **A** cannot assume a rigid half-chair structure. For this reason, the observed level of diastereoselectivity is lower than in other systems with a more adequate structural arrangement, such as β-keto phosphane oxides,[16] β-keto esters,[17] β-keto sulfones,[15] and α-nitroketones.[22]

Synthesis of *anti*-α-Alkyl-β-hydroxy Carbonitriles

We carried out this reaction under the classical conditions adopted for the reduction of various functionalized ketones:[15−17] a THF solution of $LiBH_4$ was dropped into the mixture of α-alkyl-β-keto carbonitriles and dry $CeCl_3$ at −78 °C. The reaction was stirred at this temperature for two hours and then quenched with 10% aqueous HCl. The usual workup afforded the *anti*-**2** isomer as the major product (Table 2). In the absence of $CeCl_3$ the reaction rate is lowered (50% conversion after 3 h). Interestingly, without cerium chloride the *syn* isomer prevails over the *anti* isomer, and the diastereoisomeric ratio (*syn*/*anti* ratio, 54:46) is similar to that reported in Table 1, entry 3. Good yields were generally obtained since, in this case, the reduction of the cyano group was negligible. The reactions proceeded with good diastereoselectivity except when the α-alkyl substituent was an α-branched framework. Other reducing agents such as L-selectride® or Super-Hydride® were employed in conjunction with $CeCl_3$ but they did not work at all, or only retro-aldol products were recovered.

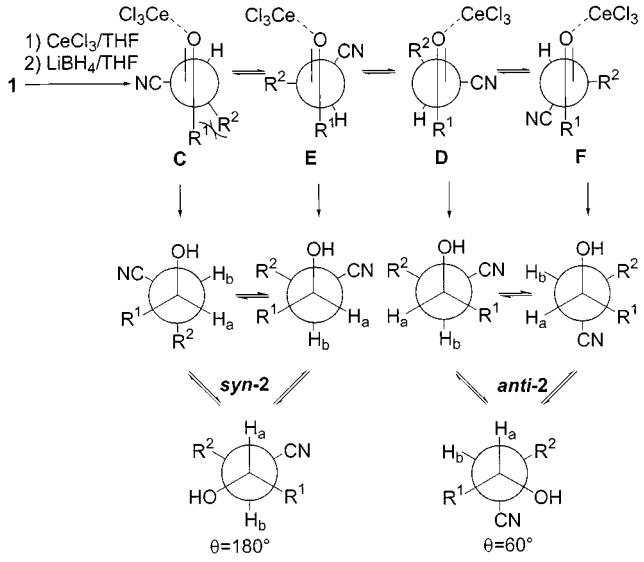
Table 2. Reduction of α-alkyl-β-keto carbonitriles with lithium borohydride (1.5:1 molar ratio) in the presence of cerium(III) chloride (1.5:1 molar ratio) in THF at −78 °C for 2 h



Entry	β-Keto carbonitriles	R^1	R^2	Product	Yield [%]	*syn*/*anti* ratio[a]
1	**1a**	Me	Ph	**2a**	75	15:85
2	**1b**	Et	Ph	**2b**	67	37:63
3	**1c**	iPr	Ph	**2c**	79	<2:98
4	**1d**	*t*Bu	Ph	**2d**	81	17:83
5	**1e**	Ph	Me	**2e**	67	14:86
6	**1f**	Ph	Pr	**2f**	45	20:80
7	**1g**	Ph	iPr	**2g**	68	48:52
8	**1h**	*t*Bu	Pr	**2h**	76	<2:98

[a] The *syn*/*anti* ratio was determined by NMR analysis of the crude mixture and re-determined after chromatography, without modifications. The diastereoisomers can be separated by preparative TLC provided at least 10% of the minor isomer is present.

In analogy to our previous interpretation in closely related systems,[15−17] we justified the observed stereochemical outcome by assuming that the reductions follow a Felkin−Ahn pathway. In such a mechanism four conformations can be proposed where the orthogonal position to the carbonyl function is occupied by the most electronegative group (in this case the cyano group) or by the most encumbered alkyl R^2 group: **C** and **D** or **E** and **F** conformations, respectively. The attack of the hydride at the **D** and **F** conformations, or at the **C** and **E** ones, from the less-hindered side gives the *anti*- and *syn*-isomers, respectively (Scheme 2).



Scheme 2

When R^2 = Ph, the lowest electron repulsion arises in the **C** and **F** conformations, where the π-clouds of the nitrile and phenyl frameworks are far from the carbonyl moiety. In such an arrangement, the steric repulsions between the R^1 and R^2 groups must disfavor the **C** conformation over the **F** conformation with increasing bulkiness of R^1. The results reported in entries 1−3 of Table 2 are in agreement with this interpretation. When R^2 = Ph and R^1 = *t*Bu (Table 2, entry 4), however, the *anti* selectivity is lowered considerably. A possible explanation could be that the highly symmetrical *tert*-butyl group cannot rotate around a C−C bond to have a hydrogen atom near to the cyano group, as an isopropyl group, for instance, can. Conformation **E**, where the small hydrogen atom is near to the bulky *tert*-butyl group thus becomes more populated, increasing the formation of *syn*-isomer. In fact, the spatial arrangement of the substituents in conformations **A** and **E** is the same, the only difference being the presence of different Lewis acids.

When R^1 = Ph, the increase in the bulkiness of R^2 causes a dramatic decrease in stereoselectivity; in fact, when R^2 becomes large it can compete with the cyano group in as-

suming the less-hindered orthogonal position as in conformation **E** (Table 2, entries 5−7). The corresponding conformation **F** is disfavored by electronic repulsions between the π-clouds of the cyano and phenyl frameworks.

Finally, when both substituents are alkyl chains (Table 2, entry 8), and in particular when R^1 is the very encumbered *tert*-butyl group, both the **C** and **E** conformations leading to the *syn*-isomer are disfavored by steric or electronic repulsions, respectively.

These results agree with those previously observed in the $CeCl_3$-mediated reduction of β-keto phosphane oxides.[16] In addition they are also in agreement with Canceill's explanation[18] of the stereochemical outcome shown in the reduction of the same substrates with potassium borohydride. In fact, both reactions show an increase in *syn*-selectivity by increasing the bulkiness of the R^2 group. In our opinion, the higher proportion of *syn*-isomer observed by Canceill can easily be accounted for by considering that the reductions with KBH_4 were carried out in methanol at room temperature: it has been demonstrated that the *syn*/*anti* ratio is strongly influenced by the polarity of the solvent and by the reaction temperature.[16] The same differences in stereoselectivity were already observed by comparing the results arising from the reduction of β-keto phosphane oxides in THF with $LiBH_4$ at −78 °C[16] with the ones in MeOH with $LiBH_4$ at room temperature.[23]

The present results confirm the hypothesis that cerium(III) salts in the presence of reducing agents cannot undergo chelation in a coordinating solvent such as THF, which is in contrast to alkylcerium reagents which are able to give chelate complexes.[24] The $CeCl_3$-mediated reduction of a large variety of bidentate compounds in THF shows a stereochemical outcome which is properly interpreted in terms of an open-chain mechanism.

Conclusions

In conclusion, both protocols previously proposed for the *syn*- and *anti*-reduction of various classes of functionalized ketones can be successfully applied to β-keto carbonitriles, thus offering a straightforward approach to the synthesis of both *syn*- and *anti*-α-alkyl-β-hydroxy carbonitriles, a key entry point to many β-functionalized alcohols. The synthetic value of this procedure relative to the use of *syn*-hydroxy carbonitriles is noteworthy in the absence of an alternative efficient methodology. In fact, the present protocol shows a general applicability that is not restricted to substrates that have both the R^1 and R^2 substituents as aromatic groups.

Experimental Section

General: ^1H NMR spectra were recorded at 300 MHz in $CDCl_3$ solution using tetramethylsilane as internal standard. Chemical shifts are given in ppm and coupling constants in Hz. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ (δ = 77.05) as reference. Total ion chromatograms and mass spectra were recorded with a Hewlett−Packard 5975 workstation. All reaction were performed in flame-dried glassware under a positive pressure of nitrogen and stirred magnetically. Starting α-alkyl-β-keto carbonitriles were synthesized from lithiated (by means of LTMP) commercial phenylacetonitrile, propionitrile, valeronitrile and isovaleronitrile, and the corresponding commercial esters at 0 °C. Other reagents are commercially available (Aldrich) and were used without purification. Solvents were dried before use: CH_2Cl_2 by distillation over calcium hydride and THF by double distillation over sodium wire and sodium/benzophenone.

Reduction of α-Alkyl-β-keto Carbonitriles 1 Mediated by Titanium Tetrachloride: $TiCl_4$ (7.5 mmol, 1 M solution in CH_2Cl_2) was added to a cold (−30 °C) solution of **1** (5 mmol) in 15 mL of dry CH_2Cl_2. The mixture was stirred for 1 h at this temperature, before cooling to −78 °C. The complex BH_3/py (7.5 mmol in 1 mL of dry CH_2Cl_2) was then added. The mixture was allowed to stir for an additional 2 h and then 10% aqueous HCl was added dropwise and the reaction mixture warmed to room temperature. The crude product was extracted with CH_2Cl_2, which was then dried over Na_2SO_4 and the resulting solution concentrated under reduced pressure. Flash column chromatography (eluent light petroleum/diethyl ether, 9:1) gave diastereoisomeric mixtures of *syn*- and *anti*-α-alkyl-β-hydroxy carbonitriles: **2a** (0.298 g, 37% from $LiBH_4$; 0.555 g, 69% from BH_3/py); **2b** (0.569 g, 65% of essentially pure *syn*-isomer); **2c** (0.633 g, 67% of essentially pure *syn*-isomer); **2d** (0.619 g, 61%); **2e** (0.499 g, 62%); **2f** (0.728 g, 77%); **2g** (0.661 g, 70%). The ratios are reported in Table 1. The pure diastereoisomers can be obtained by preparative TLC of the pure diastereomeric mixture (eluent light petroleum/diethyl ether, 95:5).

Experiments with different reducing agents were carried out with the same procedure described above and for the reaction times reported in Table 1.

A reduction of **1a** was monitored every 2 h for 12 h, and then again after 24 h. The GC/MS chromatogram showed always the same isomeric ratio for compounds **2a**. After 6 h two more peaks in the same isomer ratio appeared. The fragmentation patterns of these new peaks were in agreement with amino alcohols from complete reduction. Quenching of the mixture either with 10% HCl or with NH_4Cl_{sat} did not allow separation of the products from pyridine. Quenching with $NaHCO_3$ did not allow the product to be recovered from the organic layer.

Reduction of α-Alkyl-β-keto Carbonitriles 1 Mediated by Anhydrous Cerium Trichloride: A THF solution (10 mL) of **1** (5 mmol) was added dropwise at −30 °C to a suspension of dry $CeCl_3$,[25] and stirring was continued for 1 h. The mixture was then cooled to −78 °C and a commercial THF solution of $LiBH_4$ (7.5 mmol) added. Stirring was continued for 2 h, then 10% aqueous HCl added dropwise and the reaction warmed to room temperature. The crude reaction mixture was extracted with CH_2Cl_2, which was then dried over Na_2SO_4 and the resulting solution concentrated under reduced pressure. Flash column chromatography (eluent: light petroleum/diethyl ether, 9:1) gave diastereoisomeric mixtures of *syn*- and *anti*-α-alkyl-β-hydroxy carbonitriles: **2a** (0.603 g, 75%); **2b** (0.586 g, 67%); **2c** (0.746 g, 79% of essentially pure *anti*-isomer); **2d** (0.822 g, 81%); **2e** (0.539 g, 67%); **2f** (0.425 g, 45%); **2g** (0.642 g, 68%); **2h** (0.642 g, 76% of essentially pure *anti*-isomer). Ratios are reported in Table 2. The pure diastereoisomers can be obtained by preparative TLC (eluent light petroleum/diethyl ether, 95:5) of the pure diastereomeric mixture.

Compound Characterization: *syn*- and *anti*-3-Hydroxy-2-phenylbutanenitrile (**2a**),[19] 3-hydroxy-2-phenylpentanenitrile (**2b**),[9] 4,4-dimethyl-3-hydroxy-2-phenylpentanenitrile (**2d**),[25] 3-hydroxy-2-methyl-3-phenylpropanenitrile (**2e**)[18] 3-hydroxy-2-(1-methylethyl)-3-phenylpropanenitrile (**2g**)[18] were identified by comparison with literature data. The *syn*- and *anti*-configurations were assigned according to the H_a and H_b coupling constants[20] reported in Table 3.

Table 3. Comparison of coupling constants of *syn*- and *anti*-α-alkyl-β-hydroxy carbonitriles

Entry	Product	R^1	R^2	$J_{ab\text{-}syn}$	$J_{ab\text{-}anti}$
1	**2a**	Me	Ph	5.38	5.12
2	**2b**	Et	Ph	6.12	5.01
3	**2c**	iPr	Ph	8.11	4.91
4	**2d**	*t*Bu	Ph	7.35	6.46
5	**2e**	Ph	Me	6.65	5.83
6	**2f**	Ph	Pr	6.14[a]	6.14[b]
7	**2g**	Ph	iPr	8.91	7.36
8	**2h**	*t*Bu	Pr	7.02	1.21

[a] J_{cis} = 2.0 Hz for the carbamate from cyclisation of the *syn*-amino alcohol with triphosgene.[2a] – [b] J_{trans} = 7.7 Hz for the carbamate from cyclisation of the *anti*-amino alcohol with triphosgene.[2a]

3-Hydroxy-4-methyl-2-phenylpentanenitrile (2c, *syn*/*anti*-mixture): MS: *m*/*z* (%) = 170 (0.1) [M^+ – 19], 156 (0.2), 129 (1), 117 (100), 90 (12), 77 (3), 73 (6). – $C_{12}H_{15}NO$ (189.26): C 76.16, H 7.99, N 7.40; found C 76.20, H 8.05, N 7.40 (from reaction with $TiCl_4/BH_3$/py); C 76.10, H 8.00, N 7.35 (from reaction with $CeCl_3/LiBH_4$).

***syn* Isomer:** ^{1}H NMR ($CDCl_3$): δ = 1.01 (d, *J* = 6.50, 3 H, 4-Me), 1.04 (d, *J* = 6.15, 3 H, 4-Me), 1.97 (d, *J* = 5.10, 1 H, OH), 1.99–2.10 (m, 1 H, 4-H), 3.69–3.76 (m, 1 H, 3-H), 3.79 (d, *J* 8.11, 1 H, 2-H), 7.30–7.40 (m, 5 H, ArH). – ^{13}C NMR ($CDCl_3$): δ = 15.2 (Me), 19.9 (Me), 30.9 (C-4), 42.2 (C-2), 77.7 (C-3), 119.4 (C-1) 129.0 (CH-Ar), 129.1 (CH-Ar), 129.5 (CH-Ar), 133.1 (C-Ar).

***anti* Isomer:** ^{1}H NMR ($CDCl_3$): δ = 1.00 (d, *J* = 6.70, 6 H, 4-Me), 1.73–1.86 (m, 1 H, 4-H), 2.57 (br. s, 1 H, OH), 3.50 (dd, *J* = 6.60, 4.91, 1 H, 3-H), 3.98 (d, *J* = 4.91, 1 H, 2-H), 7.30–7.40 (m, 5 H, ArH). – ^{13}C NMR ($CDCl_3$): δ = 17.3 (Me), 19.3 (Me), 31.4 (C-4), 42.7 (C-2), 78.7 (C-3), 118.9 (C-1) 128.0 (CH-Ar), 128.6 (CH-Ar), 129.0 (CH-Ar), 133.6 (C-Ar).

3-Hydroxy-3-phenyl-2-propylpropionitrile (2f, *syn*/*anti*-mixture): MS: *m*/*z* (%) = 189 (0.1) [M^+], 146 (0.2), 128 (0.5), 115 (1), 107 (100), 79 (60), 51 (12). – $C_{12}H_{15}NO$: C 76.16, H 7.99, N 7.40; found C 76.20, H 7.95, N 7.35 (from reaction with $TiCl_4/BH_3$/py); C 76.15, H 8.00, N 7.35 (from reaction with $CeCl_3/LiBH_4$).

***syn* Isomer:** ^{1}H NMR ($CDCl_3$): δ = 0.90 (t, *J* = 7.00, 3 H, Me), 1.30–1.60 (m, 4 H, CH_2CH_2), 2.88–3.02 (m, 1 H, 2-H), 3.19 (br. s, 1 H, OH), 4.79 (d, *J* = 6.14, 1 H, 3-H), 7.20–7.40 (m, 5 H, ArH). – ^{13}C NMR ($CDCl_3$): δ = 13.4 (Me), 20.3 (CH_2), 29.8 (CH_2), 40.1 (C-2), 73.5 (C-3), 120.1 (C-1) 126.1 (CH-Ar), 126.4 (CH-Ar), 128.5 (CH-Ar), 140.1 (C-Ar).

***anti* Isomer:** ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 7.00, 3 H, Me), 1.35–1.65 (m, 4 H, CH_2CH_2), 2.73–2.84 (m, 1 H, 2-H), 3.00 (br. s, 1 H, OH), 4.74 (d, *J* = 6.14, 1 H, 3-H), 7.20–7.40 (m, 5 H, ArH). – ^{13}C NMR ($CDCl_3$): δ = 13.3 (Me), 20.2 (CH_2), 30.8 (CH_2), 40.7 (C-2), 73.6 (C-3), 104.0 (C-1) 126.1 (CH-Ar), 128.4 (CH-Ar), 128.5 (CH-Ar), 140.5 (C-Ar).

syn- and *anti*-**2f** were distinguished by complete reduction with $AlCl_3/LiAlH_4$ and cyclization of the mixture arising from both reduction methods with triphosgene according to Carlier's procedure.[2–4,11] The range δ = 5–7 of the ^{1}H NMR spectrum contains only doublets, which can be attributed to the C*H*O atom in the same ratio as reported in Table 1 and 2. We attributed the doublet with the typical axial-equatorial coupling constant (2.0 Hz) to the *syn*-configuration and the doublet with the typical axial-axial coupling constant (7.7 Hz) to the *anti*-configuration.

***anti*-3-Hydroxy-2-propyl-4,4-dimethylpentanenitrile (2h):** m.p. 64–65 °C. – ^{1}H NMR ($CDCl_3$): δ = 0.97 (t, *J* = 7.17, 3 H, Me), 1.01 (s, 9 H, Me_3C), 1.30–1.70 (m, 3 H, CH_2C*H*-H), 1.91 (ddt, *J* = 10.00, 9.60, 7.60, 1 H, CH_2CH-*H*), 2.43 (br. s, 1 H, OH), 2.75 (ddd, *J* = 9.60, 4.44, 1.21, 1 H, 2-H), 3.23 (d, *J* = 1.21, 1 H, 3-H). – ^{13}C NMR ($CDCl_3$): δ = 13.4 (Me), 20.3 (CH_2), 25.9 (Me_3), 33.4 (CH_2), 34.2 (C-2), 35.6 (C), 79.1 (C-3), 120.5 (C-1). – MS: *m*/*z* (%) = 154 (1) [M^+ – 15], 87 (58), 86 (70), 71 (15), 69 (19), 57 (100), 54 (20), 41 (30). – $C_{10}H_{19}NO$ (169.27): C 71.00, H 11.24, N 8.28; found C 71.15, H 11.20, N 8.30.

[1] See for example: [1a] M. H. Seo, Y. Y. Lee, Y. M. Goo, *Synthetic Comm.* **1994**, *20*, 1433–1439. – [1b] P. A. Wade, J. F. Bereznak, *J. Org. Chem.* **1987**, *52*, 2973–2977.

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[20] The *syn*- and *anti*-configurations were assigned according to well-established, previously reported studies, affirming that in the most-stable conformation of both isomers, the R^1 and R^2 groups should be in an antiperiplanar relationship (Schemes 1 and 2).[3,11,17] In this conformation the 2,3-*anti*-isomer will have an H–C–C–H dihedral angle (θ) of approximately 60°, giving rise to a small coupling constant. On the other hand, in the 2,3-*syn*-relationship, a dihedral angle of θ·= 180° gives rise to a large coupling constant (Table 3). Only when R^2 = propyl

are the two coupling constants very similar; the configurational assignment was then attributed as described in the Exp. Sect.
[21] Partial decomposition during reduction did not affect the diastereoisomeric ratio. In fact, monitoring a reduction of **1a**, the 94:6 ratio is maintained throughout the reaction by both signals of **2a** and two more peaks (whose fragmentation is in agreement with amino alcohols from complete reduction). At the end of the reaction, when the chromatographic peaks of **1a** disappeared, the two remaining ones still showed a 94:6 ratio.
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