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Hydroxynitrile lyase-catalyzed addition of HCN to 2- and 3-substituted cyclohexanones☆

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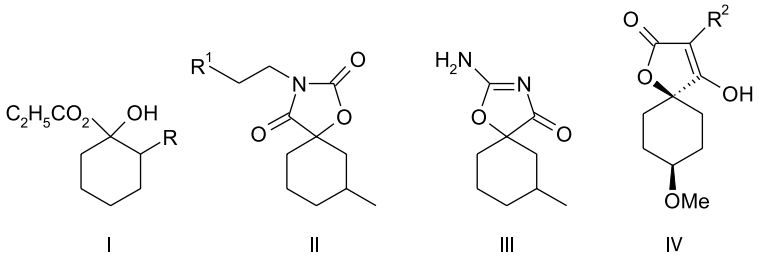
Abstract—The addition of HCN to monosubstituted cyclohexanones yielding cyanohydrins is strongly catalyzed by hydroxynitrile lyases (HNLs). With PaHNL from bitter almonds, the addition to 2-alkyl cyclohexanones **1b–g** is highly (*R*)-selective, whereas the methyl compound **1a** reacts (*S*)-selectively. With MeHNL from cassava, all 2-alkyl derivatives **1** react (*S*)-selectively. The catalytic activity of both PaHNL and MeHNL decreases with increasing size of the substituent in substrates **1**. The diastereoselectivity of HCN additions to 2-alkoxy cyclohexanones **4** and 3-substituted cyclohexanones **6**, however, is only moderate. The absolute configuration of the synthesized cyanohydrins was determined by X-ray crystallography of *O*-*p*-bromobenzoyl derivatives.

1. Introduction

Monosubstituted cyclohexanone cyanohydrins, which can be hydrolyzed easily to the corresponding α-hydroxy-carboxylic acids, are important starting materials for the synthesis of pharmaceuticals and plant protective agents. 2-Alkyl-1-hydroxy-1-carbalkoxy-cyclohexanes **I**, for example, are repellents against mosquitos.[3] The spirocyclic cyclohexanone derivatives **II** and **III** are applied as pharmaceuticals in central nervous system diseases,[4] while 4-substituted-1,1-tetronic acid cyclo-hexanes **IV** are interesting herbicides (Scheme 1).[5]

Since the different stereoisomers of one compound often reveal very distinct biological activities, the stereoselective preparation of exclusively one isomer is an important target. Although each of the compounds **I**, **II** and **III** has two stereogenic centres, until now not a single stereo-selective chemical synthesis for these interesting products is described in the literature. The hydroxynitrile lyase (HNL) catalyzed addition of HCN to 3-methyl cyclohexanone **5a** has been performed, but the stereochemistry of the corresponding cyanohydrin obtained could not be determined.[6]

In a recent publication we have described the hydroxynitrile lyase-catalyzed addition of HCN to 4-substituted cyclo-hexanones, which unexpectedly results in a high



I II III IV

Scheme 1.

☆ Enzyme-catalyzed reactions, part 49; for part 48 see ref. 1.

Keywords: Enzyme; Hydroxynitrile lyase; Cyclohexanones; Cyanohydrins; Stereochemistry.
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cis/*trans*-selectivity.[7] In the present paper we report on our systematic investigations of HNL-catalyzed HCN additions to 2- as well as to 3-substituted cyclohexanones.

2. Results and discussion

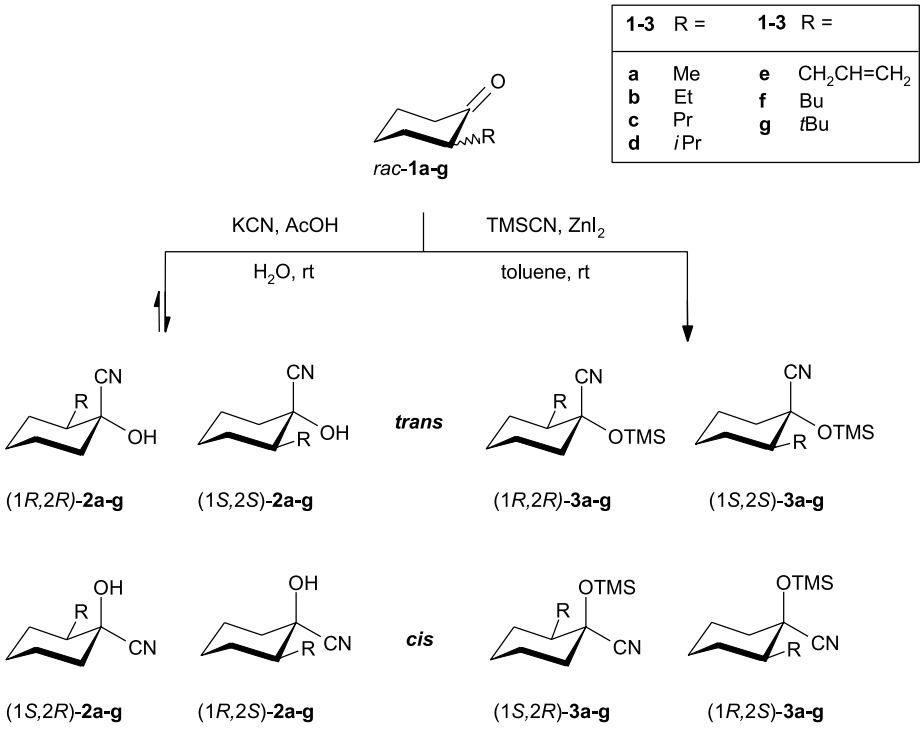
2.1. Chemical addition of HCN to 2- and 3-substituted cyclohexanones 1, 4 and 6

Prior to starting enzyme-catalyzed reactions we have investigated the chemical addition of HCN, prepared in situ in aqueous solution from KCN with acetic acid,[8] to racemic 2-alkyl cyclohexanones *rac*-**1a–g** (Scheme 2, Table 1).

Table 1 reveals *trans*-selectivity of the HCN addition to racemic 2-alkyl cyclohexanones *rac*-**1a–f** to give the corresponding cyclohexanone cyanohydrins **2a–f**. The 2-*tert*-butyl cyclohexa-none **1g**, however, could not be converted. An alternative chemical method is the addition of trimethylsilyl cyanide (TMSCN) to 2-alkyl cyclohexanones **1a–g** using ZnI_2 as a catalyst.[9] Analogously to the HCN addition, the reaction with TMSCN yielded the *trans* isomers of the *O*-trimethylsilyl cyanohydrins **3a–f** as major products (Table 1). The reaction of the *tert*-butyl compound turns out to be unselective, giving the *cis* and *trans* isomers of **3g** in almost equal amounts.

In contrast to 2-alkyl cyclohexanones, the reaction of 2-alkoxy cyclohexanones **4a–e** with KCN and acetic acid shows, with the exception of **4a**, a slight preference for *cis*-products (Scheme 3, Table 2).

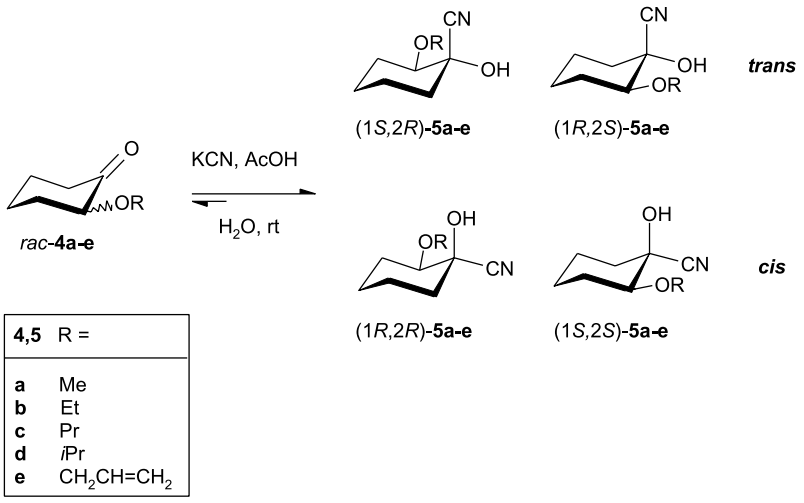
In the chemical HCN addition to 3-substituted cyclohexanones **6a–c** (Scheme 4) the formation of *cis*-products dominates (Table 2). This result may be explained by an



Scheme 2.

Table 1. *cis*/*trans*-Selectivities and yields of the HCN and TMSCN addition to racemic 2-alkyl cyclohexanones *rac*-**1a–g**

Ketones *rac*-**1**		Cyanohydrins **2**			*O*-Silylated cyanohydrins **3**		
	R=		Yield	*rac-cis*:*rac-trans*		Yield	*rac-cis*:*rac-trans*
1a	Methyl-	**2a**	90	22:78	**3a**	65	25:75
1b	Ethyl-	**2b**	70	24:76	**3b**	73	22:78
1c	*n*-Propyl-	**2c**	83	25:75	**3c**	53	23:77
1d	*iso*-Propyl-	**2d**	64	28:72	**3d**	37	36:64
1e	Allyl-	**2e**	61	14:86	**3e**	53	25:75
1f	*n*-Butyl-	**2f**	84	35:65	**3f**	83	26:74
1g	*tert*-Butyl	**2g**	—	—	**3g**	27	51:49



Scheme 3.

Table 2. *cis*/*trans*-Selectivities and yields of the HCN addition to racemic 2-alkoxy cyclohexanones *rac*-**4** and racemic 3-substituted cyclohexanones *rac*-**6**

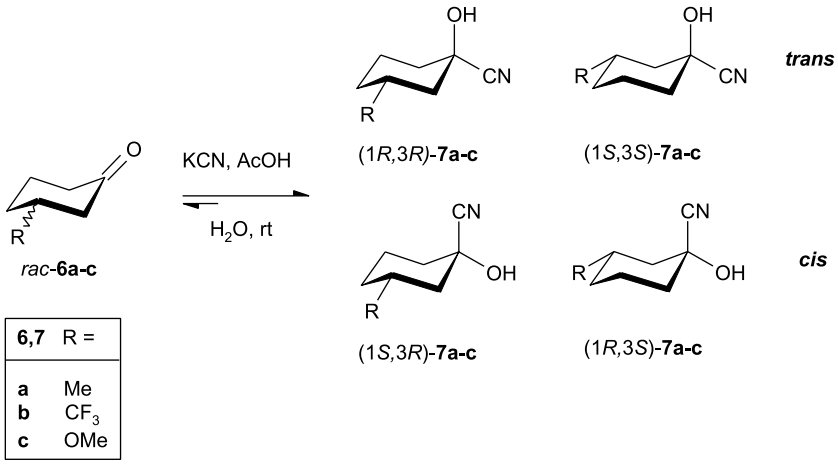
rac-**4**	Cyanohydrins **5**			*rac*-**6**	Cyanohydrins **7**		
		Yield	*rac-cis*:*rac-trans*			Yield	*rac-cis*:*rac-trans*
4a	**5a**	84	39:61	**6a**	**7a**	95	86:14
4b	**5b**	82	54:46	**6b**	**7b**	92	59:41
4c	**5c**	96	58:42	**6c**	**7c**	87	92:8
4d	**5d**	91	59:41				
4e	**5e**	86	54:46				

electronically favored axial attack of the carbonyl group by the cyanide nucleophile.[10]

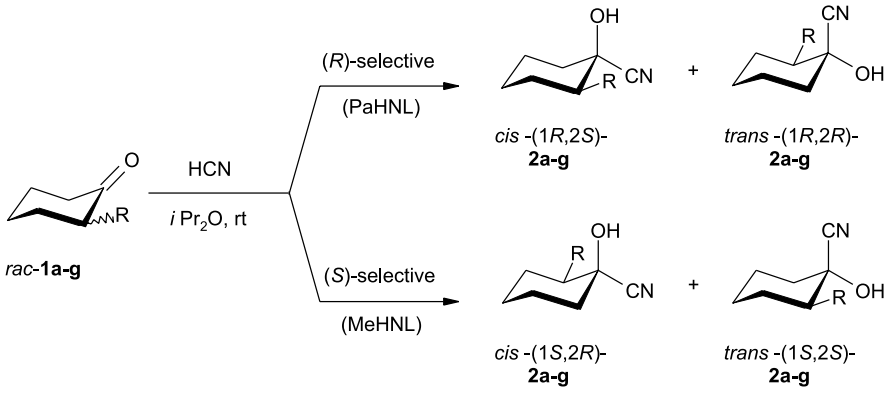
2.2. (*R*)-PaHNL- and (*S*)-MeHNL-catalyzed addition of HCN to racemic 2-alkyl cyclohexanones, *rac*-1

Both the hydroxynitrile lyases (*R*)-PaHNL from bitter almond and (*S*)-MeHNL from cassava were used for the HCN addition to cyclohexanones **1**. In contrast to the chemical reactions described above, where *cis*/*trans*-selectivity is observed, the enzyme-catalyzed additions reveal *R*/*S*-selectivity concerning the new stereogenic center formed in the 1-position. One should expect (*R*)-selectivity by using (*R*)-PaHNL[11a] yielding the *cis*-(1*R*,2*S*)- and *trans*-(1*R*,2*R*)-diastereomers and (*S*)-selectivity by applying (*S*)-MeHNL[11b] to give the *cis*-(1*S*,2*R*)- and *trans*-(1*S*,2*S*)-diastereomers **2** as shown in Scheme 5.

All HNL-catalyzed cyanohydrin formations have been performed under optimized standard conditions.[12] In order to estimate the contribution of chemical addition, for each substrate the reaction was also performed under the same conditions without enzyme (Section 4.4). Table 3 summarizes the results of (*R*)-PaHNL-catalyzed addition of HCN to racemic 2-alkyl cyclohexanones *rac*-**1a**–**g**.



Scheme 4.



Scheme 5.

Table 3. (*R*)-PaHNL catalyzed addition of HCN to *rac*-2-alkyl cyclohexanones **1a–g**

rac-**1**	*t* [h]	Cyanohydrins **2**					Blank exp.	
			Conv. [%]	*cis*:*trans*	*cis*-(1*R*,2*S*) de [%]	*trans*-(1*R*,2*R*) de [%]	Conv. [%]	*cis*:*trans*
1a	18	**2a**	98	51:49	98[a]	93[b]	3	36:64
1b	216	**2b**	95	52:48	93	79	4	35:65
1c	336	**2c**	50	48:52	67	79	5	39:61
1d	336	**2d**	< 2	22:78	—	—	< 2	29:71
1e	96	**2e**	92	42:58	93	91	4	30:70
1f	192	**2f**	2	45:55	—	—	< 2	44:56
1g	336	**2g**	< 1	n.d.	—	—	< 1	n.d.

[a] de (*cis*-(1*S*,2*R*)).
[b] de (*trans*-(1*S*,2*S*)).

The cyclohexanones **1b**, **1c** and **1e** react as expected with high (*R*)-selectivity to give the *cis*-(1*R*,2*S*) and *trans*-(1*R*,2*R*)-diastereomers of **2b**, **2c** and **2e**, respectively (Table 3). Since there is no *cis*/*trans*-selectivity observed, both (1*R*)-diastereomers are obtained in almost equal amounts. The reaction behavior of the methyl derivative **1a**, however, is absolutely unexpected. The (*R*)-PaHNL-* catalyzed reaction turns out to be completely (*S*)-selective, affording the *cis*-(1*S*,2*R*)- and *trans*-(1*S*,2*S*)-**2a** diastereomers in a 1:1 ratio (Table 3). Because the precise structure of the active site of (*R*)-PaHNL is not yet known,[13] a convincing explanation for the inversion of stereoselectivity in the case of the methyl compound **1a** is not currently possible.

From Table 3 it is also apparent that the catalytic activity of the enzyme is reduced with increasing size of the alkyl substituent R. Even after a reaction time of 336 h, the conversion of the *n*-propyl derivative **1c** is only 50% and the corresponding cyanohydrin of the isopropyl compound **1d** could not be detected at all under these conditions. Similar results are found for the butyl derivatives **1f** and **1g**, respectively, whereas the allyl compound **1e** turned out to be a good substrate for (*R*)-PaHNL giving high conversions in shorter reaction times. It must be noted that under the standard conditions the chemical addition of HCN to ketones **1** can be suppressed almost completely, even at long reaction times (Table 3).

In Table 4, the results of the (*S*)-MeHNL-catalyzed addition of HCN to the racemic 2-alkyl cyclohexanones **1a–g** (Scheme 5) are listed. The (*S*)-MeHNL-catalyzed conversion of cyclohexanone derivatives **1a–c**,**e**,**f** afforded selectively the corresponding (1*S*)-cyanohydrins, including the methyl derivative **1a**, to give *cis*-(1*S*,2*R*)- and *trans*-(1*S*,2*S*)-**2a–c**, **2e**, **f** (Table 4). Obviously 2-alkyl cyclo-hexanones **1** with the exception of **1d** and **1g** are better substrates for (*S*)-MeHNL than for (*R*)-PaHNL. The reaction times, for example, are considerably shorter and the dependence on bulky substituents is lower as can be demonstrated by

Table 4. (*S*)-MeHNL catalyzed addition of HCN to *rac*-2-alkyl cyclohexanones **1a–g**

rac-**1**	*t* [h]	Cyanohydrins **2**					Blank exp.	
			Conv. [%]	*cis*:*trans*	*cis*-(1*S*,2*R*) de [%]	*trans*-(1*S*,2*S*) de [%]	Conv. [%]	*cis*:*trans*
1a	3	**2a**	96	60:40	74	33	<1	34:66
1b	24	**2b**	98	38:62	94	88	1	32:68
1c	24	**2c**	97	55:45	99	74	1	n.d.
1d	48	**2d**	<1	n.d.	—	—	<1	n.d.
1e	24	**2e**	90	43:57	97	87	1	24:76
1f	48	**2f**	15	76:24	94	76	≪1	38:62
1g	48	**2g**	≪1	n.d.	—	—	≪1	n.d.

comparing the reactions of the *n*-propyl derivative **1c**. Only 50% of **1c** was converted after 336 h reaction time applying PaHNL, whereas the corresponding cyanohydrin **2c** is obtained in 97% yield after 24 h using MeHNL (Table 4).

The exclusive (*S*)-selectivity of MeHNL-catalyzed additions of HCN to 2-alkyl cyclohexanones **1** can be rationalized by the mechanism of cyanogenesis.[14] From the X-ray crystal structure of (*S*)-MeHNL it is known that the active site is accessible via a narrow channel and consists of a small (S1) and a larger (S2) binding pocket. In the active site the carbonyl group of the incoming substrate is fixed by two hydrogen bonds from Thr11 and from Ser80.[14] Cyclohexanones are assumed to bind to the active site of the enzyme in the channel either in an upright or in a flat mode.[7a] In both cases, the cyanide ion attacks the substrate from below, where His236 is located as a base.[14] From Figure 1 it is apparent that for steric reasons fixation of substrates with equatorial alkyl substituentes[15] in the larger pocket, S2, is strongly favored, thus leading to the *cis*-(1*S*,2*R*) configuration with the cyclohexanone ring in an upright position (Fig. 1a), whereas the *trans*-(1*S*,2*S*)-configuration results from the flat position (Fig. 1b).

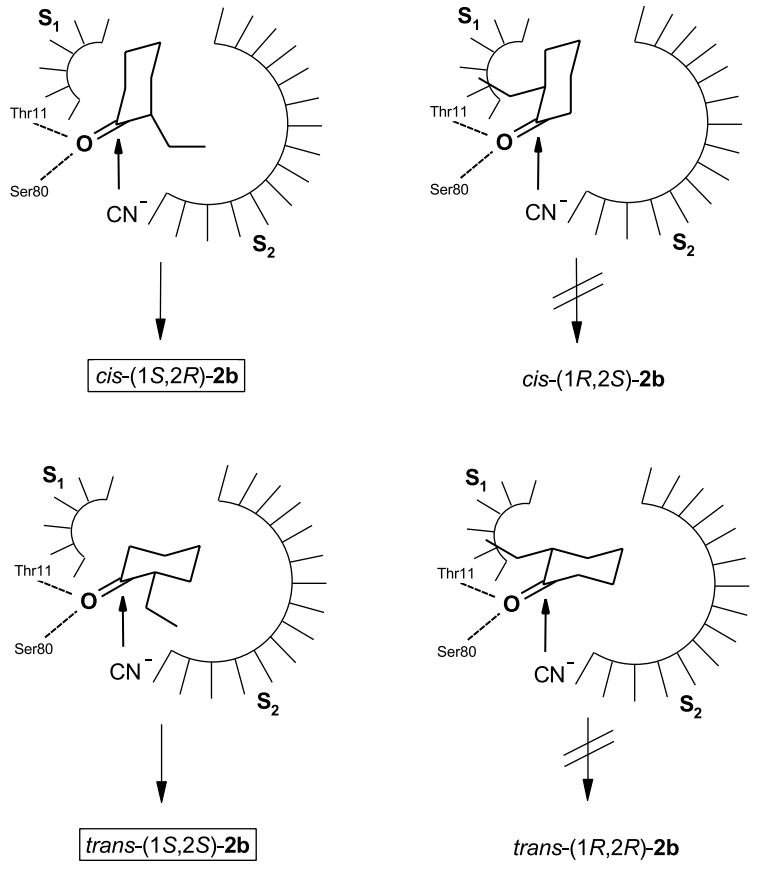
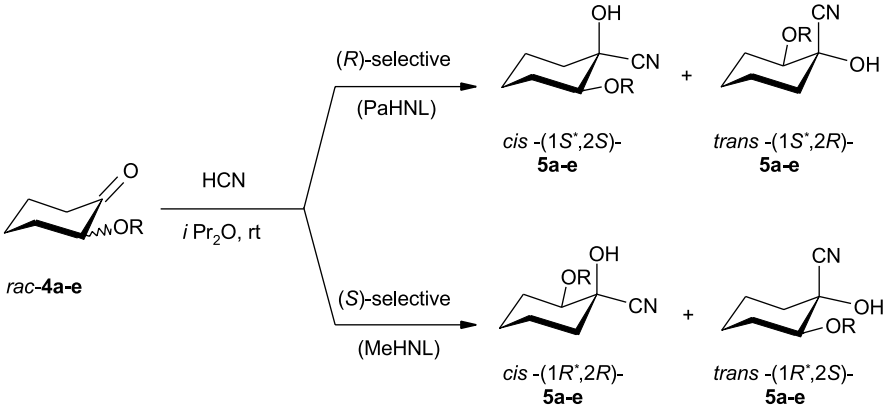


Figure 1. Schematic illustration of HCN addition to 2-ethyl cyclohexanone **1b** in the active site of (*S*)-MeHNL. Configurations of 2-ethyl cyclohexanone cyanohydrin **2b** obtained in upright position (a) and in flat position (b).



*The apparent inversion of configuration at C1 is an artefact of the CIP-priority rules.

Scheme 6.

Table 5. (*R*)-PaHNL catalyzed addition of HCN to *rac*-2-alkoxy cyclohexanones **4a–e** to form the corresponding cyanohydrins **5a–e**

rac-**4**	*t* [h]	Cyanohydrins **5**					Blank exp.	
			Conv. [%]	*cis*:*trans*	*cis*-(1S[a],2*S*) *de*[%]	*trans*-(1S[a],2*R*) de [%]	Conv. [%]	*cis*:*trans*
4a	5	**5a**	19	64:36	48	8	7	58:42
4b	48	**5b**	34	48:52	8	16	8	60:40
4c	48	**5c**	3	45:55	—	—	1	65:35
4d	48	**5d**	10	62:38	—	—	2	61:39
4e	48	**5e**	19	50:50	14	18	5	58:42

[a] The apparent inversion of configuration at C_1 is an artefact of the CIP-priority rules.

Table 6. (*S*)-MeHNL catalyzed addition of HCN to *rac*-2-alkoxy cyclohexanones **4a–e** to form the cyanohydrins **5a–e**

rac-**4**	*t* [h]	Cyanohydrins **5**					Blank exp.	
			Conv. [%]	*cis*:*trans*	*cis*-(1R[a],2*R*) de [%]	*trans*-(1R[a],2*S*) de [%]	Conv. [%]	*cis*:*trans*
4a	5	**5a**	84	59:41	98	83	7	58:42
4b	48	**5b**	23	62:38	37	5[b]	8	60:40
4c	24	**5c**	1	58:42	—	—	< 1	65:35
4d	48	**5d**	5	63:37	—	—	2	61:39
4e	48	**5e**	27	61:39	50	13	5	58:42

[a] The apparent inversion of configuration at C_1 is an artefact of the CIP-priority rules.
[b] de (*cis*-(1*S*,2*S*)).

Owing to the reduced steric demand of the methyl group in **1a**, a fixation of the substrate with the methyl group in the small pocket S1 is also possible, resulting in a diminished stereo-selectivity of the HCN addition (Table 4).

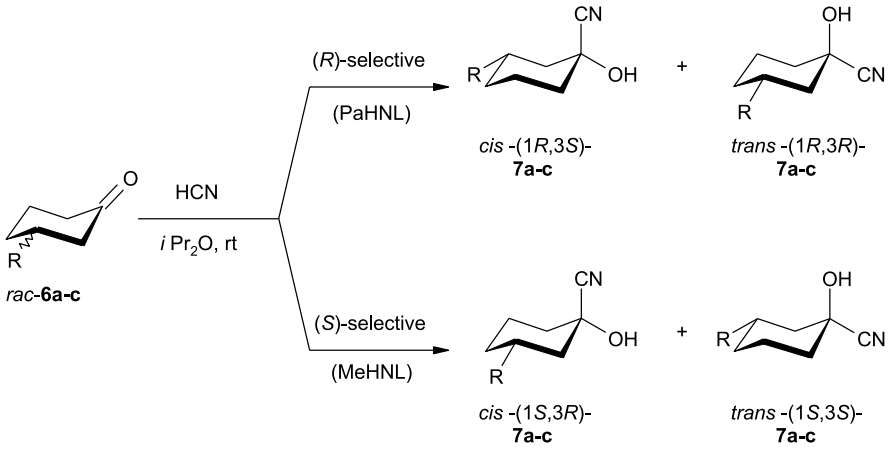
2.3. (*R*)-PaHNL- and (*S*)-MeHNL-catalyzed addition of HCN to racemic 2-alkoxy cyclohexanones, *rac*-4

HNL-catalyzed additions of HCN to racemic 2-alkoxy cyclohexanones *rac*-**4** are depicted in Scheme 6. In contrast to the 2-alkyl cyclohexanones **1**, the comparable 2-alkoxy compounds **4** are poorer substrates for both PaHNL and MeHNL. Due to the fast chemical addition of HCN to the alkoxy derivatives **4** not only the yields, but also the stereoselectivities of HNL-catalyzed cya-nohydrin formations of 2-alkoxy cyclohexanones are unsatisfactory (Tables 5 and 6).

The only exception is the MeHNL-catalyzed addition of HCN to 2-methoxy cyclohexanone (**5a**) which occurs relatively quickly with high diastereoselectivity (Table 6). A comparison of these investigations with additions of HCN to α- and β-substituted aldehydes catalyzed by the hydroxynitrile lyase from *Hevea brasiliensis* (HbHNL)[16] gave similar results. Whereas alkyl substituted aldehydes reacted highly diastereoselectively, the corresponding O-analogues gave only low de values.[16]

2.4. (*R*)-PaHNL- and (*S*)-MeHNL-catalyzed addition of HCN to racemic 3-substituted cyclohexanones *rac*-6

The 3-substituted cyclohexanones **6a–c** were reacted with HCN in the presence of both (*R*)-PaHNL and (*S*)-MeHNL as biocatalyst (Scheme 7, Tables 7 and 8). As can be seen from Table 7, the PaHNL-catalyzed additions are highly (*R*)-selective for the (3*S*)-enantiomers of *rac*-**6a–c** leading to the *cis*-(1*R*,3*S*) diastereomers of **7a–c** (Table 7). The (*R*)-selectivity, however, is only moderate for the



Scheme 7.

Table 7. (*R*)-PaHNL catalyzed addition of HCN to racemic 3-substituted cyclohexanones **6a–c** to form cyanohydrins **7a–c**

rac-**4**	*t* [h]	Cyanohydrins **5**					Blank exp.	
			Conv. [%]	*cis*:*trans*	*cis*-(1*R*,3*S*) de [%]	*trans*-(1*R*,3*R*) de [%]	Conv. [%]	*cis*:*trans*
6a	5	**7a**	99	61:39	87	49	2	78:22
6b	6	**7b**	88	64:36	99	73	4	88:12
6c	3	**7c**	99	92:8	95	69[a]	15	88:12

[a] de (*cis*-(1*S*,3*R*)).

Table 8. (*S*)-MeHNL catalyzed addition of HCN to racemic 3-substituted cyclohexanones **6a–c** to form the corresponding cyanohydrins **7a–c**

rac-**4**	*t* [h]	Cyanohydrins **5**					Blank exp.	
			Conv. [%]	*cis*:*trans*	*cis*-(1*S*,3*R*) de [%]	*trans*-(1*S*,3*S*) de [%]	Conv. [%]	*cis*:*trans*
6a	5	**7a**	99	42:58	61	94	2	78:22
6b	6	**7b**	99	46:54	77	88	4	88:12
6c	1	**7c**	98	55:45	90	76	14	88:12

(3*R*)-enantiomers of *rac*-**6a**,**b** and even inverted for *rac*-**6c**, which reacts preferentially to give the *cis*-(1*S*,3*R*) diastereomer (Table 7). In Table 8, the results of (*S*)-MeHNL-catalyzed additions of HCN to racemic 3-substituted cyclohexanones **6a–c** are summarized.

For all substrates **6a–c** the reaction is (*S*)-selective as expected, yielding the *cis*-(1*S*,3*R*)- and the *trans*-(1*S*,3*S*)-diastereomers as major products (Table 8).

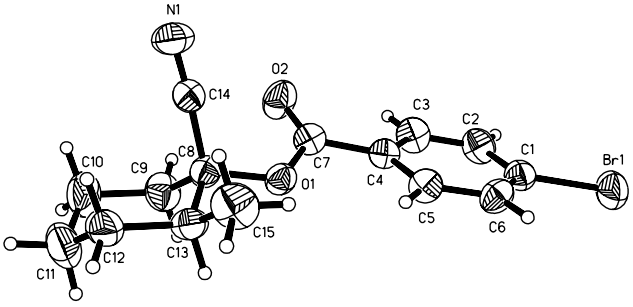


Figure 3. ORTEP view of *trans*-(1*S*,2*S*)-1-(4-bromobenzoyloxy)-2-methylcyclohexanecarbonitrile (*trans*-(1*S*,2*S*)-**2a**′).

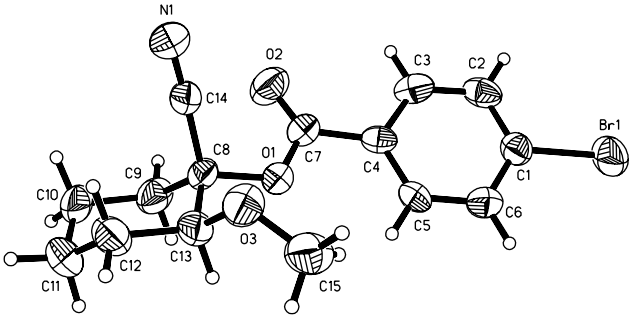


Figure 4. ORTEP view of *trans*-(1*R*,2*S*)-1-(4-bromobenzoyloxy)-2-methoxycyclohexanecarbonitrile (*trans*-(1*R*,2*S*)-**5a**′).

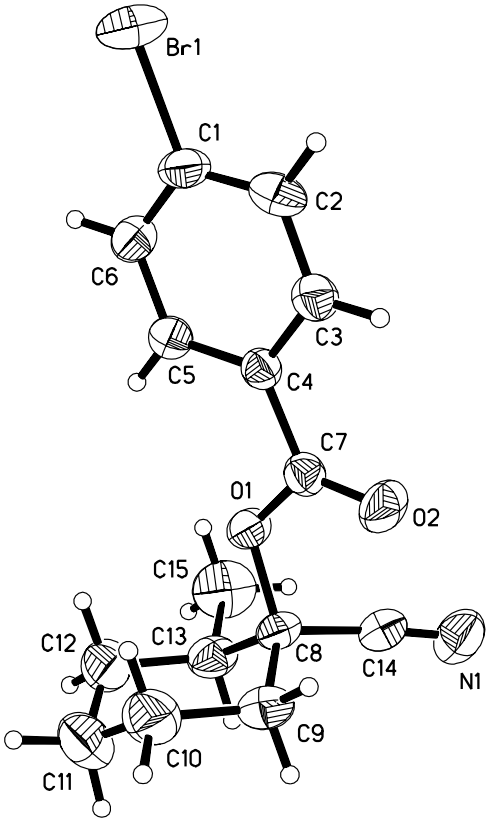


Figure 2. ORTEP view of *cis*-(1*S*,2*R*)-1-(4-bromobenzoyloxy)-2-methylcyclohexanecarbonitrile (*cis*-(1*S*,2*R*)-**2a**′).

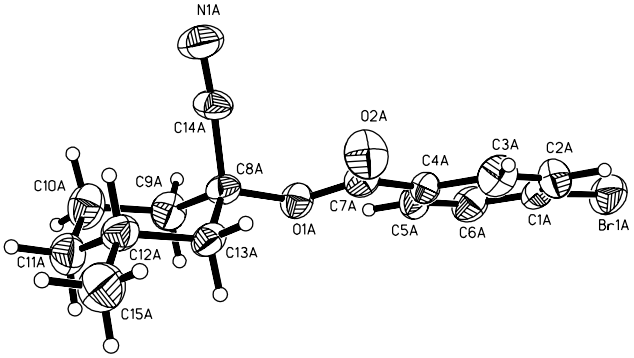


Figure 5. ORTEP view of *cis*-(1*S*,3*R*)-1-(4-bromobenzoyloxy)-3-methylcyclohexanecarbonitrile (*cis*-(1*S*,3*R*)-**7a**′).

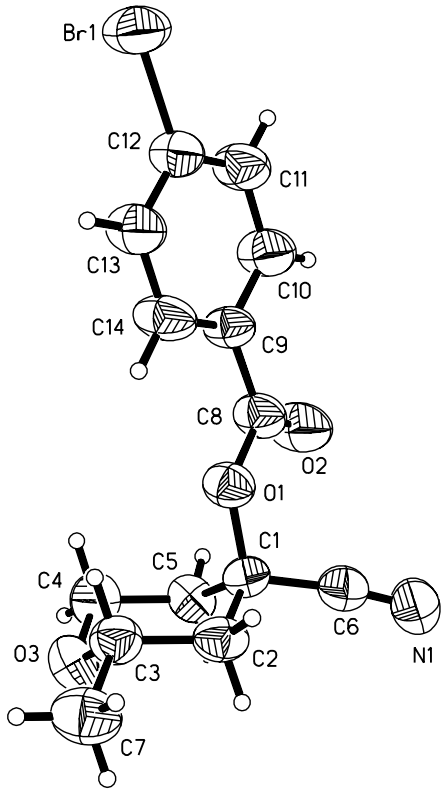


Figure 6. ORTEP view of *trans*-(1*S*,3*S*)-1-(4-bromobenzoyloxy)-3-methylcyclohexanecarbonitrile (*trans*-(1*S*,3*S*)-**7a**′).

2.5. Structural assignment of 2- and 3-substituted cyanohydrins 2, 5 and 7, respectively

Structure determinations were performed on the 2-methyl, the 2-methoxy and the 3-methyl compounds **2a**, **5a** and **7a**, respectively. The *cis*/*trans*-mixtures obtained in the HNL-catalyzed reactions were reacted with *p*-bromobenzoyl chloride to give the corresponding *O*-benzoyl derivatives, which could be separated by column chromatography. After recrystallization, the pure enantiomers *cis*-(1*S*,2*R*)-**2a**′, *trans*-(1*S*,2*S*)-**2a**′, *trans*-(1*R*,2*S*)-**5a**′, *cis*-(1*S*,3*R*)-**7a**′, and *trans*-(1*S*,3*S*)-**7a**′ were obtained as single crystals suitable for X-ray structure determination (Figs. 2–6, Table 9).[17] The absolute configurations were elucidated from diffraction data using anomalous dispersion.

By correlation of GC-data on achiral and chiral phases and analyses of NMR-data, an unambiguous assignment of structures for all the prepared cyanohydrins **2**, **5** and **7** was possible (Section 4). X-ray structure determinations were also performed on the *O*-benzoyl derivatives of the MeHNL-catalyzed reaction products of **7b** and **7c**, respectively.[17]

3. Conclusions

Cyanohydrins of 2- and 3-monosubstituted cyclohexanones contain two stereogenic centers with the implication of four possible stereoisomers. Although derivatives of the corresponding carboxylic acids are applied as pharmaceuticals, stereoselective syntheses of these interesting compounds are not described in the literature. For the enantioselective

Table 9. X-Ray crystal data collection and refinement for *cis*-(1*S*,2*R*)-**2a**′, *trans*-(1*S*,2*S*)-**2a**′, *trans*-(1*R*,2*S*)-**5a**′, *cis*-(1*S*,3*R*)-**7a**′ *trans*-(1*S*,3*S*)-**7a**′

	cis-(1*S*,2*R*)-**2a**′	*trans*-(1*S*,2*S*)-**2a**′	*trans*-(1*R*,2*S*)-**5a**′	*cis*-(1*S*,3*R*)-**7a**′	*trans*-(1*S*,3*S*)-**7a**′
Formula	$C_{15}H_{16}NO_2Br$	$C_{15}H_{16}NO_2Br$	$C_{15}H_{16}NO_3Br$	$C_{15}H_{16}NO_2Br$	$C_{15}H_{16}NO_2Br$
FW	322.18	322.18	338.21	322.18	322.18
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Monoclinic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
a (Å)	9.764(2)	7.1676(9)	7.303(2)	7.5856(13)	7.115(3)
b (Å)	11.889(3)	7.6999(12)	11.350(3)	7.2175(12)	12.274(5)
c (Å)	12.922(2)	27.057(4)	18.455(4)	27.630(4)	17.334(6)
α (°)	90	90	90	90	90
β (°)	90	90	90	90.809(12)	90
γ (°)	90	90	90	90	90
V (Å^3)	1500.1(5)	1493.3(4)	1529.8(6)	1512.5(4)	1513.7(10)
Z	4	4	4	4	4
ρ_{calc} (mg m^{-3})	1.427	1.433	1.468	1.415	1.414
F(000)	656	656	688	656	656
μ (mm^{-1})	2.738	2.750	2.693	2.715	2.713
θ range (°)	2.33–27.50	1.51–25.99	2.11–26.00	1.47–26.00	2.03–27.49
Data collection[a]					
Reflections collected/unique	13726/3442	6316/2932	1736/1736	3469/3220	2004/2004
Data/restraints/parameters	3238/0/173	2835/0/173	1590/0/182	2928/1/344	1809/0/173
Goodness-of-fit on F^2	1.052	1.039	1.111	1.094	1.100
Final *R* indices					
[$I>2\sigma(I)$]	$R1=0.0433$	$R1=0.0452$	$R1=0.0538$	$R1=0.0549$	$R1=0.0608$
	$wR2=0.0813$	$wR2=0.1031$	$wR2=0.1003$	$wR2=0.0880$	$wR2=0.1060$
R indices (all data)	$R1=0.0749$	$R1=0.0615$	$R1=0.0898$	$R1=0.1018$	$R1=0.1121$
	$wR2=0.0930$	$wR2=0.1149$	$wR2=0.1288$	$wR2=0.1151$	$wR2=0.1294$
Absolute structure parameter	0.006(11)	−0.01(2)	0.02(2)	0.01(2)	0.01(3)
Largest diff.	0.297	0.539	0.360	0.306	0.389
Peak and hole (e Å^{-3})	−0.373	−0.354	−0.285	−0.359	−0.362

[a] $T=293$ K, Nicolet P3 diffractometer, Mo Kα ($l=0.71073$) or Siemens P4 diffractometer, Cu Kα ($l=1.54178$) radiation.

Table 10. Spectroscopic data of the 2- and 3-substituted cyclohexanone cyanohydrins **2**, **5**, and **7**

Compound	^{1}H NMR (250 MHz) (J in Hz) δ	^{13}C NMR (125.8 MHz) δ
rac-**2a**	1.12 (d, ^3J=6.8, 0.7H, *cis*-CH_3), 1.15 (d, ^3J=6.6, 2.3H, *trans*-CH_3), 1.22–1.45 (m, 2H, 2CH), 1.52–1.91 (m, 6H, 6CH), 2.09–2.25 (m, 1H, C^6H_{eq}), 2.55, 2.93 (br s, 1H, OH)	16.01 (*cis*-CH_3), 16.10 (*trans*-CH_3), 19.97 (*cis*-C^5H_2), 23.62 (*trans*-C^5H_2), 24.28 (*cis*-C^4H_2), 24.80 (*trans*-C^4H_2), 28.21 (*cis*-C^3H_2), 31.68 (*trans*-C^3H_2), 37.05 (*cis*-C^6H_2), 38.62 (*trans*-C^6H_2), 39.19 (*cis*-C^2H), 41.65 (*trans*-C^2H), 70.77 (*cis*-C^1), 74.84 (*trans*-C^1), 120.21 (*trans*-CN), 122.51 (*cis*-CN)
rac-**2b**	0.97 (t, ^3J=7.4, 2.3H, *trans*-CH_2CH_3), 0.98 (t, ^3J=7.3, 0.7H, *cis*-CH_2CH_3), 1.11–1.44 (m, 4H, 4CH), 1.53–2.02 (m, 6H, 6CH), 2.08–2.24 (m, 1H, C^6H_{eq}), 2.62 and 3.03 (br s, 1H, OH)	11.59 (*trans*-CH_2CH_3), 11.86 (*cis*-CH_2CH_3), 20.24 (*cis*-C^5H_2), 22.85 (*trans*-C^5H_2), 23.29 (*cis*-CH_2CH_3), 23.44 (*trans*-CH_2CH_3), 24.18, 24.66, 24.71, 27.81 (C^4H_2), (C^3H_2), 37.49 (*cis*-C^6H_2), 39.08 (*trans*-C^6H_2), 45.99 (*cis*-C^2H), 48.33 (*trans*-C^2H), 71.40 (*cis*-C^1), 74.20 (*trans*-C^1), 120.50 (*trans*-CN), 122.66 (*cis*-CN)
rac-**2c**	0.94 (t, ^3J=7.1, 2.3H, *trans*-CH_2CH_3), 0.95 (t, ^3J=7.0, 0.7H, *cis*-$CH_2CH_2CH_3$), 1.12–1.36 (m, 4H, 1CH, $CH_2CH_2CH_3$, $CH_AHCH_2CH_3$), 1.41–1.98 (m, 8H, 7CH, $CH_BCH_2CH_3$), 2.09–2.27 (m, 1H, $1C^6H_{eq}$), 2.55 and 2.95 (br s, 1H, OH)	14.12 (*cis*-$CH_2CH_2CH_3$), 14.20 (*trans*-$CH_2CH_2CH_3$), 20.19 ($CH_2CH_2CH_3$), 20.35 (*cis*-C^5H_2), 23.41 (*trans*-C^5H_2), 24.22 (*cis*-C^4H_2), 24.73 (*trans*-C^4H_2), 25.29 (*cis*-C^3H_2), 28.42 (*trans*-C^3H_2), 32.24 (*trans*-$CH_2CH_2CH_3$), 32.59 (*cis*-$CH_2CH_2CH_3$), 37.49 (*cis*-C^6H_2), 39.04 (*trans*-C^6H_2), 43.97 (*cis*-C^2H), 46.41 (*trans*-C^2H), 71.44 (*cis*-C^1), 74.20 (*trans*-C^1), 120.52 (*trans*-CN), 122.64 (*cis*-CN)
rac-**2d**	0.97–1.04 (m, 6H, $CH(CH_3)_2$), 1.18–1.90 (m, 8H, 8CH), 2.02 (br s, 0.3H, OH), 2.09–2.26 (m, 2H, C^6H_{eq}, 1CH), 2.47 (br s, 0.7H, OH)	17.45, 18.67, 23.23, 23.32 ($CH(CH_3)_2$)*), 20.13, 20.26, 23.65, 23.90, 25.28, 25.33 (C^5H_2), (C^4H_2), (C^3H_2), 26.29, 29.71 ($CH(CH_3)_2$), 39.71 (*cis*-C^6H_2), 41.07 (*trans*-C^6H_2), 49.42 (*cis*-C^2H), 52.36 (*trans*-C^2H), 71.20 (*cis*-C^1), 72.53 (*trans*-C^1), 121.23 (*trans*-CN), 121.69 (*cis*-CN)*) rotamers
rac-**2e**	1.11–1.40 (m, 2H, 2CH), 1.53–1.92 (m, 6H, 6CH), 2.03–2.36 (m, 2H, 2CH), 2.47–2.73 (m, 1H, 1CH), 3.19 (br s, 1H, OH), 5.06–5.28 (m, 2H, $CH_2CH{=}CH_2$), 5.74–5.97 (m, 1H, $CH_2CH{=}CH_2$)	20.15 (*cis*-C^5H_2), 23.29 (*trans*-C^5H_2), 24.23 (*cis*-C^4H_2), 24.75 (*trans*-C^4H_2), 25.03 (*cis*-C^3H_2), 29.20 (*trans*-C^3H_2), 35.36 (*cis*-$CH_2CH{=}CH_2$), 36.19 (*trans*-$CH_2CH{=}CH_2$), 37.59 (*cis*-C^6H_2), 38.80 (*trans*-C^6H_2), 43.97 (*cis*-C^2H), 46.38 (*trans*-C^2H), 71.17 (*cis*-C^1), 74.68 (*trans*-C^1), 117.62 (*cis*-$CH_2CH{=}CH_2$), 117.79 (*trans*-$CH_2CH{=}CH_2$), 120.21 (*trans*-CN), 122.35 (*cis*-CN), 136.00 (*cis*-$CH_2CH{=}CH_2$), 136.86 (*trans*-$CH_2CH{=}CH_2$)
rac-**2f**	0.91 (t, ^3J=7.1, 2H, *trans*-$CH_2CH_2CH_2CH_3$), 0.92 (t, ^3J=7.0, 1H, *cis*-$CH_2CH_2CH_2CH_3$), 1.11–1.47 (m, 7H, 3CH, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$), 1.52–1.95 (m, 7H, 7CH), 2.09–2.23 (m, 1H, C^6H_{eq}), 2.45 and 2.90 (br s, 1H, OH)	14.00 (*cis*-$CH_2CH_2CH_2CH_3$), 14.03 (*trans*-$CH_2CH_2CH_2CH_3$), 20.21 (*cis*-C^5H_2), 22.74 (*trans*-C^5H_2), 22.83, 23.42 ($CH_2CH_2CH_2CH_3$), 24.24 (*cis*-C^4H_2), 24.74 (*trans*-C^4H_2), 25.31 (*cis*-C^3H_2), 28.45 (*trans*-C^3H_2), 29.23, 29.40, 29.73, 30.12 ($CH_2CH_2CH_2CH_3$), ($CH_2CH_2CH_2CH_3$), 37.50 (*cis*-C^6H_2), 39.05 (*trans*-C^6H_2), 44.19 (*cis*-C^2H), 46.66 (*trans*-C^2H), 71.47 (*cis*-C^1), 74.23 (*trans*-C^1), 120.50 (*trans*-CN), 122.61 (*cis*-CN)
rac-**5a**	1.19–1.97 (m, 6H, 6CH), 2.14–2.26 (m, 2H, C^6H_{ax}, C^6H_{eq}), 3.13 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.1 Hz, ^3J (C^2H_{ax}, C^3H_{ax})=11.0, 0.6H, *trans*-C^2H_{ax}), 3.39 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.4, ^3J (C^2H_{ax}, C^3H_{ax})=10.1, 0.4H, *cis*-C^2H_{ax}), 3.46 and 3.52 (s, 3H, OCH_3), 3.70 (br s, 1H, OH)	19.59 (*cis*-C^5H_2), 22.38 (C^4H_2), 23.24 (*trans*-C^5H_2), 25.19 (*cis*-C^3H_2), 26.85 (*trans*-C^3H_2), 35.01 (*cis*-C^6H_2), 35.40 (*trans*-C^6H_2), 56.88 (*trans*-OCH_3), 57.60 (*cis*-OCH_3), 69.94 (*cis*-C^1), 73.92 (*trans*-C^1), 81.18 (*cis*-C^2H), 84.24 (*trans*-C^2H), 119.75 (*trans*-CN), 121.79 (*cis*-CN)
rac-**5b**	1.22–1.96 (m, 6H, 6CH), 1.25 (t, ^3J=7.0, 3H, OCH_2CH_3), 2.10–2.25 (m, 2H, C^6H_{ax}, C^6H_{eq}), 3.21 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.2, ^3J (C^2H_{ax}, C^3H_{ax})=11.1, 0.5H, C^2H_{ax}), 3.40–3.52 (m, 0.5H, C^2H_{ax}), 3.62–3.83 (m, 3H, OCH_2CH_3, OH)	15.38 (OCH_2CH_3), 15.47 (OCH_2CH_3), 19.54 (C^5H_2), 22.39 (C^4H_2), 22.58 (C^4H_2), 23.37 (C^5H_2), 26.12 (C^3H_2), 27.68 (C^3H_2), 35.02 (C^6H_2), 35.34 (C^6H_2), 64.62 (OCH_2CH_3), 65.64 (OCH_2CH_3), 70.10 (C^1), 73.91 (C^1), 79.38 (C^2H), 82.61 (C^2H), 119.87 (CN), 121.91 (CN)
rac-**5c**	0.95 (t, ^3J=7.4, 1.5H, $OCH_2CH_2CH_3$), 0.96 (t, ^3J=7.4, 1.5H, $OCH_2CH_2CH_3$), 1.21–1.31 (m, 1H, $OCH_2CH_2CH_3$), 1.42–1.90(m, 7H, 6CH, $OCH_2CH_2CH_3$), 2.09–2.24 (m, 2H, C^6H_{ax}, C^6H_{eq}), 3.19 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.2, ^3J (C^2H_{ax}, C^3H_{ax})=11.3, 0.5H, C^2H_{ax}), 3.23 (bs, 0.5H, OH), 3.33–3.38 (m, 0.5H, $OCH_AHCH_2CH_3$), 3.46 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.5, ^3J (C^2H_{ax}, C^3H_{ax})=10.2, 0.5H, C^2H_{ax}), 3.55–3.66 (m, 2H, $OCH_AHCH_2CH_3$, OH, $OCH_BCH_2CH_3$)	10.53 ($OCH_2CH_2CH_3$), 19.60, 22.39, 22.51, 23.08, 23.17, 23.34 (C^5H_2), (C^4H_2), ($OCH_2CH_2CH_3$), 26.02 (*cis*-C^3H_2), 27.58 (*trans*-C^3H_2), 35.01 (*cis*-C^6H_2), 35.31 (*trans*-C^6H_2), 70.12 (*trans*-$OCH_2CH_2CH_3$), 70.82 (*cis*-$OCH_2CH_2CH_3$), 71.83 (*cis*-C^1), 74.03 (*trans*-C^1), 79.54 (*cis*-C^2H), 82.73 (*trans*-C^2H), 119.85 (*trans*-CN), 121.88 (*cis*-CN)
rac-**5d**	1.17–1.24 (m, 6H, $OCH(CH_3)_2$), 1.42–1.83 (m, 6H, 6CH), 2.02–2.09 (m, 1H, C^6H_{ax}, C^6H_{eq}), 2.25–2.35 (m, 1H, C^6H_{ax}, C^6H_{eq}), 3.22–3.28 (br s, 0.5H, OH), 3.24 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.1 Hz, ^3J (C^2H_{ax}, C^3H_{ax})=10.8, 0.5H, C^2H_{ax}), 3.51 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.2 Hz, ^3J (C^2H_{ax}, C^3H_{ax})=10.2, 0.5H, C^2H_{ax}), 3.60 (br s, 0.5H, OH), 3.78 (sept, ^3J=6.1, 0.4H, *trans*-$OCH(CH_3)_2$), 3.91 (sept, ^3J=5.9, 0.6H, *cis*-$OCH(CH_3)_2$)	19.42, 21.87, 22.31, 22.38, 22.82, 23.09, 23.41, 23.54 (C^5H_2), (C^4H_2), ($OCH(CH_3)_2$)*), 27.19 (*cis*-C^3H_2), 28.54 (*trans*-C^3H_2), 35.01 (*cis*-C^6H_2), 35.28 (*trans*-C^6H_2), 70.08 (*trans*-$OCH(CH_3)_2$), 70.35 (*cis*-$OCH(CH_3)_2$), 71.66 (*cis*-C^1), 73.94 (*trans*-C^1), 77.26 (*cis*-C^2H), 80.33 (*trans*-C^2H), 119.95 (*trans*-CN), 122.01 (*cis*-CN)*) rotamers
rac-**5e**	1.43–1.88 (m, 6H, 6CH), 2.09–2.14 (m, 1H, CH), 2.21–2.27 (m, 1H, CH), 3.21 (br s, 0.5H, OH), 3.25–3.29 (m, 0.5H, C^2H_{ax}), 3.52–3.55 (m, 0.5H, C^2H_{ax}), 3.63 (br s, 0.5H, OH), 3.99–4.03 (m, 0.5H, $OCH_AHCH{=}CH_2$), 4.15–4.25 (m, 1.5H, $OCH_AHCH{=}CH_2$, $OCH_BCH{=}CH_2$), 5.22-5.24 (m, 1H, $OCH_2CH{=}CH_AH$), 5.30–5.34 (m, 1H, $OCH_2CH{=}CH_BH$), 5.88–5.98 (m, 1H, $OCH_2CH{=}CH_2$)	19.53, 22.37, 22.55, 23.33 (C^5H_2), (C^4H_2), 26.09 (*cis*-C^3H_2), 27.70 (*trans*-C^3H_2), 35.08 (*cis*-C^6H_2), 35.44 (*trans*-C^6H_2), 70.05, 70.87 ($OCH_2CH{=}CH_2$), 70.13 (*cis*-C^1), 73.95 (*trans*-C^1), 78.75 (*cis*-C^2H), 82.11 (*trans*-C^2H), 117.88, 118.02 ($OCH_2CH{=}CH_2$), 119.76 (*trans*-CN), 121.81 (*cis*-CN), 134.14, 134.21 ($OCH_2CH{=}CH_2$)
rac-**7a**	0.82–1.04 (m, 1H, CH), 0.92 (d, ^3J=6.4 Hz, 0.5H, *trans*-CH_3), 0.98 (d, ^3J=6.3 Hz, 2.5H, *cis*-CH_3), 1.16–1.26 (m, 1H, CH), 1.38–1.90 (m, 5H, 5CH), 2.06–2.21 (m, 2H, C^2H_{eq}, C^6H_{eq}), 3.14 (br s, 1H, OH)	19.89 (*trans*-C^5H_2), 21.64 (*cis*-C^5H_2), 21.80 (*trans*-CH_3), 22.91 (*cis*-CH_3), 26.25 (*trans*-C^3H), 30.14 (*cis*-C^3H), 33.19 (*trans*-C^4H_2), 33.39 (*cis*-C^4H_2), 36.21 (*trans*-C^6H_2), 37.78 (*cis*-C^6H_2), 44.48 (*trans*-C^2H_2), 46.15 (*cis*-C^2H_2), 67.25 (*trans*-C^1), 70.54 (*cis*-C^1), 121.89 (*cis*-CN), 122.95 (*trans*-CN)

Table 10 (*continued*)

Compound	^{1}H NMR (250 MHz) (J in Hz) δ	^{13}C NMR (125.8 MHz) δ
rac-**7b**	1.22–1.38 (m, 1H, CH), 1.45–1.81 (m, 3H, 3CH), 1.95–2.03 (m, 2H, 2CH), 2.13–2.16 (m, 0.4H, *trans*-CH), 2.23–2.27 (m, 0.6H, *cis*-CH), 2.32–2.56 (m, 2H, CH, C^3H_{ax}), 3.09 (br s, 1H, *trans*-OH), 3.40 (br s, 1H, *cis*-OH)	18.45 (s, *trans*-CH_2), 21.51 (s, *cis*-CH_2), 23.38 (q, ^3J(C,F)=2.0 Hz, *cis*-C^4H_2), 23.46 (q, ^3J(C,F)=2.1 Hz, *trans*-C^4H_2), 34.93 (q, ^3J(C,F)=2.2 Hz, *trans*-C^2H_2), 35.80 (s, *cis*-C^2H_2), 36.30 (q, ^2J(C,F)=27.7 Hz, *trans*-C^3H), 36.62 (q, ^3J(C,F)=2.5 Hz, *trans*-CH_2), 37.39 (s, *cis*-CH_2), 39.87 (q, ^2J(C,F)=27.9 Hz, *cis*-C^3H), 65.98 (*trans*-C^1), 69.47 (*cis*-C^1), 120.61 (*cis*-CN), 121.78 (*trans*-CN), 126.55 (q, ^1J(C,F)=278.4 Hz, *cis*-CF_3), 127.11 (q, ^1J(C,F)=278.3 Hz, *trans*-CF_3)
rac-**7c**	1.52–1.70 (m, 3H, 3CH), 1.85–2.08 (m, 4H, 4CH), 2.17–2.20 (m, 1H, *cis*-CH), 3.37 (s, 3H, *cis*-OCH_3), 3.58–3.63 (m, 1H, *cis*-C^3H_{ax}), 4.35 (br s, 1H, OH)	16.69 (*cis*-C^5H_2), 28.22 (*cis*-C^4H_2), 37.21 (*cis*-C^2H_2), 40.61 (*cis*-C^6H_2), 56.46 (*cis*-OCH_3), 68.50 (*cis*-C^1), 75.86 (*cis*-C^3H), 121.84 (*cis*-CN)

Table 11. Spectroscopic data of the racemic silylated 2-substituted cyclohexanone cyanohydrins **3**

Compound	^{1}H NMR (500 MHz) (J in Hz) δ	^{13}C NMR (125.8 MHz) δ
rac-**3a**	0.24 (s, 6.8H, *trans*-$Si(CH_3)_3$), 0.25 (s, 2.2H, *cis*-$Si(CH_3)_3$), 1.03 (d, ^3J=6.7, 0.8H, *cis*-CH_3), 1.08 (d, ^3J=6.5, 2.2H, *trans*-CH_3), 1.18–1.42 (m, 2H, 2CH); 1.50–1.85 (m, 6H, 6CH); 2.06–2.22 (m, 1H, C^6H_{eq})	1.08 (*cis*-$Si(CH_3)_3$), 1.42 (*trans*-$Si(CH_3)_3$), 16.40 (CH_3), 20.15 (*cis*-C^5H_2), 23.72 (*trans*-C^5H_2), 24.45 (*cis*-C^4H_2), 24.87 (*trans*-C^4H_2), 28.26 (*cis*-C^3H_2), 31.50 (*trans*-C^3H_2), 38.14 (*cis*-C^6H_2), 39.70 (*trans*-C^6H_2), 40.81 (*cis*-C^2H), 43.13 (*trans*-C^2H), 71.60 (*cis*-C^1), 75.98 (*trans*-C^1), 120.17 (*trans*-CN), 122.45 (*cis*-CN)
rac-**3b**	0.24 (s, 9H, $Si(CH_3)_3$), 0.93 (t, ^3J=7.3, 3H, CH_2CH_3), 1.03–1.36 (m, 4H, 4CH), 1.48–1.83 (m, 4H, 4CH), 1.85–2.03 (m, 2H, 2CH), 2.06–2.12 (m, 0.25H, *cis*-C^6H_{eq}), 2.15–2.20 (m, 0.75H, *trans*-C^6H_{eq})	1.12 (*cis*-$Si(CH_3)_3$), 1.46 (*trans*-$Si(CH_3)_3$), 11.71 (CH_2CH_3), 20.47 (*cis*-C^5H_2), 22.92, 23.47, 23.56 ((*trans*-C^5H_2), (CH_2CH_3)), 24.26 (*cis*-C^4H_2), 24.63 (*cis*-C^4H_2), 24.79 (*trans*-C^5H_2), 27.70 (*trans*-C^3H_2), 38.46 (*cis*-C^6H_2), 39.99 (*trans*-C^6H_2), 47.57 (*cis*-C^2H), 49.81 (*trans*-C^2H), 72.25 (*cis*-C^1), 75.50 (*trans*-C^1), 120.49 (*trans*-CN), 122.71 (*cis*-CN)
rac-**3c**	0.24 (s, 9H, $Si(CH_3)_3$), 0.91 (t, ^3J=7.0, 3H, $CH_2CH_2CH_3$), 1.10–1.31 (m, 4H, $CH_2CH_2CH_3$, 2CH), 1.36–1.92 (m, 8H, $CH_2CH_2CH_3$, 6CH), 2.03–2.12 (m, 0.25H, *cis*-C^6H_{eq}), 2.15–2.20 (m, 0.75H, *trans*-C^6H_{eq})	1.18 (*cis*-$Si(CH_3)_3$), 1.51 (*trans*-$Si(CH_3)_3$), 14.24 (*cis*-($CH_2CH_2CH_3$)), 14.31 (*trans*-($CH_2CH_2CH_3$)), 20.24 (*cis*-($CH_2CH_2CH_3$)), 20.32 (*trans*-($CH_2CH_2CH_3$)), 20.50 (*cis*-C^5H_2), 23.58 (*trans*-C^5H_2), 24.34 (*cis*-C^4H_2), 24.85 (*trans*-C^4H_2), 25.32 (*cis*-C^3H_2), 28.45 (*trans*-C^3H_2), 32.48 (*trans*-($CH_2CH_2CH_3$)), 32.86 (*cis*-($CH_2CH_2CH_3$)), 38.52 (*cis*-C^6H_2), 40.01 (*trans*-C^6H_2), 45.56 (*cis*-C^2H), 47.84 (*trans*-C^2H), 72.35 (*cis*-C^1), 75.55 (*trans*-C^1), 120.59 (*trans*-CN), 122.76 (*cis*-CN)
rac-**3d**	0.24 (s, 5.8H, *trans*-$Si(CH_3)_3$), 0.25 (s, 3.2H, *cis*-$Si(CH_3)_3$), 0.90–0.99 (m, 6H, $CH(CH_3)_2$)), 1.13–1.61 (m, 6H, 6CH), 1.69–1.83 (m, 2H, 2CH), 2.05–2.34 (m, 2H, C^6H_{eq}, $CH(CH_3)_2$)	1.16 (*cis*-$Si(CH_3)_3$), 1.52 (*trans*-$Si(CH_3)_3$), 17.11, 18.20, 23.40, 23.51 ($CH(CH_3)_2^*$)), 20.22, 20.35, 23.55, 23.77, 25.38, 25.46, (C^5H_2, C^4H_2, C^3H_2), 25.83, 29.85 ($CH(CH_3)_2$), 39.77 (*cis*-C^6H_2), 41.08 (*trans*-C^6H_2), 51.01 (*cis*-C^2H), 53.71 (*trans*-C^2H), 73.52 (*cis*-C^1), 73.80 (*trans*-C^1), 121.38 (*trans*-CN), 122.86 (*cis*-CN)*) rotamers
rac-**3e**	0.24 (s, 6.8H, *trans*-$Si(CH_3)_3$), 0.25 (s, 2.2H, *cis*-$Si(CH_3)_3$), 1.11–1.36 (m, 2H, 2CH), 1.43–2.22 (m, 8H, 6CH, $CH_2CH{=}CH_2$), 2.43–2.51 (m, 0.25H, *cis*-C^6H_{eq}), 2.65–2.76 (m, 0.75H, *trans*-C^6H_{eq}), 5.01–5.10 (m, 2H, $CH_2CH{=}CH_2$), 5.65–5.85 (m, 1H, $CH_2CH{=}CH_2$)	1.13 (*cis*-$Si(CH_3)_3$), 1.45 (*trans*-$Si(CH_3)_3$), 20.42 (*cis*-C^5H_2), 23.63 (*trans*-C^5H_2), 24.13 (*cis*-C^4H_2), 24.74 (*trans*-C^4H_2), 25.04 (*cis*-C^3H_2), 28.46 (*trans*-C^3H_2), 34.89 (*trans*-$CH_2CH{=}CH_2$), 35.35 (*cis*-$CH_2CH{=}CH_2$), 38.35 (*cis*-C^6H_2), 39.97 (*trans*-C^6H_2), 45.63 (*cis*-C^2H), 47.90 (*trans*-C^2H), 71.87 (*cis*-C^1), 75.14 (*trans*-C^1), 116.64 ($CH_2CH{=}CH_2$), 120.21 (*trans*-CN), 122.42 (*cis*-CN), 136.42 (*cis*-$CH_2CH{=}CH_2$), 136.48 (*trans*-$CH_2CH{=}CH_2$)
rac-**3f**	0.23 (s, 6.7H, *trans*-$Si(CH_3)_3$), 0.24 (s, 2.3H, *cis*-$Si(CH_3)_3$), 0.90 (t, ^3J=7.0, 3H, $CH_2CH_2CH_2CH_3$), 1.06–1.44 (m, 8H, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, 4CH), 1.48–1.94 (m, 6H, $CH_2CH_2CH_2CH_3$, 4CH), 2.01–2.12 (m, 0.25H, *cis*-C^6H_{eq}), 2.15-2.20 (m, 0.75H, *trans*-C^6H_{eq})	1.18 (*cis*-$Si(CH_3)_3$), 1.51 (*trans*-$Si(CH_3)_3$), 13.99 (*trans*-$CH_2CH_2CH_2CH_3$), 14.05 (*cis*-$CH_2CH_2CH_2CH_3$), 20.47 (*cis*-C^5H_2), 22.79 ($CH_2CH_2CH_2CH_3$), 23.55 (*trans*-C^5H_2), 24.27 (*cis*-C^4H_2), 24.82 (*trans*-C^4H_2), 25.30 (*cis*-C^3H_2), 28.43 (*trans*-C^3H_2), 29.31, 29.79 ($CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$), 38.45 (*cis*-C^6H_2), 39.98 (*trans*-C^6H_2), 45.71 (*cis*-C^2H), 48.00 (*trans*-C^2H), 72.32 (*cis*-C^1), 75.51 (*trans*-C^1), 120.55 (*trans*-CN), 122.72 (*cis*-CN)
rac-**3g**	0.25 (s, 4.5H, $Si(CH_3)_3$), 0.27 (s, 4.5H, $Si(CH_3)_3$), 1.06 (s, 4.5H, $C(CH_3)_3$), 1.07 (s, 4.5H, $C(CH_3)_3$), 1.14–1.94 (m, 8H, 8CH), 2.13–2.25 (m, 1H, 1CH)	1.48, 1.87 ($Si(CH_3)_3$), 20.71, 23.08 (C^5H_2), 24.08, 25.92, 26.00, 26.06 (C^4H_2, C^3H_2), 29.56, 30.08 ($C(CH_3)_3$), 34.15, 34.52 ($C(CH_3)_3$), 42.71, 43.40 (C^6H_2), 53.56, 56.63 (C^2H), 71.24, 75.75 (C^1), 121.64, 124.65 (CN)

preparation of optically active cyanohydrins, hydroxynitrile lyases (HNLs) are excellent biocatalysts. With (*R*)-PaHNL from bitter almonds, (*R*)-selective addition of HCN to 2- as well as 3-substituted cyclohexanones is possible, enabling specifically the preparation of two diastereomers which can be separated by column chromatography after *O*-acylation. With the enzyme (*S*)-MeHNL from cassava, the complementary two diastereomers can be synthesized and separated analogously. Increasing bulkiness of the substituents in the 2- as well as in the 3-position diminishes the catalytic activity of both enzymes.

4. Experimental

4.1. Materials and methods

Melting points were determined on a Büchi SMP-20 and are

Table 12. Spectroscopic data of the acetylated 2- and 3-substituted cyclohexanone cyanohydrins **5″**, and **7″**

Compound	^{1}H NMR (250 Hz) (J in Hz) δ	^{13}C NMR (62.9 MHz) δ
rac-**5a″**	1.29–1.37 (m, 0.5H, CH), 1.39–1.45 (m, 0.5H, CH), 1.53–1.96 (m, 6H, 6CH), 2.13, 2.15 (s, 3H, OCOCH_3), 2.36–2.40 (m, 0.5H, C^{6}H$_{eq}$), 2.54–2.59 (m, 0.5H, C^{6}H$_{eq}$), 3.45, 3.51 (s, 3H, OCH_3), 3.52–3.55 (m, 0.5H, C^{2}H$_{ax}$), 3.59–3.81 (m, 0.5H, C^{2}H$_{ax}$)	20.24, 21.12, 21.26, 21.35 (C^{5}H$_2$), (C^{4}H$_2$), (OCOCH$_3$), 26.09 (*cis*-C^{3}H$_2$), 26.75 (*trans*-C^{3}H$_2$), 31.01 (*cis*-C^{6}H$_2$), 32.02 (*trans*-C^{6}H$_2$), 56.26 (*cis*-OCH$_3$), 58.58 (*trans*-OCH$_3$), 74.30 (*cis*-C^1), 76.34 (*trans*-C^1), 78.93 (*cis*-C^{2}H), 79.90 (*trans*-C^{2}H), 116.85 (*trans*-CN), 117.89 (*cis*-CN), 168.62 (*trans*-OCOCH$_3$), 168.95 (*cis*-OCOCH$_3$)
rac-**5b″**	1.21 (t, ^3J=7.0 Hz, 1.5H, *cis*-OCH$_2$CH$_3$), 1.23 (t, ^3J=7.0 Hz, 1.5H, *trans*-OCH$_2$CH$_3$), 1.26–1.97 (m, 7H, 7CH), 2.13 (s, 1.5H, *cis*-OCOCH_3), 2.15 (s, 1.5H, *trans*-OCOCH_3), 2.35–2.49 (m, 0.5H, C^{6}H$_{eq}$), 2.51–2.60 (m, 0.5H, C^{6}H$_{eq}$), 3.52–3.73 (m, 2.5H, OCH_2CH$_3$, C^{2}H), 3.87–3.91 (m, 0.5H, C^{2}H)	15.51, 15.53 (OCH$_2$CH$_3$), 20.39, 21.11, 21.22 (C^{5}H$_2$), (C^{4}H$_2$), 21.14, 21.24 (OCOCH$_3$), 27.06 (*cis*-C^{3}H$_2$), 27.48 (*trans*-C^{3}H$_2$), 31.05 (*cis*-C^{6}H$_2$), 31.85 (*trans*-C^{6}H$_2$), 66.24 (*cis*-OCH$_2$CH$_3$), 66.58 (*trans*-OCH$_2$CH$_3$), 74.37 (*cis*-C^1), 76.18 (*trans*-C^1), 77.08 (*cis*-C^{2}H), 77.75 (*trans*-C^{2}H), 117.09 (*trans*-CN), 118.04 (*cis*-CN), 168.63 (*trans*-OCOCH$_3$), 169.01 (*cis*-OCOCH$_3$)
rac-**5c″**	0.93 (t, ^3J=7.4 Hz, 1.8H, *cis*-OCH$_2$CH$_2$CH$_3$), 0.95 (t, ^3J=7.4 Hz, 1.2H, *trans*-OCH$_2$CH$_2$CH$_3$), 1.25–1.99 (m, 9H, 7CH, OCH$_2$CH$_2$CH$_3$), 2.13 (s, 1.8H, *cis*-OCOCH_3), 2.14 (s, 1.2H, *trans*-OCOCH_3), 2.30–2.41 (m, 0.6H, *cis*-C^{6}H$_{eq}$), 2.48–2.58 (m, 0.4H, *trans*-C^{6}H$_{eq}$), 3.40–3.66 (m, 2.5H, OCH_2CH$_2$CH$_3$, C^{2}H), 3.90–4.00 (m, 0.5H, C^{2}H)	10.59 (OCH$_2$CH$_2$CH$_3$), 20.11, 21.08, 21.26, 23.20 (C^{5}H$_2$), (C^{4}H$_2$), (OCH$_2$CH$_2$CH$_3$), 21.14, 21.23 (OCOCH$_3$), 26.90 (*cis*-C^{3}H$_2$), 27.18 (*trans*-C^{3}H$_2$), 30.93 (*cis*-C^{6}H$_2$), 31.79 (*trans*-C^{6}H$_2$), 72.42 (*cis*-OCH$_2$CH$_2$CH$_3$), 72.77 (*trans*-OCH$_2$CH$_2$CH$_3$), 74.47 (C^1), 76.94 (*cis*-C^{2}H), 77.83 (*trans*-C^{2}H), 117.14 (*trans*-CN), 118.01 (*cis*-CN), 168.62 (*trans*-OCOCH$_3$), 169.02 (*cis*-OCOCH$_3$)
rac-**5d″**	1.16, 1.17, 1.22 (d*), $^3J_{d1}$=$^3J_{d2}$=$^3J_{d3}$= 6.1 Hz, 3H, OCH(CH_3)$_2$), 1.24–1.97 (m, 7H, 7CH), 2.12 (s, 1.5H, OCOCH_3), 2.14 (s, 1.5H, OCOCH_3), 2.32–2.43 (m, 0.6H, *cis*-C^{6}H$_{eq}$), 2.46–2.56 (m, 0.4H, *trans*-C^{6}H$_{eq}$), 3.69–3.88 (m, 1.5H, OCH(CH$_3$)$_2$, C^{2}H), 3.90–3.98 (m, 0.5H, C^{2}H)*) rotamers	20.31, 20.98, 21.08, 21.16, 22.35, 22.43, 22.86, 22.95 (C^{5}H$_2$), (C^{4}H$_2$), (OCOCH$_3$), (OCH(CH_3)$_2$)*), 28.16 (*cis*-C^{3}H$_2$), 28.36 (*trans*-C^{3}H$_2$), 30.87 (*cis*-C^{6}H$_2$), 31.72 (*trans*-C^{6}H$_2$), 72.32 (*cis*-OCH(CH$_3$)$_2$), 72.68 (*trans*-OCH(CH$_3$)$_2$), 74.52, 75.08, 75.52, 76.08 (C^1), (C^{2}H), 117.28 (*trans*-CN), 118.11 (*cis*-CN), 168.63 (*trans*-OCOCH$_3$), 169.05 (*cis*-OCOCH$_3$)*) rotamers
rac-**5e″**	1.29–2.00 (m, 7H, 7CH), 2.13 (s, 1.8H, *cis*-OCOCH_3), 2.14 (s, 1.2H, *trans*-OCOCH_3), 2.36–2.45 (m, 0.6H, *cis*-C^{6}H$_{eq}$), 2.53–2.63 (m, 0.4H, *trans*-C^{6}H$_{eq}$), 3.66–3.71 (m, 0.5H, C^{2}H), 3.94–4.21 (m, 2.5H, C^{2}H, OCH_2CH=CH$_2$), 5.17–5.37 (m, 2H, OCH$_2$CH=CH_2), 5.83–6.00 (m, 1H, OCH$_2$CH=CH$_2$)	20.27, 21.10, 21.15, 21.24, 21.34 (C^{5}H$_2$), (C^{4}H$_2$), (OCOCH$_3$), 27.00 (*cis*-C^{3}H$_2$), 27.51 (*trans*-C^{3}H$_2$), 30.99 (*cis*-C^{6}H$_2$), 31.99 (*trans*-C^{6}H$_2$), 71.57, 71.85 (OCH$_2$CH=CH$_2$), 74.36 (*cis*-C^1), 76.27 (*trans*-C^1), 77.31 (C^{2}H), 116.92 (*trans*-CN), 117.28 (*cis*-OCH$_2$CH=CH$_2$), 117.52 (*trans*-OCH$_2$CH=CH$_2$), 117.91 (*cis*-CN), 134.38 (*trans*-OCH$_2$CH=CH$_2$), 134.57 (*cis*-OCH$_2$CH=CH$_2$), 168.59 (*trans*-OCOCH$_3$), 168.96 (*cis*-OCOCH$_3$)
rac-**7c″**	1.13–1.30 (m, 1H, 1CH), 1.52–2.02 (m, 4H, 4CH), 2.06–2.13 (m, 1H, 1CH), 2.11 (s, 3H, *cis*-OCOCH$_3$), 2.41–2.48 (m, 1H, *cis*-CH), 2.74–2.82 (m, 1H, *cis*-C^{2}H$_{eq}$), 3.33–3.51 (m, 1H, *cis*-C^{3}H$_{ax}$), 3.37 (s, 3H, OCH$_3$)	19.07 (*cis*-C^{5}H$_2$), 21.12 (OCOCH$_3$), 30.45 (*cis*-C^{4}H$_2$), 34.88 (*cis*-C^{2}H$_2$), 39.76 (*cis*-C^{6}H$_2$), 56.38 (*cis*-OCH$_3$), 72.12 (*cis*-C^1), 75.39 (*cis*-C^{3}H), 118.06 (*cis*-CN), 168.75 (OCOCH$_3$)

Table 13. Elemental analysis of racemic silylated cyanohydrins **3** and racemic acetylated cyanohydrins **5″** and **7″**

Compound	Mol. formula (Mol. weight)	Calcd/found			
		C	H	N	O
rac-**3a**	$C_{11}H_{21}NOSi$ (211.38)	62.50	10.01	6.63	7.57
		62.49	10.06	6.57	
rac-**3b**	$C_{12}H_{23}NOSi$ (225.41)	63.94	10.28	6.21	7.10
		63.85	10.16	6.31	
rac-**3c**	$C_{13}H_{25}NOSi$ (239.43)	65.21	10.52	5.85	6.68
		65.24	10.60	5.79	
rac-**3d**	$C_{13}H_{25}NOSi$ (239.43)	65.21	10.52	5.85	6.68
		65.14	10.44	5.81	
rac-**3e**	$C_{13}H_{23}NOSi$ (237.42)	65.77	9.76	5.90	6.74
		66.03	9.69	5.85	
rac-**3f**	$C_{14}H_{27}NOSi$ (253.46)	66.34	10.74	5.53	6.31
		66.46	10.78	5.41	
rac-**3g**	$C_{14}H_{27}NOSi$ (197.23)	66.34	10.74	5.53	6.31
		66.35	10.72	5.31	
rac-**5a″**	$C_{10}H_{15}NO_3$ (197.23)	60.90	7.67	7.10	24.34
		60.81	7.69	7.00	
rac-**5b″**	$C_{11}H_{17}NO_3$ (211.26)	62.54	8.11	6.63	22.72
		62.24	7.91	6.29	
rac-**5c″**	$C_{12}H_{19}NO_3$ (225.29)	63.98	8.50	6.22	21.31
		64.05	8.51	6.04	
rac-**5d″**	$C_{12}H_{19}NO_3$ (225.29)	63.98	8.50	6.22	21.31
		63.88	8.43	6.16	
rac-**5e″**	$C_{12}H_{17}NO_3$ (223.27)	64.55	7.67	6.27	21.50
		64.40	7.76	6.16	
rac-**7c″**	$C_{10}H_{15}NO_3$ (197.23)	60.90	7.66	7.10	24.34
		61.00	7.71	6.82	

uncorrected. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 F (250 MHz) or ARX 500 (500 MHz) spectrometer in $CDCl_3$ with TMS as internal standard. ^{13}C NMR multiplicities were determined with DEPT experiments. Optical rotations were measured with a Perkin–Elmer polarimeter 241 LC in a thermostated glass cuvette $l=10$ cm). Chromatography was performed using silica gel, grain size 0.040–0.063 mm (Fluka). Diastereomeric excess:GC separations were conducted using (a) capillary glass columns (20 m) with OV 1701, carrier gas 0.4–0.6 bar hydrogen; (b) a Chiraldex B-PM (permethylated) column (30 m×0.32 mm), carrier gas 0.6–1.0 bar hydrogen; (c) a Chiraldex B-TA and G-TA column (30 m×0.32 mm), carrier gas hydrogen.

Cyclohexanones **1b–f**,[18] **1g**,[19] **4a–e**,[20] and **6c**[21] were prepared according to literature procedures. Ketones **1a** and **6a** are commercially available, **6b** was donated by Bayer A. G. Racemic cyanohydrins were prepared according to a procedure developed by van der Gen et al.,[8] but reaction time was always 48 h. ^{1}H and ^{13}C NMR data of the racemic cyanohydrins are reported in Tables 10–12.

To obtain elemental analyses of the cyanohydrins (Table 13), either the *O*-silylated derivatives (**3a–g**) or the *O*-acetylated cyanohydrins (**5a″–e″**, **7c″**) were used. Cyanosilylation[9] was performed according to known literature procedures but purification was accomplished either by chromatography on silica gel with CH_2Cl_2 or distillation. The *O*-acetylated derivatives were prepared using acetic anhydride and dimethylaminopyridine (for conditions see determination of conversion rates and isomeric ratio). All yields are not optimized.

4.2. General procedure for the (*R*)-PaHNL-catalyzed preparation of cyclohexanone cyanohydrins 2, 5 and 7

A solution of (*R*)-PaHNL (100 U per 100 mg support, total 200 U, 78 μL) was added to cellulose [Elcema-Cellulose P100PSC (Degussa): 1 g soaked in 10 mL of 0.02 M sodium citrate buffer, pH 3.3, for 2 h, and filtered off], followed by addition of diisopropyl ether (5 mL), substrate **1**, **4** or **6** (1 mmol), and anhydrous HCN[22] (150 μL, 3.9 mmol). After stirring at room temperature for the times given in Tables 3, 5 and 8, the support was removed by filtration, washed twice with diethyl ether, and the combined filtrates were concentrated under vacuum.

4.3. General procedure for the (*S*)-MeHNL-catalyzed preparation of cyclohexanone cyanohydrins 2, 5 and 7

A solution of (*S*)-MeHNL (100 U per 100 mg support, total 200 U, 93 μL) was added to nitrocellulose [Pro-Celloidin (Fluka): 1 g (dry), soaked in 50 μL of 0.02 M sodium citrate buffer, pH 3.3, for 0.5 h; the buffer was decanted and nitrocellulose centrifuged (5700×*g* for 30 min) and dried under high vacuum for 5 h], followed after 15 min by addition of diisopropyl ether (5 μL), substrate **1**, **4** or **6** (1 mmol), and anhydrous HCN[22] (150 μL, 3.9 mmol). The reaction was then performed as described above.

4.4. Blank experiment

The chemical HCN addition was performed analogously to the enzymatic reaction, however, the enzyme solution was replaced by the same volume of 0.02 M sodium acetate buffer, pH 5.4. The reaction times correspond with those of the (*R*)-PaHNL- and (*S*)-MeHNL-catalyzed reaction. ^{1}H and ^{13}C NMR data of the enzyme-catalyzed and the chemically prepared cyanohydrins are identical.

4.5. Determination of conversion rates and isomeric ratio (acetylation)

To a solution of the crude cyclohexanone cyanohydrins **2**, **5**, or **7** (10 μL) in CH_2Cl_2 (500 μL) was added acetic anhydride (50 μL) and dimethylaminopyridine (15 mg). The reaction mixture was allowed to stand at room temperature for 30 min. The mixture was then filtered through a silica gel column (3×0.5 cm) with CH_2Cl_2 (4 mL). Conversion and isomeric ratio were directly determined from the filtrate by gas chromatography.

4.6. General procedure for the preparation of the *p*-bromobenzoylated derivatives 2a′, 5a′, and 7a′–c′

To a solution of **2a**, **5a** or **7a–c** (9.56, 7.47 or 3.35–8.12 mmol), diastereomeric ratio given in Tables 2, 5, and 7 in pyridine (25–70 mL) or in 1:1 pyridine/CH_2Cl_2 (25–70 mL) was added dimethylaminopyridine (ca. 0.2 equiv) and *p*-bromobenzoyl chloride (2.0 equiv), and the reaction mixture was stirred for the time specified. Then water (20–50 mL) was added, the layers were separated, and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined extracts were washed with diluted HCl until neutral, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel with petroleum ether–ethyl acetate (15:1 for **7b**, 50:1 for others) and recrystallized.

4.6.1. *cis*-(1*S*,2*R*)-1-(4-Bromobenzoyloxy)-2-methylcyclohexanecarbonitrile (*cis*-(1*S*,2*R*)-2a′). Reaction time: 14 d at room temperature, $R_f=0.08$, yield: 22% (*cis*-**2a′**, colorless solid), mp 97 °C (diisopropyl ether), $[\alpha]_D^{20}=+3.7$ (*c* 1.0, $CHCl_3$), ^{1}H NMR (500 MHz): δ 1.24 (d, $^{3}J=6.8$ Hz, 3H, CH_3), 1.36–1.47 (m, 2H, C^4H_{ax}, C^5H_{ax}), 1.54–1.66 (m, 2H, CH, C^3H_{ax}), 1.72–1.89 (m, 3H, CH, C^3H_{eq}, C^6H_{ax}), 2.11–2.18 (m, 1H, C^2H_{ax}), 2.85–2.88 (m, 1H, C^6H_{eq}), 7.61–7.90 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 16.33 (CH_3), 20.26 (C^5H), 23.87 (C^4H_2), 29.08 (C^3H_2), 32.78 (C^6H_2), 39.82 (C^2H), 74.88 (C^1), 118.73 (CN), 128.24, 128.95, 131.13, 132.04 (C_{Ph}), 163.56 (OCO). Anal. Calcd for $C_{15}H_{16}NO_2Br$ (322.18):C, 55.92; H, 5.00; N, 4.35; Br, 24.80; O, 9.93. Found: C, 55.96; H, 5.02; N 4.38; Br, 25.01.

4.6.2. *trans*-(1*S*,2*S*)-1-(4-Bromobenzoyloxy)-2-methylcyclohexanecarbonitrile (*trans*-(1*S*,2*S*)-2a′). Reaction conditions see *cis*-(1*S*,2*R*)-**2a′**, $R_f=0.11$, yield: 17% (*trans*-**2a′**, colorless solid), mp 103 °C (diisopropyl ether), $[\alpha]_D^{20}=+44.7$ (*c* 1.0, $CHCl_3$), ^{1}H NMR (500 MHz): δ 1.23 (d, $^{3}J=6.6$ Hz, 3H, CH_3), 1.26–1.39 (m, 1H, C^4H_{ax}), 1.43–1.64 (m, 2H, C^3H_{ax}, C^6H_{ax}), 1.67–1.90 (m, 4H, C^5H_{ax}, C^4H_{eq}, C^3H_{eq}, C^5H_{eq}), 2.08–2.15 (m, 1H, C^2H_{ax}), 2.91–2.94 (m, 1H, C^6H_{eq}), 7.59–7.88 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 16.42 (CH_3), 23.05 (C^5H), 24.45 (C^4H_2),

31.12 (C^3H_2), 34.35 (C^6H_2), 40.26 (C^2H), 78.97 (C^1), 116.37 (CN), 128.30, 128.83, 131.18, 131.92 (C_{Ph}), 163.64 (OCO). Anal. Calcd for $C_{15}H_{16}NO_2Br$ (322.18):C, 55.92; H, 5.00; N, 4.35; Br, 24.80; O, 9.93. Found: C, 56.16; H, 5.02; N 4.31; Br, 24.63.

4.6.3. *cis*-1-(4-Brombenzoyloxy)-2-methoxycyclohexanecarbonitrile (*cis*-5a′). Reaction time: 10 d at room temperature, R_f=0.05, yield: 22% (light yellow oil), ^1H NMR (500 MHz): δ 1.35–1.43 (m, 1H, C^4H_{ax}), 1.64–1.84 (m, 4H, 2CH, C^5H_{ax}, C^6H_{ax}), 1.93–1.98 (m, 2H, 2CH), 2.64–2.69 (m, 1H, C^6H_{eq}), 3.57 (s, 3H, OCH_3), 3.71–3.75 (m, 1H, C^2H_{ax}), 7.61–7.88 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 20.36, 21.06 (C^5H_2, C^4H_2), 26.31 (C^6H_2), 31.93 (C^3H_2), 58.36 (CH_3), 74.83 (C^1), 79.15 (C^2H), 117.78 (CN), 128.07, 128.98, 131.36, 131.96 (C_{Ph}), 163.81 (OCO). Anal. Calcd for $C_{15}H_{16}NO_3Br$ (338.21):C, 53.27; H, 4.77; N, 4.14; Br, 23.63; O, 14.19. Found: C, 53.09; H, 4.73; N 4.08; Br, 23.83.

4.6.4. *trans*-(1*R*,2*S*)-1-(4-Bromobenzoyloxy)-2-methoxycyclohexanecarbonitrile (*trans*-(1*R*,2*S*)-5a′). Reaction conditions see *cis*-5a′, R_f=0.02, yield: 12% (*trans*-5a′, colorless solid), mp 112 °C (ethanol), $[\alpha]_D^{20}=+31.4$ (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz): δ 1.35–1.43 (m, 1H, C^4H_{ax}), 1.64–1.84 (m, 4H, C^5H_{ax}, C^6H_{ax}, 2CH), 1.93–1.98 (m, 2H, 2CH), 2.64–2.69 (m, 1H, C^6H_{eq}), 3.57 (s, 3H, OCH_3), 3.71–3.75 (m, 1H, C^2H_{ax}), 7.61–7.88 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 21.10, 21.27 (C^5H_2, C^4H_2), 26.70 (C^6H_2), 32.03 (C^3H_2), 58.68 (CH_3), 77.15 (C^1), 79.71 (C^2H), 116.83 (CN), 128.09, 129.04, 131.25, 132.00 (C_{Ph}), 163.51 (OCO). Anal. Calcd for $C_{15}H_{16}NO_3Br$ (338.21):C, 53.27; H, 4.77; N, 4.14; Br, 23.63; O, 14.19. Found: C, 53.25; H, 4.88; N, 3.88; Br, 23.48.

4.6.5. *cis*-(1*S*,3*R*)-1-(4-Bromobenzoyloxy)-3-methylcyclohexanecarbonitrile (*cis*-(1*S*,3*R*)-7a′). Reaction time: 14 d at room temperature, R_f=0.15, yield: 34% (*cis*-7a′, colorless solid), mp 86 °C (petroleum ether), $[\alpha]_D^{20}=+1.6$ (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz): δ 0.95 (m, 1H, C^4H_{ax}), 1.02 (d, ^3J=6.5 Hz, 3H, CH_3), 1.39 (dd, $^2J(C^2H_{ax}, C^2H_{eq})$-$\approx{}^3J(C^2H_{ax}, C^3H_{ax})$=12.6 Hz, 1H, C^2H_{ax}), 1.60–1.67 (m, 1H, C^6H_{ax}), 1.72–1.82 (m, 2H, C^4H_{eq}, C^5H_{ax}), 1.88–1.96 (m, 2H, C^3H_{ax}, C^5H_{eq}), 2.63–2.66 (m, 2H, C^2H_{eq}, C^6H_{eq}), 7.59–7.88 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 21.62 (CH_3), 22.41 (C^5H_2), 29.69 (C^3H), 33.33 (C^4H_2), 35.09 (C^6H_2), 43.13 (C^2H_2), 74.48 (C^1), 118.17 (CN), 128.13, 128.89, 131.26, 131.89 (C_{Ph}), 163.59 (OCO). Anal. Calcd for $C_{15}H_{16}NO_2Br$ (322.18):C, 55.92; H, 5.00; N, 4.35; Br, 24.80; O, 9.93. Found: C, 55.98; H, 5.00; N, 4.33; Br, 24.57.

4.6.6. *trans*-(1*S*,3*S*)-1-(4-Bromobenzoyloxy)-3-methylcyclohexanecarbonitrile (*trans*-(1*S*,3*S*)-7a′). Reaction conditions see *cis*-(1*S*,3*R*)-7a′, R_f=0.09, yield: 37% (*trans*-7a′, colorless solid), mp 102 °C (diisopropyl ether), $[\alpha]_D^{20}=+19.3$ (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz): δ= 0.96 (d, ^3J=6.5 Hz, 3H, CH_3), 1.02 (m, 1H, C^4H_{ax}), 1.52–1.65 (m, 2H, C^2H_{ax}, C^5H_{ax}), 1.70–1.85 (m, 4H, C^5H_{eq}, C^3H_{ax}, C^4H_{eq}, C^6H_{ax}), 2.63–2.68 (m, 2H, C^2H_{eq}, C^6H_{eq}), 7.61–7.90 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 20.47 (C^5H), 21.77 (CH_3), 26.99 (C^3H), 33.12 (C^4H_2), 34.08 (C^6H_2), 42.12 (C^2H_2), 71.37 (C^1), 119.26 (CN), 128.10, 128.98, 131.22, 132.00 (C_{Ph}), 163.51 (OCO). Anal. Calcd for $C_{15}H_{16}NO_2Br$ (322.18):C, 55.92; H, 5.00; N, 4.35; Br, 24.80; O, 9.93. Found: C, 55.84; H, 4.99; N, 4.34; Br, 24.47.

4.6.7. *cis*-(1*S*,3*R*)-1-(4-Bromobenzoyloxy)-3-trifluoromethylcyclohexanecarbonitrile (*cis*-(1*S*,3*R*)-7b′). Reaction time: 24 h at 50 °C, R_f=0.23, yield: 25% (*cis*-7b′, colorless solid), mp 106 °C (diisopropyl ether), $[\alpha]_D^{20}=+5.4$ (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz): δ 1.37 (m, 1H, C^4H_{ax}), 1.58–1.87 (m, 3H, C^5H_{ax}, C^6H_{ax}, C^2H_{ax}), 2.06–2.09 (m, 2H, C^4H_{eq}, C^5H_{eq}), 2.54–2.64 (m, 1H, C^3H_{ax}), 2.72–2.75 (m, 1H, C^6H_{eq}), 2.89–2.92 (m, 1H, C^2H_{eq}), 7.60–7.88 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 21.11 (s, C^5H_2), 23.69 (s, C^4H_2), 34.24 (s, C^2H_2), 34.83 (s, C^6H_2), 39.53 (q, ^2J(C,F)=28.1 Hz, C^3H), 73.03 (C^1), 117.15 (CN), 126.56 (q, ^1J(C,F)=278.5 Hz, CF_3), 127.63, 129.46, 131.44, 132.16 (C_{Ph}), 163.56 (OCO). Anal. Calcd for $C_{15}H_{13}NO_2BrF_3$ (376.17):C, 47.89; H, 3.48; N, 3.72; Br, 21.24; O, 8.51; F, 15.15. Found: C, 47.84; H, 3.56; N, 3.69; Br, 21.11.

4.6.8. *trans*-(1*S*,3*S*)-1-(4-Bromobenzoyloxy)-3-trifluoromethylcyclohexanecarbonitrile (*trans*-(1*S*,3*S*)-7b′). Reaction conditions see *cis*-(1*S*,3*R*)-7b′, R_f=0.17, yield: 13% (*trans*-7b′, colorless solid), mp 153 °C (diisopropyl ether), $[\alpha]_D^{20}=+5.7$ (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz): δ 1.43 (m, 1H, C^4H_{ax}), 1.62 (m, 1H, C^5H_{ax}), 1.85–1.97 (m, 3H, C^5H_{eq}, C^2H_{ax}, C^6H_{ax}), 2.02–2.05 (m, 1H, C^4H_{eq}), 2.35–2.45 (m, 1H, C^3H_{ax}), 2.76–2.79 (m, 1H, C^6H_{eq}), 2.89–2.92 (m, 1H, C^2H_{eq}), 7.61–7.89 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 19.04 (s, C^5H_2), 23.27 (q, ^3J(C,F)= 2.6 Hz, C^4H_2), 33.23 (q, ^3J(C,F)=2.8 Hz, C^2H_2), 33.53 (s, C^6H_2), 37.10 (q, ^2J(C,F)=27.9 Hz, C^3H), 69.96 (C^1), 118.12 (CN), 126.69 (q, ^1J(C,F)=278.6 Hz, CF_3), 127.41, 129.51, 131.25, 132.21 (C_{Ph}), 163.22 (OCO). Anal. Calcd for $C_{15}H_{13}NO_2BrF_3$ (376.17):C, 47.89; H, 3.48; N, 3.72; Br, 21.24; O, 8.51; F, 15.15. Found: C, 48.18; H, 3.56; N, 3.74; Br, 21.22.

4.6.9. *cis*-(1*S*,3*R*)-1-(4-Bromobenzoyloxy)-3-methoxycyclohexanecarbonitrile (*cis*-(1*S*,3*R*)-7c′). Reaction time: 10 d at room temperature, R_f=0.02, yield: 16% (*cis*-7c′, colorless solid), mp 105 °C (ethanol), $[\alpha]_D^{20}=+24.6$ (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz): δ 1.30–1.37 (m, 1H, C^4H_{ax}), 1.66–1.74 (m 1H, C^5H_{ax}), 1.79–1.90 (m, 2H, C^6H_{ax}, C^2H_{ax}), 1.96–2.02 (m, 1H, C^5H_{eq}), 2.08–2.12 (m, 1H, C^4H_{eq}), 2.54–2.56 (m, 1H, C^6H_{eq}), 2.84–2.87 (m, 1H, C^2H_{eq}), 3.37 (s, 3H, OCH_3), 3.51–3.57 (m, 1H, C^3H_{ax}), 7.60–7.88 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 18.90 (C^5H_2), 30.37 (C^4H_2), 34.95 (C^6H_2), 39.55 (C^2H_2), 56.43 (CH_3), 72.71 (C^1), 75.28 (C^3H), 117.99 (CN), 127.95, 129.03, 131.31, 131.95 (C_{Ph}), 163.63 (OCO). Anal. Calcd for $C_{15}H_{16}NO_3Br$ (338.21):C, 53.27; H, 4.77; N, 4.14; Br, 23.63; O, 14.19. Found: C, 53.24; H, 4.80; N, 4.12; Br, 23.34.

4.6.10. *trans*-1-(4-Bromobenzoyloxy)-3-methoxycyclohexanecarbonitrile (*trans*-7c′). Reaction conditions see *cis*-(1*S*,3*R*)-7c′, R_f=0.04, yield: 26% (*trans*-7c′, colorless solid), mp 76 °C (ethanol), ^1H NMR (250 MHz): δ 1.39–1.72 (m, 2H, C^4H_{ax}, C^5H_{ax}), 1.85–2.15 (m, 4H, C^6H_{ax}, C^2H_{ax}, C^5H_{eq}, C^4H_{eq}), 2.43–2.49 (m, 1H, C^6H_{eq}), 2.68–2.75 (m, 1H, C^2H_{eq}), 3.38 (s, 3H, OCH_3), 3.41–3.51 (m, 1H, C^3H_{ax}), 7.60–7.89 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 18.65 (C^5H_2), 30.22 (C^4H_2), 34.41 (C^6H_2), 38.77 (C^2H_2), 56.12 (CH_3), 71.91 (C^1), 74.03 (C^3H),118.40 (CN), 127.88,

129.17, 131.23, 132.07 (C_{Ph}), 163.39 (OCO). HRMS (EI, 70 eV): Mol. mass Calcd 337.0314 (for $C_{15}H_{16}NO_3Br$), found 337.0313 (M^+).

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