Attempted enantiotopic group selective cyanohydrin formation from α-alkoxy aldehydes by double stereodifferentiation

Dale E. Ward, Marcelo Sales, and Matthew J. Hrapchak

Abstract: Enantiotopic group selectivity can result from the competition between substrate and reagent double stereodifferentiation. We have examined this approach for enantioselective hydrocyanation of racemic α-alkoxy aldehydes (e.g., 2-(phenylmethoxy)heptanal (**1**)). Reaction of **1** with TMSCN mediated by chiral nonracemic alkoxy Ti(IV) reagents under conditions known to be reasonably enantioface selective in reactions with achiral aldehydes, proceeded with very low enantiotopic group selectivity (<2:1). It was established that TMSCN can react with Ti(IV) reagents to produce "TiCN" adducts that are capable of hydrocyanation but with low substrate-controlled diastereoselectivity in reactions with **1**. The poor enantiotopic group selectivity observed can be rationalized to result from this low diastereoselectivity despite the respectable levels of enantioface selectivity associated with these reagents in hydrocyanation of achiral aldehydes. Highly diastereoselective hydrocyanation of α-alkoxy aldehydes can be achieved with TMSCN in the presence of excess $MgBr_2 \cdot OEt_2$. High diastereoselectivity was also observed using achiral and chiral TiCN adducts in place of TMSCN. Although the putative TiCN adducts obtained from nonracemic alkoxy Ti(IV) reagents are implicated in enantioface selective hydrocyanation, these reagents were not enantiotopic group selective under these conditions and showed no evidence of double stereodifferentiation. The use of nonracemic bisoxazoline ligands for Mg(II) was also ineffective.

Key words: cyanohydrin, 2-alkoxyalkanal, double stereodifferentiation, enantiotopic group selective reaction, kinetic resolution.

Résumé : La sélectivité énantiotopique de groupe peut découler d'une compétition entre la stéréodifférenciation double entre le substrat et le réactif. On a examiné cette approche pour l'hydrocyanuration énantiosélective d'α-alkoxyaldéhydes racémiques (par exemple, le 2-(phénylméthoxy)heptanal (**1**)). Lors de la réaction avec le TMSCN, sous l'influence de réactifs chiraux non racémiques de type alkoxy Ti(IV), dans des conditions reconnues pour être énantiosélectives au cours de réactions avec les faces d'aldéhydes achiraux, la sélectivité énantiotopique de groupe était très faible (< 2:1). Il a été établi que le TMSCN peut réagit avec les réactifs du Ti(IV) pour conduire à la production d'adduits "TiCN" qui, lors de réactions avec le composé **1**, peuvent donner lieu à une hydrocyanuration pour laquelle la diastéréosélectivité contrôlée par le substrat est faible. On peut imaginer que la faible sélectivité énantiotopique de groupe observée résulte de cette faible diastéréosélectivité malgré les niveaux respectables de énantiosélectivité par rapport aux faces qui sont associées à ces réactifs dans l'hydrocyanuration d'aldéhydes achiraux. On peut réaliser des hydrocyanurations hautement diastéréosélectives d'α-alkoxyaldéhydes à l'aide de TMSCN, en présence d'un excès de $MgBr_2 \cdot OEt_2$. On a aussi observé une diastéréosélectivité lorsqu'on a utilisé des adduits TiCN achiraux et chiraux à la place du TMSCN. Les adduits TiCN présumés, obtenus à partir de réactifs non racémiques de type alkoxy Ti(IV), sont impliqués dans des hydrocyanurations énantiosélectives par rapport aux faces; toutefois, dans ces conditions, ces réactifs ne donnent pas lieu à de la sélectivité énantiotopique de groupe et ne présentent pas de signe de double stéréodifférenciation. L'utilisation de ligands bisaxozolines non racémiques pour des composés de type Mg(II) est aussi inefficace.

Mots clés : cyanohydrine, 2-alkoxyalcanal, double stéréodifférenciation, réaction avec sélectivité énantiotopique de groupe, dédoublement cinétique.

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This paper is dedicated to Professor Victor Snieckus in celebration of his numerous contributions to chemistry and to the chemistry community in Canada.

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Introduction

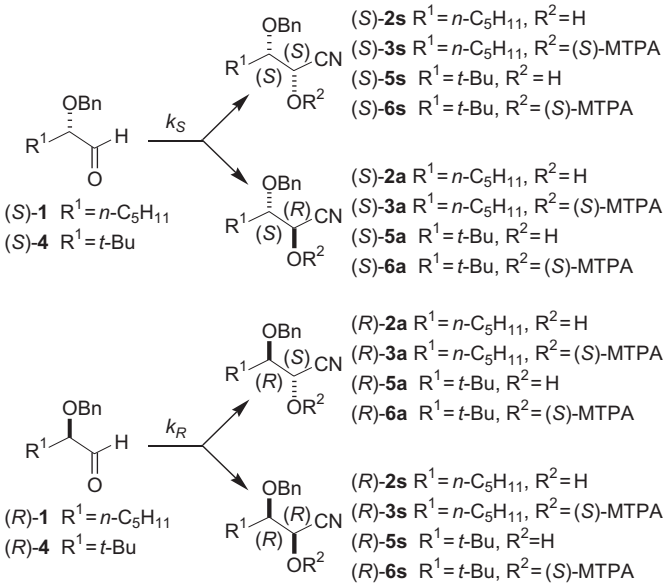
The development of new methods for asymmetric synthesis continues to attract considerable attention (1). Although the majority of known methods involve enantioselective addition to a π-bond of an achiral substrate (i.e., an enantiotopic face selective reaction), the use of enantiotopic group selective reactions for desymmetrization of achiral C_s (or C_i) symmetric substrates has recently emerged as an alternative strategy (2). This approach is particularly effective when the enantiotopic groups can react sequentially thereby coupling an asymmetric synthesis with a kinetic resolution and producing products with high stereoisomeric purity (3). We have previously shown that such processes can yield products with very high stereoisomeric purity from reactions with modest enantioselectivity (4) and even from mixtures of substrate stereoisomers (5). Both the efficiency and efficacy of these processes are improved with recycling, especially if the enantioselectivity is modest (4, 5). Because recycling requires that the product(s) (or byproducts) be efficiently converted back into the starting material(s), enantiotopic group selective reactions that are easily "reversed" are desirable. We have previously targeted enantioselective reduction of chiral aldehydes (reversed by oxidation of the product alcohols) (4) and enantioselective enolization (reversed by protonation of the enolate derivative) (6) as reactions for development. The potential for stereoselective formation of cyanohydrins from aldehydes (vide infra) and the facile loss of HCN from such cyanohydrins prompted us to examine enantiotopic group selective cyanohydrin formation from α-alkoxy aldehydes.

Few design elements are available to guide the development of enantiotopic group selective reactions and many of the successful examples (2) involve application of previously established "reagent-controlled" enantioface selective reactions to chiral[2] or C_s symmetric substrates that impart significant "substrate-controlled" diastereoface selectivity (7).[3] In such cases, enantiotopic group selectivity can be rationalized to result from the matching and mismatching of substrate diastereotopic face selectivity with reagent enantiotopic face selectivity (4, 8, 9). The magnitude of the enantiotopic group selectivity (E) can be estimated from eq. [1] where **r** is the enantiotopic face selectivity associated with the chiral reagent acting on a "model" achiral substrate and **s** is the diastereotopic face selectivity of the chiral substrate with a model achiral reagent (4, 9).[4]

$$[1] \qquad E = \frac{(\mathbf{r})(\mathbf{s}) + 1}{\mathbf{r} + \mathbf{s}}$$

The stereoselective formation of cyanohydrins from aldehydes dates back to the late 19th century when Emil Fischer reported that addition of HCN to L-arabinose gave a 2:1 mixture of cyanohydrins in favor of the *manno* (i.e., 2,3-*anti*) diastereomer (10). Subsequently, this reaction has proven to be quite useful for the chain extension of monosaccharides (11). Cyanohydrins are generally recognized as versatile synthetic intermediates for the preparation of a variety of useful compounds (12, 13). As a consequence, the development of methods for enantioselective formation of cyanohydrins from achiral aldehydes has attracted considerable attention (13) and several highly enantioselective methods using chiral Lewis acid catalysts have been reported recently (14). By contrast, cyanohydrins are often formed with poor diastereoselectivity from chiral aldehydes (15), even in enzyme-mediated processes (16). For example, diastereoselectivities of only 1.5–5:1 in favor of the *syn* isomer have been reported for cyanohydrin formation from α-alkoxy aldehydes using trimethylsilylcyanide (TMSCN) in the presence of various Lewis acids (17). Because the predicted selectivity (*E*) is limited by the lower of **r** and **s** (eq. [1]), the low substrate diastereoselectivity noted above suggested that cyanohydrin formation from α-alkoxy aldehydes would result in poor enantiotopic group selectivity even using methods with excellent enantioface selectivity. We now report several experiments which support this hypothesis and on our efforts to improve on the substrate diastereoselectivity in an attempt to achieve enantiotopic group selective cyanohydrin formation by double stereodifferentiation.

Scheme 1



Results and discussion

We selected the racemic α-alkoxy aldehydes **1** and **4** as substrates to investigate enantiotopic group selective cyanohydrin formation. Under the influence of a chiral nonracemic reagent or catalyst, the individual enantiomers of the aldehyde

[2] Enantiotopic group selective reaction of chiral substrates is equivalent to kinetic resolution. In this case, groups on enantiomeric substrates are enantiotopic by external comparison.

[3] For a discussion and definition of reagent- and substrate-controlled stereoselectivity, see ref. 8.

[4] The face selectivity for one group will be (**r**)(**s**):1 (i.e., "matched"); total reactivity is (**r**)(**s**) + 1. The face selectivity for the enantiotopic group will be (**r**):(**s**) (i.e., "mismatched"); total reactivity is (**r**) + (**s**). The accuracy of this estimation depends on the suitability of the models used for the determination of **r** and **s**. For a detailed discussion of the derivation, assumptions, and sources of error in the above multiplicativity rule, see ref. 8.

Table 1. Enantiotopic group selective hydrocyanation of **1** and **4** with TMSCN–(*i*-Pr-O)$_2$TiCl$_2$–TADDOL at –23°C.[a]

Entry	Aldehyde	Time (h)	(*C*)[b,c]	(*R*)-**2s**[c,d] (%)	(*R*)-**2a**[c,d] (%)	(*S*)-**2s**[c,d] (%)	(*S*)-**2a**[c,d] (%)	k_S/k_R[e]
1	**1**	1	0.31	27	10	42	21	2.0
2	**1**	3	0.68	33	11	39	16	1.5
3	**1**	8	0.87	35	12	37	17	1.6
4	**4**	3	0.71	20[f]	25[f]	43[f]	13[f]	1.5
5	**1**[g]	3	0.20	46	6	23	25	0.91

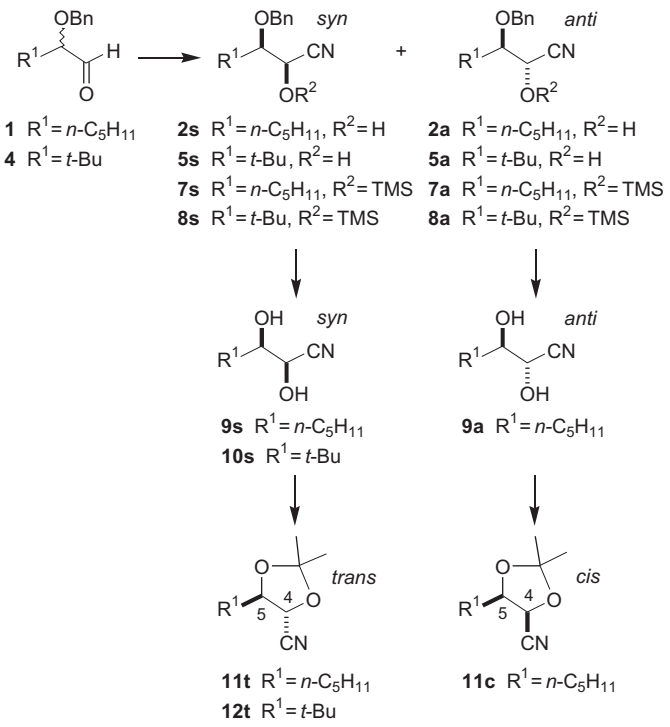
[a]Reagent preparation: TADDOL (1.5 equiv) was added to a toluene solution of (*i*-Pr-O)$_2$TiCl$_2$ (1.5 equiv) at room temperature. After 1 h, MS4A and TMSCN were added.
[b]Determined by ^{1}H NMR of the crude reaction mixture.
[c]Estimated relative error of ±10%.
[d]Determined by ^{1}H NMR of the corresponding Mosher's esters.
[e]Calculated according to footnote 5.
[f]Refers to cyanohydrins **6** (not **2**).
[g](+)-BINOL was used instead of TADDOL.

(e.g., **1**) should form cyanohydrins at different rates (i.e., a kinetic resolution) and with different diastereoselectivities to produce the four possible stereoisomeric products (e.g., (*R*)-**2a**, (*R*)-**2s**, (*S*)-**2a**, and (*S*)-**2s**) (18).

The relative amounts of the product stereoisomers from a reaction of low or known conversion can be used to calculate the relative rates of hydrocyanation of the individual substrate enantiomers (i.e., the enantiotopic group selectivity).[5] Alternatively, the enantiomeric purity of the recovered α-alkoxy aldehyde from a hydrocyanation reaction of known conversion can be used to determine the selectivity.[6] Thus, a method to analyze the composition of the four stereoisomeric cyanohydrins was required.

The relative stereochemical configurations of the cyanohydrins **2** and **5** were determined via NMR analysis of the derived acetonides (17*a*). Reaction of **1** with trimethylsilylcyanide (TMSCN) in the presence of Et_3N (19) gave **7** as a 2:1 mixture of racemic diastereomers in quantitative yield. Hydrolysis of **7** (a 2:1 mixture of diastereomers) with dilute acid gave a 2:1 mixture of cyanohydrins **2.** Alternatively, treatment of **7** with $TiCl_4$ gave the diols **9**, also as a 2:1 mixture of diastereomers, which produced a 2:1 mixture of acetonides **11**. The minor acetonide was assigned as *cis* (i.e., **11c**) on the basis of an 8% nOe observed for HC-5 upon irradiation of HC-4 (nOe was not observed between HC-4 and HC-5 in the major acetonide, **11t**); thus, the major cyanohydrin formed was assigned as the *syn* diastereomer **2s**. Similar processing of **4** gave a separable 3:1 mixture of cyanohydrins **5**; the major diastereomer was assigned as *syn* (i.e., **5s**) on the basis of an 18% nOe observed for HC-4 upon irradiation of the $(H_3C)_3C$ protons in the derived acetonide **12t**. A method for determining the absolute configurations of the four stereoisomers of **2** was established by conversion (20) of a 2.4:1 mixture of racemic **2s** and **2a**, respectively, to a 2.6:2.6:1:1 mixture of diastereoisomeric Mosher's esters (21) **3** in 88% yield from excess (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid [(*S*)-MTPA-OH].[7] Assignment of individual signals in the ^{1}H NMR spectrum of the mixture of esters to individual diastereomers was possible on the basis of intensity (i.e., major signals from *syn* diastereomers and minor signals from *anti* diastereomers), homonuclear decoupling experiments (i.e., identifying the pairs of HC-2–HC-3 and H_2CO signals for individual diastereomers), and application of the advanced Mosher's method (22).[8] The same strategy was successfully applied for analysis of the four stereoisomers of **6**.

Scheme 2.



[5]At low conversion, k_S/k_R (= *E*) is closely approximated by ([(*S*)-**2a**] + [(*S*)-**2s**])/([(*R*)-**2a**] + [(*R*)-**2s**]). At higher conversions (*C*) with product stereoisomeric excess (se = ([(*S*)-**2a**] + [(*S*)-**2s**] – [(*R*)-**2a**] – [(*R*)-**2s**])/([(*S*)–**2a**] + [(*S*)-**2s**] + [(*R*)-**2a**] + [(*R*)-**2s**])), $E = \{\ln (1 - C(1 + se)\}/\{\ln (1 - C(1 - se)\}$. For a discussion, see ref. 18.
[6]If the ee of recovered **1** is ([(*R*)-**1**] – [(*S*)-**1**])/([(*R*)-**1**] + [(*S*)-**1**]) at conversion *C*, then $k_S/k_R = E = \{\ln [(1 - C)(1 - ee)]\}/\{\ln [(1 - C)(1 + ee)]\}$. For a discussion, see ref. 18.
[7]A control experiment established that acetylation of **2** under these conditions occurred without loss of stereochemical integrity.
[8]This method predicts that for the (*S*)-MTPA esters **3** (and **6**), the HC-2 and H_2CO (and *t*-Bu) signals for the (1*S*) diastereomers will appear downfield relative to the (1*R*) diastereomers.

With an analytical method in place, we chose to examine cyanohydrin formation using TMSCN mediated by the chiral alkoxytitanium generated in situ by mixing (*i*-Pr-O)$_2$TiCl$_2$ and (2*R*,3*R*)-2,3-*O*-(1-phenylethylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol (**13**, TADDOL) in the presence of 4 Å molecular sieves (MS4A) as described by Narasaka and co-workers (23). Using this system, 3-phenylpropanal was reported to give the (*R*)-cyanohydrin in high yield and in 74–91% ee depending on the procedure employed. In our hands, the same cyanohydrin was obtained in >80% yield under the reported conditions but in only 60 ± 5% ee despite numerous attempts including using alternative methods (24) for preparing the precatalyst **14a**. Despite this modest result (i.e., 4:1 selectivity for addition of cyanide to the *si* face of the aldehyde), we attempted enantiotopic group selective hydrocyanation of **1** using the Narasaka reagent; the results are presented in Table 1.[9] Although the selectivity (i.e., k_S/k_R) was predictably low,[10] it was surprising that hydrocyanation of **1** occurred without evidence of double stereodifferentiation (8). That is, the cyanohydrins from (*R*)-**1** and (*S*)-**1** were formed with comparable levels of *syn* diastereoselectivity (i.e., 2–3:1; compare (*R*)-**2s**:(*R*)-**2a** with (*S*)-**2s**:(*S*)-**2a** in Table 1, entries 1–3) with the *slower* reacting (*R*)-enantiomer giving slightly higher diastereoselectivity. A 1.5–2:1 enantiotopic group selectivity for hydrocyanation of **1** under these conditions was observed at three different conversions and was confirmed by measuring the ee of the recovered aldehyde.[11]

Formation of cyanohydrins from **4** using the Narasaka reagent also proceeded with low enantiotopic group selectivity (Table 1, entry 4). However in this case, the reaction occurred with the expected double stereodifferentiation (8). Thus, the faster reacting (*S*)-**4** gave cyanohydrins with 3.3:1 *syn* diastereoselectivity (i.e., (*S*)-**4s**/(*S*)-**4a**) whereas the slower reacting (*R*)-**4** was slightly *anti* selective (i.e., (*R*)-**4a**/(R*S*)-**4s** = 1.25); addition of cyanide occurred preferentially to the *si* face of both enantiomers of **4** as expected for this reagent (23) and indicating that the reagent *si* face selectivity was higher than the substrate *syn* diastereoselectivity. We also attempted cyanohydrin formation by replacing TADDOL with (*R*)-(+)-1,1′-bi-2-naphthol (BINOL) in the Narasaka protocol (25).[12] Hydrocyanation of **1** with this modified procedure also showed double stereodifferentiation but very low enantiotopic group selectivity (Table 1, entry 5).

Although the observation of double stereodifferentiation in the hydrocyanation of **1** was encouraging, the very low enantiotopic group selectivity obtained suggested that both the reagent enantioselectivity and the substrate diastereoselectivity required improvement. The low diastereoselectivity observed for cyanohydrin formation from α-alkoxy aldehydes on reaction with TMSCN in the presence of various Lewis acids (17) is in stark contrast to the excellent selectivity often associated with nucleophilic additions to these aldehydes under chelation-controlled conditions (26). For example, Reetz et al. (17*a*) reported that reaction of 2-(phenylmethoxy)propanal with TMSCN mediated by TiCl$_4$ (1 equiv) at –78°C gave a 4:1 mixture of *syn:anti* cyanohydrins in good yield. We obtained the same diastereoselectivity (i.e., a 4:1 mixture of **2s** and **2a**) on hydrocyanation of **1** under these conditions (27). This moderate diastereoselectivity prompted us to investigate this reaction more closely.

Varying amounts of TMSCN were added to a solution of TiCl$_4$ in CDCl$_3$ to determine if these two reagents undergo any reaction. The ^{1}H NMR spectra of the yellow solutions obtained after addition of 1, 2, or 4 equiv of TMSCN showed a single signal (δ 0.43) indistinguishable from chlorotrimethylsilane (TMSCl);[13] addition of 10 equiv of TMSCN gave a 3:2 ratio signals assigned[13] to TMSCN (δ 0.36) and TMSCl, respectively. The propensity of mixtures of TiCl$_4$ and TMSCN to produce cyanohydrins from benzaldehyde and from **1** was assessed (Table 2). Clearly, excess TMSCN was required for high conversions (Table 2, entries 1–3) although the diastereoselectivity was unchanged (Table 2, entries 4–5). Interestingly, the cyanohydrin **2** was produced in similar yield and diastereoselectivity by addition of TMSCN to a solution of **1** and TiCl$_4$ or by addition of **1** to a premixed solution of TiCl$_4$ and TMSCN (cf. entries 5 and 6). To obtain further information on the nature of this reagent, solutions of TMSCN (2, 4, and 6 equiv) and TiCl$_4$ in C$_6$D$_6$ were concentrated in vacuo (0.2 torr 1 torr = 133.322 Pa)) collecting the volatile components in a cold trap. Analysis of the resulting yellow residue by ^{1}H NMR (in C$_6$D$_6$) consistently showed the presence of a single signal at ca. 0.18 indistinguishable from TMSCl.[13] The ^{1}H NMR spectrum (in C$_6$D$_6$) of the volatile components obtained from the 2:1 mixture of TMSCN:TiCl$_4$ indicated the absence of both TMSCl and TMSCN, whereas that from the 4:1 mixture showed the presence of ca. 2 equiv of TMSCl[13] and that from the 6:1 mixture contained ca. 2 equiv each of TMSCl and TMSCN δ (–0.17).[13,14] These ex-

[9] The configurational stability of the cyanohydrins under the reaction conditions was confirmed by control experiments.

[10] Reaction of **1** with TMSCN (2 equiv) in the presence of (*i*-Pr-O)$_2$Cl$_2$Ti(IV) (1 equiv) at 0°C in CH$_2$Cl$_2$ gave a 2.5:1 mixture of *syn:anti* cyanohydrins **2s** and **2a** (cf. 4:1, *syn:anti* diastereoselectivity in TiCl$_4$ mediated reaction of α-alkoxy aldehydes with TMSCN (17*a*)). Assuming a reagent enantioselectivity of 4:1 and a substrate diastereoselectivity of 2.5:1, eq. [1] predicts an enantiotopic group selectivity of 1.5:1.

[11] Aldehyde **1** was recovered (50% yield) from a hydrocyanation reaction proceeding to 35% conversion (^{1}H NMR) and found to have 15% ee in favor of (*R*)-**1** by ^{1}H NMR of the Mosher's ester of the corresponding alcohol (NaBH$_4$, 0°C, MeOH; quantitative). Using the equation in footnote 6, the calculated enantiotopic group selectivity from this data (C = 0.35, ee = 0.15) is 2:1.

[12] Subsequent to our work, Nakai and co-workers (25) reported hydrocyanation of aldehydes with the reagent prepared by mixing (*R*)-BINOL and (*i*-Pr-O)$_4$Ti(IV) (0.2 equiv each, rt, 0.5 h) in CH$_2$Cl$_2$ followed by addition of TMSCN (2.5 equiv, 0°C, 0.5 h) (putative catalyst: (BINOL)(CN)$_2$Ti(IV)). With this reagent, addition of cyanide was *re* face selective giving (*S*) cyanohydrins (10–75% ee) from simple aliphatic aldehydes.

[13] Confirmed by addition of an authentic sample(s).

[14] Experiments were conducted at least in triplicate. Quantification was achieved by addition of internal standards (TMSCN and (or) TMSCl). Varying amounts of TMSOH (δ 0.12) were observed; this signal was counted as being derived from TMSCl which was confirmed (^{1}H NMR) by adding controlled amounts of water to a C$_6$D$_6$ solution of TMSCl and TMSCN. Variation of the calculated stoichiometry among "identical" experiments was ca. ±15%.

Table 2. Hydrocyanation of **1** and benzaldehyde with TiCN reagents.

Entry	Aldehyde	TiCN reagent (equiv)	**15**[a,b] (%)	**2** (**2s**:**2a**)[a,b] (%)
1	PhCHO	$TiCl_4$ (1)/TMSCN (1)[c]	50	
2		$TiCl_4$ (1)/TMSCN (2)[c]	78	
3		$TiCl_4$ (1)/TMSCN (4)[c]	92	
4	**1**	$TiCl_4$ (1)/TMSCN (1)[d]		70 (4:1)
5		$TiCl_4$ (1)/TMSCN (2)[d]		90 (4:1)
6		$TiCl_4$ (1)/TMSCN (2)[d,e]		88 (3.3:1)
7	PhCHO	$TiCl_4CN_2^{2-}(TMS^+)_2$[f] (0.16)[g]	21	
8	**1**	$TiCl_4CN_2^{2-}(TMS^+)_2$[f] (0.5)[g]		63 (2:1)
9	PhCHO	$TiCl_2CN_4^{2-}(TMS^+)_2$[h] (0.16)[g]	50	
10	**1**	$TiCl_2CN_4^{2-}(TMS^+)_2$[h] (0.5)[g]		92 (3:1)
11	**1**	(*i*-Pr-O)$_3$TiCN[i] (1)[g]		75 (1:1.2)

[a]Determined by ^{1}H NMR of the crude reaction mixture; the remainder is aldehyde.
[b]Estimated relative error of ±10%.
[c]Conditions: TMSCN was added to a $CDCl_3$ solution of $TiCl_4$ at room temperature. After 1 h, aldehyde was added; water was added after an additional 1 h.
[d]Aldehyde added at –78°C; reaction at –78 to –25°C over 3 h.
[e]TMSCN added to **1** and $TiCl_4$ at –78°C.
[f]Prepared by concentration of a 2:1 mixture of TMSCN:$TiCl_4$.
[g]Reaction for 30 min at room temperature.
[h]Prepared by concentration of a 4:1 mixture of TMSCN:$TiCl_4$.
[i]Prepared by concentration of a 6:1 mixture of TMSCN:(*i*-Pr-O)$_4$Ti.

Table 3. Hydrocyanation of **1** and with TiCN reagents in the presence of $MgBr_2 \cdot OEt_2$ (5 equiv).[a]

Entry	Reagent (equiv)	**2**[b,c] (%)	(*R*)-**2s**[c,d] (%)	(*R*)-**2a**[c,d] (%)	(*S*)-**2s**[c,d] (%)	(*S*)-**2a**[c,d] (%)	k_S/k_R[e]
1	TMSCN (1.1)[f]	95		**2s**:**2a** = 9:1			
2	Et_4NCN (1.1)[f]	65		**2s**:**2a** = 4:1			
3	$TiCl_2CN_4^{2-}(TMS^+)_2$[g] (1)	60		**2s**:**2a** = 3:1			
4	(*i*-Pr-O)$_3$TiCN[h] (1)	51		**2s**:**2a** = 7.5:1			
5	(*i*-Pr-O)$_4$Ti (1) – Et_4NCN (1)[i]	95		**2s**:**2a** = 8.8:1			
6	**14b** (0.3) – Et_4NCN (0.3)[i]	25	45	6	43	6	0.95
7	**14b** (1) – TMSCN (6)[j]	19	46	4	46	4	1.0
8	**16** (1) – TMSCN (0.33)	30	45	5	44	5	0.98
9	**17** (1) – TMSCN (0.33)	24	31	18	34	17	1.05

[a]Conditions: cyanide reagent added to a suspension of Mg(II) and **1** in CH_2Cl_2 solution, 0°C, 1 h. [b]Determined by ^{1}H NMR of the crude reaction mixture.
[c]Estimated relative error of ±10%.
[d]Determined by ^{1}H NMR of the corresponding Mosher's esters.
[e]Calculated according to footnote 5.
[f]Reference 27.
[g]Prepared by concentration of a 6:1 mixture of TMSCN:$TiCl_4$.
[h]Prepared by concentration of a 6:1 mixture of TMSCN:(*i*-Pr-O)$_4$TiCN.
[i]Addition of Et_4NCN over 30 min
[j]Concentrated prior to use.

periments suggest that reaction of $TiCl_4$ with TMSCN produces an initial 1:2 adduct (e.g., $TiCl_4CN_2^{2-}(TMS^+)_2$) and that additional TMSCN results in the substitution of two Cl ligands with two CN ligands [e.g., $TiCl_2CN_4^{2-}(TMS^+)_2$] with concomitant formation of TMSCl. The capability of the residues obtained after concentration of mixtures of $TiCl_4$ and TMSCN to produce cyanohydrins was confirmed by reactions with benzaldehyde and with **1** (Table 2, entries 7–10). The reagents derived from 6:1 and from 4:1 mixtures of TMSCN:$TiCl_4$ (nominal stoichiometry $TiCl_2CN_4^{2-}(TMS^+)_2$) generated 3 equiv (based on Ti) of mandelonitrile (**15**) from benzaldehyde within 30 min at room temperature. Reaction of excess benzaldehyde with the reagent obtained from a 2:1 mixture of TMSCN:$TiCl_4$ (nominal stoichiometry $TiCl_4CN_2^{2-}(TMS^+)_2$) under similar conditions produced 1.3 equiv of mandelonitrile (**15**); reaction of the same reagent with **1** gave a 2:1 mixture of **2s** and **2a**. We also briefly examined cyanohydrin formation using a reagent prepared by addition of TMSCN (6 equiv) to a solution of (*i*-Pr-O)$_4$Ti in C_6D_6. After 15 min, the pale yellow solution was concentrated in vacuo to produce a residue with a nominal stoichiometry of "(*i*-Pr-O)$_3$TiCN" based on analysis of the volatile components by ^{1}H NMR.[15] Addition of **1** (1 equiv based on Ti) to a CH_2Cl_2 solution of the above residue gave a 1:1.2 mixture of **2s** and **2a** (75%) (Table 2, entry 11).

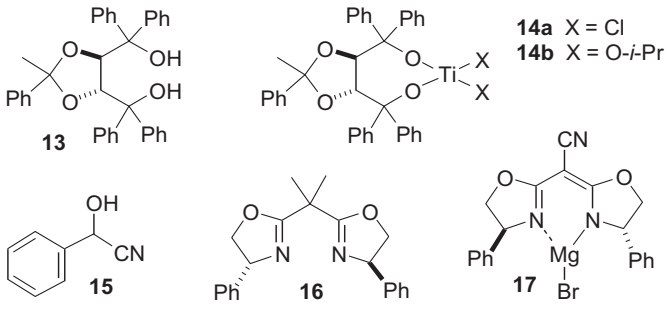
[15]The amounts of *i*-Pr-OR (*R* = H, TMS, 0.9 to 1.1 equiv), and TMSCN (4.5 to 5.1 equiv) in the "distillate" were quantified using an internal standard.

To summarize, TMSCN reacts with $TiCl_4$ and with (*i*-Pr-O)$_4$Ti to give adducts that can generate cyanohydrins from benzaldehyde and from **1**. The low diastereoselectivity observed in reactions with **1** can be rationalized by considering the decreased Lewis acidity of these adducts due to the strongly donating CN ligand(s) which disfavors a "chelation-controlled" pathway. Furthermore, the formation of such adducts suggests that the primary role of the Ti(IV) in these reactions may be to activate the TMSCN rather than the aldehyde. In any event, it seemed apparent that realization of enantiotopic group selective cyanohydrin formation from α-alkoxy aldehydes would require conditions to achieve cyanohydrin formation with much higher diastereoselectivity. We undertook a systematic investigation of cyanohydrin formation from **1** using a variety of cyanide sources (TMSCN, Et_4NCN, $Et_4NAg(CN)_2$), Lewis acids ($BF_3\cdot OEt_2$, $TiCl_4$, $SnCl_4$, $ZnBr_2$, $MgBr_2$), and reaction conditions (27). This study revealed Mg(II) as a unique promoter of hydrocyanation as it is capable of chelation of **1** and does not react appreciably with the cyanide source. Under optimized conditions (27), the cyanohydrin **2** was obtained in high yield as a 24:1 mixture of *syn:anti* diastereomers **2s** and **2a**, respectively.[16] Adapting this diastereoselective method to achieve enantiotopic group selectivity would require a chiral nonracemic version of $MgBr_2$ and (or) a chiral nonracemic cyanide source. The latter strategy appeared more promising because optimal diastereoselectivity requires the use of excess solid $MgBr_2\cdot OEt_2$ (27) and chiral nonracemic Ti(IV) cyanides are readily available and have been implicated in enantioselective hydrocyanation (14*d*, 23, 25).

Initial experiments evaluated the possibility for diastereoselective cyanohydrin formation from **1** using an achiral "TiCN" reagent in the presence of $MgBr_2\cdot OEt_2$ (Table 3). Although the reagent obtained by concentration of a 6:1 mixture of TMSCN and $TiCl_4$ (nominal stoichiometry $TiCl_2CN_4^{2-}(TMS^+)_2$) gave **2** with poor diastereoselectivity (Table 3, entry 3), the reagent prepared from a 6:1 mixture of TMSCN and (*i*-Pr-O)$_4$Ti (nominal stoichiometry (*i*-Pr-O)$_3$TiCN) generated **2** with a diastereoselectivity nearly as high as that obtained with TMSCN (Table 3, cf. entries 1 and 4). The reagent obtained analogously from a 6:1 mixture of TMSCN and **14b** was also very diastereoselective in the presence of $MgBr_2\cdot OEt_2$ but produced **2** with very low enantiotopic group selectivity and without evidence for double stereodifferentiation (Table 3, entry 7). We also examined reagents derived from Et_4NCN and Ti(IV) alkoxides in the presence of excess $MgBr_2\cdot OEt_2$ for hydrocyanation. The Mg(II) mediated hydrocyanation of **1** with Et_4NCN is a relatively poor method (Table 3, entry 2) (27). However, slow addition of Et_4NCN to a suspension of **1** and $MgBr_2\cdot OEt_2$ in the presence of (*i*-Pr-O)$_4$Ti was as effective as TMSCN–$MgBr_2\cdot OEt_2$ for stereoselective synthesis of **2s** (Table 3, cf. entries 1 and 5). The successful moderation of the reactivity of Et_4NCN towards $MgBr_2$ (27) by (*i*-Pr-O)$_4$Ti suggests the possible formation of a TiCN reagent under these conditions. Although the chiral titanium alkoxide **14b** was also effective for diastereoselective hydrocyanation of **1** under analogous conditions, the reaction proceeded with very low enantiotopic group selectivity and without double stereodifferentiation.[17]

We briefly examined enantiotopic group selective hydrocyanation using TMSCN in the presence of "chiral versions" of Mg(II). Hydrocyanations of **1** with TMSCN–$MgBr_2\cdot OEt_2$ in the presence or absence of the nonracemic bisoxazoline ligand **16** (28) were virtually indistinguishable (cf. Table 3, entries 1 and 8). Finally, the use of the nonracemic Mg(II) reagent **17** (29) in place of $MgBr_2\cdot OEt_2$ resulted in low diastereoselectivity (**2s**:**2a** = 2:1), very low enantiotopic group selectivity, and proceeded without double stereodifferentiation (Table 3, entry 9).

In conclusion, attempted hydrocyanations of α-alkoxy aldehydes with TMSCN using chiral nonracemic alkoxy Ti(IV) reagents proceeded with low enantiotopic group selectivity (<2:1). It was established that TMSCN can react with Ti(IV) reagents to produce TiCN adducts that are capable of hydrocyanation but with low substrate-controlled diastereoselectivity in reactions with α-alkoxy aldehydes. The poor enantiotopic group selectivity observed can be rationalized to result from this low diastereoselectivity despite the respectable levels of enantioface selectivity associated with these reagents in hydrocyanation of achiral aldehydes. Highly diastereoselective hydrocyanation of α-alkoxy aldehydes can be achieved with TMSCN in the presence of excess $MgBr_2\cdot OEt_2$ (27). High diastereoselectivity was also observed using achiral and chiral TiCN adducts in place of TMSCN. Although the putative TiCN adducts obtained from nonracemic alkoxy Ti(IV) reagents are implicated in enantioface selective hydrocyanation, these reagents were not enantiotopic group selective under these conditions and showed no evidence of double stereodifferentiation. The use of nonracemic bisoxazoline ligands for Mg(II) was also ineffective.



Experimental

General methods

All solvents were distilled prior to use. Et_3N was distilled from CaH_2 and stored over KOH pellets. Anhydrous solvents were distilled under argon as follows: ether and tetrahydrofuran (THF) from benzophenone potassium ketyl; benzene, toluene, and CH_2Cl_2 from P_2O_5 and stored over 3 Å molecular sieves; MeOH from $Mg(OMe)_2$. Unless otherwise

[16]Conditions: $MgBr_2\cdot OEt_2$ (5 equiv), $Et_4NAg(CN)_2$ (2 equiv) in CH_2Cl_2, –78 to –20°C, 2 h. This level of diastereoselectivity is five times greater than previously reported for α-alkoxy aldehydes.
[17]Reaction of benzaldehyde under these conditions gave **15** with <10% ee.

noted, reactions were carried out under an atmosphere of argon and reaction temperatures refer to the bath. Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator.

Preparative TLC (PTLC) was carried out on glass plates (20 × 20 cm) precoated (0.25 mm) with silica gel 60 F_{254}. Materials were detected by visualization under an ultraviolet lamp (254 nm) and (or) by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aqueous sulfuric acid (5% v/v), followed by charring on a hot plate. Flash column chromatography (FCC) was performed according to Still et al. (30) with Merck silica gel 60 (40–63 μm). Dry FCC was performed according to Harwood (31). All mixed solvent eluents are reported as v/v solutions.

Spectral data

High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a VG 70E double focussing high resolution spectrometer; only partial data are reported. EI ionization was accomplished at 70 eV and CI at 50 eV with ammonia as the reagent gas; only partial data are reported. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and (or) intense peaks are reported. Unless otherwise noted, NMR spectra were measured in $CDCl_3$ solution at 300 MHz for ^{1}H and 75 MHz for ^{13}C. For ^{1}H NMR, residual $CHCl_3$ in $CDCl_3$ was employed as the internal standard (7.26 δ); for ^{13}C NMR, $CDCl_3$ was employed (77.2 δ). The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. ^{1}H NMR spectra were normally obtained with a digital resolution of 0.244 Hz/pt (sweep width = 4000 Hz, FID = 32 K data points) and coupling constants are reported to the nearest 0.5 Hz. The ^{1}H NMR assignments were made on the basis of chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling and (or) NOE experiments. The multiplicity of ^{13}C NMR signals refers to the number of attached Hs (i.e., s = C, d = CH, t = CH_2, q = CH_3) and was determined by *J*-modulation (32).

Materials

TMSCN (33), (*i*-Pr-O)$_2$TiCl$_2$ (34), TADDOL (23), (*i*-Pr-O)$_2$Ti(TADDOL) (24), and **18** (29) were prepared according to literature procedures. The aldehydes **1** and **4** were prepared from hexanal and pivaldehyde, respectively, by addition of vinlymagnesium bromide, benzylation, and ozonolyisis according to the procedure of Midland and Koops (35). $TiCl_4$ and (*i*-Pr-O)$_4$Ti were freshly distilled prior to use. All other reagents were commercially available and, unless otherwise noted, were used as received.

General procedure for preparation Mosher's esters

A solution of (*R*)-MTPA-Cl (prepared (20) from (*S*)-MTPA-OH; 1.2 to 1.5 equiv) in CH_2Cl_2 (ca. 0.05 M) was added via syringe to a stirred solution of the alcohol, Et_3N (2.5 equiv), and DMAP (ca. 1 mg) in CH_2C_l (ca. 0.1 M in alcohol) at room temperature. After stirring for 1–3 h, the reaction mixture was concentrated to give the crude Mosher's esters (quantitative conversion was verified by ^{1}H NMR).

General procedure for hydrocyanation with TMSCN–(i-Pr-O)$_2$TiCl$_2$–TADDOL (or BINOL)

A solution of (*i*-Pr-O)$_2$TiCl$_2$ (1.5 equiv) in toluene (ca. 0.5 M) was added via syringe to a stirred solution of TADDOL (1.5 equiv) in toluene (ca. 0.5 M) at room temperature. After 1 h, MS4A (ca. 150 mg/mmol of aldehyde) and then TMSCN (5 equiv) were added and the mixture was cooled to –23°C. A solution of aldehyde (ca. 0.2 mmol) in toluene (ca. 0.1 M) was added to the mixture. After the appropriate time, phosphate buffer (pH 7) was added and the mixture was allowed to warm to room temperature (ca. 25 min) and then was filtered (Celite®) and extracted with EtOAc (×3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the crude cyanohydrin. The conversion was determined by ^{1}H NMR of the crude by integrating signals due to **1** (or **4**) and **2** (or **5**). Fractionation of the crude by PTLC (25% EtOAc in hexane) gave recovered **1** (or **4**) and the cyanohydrins **2** (or **5**) as a mixture of diastereomers; the stereoisomeric composition was determined by ^{1}H NMR of the corresponding Mosher's esters.

General procedure for hydrocyanation with TMSCN–TiCl$_4$ reagents

$TiCl_4$ (11 mg, 0.06 mmol) in $CDCl_3$ (40 μL) was added via syringe to a solution of TMSCN (1, 2, or 4 equiv) in $CDCl_3$ (0.5 mL). After standing at room temperature for 1 h, PhCHO (6 mg, 0.06 mmol) or **1** (13 mg, 0.06 mmol) was added. After standing at room temperature for 1 h, the mixture was poured over H_2O, diluted with CH_2Cl_2, filtered (Celite®), dried over Na_2SO_4, and concentrated giving **15** or **2** as a yellow oil. Analysis and fractionation were performed as described above.

General procedure for hydrocyanation with TiCN reagents

$TiCl_4$ (19 mg, 0.10 mmol) in C_6D_6 (0.2 mL) was added via syringe to a solution of TMSCN (2, 4, or 6 equiv) in C_6D_6 (0.3 mL) in an NMR tube (5 mm). After standing for 15 min, concentrated by freeze drying under high vacuum (0.2 torr (1 torr = 133.322 Pa)) with the volatile components being collected in a liquid nitrogen cooled trap and analyzed by ^{1}H NMR. The yellowish solid residue was dissolved in C_6D_6 (0.5 mL) and PhCHO (63 mg, 0.60 mmol) or **1** (44 mg, 0.20 mmol) was added via syringe. After 30 min, phosphate buffer (pH 7) was added and the mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were dried over Na_2SO_4 and concentrated to give a mixture of **15** (or **2**) as a yellow oil. Analysis and fractionation as described above. Analogous procedures using (*i*-Pr-O)$_4$Ti or **14b** in place of $TiCl_4$ were employed to prepare and use (*i*-Pr-O)$_3$TiCN or "(TADDOL)(*i*-Pr-O)TiCN", respectively.

General procedure for hydrocyanation with TiCN reagents in the presence of MgBr$_2$·OEt$_2$

A solution of **1** (20 mg, 0.091 mmol) in CH_2Cl_2 (0.5 mL) was added to a stirred suspension of $MgBr_2.OEt_2$ (115 mg,

0.45 mmol) in CH_2Cl_2 (1.5 mL) at room temperature. After stirring for 5 min, the reaction mixture was cooled to 0°C. A solution of the cyanating reagent (TMSCN or Et_4NCN or TiCN) (0.3–1 equiv) was added via syringe. After 1 h at 0°C, phosphate buffer (pH 7, 5 mL) was added and the reaction mixture processed as above to give the crude **2**. For entry 8 of Table 3, **1** was added to a suspension the $MgBr_2 \cdot OEt_2$ containing the ligand **16** (1 equiv). For entry 9 of Table 3, reagent **17** (1 equiv) was used instead of $MgBr_2 \cdot OEt_2$ (5 equiv). Analysis and fractionation were performed as described above.

*2-(Phenylmethoxy)heptanal (**1**):* LRMS (CI, NH_3) *m/z* (relative intensity): 238 ($[M + 18]^+$, 10), 221 ($[M + 1]^+$, 2), 191 (36), 108 (64), 91 (100). HRMS *m/z* calcd. for $C_{14}H_{21}O_2$: 221.1542 (= $[M + H]^+$); found: 221.1542 (CI, NH_3). IR ν_{max} (cm^{-1}): 3088, 2930, 1732, 1454, 1099, 736, 698. ^1H NMR δ: 9.65 (1H, d, *J* = 2 Hz, HC-1), 7.39–7.28 (5H, m, ArH), 4.68 (1H, d, *J* = 12 Hz, HCAr), 4.54 (1H, d, *J* = 12 Hz, HCAr), 3.76 (1H, ddd, *J* = 2, 6.5, 6.5 Hz, HC-2), 1.72–1.62 (2H, m, H_2C-3), 1.51–1.35 (2H, m, H_2C-4), 1.34–1.20 (4H, m, H_2C-5, H_2C-6), 0.92–0.83 (3H, t, *J* = 6.5 Hz, H_3C-7). ^{13}C NMR δ: 203.7 (d, C-1), 137.5 (s, Ph), 128.5 (2d, Ph), 128.3 (d, Ph), 128.0 (2d, C-2), 83.5 (d, C-2), 72.5 (t, CH_2O), 31.6 (t, C-5), 30.0 (t, C-3), 24.4 (t, C-4), 22.4 (t, C-6), 14.0 (q, C-7).

(2R,3R*)-2-Hydroxy-3-(phenylmethoxy)octanenitrile (**2s**) and (2S*,3R*)-2-hydroxy-3-(phenylmethoxy)octanenitrile (**2a**):* LRMS (CI, NH_3) *m/z* (relative intensity): 265 ($[M + 18]^+$, 1), 191 (8), 108 (13), 91 (100). HRMS *m/z* calcd. for $C_{15}H_{21}NO_2$: 265.1916 (= $[M + NH_4]^+$); found: 265.1906 (CI, NH_3). IR ν_{max} (cm^{-1}): 3426, 3031, 2930, 1454, 1073, 744, 698. ^1H NMR δ for **2s**: 7.43–7.32 (5H, m, ArH), 4.75 (1H, d, *J* = 11.5 Hz, HCAr), 4.58 (1H, d, *J* = 11.5 Hz, HCAr), 4.46 (1H, dd, *J* = 4, 9 Hz, HC-2), 3.63 (1H, ddd, *J* = 4, 7, 7 Hz, HC-3), 2.95 (1H, d, *J* = 9 Hz, OH), 1.90–1.76 (1H, m, HC-4), 1.75–1.58 (1H, m, HC-4), 1.47–1.23 (6H, m, H_2C-5, H_2C-6, H_2C-7), 0.97–0.85 (3H, m, H_3C-8); δ for **2a**: 7.43–7.32 (5H, m, ArH), 4.76 (1H, d, *J* = 11.5 Hz, HCAr), 4.71 (1H, d, *J* = 11.5 Hz, HCAr), 4.38 (1H, dd, *J* = 3, 9 Hz, HC-2), 3.68 (1H, dt, *J* = 3, 6.5 Hz, HC-3), 2.95 (1H, d, *J* = 9 Hz, OH), 1.75–1.58 (2H, m, H_2C-4), 1.47–1.23 (6H, m, H_2C-5, H_2C-6, H_2C-7), 0.97–0.85 (3H, m, H_3C-8). ^{13}C NMR δ for **2s**: 137.2 (s, Ph), 128.6 (2d, Ph), 128.2 (d 2, Ph), 128.1 (d, Ph), 119.0 (s, C-1), 79.4 (t, C-2), 73.4 (d, CH_2Ar), 63.2 (d, C-3), 31.6 (t, C-4), 30.4 (t, C-6), 24.8 (t, C-5), 22.4 (t, C-7), 13.9 (q, C-8); δ for **2a**: 137.4 (s, Ph), 128.6 (2d, Ph), 128.2 (2d, Ph), 128.0 (d, Ph), 118.0 (s, C-1), 79.4 (t, C-2), 72.8 (d, CH_2Ar), 64.1 (d, C-3), 31.7 (t, C-4), 30.4 (t, C-6), 24.7 (t, C-5), 22.4 (t, C-7), 13.9 (q, C-8). Elemental anal. calcd. for $C_{15}H_{21}NO_2$: C 72.84, H 8.56, N 5.66; found: C 72.54, H 8.53, N 5.62.

*1-Cyano-2-(phenylmethoxy)heptyl (2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**3**):* Fractionation of the crude product from reaction of **2** (a 2.4:1 mixture of racemic **2s** and **2a**; 8 mg, 0.03 mmol) with (*R*)-MTPA-Cl by PTLC (25% EtOAc in hexane) gave a 2.6:2.6:1:1 mixture of (*R*)-**3s**, (*S*)-**3s**, (*R*)-**3a**, and (*R*)-**3a** isomers, respectively, as a colorless oil (13 mg, 88%). LRMS (CI, NH_3), *m/z* (relative intensity): 481 ($[M + 18]^+$, 37), 373 (42), 279 (23), 189 (100), 108 (38), 91 (82). HRMS *m/z* calcd. for $C_{25}H_{28}F_3NO_4$: 463.1970; found: 463.1978 (EI). IR ν_{max} (cm^{-1}): 2953, 1763, 1453, 1172. ^1H NMR δ:[18] 7.51–7.25 (10H, m, ArH), 5.67† (d, *J* = 4 Hz), 5.62‡ (d, *J* = 4.5 Hz), 5.57§ (d, *J* = 6 Hz), and 5.52¶ (d, *J* = 6.5 Hz) (1H, HC-1), 4.69† (d, *J* = 11 Hz), 4.65¶ (d, *J* = 11 Hz), 4.63‡ (d, *J* = 11 Hz), 4.58¶ (d, *J* = 11 Hz), 4.53§ (d, *J* = 11 Hz), 4.51† (d, *J* = 11 Hz), 4.47§ (d, *J* = 11 Hz), and 4.42‡ (d, *J* = 11 Hz) (2H, H_2CAr), 3.81–3.71†¶ (m), and 3.71–3.61‡§ (m) (1H, HC-2), 3.59‡§ (br s), 3.54† (br s), and 3.50¶ (br s) (3H, H_3CO), 1.70–1.14 (8H, m, H_3C-3, H_2C-4, H_2C-5, H_2C-6), 0.90–0.81 (3H, m, H_3C-7).

*3,3-Dimethyl-2-(phenylmethoxy)butanal (**4**):* LRMS (CI, NH_3) *m/z* (relative intensity): 224 ($[M + 18]^+$, 100), 177 (32), 108 (21), 91 (28). HRMS *m/z* calcd. for $C_{13}H_{18}O_2$: 206.1307; found: 206.1298 (EI). IR ν_{max} (cm^{-1}): 2960, 2870, 2714, 1727, 1454, 1110. ^1H NMR δ: 9.73 (1H, d, *J* = 3.5 Hz, HC-1), 7.37–7.29 (5H, m, ArH), 4.65 (1H, d, *J* = 11.5 Hz, HCAr), 4.43 (1H, d, *J* = 11.5 Hz, HCAr), 3.29 (1H, d, *J* = 3.5 Hz, HC-2), 1.01 (9H, s, $(H_3C)_3C$). ^{13}C NMR δ: 204.9 (d, C-1), 137.8 (s, Ph), 128.2 (2d, Ph), 128.1 (3d, Ph), 90.7 (d, C-3), 73.1 (t, CH_2O), 35.6 (s, C-4), 27.0 (3q, $(H_3C)_3C$).

(2R,3R*)-2-Hydroxy-4,4-dimethyl-3-(phenylmethoxy) pentanenitrile (**5s**) and (2S*,3R*)-2-hydroxy-4,4-dimethyl-3-(phenylmethoxy)pentanenitrile (**5a**)*

TMSCN (173 mg, 1.74 mmol) and Et_3N (59 mg, 0.58 mmol) were added to a stirred solution of aldehyde **4** (120 mg, 0.580 mmol) and MS4A (100 mg) in toluene (2.5 mL) at room temperature. After 3 h, the mixture was filtered and concentrated to give **8** (a 3:1 mixture of **8s** and **8a**, respectively, by ^1H NMR; 160 mg, 90%). ^1H NMR δ for **8s**: 7.44–7.22 (5H, m, ArH), 4.89 (1H, d, *J* = 11.5 Hz, HC-Ar), 4.63 (1H, d, *J* = 11.5 Hz, HC-Ar), 4.52 (1H, d, *J* = 5.5 Hz, HC-2), 3.25 (1H, d, *J* = 5.5 Hz, HC-3), 1.04 (9H, s, $(H3C)_3C$), 0.20 (9H, s, $(H_3C)_3Si$); δ for **8a**: 7.44–7.22 (5H, m, ArH), 5.00 (1H, d, *J* = 11.5 Hz, HC-Ar), 4.62 (1H, d, *J* = 4 Hz, HC-2), 4.61 (1H, d, *J* = 11.5 Hz, HC-Ar), 3.25 (1H, d, *J* = 4 Hz, HC-3), 1.00 (9H, s, $(H_3C)_3C$), 0.25 (9H, s, $(H_3C)_3Si$). To a stirred solution of **8** (a 3:1 mixture of **8s** and **8a**, respectively; 160 mg) in Et_2O (10 mL) was added 1 M HCl (10 mL). After 14 h, the mixture was diluted with Et_2O and washed sequentially with H_2O and sat. NaCl, dried over Na_2SO_4, and concentrated to give **5** as a colorless liquid (122 mg, 90%, 3:1 mixture of **5s** and **5a** by ^1H NMR). The residue was fractionated by FCC (10% EtOAc in hexane) giving **5s** as a clear liquid (75 mg, 55%) and **5a** as a clear liquid (10 mg, 8%).

*Spectral data for **5s**:* LRMS (CI, NH_3) *m/z* (relative intensity): 251 ($[M + 18]^+$, 6), 224 (100), 108 (33), 91 (48). HRMS *m/z* calcd. for $C_{14}H_{19}NO_2$: 251.1760 (= $[M + NH_4]^+$); found: 251.1760 (CI). IR ν_{max} (cm^{-1}): 3456, 2959, 2872, 2240 (w), 1395, 1089. ^1H NMR δ: 7.46–7.35 (5H, m, ArH), 5.00 (1H, d, *J* = 10.5 Hz, HCAr), 4.89 (1H, d, *J* = 10.5 Hz, HCAr), 4.58 (1H, dd, *J* = 1.5, 10 Hz, HC-2), 3.47 (1H, d, *J* = 1.5 Hz, HC-3), 3.29 (1H, d, *J* = 10 Hz, OH), 1.00 (9H, s, H_3C). ^{13}C NMR δ: 137.0 (s, Ph), 128.6 (2d, Ph), 128.3 (d, Ph), 128.2 (2d, Ph), 120.6 (s, C-1), 86.4 (d, C-2), 76.0 (t, CH_2O), 59.3 (d, C-3), 35.9 (s, C-4), 26.4 (3q, CH_3). Elemen-

[18]Legend: † = (*R*)-**3a**, ‡ = (*S*)-**3a**, § = (*R*)-**3s**, ¶ = (*S*)-**3s**.

tal anal. calcd. for $C_{14}H_{19}NO_2$: C 72.07, H 8.21l N 6.00; found: C 72.06, H 8.18, N 5.93.

*Spectral data for **5a**:* LRMS (CI, NH_3) *m/z* (relative intensity): 251 ([M + 18]$^+$, 46), 224 (100), 108 (42), 91 (54). HRMS *m/z* calcd. for $C_{14}H_{19}NO_2$: 251.1760 (= [M + NH_4]$^+$); found: 251.1763 (CI, NH_3). IR ν_{max} (cm^{-1}): 3422, 2960, 2872, 2250 (w), 1394, 1105. ^{1}H NMR δ: 7.44–7.30 (5H, m, ArH), 4.80 (1H, d, *J* = 11.5 Hz, HCAr), 4.76 (1H, d, *J* = 11.5 Hz, HCAr), 4.58 (1H, d, *J* = 3 Hz, HC-2), 3.30 (1H, d, *J* = 3 Hz, HC-3), 2.40 (1H, br s, OH), 1.05 (9H, s, H_3C). ^{13}C NMR δ: 139.0 (s, Ph), 129.7 (2d, Ph), 129.2 (d, Ph), 129.0 (2d, Ph), 118.8 (s, C-1), 93.3 (d, C-2), 76.7 (t, CH_2O), 63.9 (d, C-3), 35.7 (s, C-4), 26.9 (3q, CH_3).

*1-Cyano-3,3-dimethyl-2-(phenylmethoxy)butyl (2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**6**):* Fractionation of the crude product from reaction of **5** (a 1.5:1 mixture of **5a** and **5s**, respectively; 10 mg, 0.043 mmol) with (*R*)-MTPA-Cl by PTLC (25% EtOAc in hexane) gave **6** as a 1.5:1.5:1:1 mixture of (*R*)-**6a**, (*S*)-**6a**, (*R*)-**6s**, and (*R*)-**6s** isomers, respectively, as a colorless oil (16 mg, 83%). IR ν_{max} (cm^{-1}): 2959, 1761, 1453, 1227, 1171, 1108, 1021. ^{1}H NMR δ: [19] 7.57–7.18 (10H, m, ArH), 5.83‡ (d, *J* = 2 Hz), 5.77† (d, *J* = 2 Hz), 5.590§ (d, *J* = 4 Hz), and 5.587¶ (d, *J* = 5.5 Hz) (1H, HC-1), 4.83¶ (d, *J* = 11 Hz), 4.76† (d, *J* = 11 Hz), 4.73§ (d, *J* = 11 Hz), 4.64‡ (d, *J* = 11 Hz), 4.58¶ (d, *J* = 11 Hz), 4.52§ (d, *J* = 11 Hz), 4.38† (d, *J* = 11 Hz), and 4.25‡ (d, *J* = 11 Hz) (2H, H_2CAr), 3.61†¶ (m), 3.52‡ (m), and 3.45§ (m) (3H, H_3CO), 3.53¶ (d, *J* = 5.5 Hz), 3.45§ (d, *J* = 4 Hz), 3.33† (d, *J* = 2 Hz), and 3.18‡ (d, *J* = 2) (1H, HC-2), 1.04¶ (s), 1.03† (s), 0.98‡ (s), and 0.89§ (s), (9H, $(H_3C)_3$). LRMS (EI) *m/z* (relative intensity): 449 ([M]$^+$, 5), 189 (22), 91 (100), 57 (21). HRMS *m/z* calcd. for $C_{24}H_{26}F_3NO_4$: 449.1814; found: 449.1812 (EI). Elemental anal. calcd. for $C_{24}H_{26}F_3NO_4$: C 64.13, H 5.83, N 3.12; found: C 64.42, H 5.82, N 3.13.

*2,3-Dihydroxyoctanenitrile (**9**):* TMSCN (100 mg, 1.01 mmol) and Et_3N (41 μL, 30 mg, 0.30 mmol) was added to a stirred solution of aldehyde (150 mg, 0.68 mmol) in toluene (10 mL) containing powdered MS4A (100 mg). After stirring for 2 h the reaction was filtered and concentrated to give a 2:1 mixture of **7s** and **7a**, respectively, (197 mg, 90%). ^{1}H NMR δ for the *syn* isomer: 7.33–7.28 (5H, m, ArH), 4.68 (1H, d, *J* = 11.5 Hz, HC-Ar), 4.63 (1H, d, *J* = 11.5 Hz, HC-Ar), 4.38 (1H, d, *J* = 5.5 Hz, HC-2), 3.46 (1H, ddd, *J* = 3, 5.5, 8.5 Hz, HC-3), 1.80–1.20 (8H, m, H_2C-4, H_2C-5, H_2C-6, H_2C-7), 0.90 (3H, m, H_3C-8), 0.19 (9H, s, $(H_3C)_3Si$); δ for the *anti* isomer: 7.33–7.28 (5H, m, ArH), 4.80 (1H, d, *J* = 11.5 Hz, HC-Ar), 4.62 (1H, d, *J* = 11.5 Hz, HC-Ar), 4.33 (1H, d, *J* = 6 Hz, HC-2), 3.59 (1H, ddd, *J* = 5, 6, 7 Hz, HC-3), 1.80–1.20 (8H, m, H_2C-4, H_2C-5, H_2C-6, H_2C-7), 0.90 (3H, m, H_3C-8), 0.22 (9H, s, $(H_3C)_3Si$). Addition of one drop of DCl to the NMR sample resulted in hydrolysis of **7** to give a 2:1 mixture of **2s** and **2a**, respectively. To a stirred solution of **7** (2:1 mixture of **7s**:**7a**; 190 mg, 0.596 mmol) in CH_2Cl_2 (20 mL) was added $TiCl_4$ (71 μL, 123 mg, 0.65 mmol). After 1 h, the reaction was quenched by addition of NH_4Cl (1 M, 20 mL). The mixture was extracted with Et_2O (×3) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and the residue fractionated by FCC (35% EtOAc in hexane) to give the diol **9** as a 2:1 mixture of **9s** and **9a**, respectively, (54 mg, 58%). LRMS (CI, NH_3) *m/z* (relative intensity): 175 ([M + 18]$^+$, 5), 148 (100), 99 (36), 83 (17). HRMS *m/z* calcd. for $C_8H_{15}NO_2$: 175.1447 (= [M + NH_4]$^+$); found: 175.1447 (CI, NH_3). IR ν_{max} (cm^{-1}): 3421, 2929, 1465, 1077. ^{1}H NMR δ for **9a**: 4.42 (1H, d, *J* = 3.0 Hz, HC-2), 3.92–3.80 (1H, m, HC-3), 1.72–1.43 (2H, m, H_2C-4), 1.42–1.24 (6H, m, H_2C-5, H_2C-6, H_2C-7), 0.94–0.85 (3H, t, *J* = 6.5 Hz, H_3C-8); for **9s**: 4.33 (1H, d, *J* = 4.5 Hz, HC-2), 3.92–3.80 (1H, m, HC-3), 1.72–1.43 (2H, m, H_2C-4), 1.42–1.24 (6H, m, H_2C-5, H_2C-6, H_2C-7), 0.94–0.85 (3H, t, *J* = 6.5 Hz, H_3C-8). ^{13}C NMR δ for **9a**: 117.9 (s, C-1), 72.6 (d, C-3), 66.0 (d, C-2), 32.6 (t, C-4), 31.5 (t, C-6), 25.0 (t, C-5), 22.4 (t, C-7), 13.9 (q, C-8); δ for **9s**: 118.8 (s, C-1), 72.6 (d, C-3), 64.9 (d, C-2), 32.1 (t, C-4), 31.5 (t, C-6), 25.0 (t, C-5), 22.4 (t, C-7), 13.9 (q, C-8).

(2R,3R*)-2,3-Dihydroxy-4,4-dimethylpentanenitrile (**10s**):* A solution of $TiCl_4$ (0.030 mL, 52 mg, 0.27 mmol) in CH_2Cl_2 (0.2 mL) was added via syringe to a stirred solution of **4s** (32 mg, 0.14 mmol) in CH_2Cl_2 (2.3 mL) at 25°C. After 0.5 h, H_2O was added and the mixture was extracted with CH_2Cl_2 (×3). The combined organic layers were filtered (Celite®), and the filtrate was dried over Na_2SO_4, concentrated, and the residue (29 mg) fractionated by dry FCC (0–50% Et_2O in hexane, gradient elution) to give **10s** as a white solid (10 mg, 51%). LRMS (CI, NH_3) *m/z* (relative intensity): 161 ([M + 18]$^+$, 62), 134 (100). HRMS *m/z* calcd. for $C_7H_{13}NO_2$: 161.1290 (= [M + NH_4]$^+$); found: 161.1284 (CI, NH_3). IR ν_{max} (cm^{-1}): 3416, 3291, 2959, 2873, 2238 (w), 1110, 1020. ^{1}H NMR δ: 4.61–4.56 (1H, br s, HC-2), 3.59–3.55 (1H, br s, HC-3), 1.00 (9H, br s, *J* = 1 Hz, $(H_3C)_3$). ^{13}C NMR: 120.1 (s, C-1), 78.9 (d, C-2), 61.8 (d, C-3), 35.2 (s, C-4), 26.4 (3q, $(CH_3)_3$). Elemental analysis calcd. for $C_7H_{13}NO_2$: C 58.72, H 9.15, N 9.78; found: C 58.86, H 8.95, N 9.51.

(4R,5R*)-2,2-Dimethyl-5-pentyl-1,3-dioxolane-4-carbonitrile (**11t**) and (4R*,5S*)-2,2-dimethyl-5-pentyl-1,3-dioxolane-4-carbonitrile (**11c**)*

TsOH (24 mg, 0.13 mmol) was added to a stirred solution of **9** (a 2:1 mixture of **9s** and **9a**; 50 mg, 0.32 mmol) in dimethoxypropane (10 mL) at room temperature. After 12 h, the reaction mixture was diluted with CH_2Cl_2 (15 mL), washed sequentially with sat. $NaHCO_3$ (×2) and H_2O, dried over Na_2SO_4, and concentrated giving a colorless oil the crude **11** as 2:1 ratio of *trans*:*cis* diastereomers by ^{1}H NMR (67 mg). The residue was fractionated by FCC (10% EtOAc in hexane) giving **11t** (25 mg), a 1:1 mixture of **11t** and **11c** (13 mg), and **11c** (12 mg, 80%).

*Spectral data for **11t**:* LRMS (CI, NH_3) *m/z* (relative intensity): 215 ([M + 18]$^+$, 8), 198 ([M + 1]$^+$, 26), 182 (78), 171 (19), 61 (100). HRMS *m/z* calcd. for $C_{11}H_{19}NO_2$: 215.1760 (= [M + NH_4]$^+$); found: 215.1758 (CI). IR ν_{max} (cm^{-1}): 2933, 1460, 1383, 1218, 1067. ^{1}H NMR δ: 4.36 (1H, ddd, *J* = 6, 6, 6 Hz, HC-5), 4.15 (1H, d, *J* = 6 Hz, HC-4), 1.72–1.63

[19] Legend: † = (*R*)-**6a**, ‡ = (*S*)-**6a**, § = (*R*)-**6s**, ¶ = (*S*)-**6s**.

(2H, m, H_2C-1′), 1.49 (3H, s, H_3CC-2), 1.45 (3H, s, H_3CC-2), 1.40–1.27 (6H, m, H_2C-2′, H_2C-3′, H_2C-4′), 0.93–0.87 (3H, m, H_3C-5′). ^{13}C NMR δ: 117.9 (s, CN), 112.3 (s, C-2), 80.3 (d, C-4), 67.7 (d, C-5), 32.8 (t, C-1′), 31.5 (t, C-3′), 26.8 (t, C-2′), 25.0 (2q, CH_3C-2), 22.4 (t, C-4′), 13.9 (q, C-5′). Elemental anal. calcd. for $C_{11}H_{19}NO_2$: C 66.97, H 9.70, N 7.10; found: C 67.21, H 9.86, N 6.89.

*Spectral data for **11c**:* LRMS (CI, NH_3) *m*/*z* (relative intensity): 215 ($[M + 18]^+$, 8), 198 ($[M + 1]^+$, 26), 182 (78), 171 (19), 61 (100). HRMS *m*/*z* calcd. for $C_{11}H_{19}NO_2$: 215.1760 (= $[M + NH_4]^+$); found: 215.1759 (CI, NH_3). IR ν_{max} (cm^{-1}): 2935, 1467, 1374, 1227, 1064. ^{1}H NMR δ: 4.73 (1H, d, *J* = 5 Hz, HC-4), 4.15 (1H, ddd, *J* = 5, 6, 7 Hz, HC-5), 1.97–1.86 (1H, m, HC-1′), 1.81–1.70 (1H, m, HC-1′), 1.56 (3H, s, H_3CC-2), 1.52–1.44 (1H, m, HC-2′), 1.37 (3H, s, H_3CC-2), 1.39–1.32 (5H, m, HC-2′, H_2C-3′, H_2C-4′), 0.90 (3H, br t, *J* = 7 Hz, H_3C-5′). ^{13}C NMR δ: 116.5 (s, CN), 111.8 (s, C-2), 77.5 (d, C-4), 68.2 (d, C-5), 31.6 (t, C-3′), 30.3 (t, C-1′), 27.2 (t, CH_3C-2), 25.8 (q, C-2′), 25.5 (q, CH_3C-2), 22.4 (t, C-4′), 13.9 (q, C-5′).

*(4*R**,5*R**)-2,2-Dimethyl-5-(1′,1′-dimethylethyl)-1,3-dioxolane-4-carbonitrile (**12t**):*

A solution of **10s** (16 mg, 0.11 mmol) and TsOH (ca. 2 mg) in dimethoxypropane (1.5 mL) was stirred a room temperature for 17 h. The reaction mixture was diluted with CH_2Cl_2, washed sequentially with sat. $NaHCO_3$ (×2) and H_2O, dried over Na_2SO_4, and concentrated to give a yellow oil (19 mg). Bulb-to-bulb distillation (Kugelrohr, 15 torr (1 torr = 133.322 Pa), 90°C) of the residue distillation gave **12t** as a colorless oil (12 mg, 60%). LRMS (CI, NH_3) *m*/*z* (relative intensity): 201 ($[M + 18]^+$, 79), 168 (100), 157 (92). HRMS *m*/*z* calcd. for $C_{10}H_{17}O_2N$: 201.1603 (= $[M + NH_4]^+$); found: 201.1606 (CI, NH_3). IR ν_{max} (cm^{-1}): 2961, 2874, 2250 (w), 1479, 1379, 1214, 1072. ^{1}H NMR δ: 4.56 (1H, d, *J* = 7 Hz, HC-4), 4.13 (1H, d, *J* = 7 Hz, HC-5), 1.50 (3H, s, H_3C-C-2), 1.45 (3H, s, H_3C-C-2), 0.96 (9H, s, $(H_3C)_3C$). ^{13}C NMR δ: 119.2 (s, CN), 112.6 (s, C-2), 88.1 (d, C-4), 64.2 (d, C-5), 33.1 (s, $C(CH_3)_3$), 26.4 (q, CH_3C-2), 25.4 (3q, $(CH_3)_3C$), 24.5 (q, CH_3C-2).

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