Tetrahedron: *Asymmetry* 20 (2009) 2279–2286

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantioselective cyanoformylation of aldehydes organocatalyzed by recyclable cinchonidine ammonium salts

Rafael Chinchilla *, Carmen Nájera *, Francisco J. Ortega, Silvia Tarí

Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo 99, 03080 Alicante, Spain

ARTICLE INFO

Article history:
Received 30 July 2009
Accepted 12 August 2009
Available online 31 August 2009

ABSTRACT

Enantiomerically enriched *O*-methoxycarbonyl cyanohydrins were obtained using an enantioselective addition of methyl cyanoformate to aldehydes organocatalyzed by a dimeric anthracenyldimethyl-derived cinchonidine ammonium salt (1 mol % catalyst loading) in the presence of substoichiometric amounts of triethylamine (20 mol %). Aromatic and heteroaromatic aldehydes usually afford high enantioselectivities (up to 96%) and quantitative yields of the corresponding *O*-methoxycarbonyl cyanohydrins, whereas aliphatic and α,β-unsaturated aldehydes give lower enantioselectivities (up to 60%) in high yields. The observed sense of the enantioselection was always the same, and the organocatalyst was almost quantitatively recovered by ether-promoted precipitation without any loss of activity. The use of resin-supported cinchonidine-derived ammonium salts as an organocatalyst in this transformation was also explored.

1. Introduction

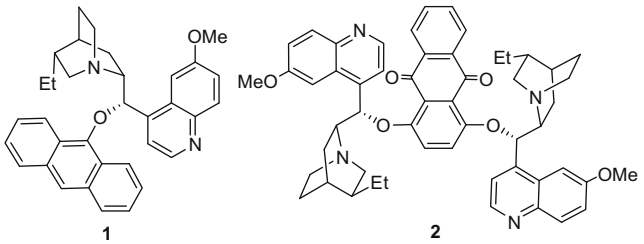
Optically active cyanohydrins are important natural products and versatile synthetic intermediates for pharmaceuticals and agrochemicals. They are present in bacteria, fungi, and insects forming part of the self-defense system.[1] In addition, they contain two functional groups that can be manipulated preserving the stereochemistry, thus producing many interesting 1,2-difunctional compounds with biological activity.[2,3] The most direct way for preparing optically active cyanohydrins is the addition of cyanide to a prochiral carbonyl compound in the presence of a synthetic chiral catalyst or an enzyme.[3,4] In this case, the choice of the cyanide source is critical in terms of economy and safety. Obviously, the simplest approach is the use of a hydrogen cyanide or a metal cyanide salt in the presence of an acid, but the high toxicity of these reagents makes it difficult to scale-up. Therefore numerous safer and easy-to-handle cyanide-based reagents have been developed. Among these reagents are trimethylsilyl cyanides, acyl cyanides, cyanoformates, and cyanophosphonates.[3,4] All of these have the advantage of overcoming the well-known reversibility of the cyanide addition to a carbonyl compound, therefore affording configurationally stable O-protected cyanohydrins which do not revert to carbonyl compounds. However, some of them still have serious disadvantages, as is the case of the popular trimethylsilyl cyanide, which is unsafe due to easy hydrolysis to hydrogen cyanide and affords cyanohydrin trimethylsilyl ethers, which are prone to decomposition when subsequent transformations are attempted. Better alternatives are cyanoformates (ROCOCN), which are less toxic and more economical and can afford O-formylated cyanohydrins which have excellent configurational stability toward chemoselective hydrolysis in acidic media,[5] in reduction processes affording β-aminoalcohols,[5] and in palladium-catalyzed allylic nucleophilic substitutions.[6]

These cyanide sources have been added enantioselectively to carbonyl compounds following different asymmetric strategies. Thus, although the use of enzymes for the catalytic enantioselective cyanation of aldehydes and ketones is a well-known process[3] (in fact the oldest for this transformation[7]), the frequent lack of flexibility of enzymes to accommodate different substrates and the difficulties in scaling-up have made more research to be focused on other methodologies. Over the last few years, numerous procedures involving chiral metal complex-catalyzed enantioselective synthesis of cyanohydrins derived from aldehydes or ketones have appeared.[3,4] Thus, chiral complexes of B, V, Al, Ti, Sn, Mg, Y, Mn, Bi, Zr, Co or Re have been employed, mainly for the enantioselective addition of different cyanide sources to aldehydes, some of them achieving impressive degrees of enantioselectivity.[3,4] However, there are disadvantages associated with the use of metal complexes, which hamper their use on a large scale. Thus, most of them are air and moisture sensitive, which makes the use of strict reaction conditions necessary. In addition, they are not recoverable, while the presence of large amounts of chiral ligands and also the presence of some additives is required. Thus, the development of efficient and versatile metal-free enantioselective cyanoformylation of carbonyl compounds is a good synthetic challenge.

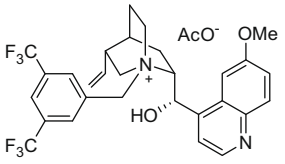
* Corresponding authors. Tel.: +34 96 5903728; fax: +34 96 5903549.
E-mail addresses: chinchilla@ua.es (R. Chinchilla), cnajera@ua.es (C. Nájera).

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.08.007

Although the organocatalyzed enantioselective cyanohydrin synthesis is an old field, which began with the use of *Cinchona* alkaloids as organocatalysts,[8] the recent upsurge in interest in asymmetric organocatalysis in general[9] has prompted the discovery of new organocatalyzed procedures.[3,4h] In particular, the use of organocatalysis in the enantioselective addition of cyanoformates to carbonyl compounds leading to O-formylated cyanohydrins is a scarcely explored field where *Cinchona* alkaloids have shown their abilities as asymmetry-inductors. Thus, monomeric and dimeric O-arylated dihydroquinidine derivatives **1** and **2** have been employed by Deng et al. as excellent chiral amines for the enantioselective addition of ethyl cyanoformate to aliphatic ketones achieving enantioselectivities of up to 97%, although using rather large amounts of catalysts (up to 30%) and long reaction times (up to 7 d).[10] Recently, Feng et al. have reported the use of a quinidine-derived quaternary ammonium salt **3** in the enantioselective cyanoformylation of aldehydes in the presence of triethylamine, achieving moderate enantioselectivities (up to 72%) in long reaction times (1–6 d) and working at low temperatures (−78 °C).[11]

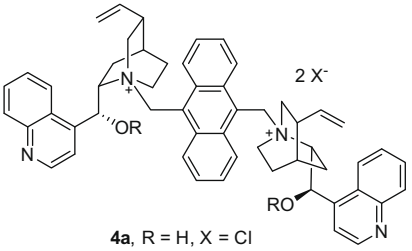


1 **2**



3

Our group has been working on the use of unsupported[12,13] and supported[14] recoverable *Cinchona* alkaloid-derived ammonium salts in organocatalyzed enantioselective transformations. Among them are a series of dimeric anthracenyldimethyl-derived ammonium salts from *Cinchona* alkaloids, such as the cinchonidine-derivative **4a**, which have been used as recoverable chiral phase-transfer catalysts for the asymmetric alkylation[12] and Michael addition[13] reactions of glycinate Schiff bases for the enantioselective synthesis of α-amino acids.[15] Herein, we explore the use of our recoverable ammonium salts as organocatalysts in the enantioselective formylation of aldehydes.[16]



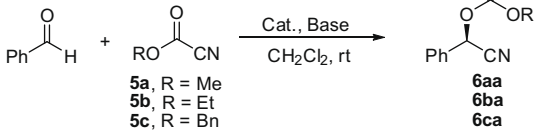
4a, R = H, X = Cl
4b, R = allyl, X = Br
4c, R = H, X = BF_4

2. Results and discussion

Benzaldehyde was chosen as a model substrate for the cyanoformylation reaction of aldehydes, using our reported dimeric cinchonidine-derived ammonium salt **4a**[12] (10 mol %) as an organocatalyst under the conditions described by Feng,[11] although initially at room temperature (5 equiv). Thus, methyl cyanoformate **5a** was used as a cyanide source in the presence of triethylamine (20 mol %) as a base in dichloromethane as solvent. Under these conditions, the corresponding (*R*)-O-formylated cyanohydrin **6aa** was obtained quantitatively in 2 h reaction time and in 60% ee (Table 1, entry 1),[16] a good starting point considering the reported 44% ee obtained using **3** as an organocatalyst but working at −15 °C.[11] However, when the O-allylated cinchonidine-derived ammonium salt **4b**[12a] was used as a catalyst under these reaction conditions, racemic **6aa** was obtained quantitatively (Table 1, entry 2), the presence of a free OH group on the catalysts shown to be critical. In addition, the counteranion on the ammonium salt was also revealed to be important. Thus, a change from the chloride to the tetrafluoroborate anion in ammonium salt **4c**[12b] gave place to a lower enantioselection for **6aa** (Table 1, entry 3).

Lowering the catalyst loading of **4a** from 10 mol % to 5 mol % had no effect on the enantioselectivity of the process (Table 1, compare entries 1 and 4). However, when a loading of just 1 mol % of **4a**

Table 1
Organocatalytic addition of alkyl cyanoformates to benzaldehyde



5a, R = Me
5b, R = Et
5c, R = Bn

6aa
6ba
6ca

Entry	Cat. (mol %)	5	Base (20 mol %)	*t* (h)	No.	Yield[a] (%)	ee[b] (%)
1	**4a** (10)	**5a**	Et_3N	2	**6aa**	99	60
2	**4b** (10)	**5a**	Et_3N	2	**6aa**	99	0
3	**4c** (10)	**5a**	Et_3N	2	**6aa**	99	44
4	**4a** (5)	**5a**	Et_3N	2	**6aa**	99	60
5	**4a** (1)	**5a**	Et_3N	2	**6aa**	99	69
6	**4a** (1)	**5b**	Et_3N	3	**6ba**	99	56
7	**4a** (1)	**5c**	Et_3N	3	**6ca**	99	65
8	**4a** (1)	**5a**	C_6H_5N	3	**6aa**	0	0
9	**4a** (1)	**5a**	Cy_2MeN	3	**6aa**	99	16
10	**4a** (1)	**5a**	Imidazole	3	**6aa**	63[c]	58
11	**4a** (1)	**5a**	*N*-Me-imidazole	3	**6aa**	99	48

Optimization reactions.
[a] Isolated as pure crude products according to ^1H NMR (300 MHz) and with >95% purity according to GLC.
[b] Determined by chiral HPLC.
[c] Determined by ^1H NMR (300 MHz).

was used, the enantioselectivity of the process increased and **6aa** was isolated in 69% ee in the same yield and reaction time (Table 1, entry 5). Other cyanoformates were also attempted as cyanide sources under these conditions, such as ethyl cyanoformate **5b** (Table 1, entry 6) and benzyl cyanoformate **5c** (Table 1, entry 7), although the ee's for **6ba** and **6ca** were lower than in the case of **4aa** and the reaction time increased. In addition, the use of other bases in the process was explored. Thus, the use of pyridine gave no reaction (Table 1, entry 8), whereas the use of dicyclohexylmethylamine gave a quantitative yield of **6aa** but with poor enantioselectivity (Table 1, entry 9), and the use of imidazole and *N*-methylimidazole afforded lower enantioselectivities for **6aa** than when triethylamine was employed (Table 1, entries 10 and 11). Lowering the amount of triethylamine gave rise to higher reaction times and lower enantioselectivities, whereas the use of other solvents (toluene, THF, toluene/$CHCl_3$, and fluorobenzene) gave very low to no stereoselectivity.

Working under the most appropriate reaction conditions, 1 mol % **4a** loading, methyl cyanoformate **5a** as a cyanide source, 20 mol % triethylamine as a base, and dichloromethane as a solvent, we explored the influence of lowering the reaction temperature. Thus, the cyanoformylation of benzaldehyde was also carried out at 10, 0, −20, and −78 °C (Table 2, entries 1–4), observing longer reaction times, similar yield and an 80% ee when working at 10 °C (Table 2, entry 1). Interestingly, working at −78 °C gave rise to a lower ee than working at room temperature (compare Table 1, entry 5 and Table 2, entry 4).

We extended the study of the enantioselective cyanoformylation reaction to other aldehydes.[17,18] Thus, when the reaction was carried out using 2-methylbenzaldehyde, the corresponding cyanoformylated product **6ab** was obtained quantitatively in 81% ee at 10 °C (Table 2, entry 5). However, when this reaction was carried out at −78 °C, the enantioselectivity for **6ab** increased to 92% ee (Table 2, entry 6). As a result of this, we became suspicious that the enantioselectivity of the process could be highly dependant on the nature of the starting aldehyde. Therefore, the optimization of the reaction temperature was explored for each aldehyde. In this case, 3-methylbenzaldehyde, gave rise to an 86% ee for the corresponding product **6ac** working at 10 °C, whereas it afforded a 96% ee when working at −78 °C (Table 2, entries 7 and 8). However, in the case of the reactions of 4-methylbenzaldehyde, 4-methoxybenzaldehyde, and 3,4-dimethoxybenzaldehyde, higher enantioselections for **6ad**, **6ae,** and **6af**, respectively, were achieved when working at 10 °C compared to when working at −78 °C (Table 2, compare entries 9 and 10, entries 11 and 12, and entries 13 and 14). The case of the cyanoformylation reaction of 3,5-dimethoxybenzaldehyde is instructive, as only a 37% ee of the corresponding product **6ag** was obtained when working at 10 °C, whereas a very high 96% ee was obtained quantitatively when working at −78 °C (Table 2, entries 15 and 16).

In other cases, low differences in the enantioselectivity of the process were observed when working at 10 or −78 °C, as in the case of the cyanoformylation reaction of 3,4,5-trimethoxybenzaldehyde and heliotropin {benzo[d][1,3]-dioxole-5-carbaldehyde}, which afforded almost quantitatively **6ah** and **6ai**, respectively (Table 2, compare entries 17 and 18, as well as 19 and 20). 3-Phenoxybenzaldehyde gave a higher ee for the corresponding **6aj** when working at −78 °C (54%) than at 10 °C (32%) (Table 2, entries 21 and 22), whereas 4-acetoxybenzaldehyde[19] gave a good ee for **6ak** at −78 °C (86%) but a very poor ee at 10 °C (8%) (Table 2, entries 23 and 24). A similar case was observed in the cyanoformylation of 4-(*tert*-butyldimethylsilyloxy)benzaldehyde,[20] which gave rise to only a 4% ee for **6al** working at 10%, and a 69% ee for working at −78 °C (Table 2, entries 25 and 26). Other aromatic aldehydes such as 4-(methylsulfanyl)-benzaldehyde and 2-chlorobenzaldehyde afforded quantitative yields and moderate ee's for the corresponding products **6am** and **6an** working at 10 or −78 °C (Table 2, compare entries 27 and 28, as well as 29 and 30). However, the enantioselective cyanoformylation of 4-chloro- and 4-bromobenzaldehyde proved more effective working at low temperatures, yielding **6ao** and **6ap**, respectively, in 86% and 90% ee, respectively, at −78 °C, and only 41% and 7% ee at 10 °C (Table 2, entries 31–34).

1-Naphthaldehyde behaved similarly in the cyanoformylation reaction when working at 10 or −78 °C, giving rise to **6aq** in 78% and 79% ee, respectively, whereas 2-naphthaldehyde showed a different behavior and afforded a 75% ee for **6ar** at 10 °C and a higher 90 % ee at −78 °C (Table 2, entries 35–38). Moreover, anthracene-9-carbaldehyde gave ca. 40% ee for the formylated product **6as** independent of the reaction temperature (Table 2, entries 39 and 40).

Heteroaromatic aldehydes were also employed in the enantioselective cyanoformylation reaction. Thus, 1-phenylsulfonyl-1*H*-pyrrole-2-carbaldehyde yielded the corresponding product **6at** in 74% ee at 10 °C, whereas only a 42% ee was observed when lowering the reaction temperature to −78 °C (Table 2, entries 41 and 42). In addition, 1-acetyl-1*H*-indole-2-carbaldehyde gave a 69% ee for **6au** when working at 10 °C, and only a 29% ee when working at −78 °C (Table 2, entries 43 and 45). However, in this case, a good 80% ee for **6au** could be obtained quantitatively when the reaction temperature was set to −20 °C (Table 2, entry 44). Furthermore, furfural and thiophene-2-carbaldehyde behave similarly in the cyanoformylation reaction, and higher ee's could be obtained for the corresponding products **6av** and **6aw**, respectively, when working at −78 °C (90% and 80%, respectively) (Table 2, entries 46–49).

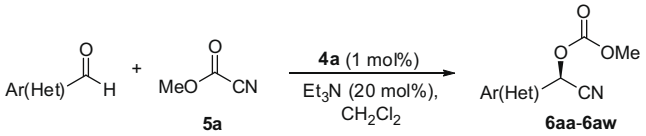
We also performed the enantioselective cyanoformylation reaction on non-aromatic aldehydes (Table 3). In this case, the combination of substrate-reaction temperature seemed not so crucial and the reaction gave rise to the highest enantioselectivities of the corresponding products **7a** when carried out at 10 °C, these values usually being lower than in the case of aromatic and heteroaromatic aldehydes.

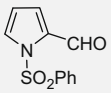
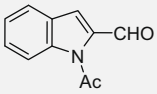
Thus, α,β-unsaturated aldehydes such as (*E*)-crotonaldehyde, (*E*)-hex-2-enal, and (*E*)-oct-2-enal afforded the corresponding products **7aa**, **7ab,** and **7ac** in high yields and with ee's of 60, 55 and 46%, respectively (Table 3, entries 1–3). Aliphatic aldehydes such as 3-methylbut-2-enal, 3-phenylpropanal, and cyclohexanecarbaldehyde always gave rise to lower enantioselectivities of the corresponding cyanoformylated products **7ad**, **7ae**, and **7af**, respectively (Table 3, entries 4–6).

As observed (Tables 2 and 3), the sense of the stereoinduction achieved using **4a** as an organocatalyst was always the same independent of the aldehyde employed as a substrate. Attempting to achieve an opposite enantioselectivity in the cyanoformylation reaction, we decided to use our previously reported *pseudoenantiomeric* cinchonine-derived dimeric ammonium salt **8**[12a] as an organocatalyst. No enantioselectivity at all was observed when the cyanoformylation reaction of several aldehydes was performed at any temperature, the cyanoformylated products being quantitatively obtained as racemic mixtures. The impossibility of obtaining the optically active enantiomeric cyanoformate counterparts of **6a** or **7a** was disappointing. However, the higher biological activity of compounds resulting from the transformation of optically active cyanoformates,[5] such as β-aminoalcohols,[21] corresponds to the enantiomers obtained when the ammonium salt **4a** is used as an organocatalyst.

This methodology proved to be scalable, which also allowed us to study the recyclability of the organocatalyst **4a**, by taking advantage of its observed low solubility in ether.[12a] Thus, the cyanoformylation procedure was carried out on a 4 mmol scale using several aldehydes (see Section 4), obtaining similar yields and

Table 2
Enantioselective cyanoformylation of aromatic and heteroaromatic aldehydes at different temperatures using **4a** as an organocatalyst



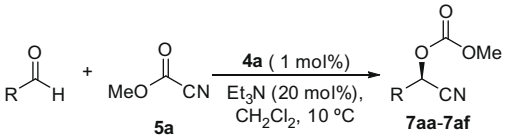
Entry	Aldehyde	*T* (°C)	*t* (h)	No.	Yield[a] (%)	ee[b] (%)
1	Benzaldehyde	10	3	**6aa**	99	80
2		0	6		99	75
3		−20	15		99	61
4		−78	15		97	62
5	2-Methylbenzaldehyde	10	3	**6ab**	99	81
6		−78	14		99	92
7	3-Methylbenzaldehyde	10	3	**6ac**	99	86
8		−78	15		99	96
9	4-Methylbenzaldehyde	10	3	**6ad**	99	83
10		−78	16		97	60
11	4-Methoxybenzaldehyde	10	3	**6ae**	99	88
12		−78	16		70[c]	74
13	3,4-Dimethoxybenzaldehyde	10	3	**6af**	99	86
14		−78	16		53[c]	62
15	3,5-Dimethoxybenzaldehyde	10	3	**6ag**	99	37
16		−78	17		99	96
17	3,4,5-Trimethoxybenzaldehyde	10	3	**6ah**	99	80
18		−78	14		96	78
19	Heliotropin	10	2	**6ai**	99	83
20		-78	17		95[c]	88
21	3-Phenoxybenzaldehyde	10	3	**6aj**	99	32
22		−78	14		90[c]	54
23	4-Acetoxybenzaldehyde	10	3	**6ak**	99	8
24		−78	14		94[c]	86
25	4-(*tert*-Butyldimethylsilyloxy)benzaldehyde	10	21	**6al**	83[c]	4
26		−78	16		44[c]	69
27	4-(Methylsulfanyl)benzaldehyde	10	3	**6am**	99	39
28		−78	14		99	52
29	2-Chlorobenzaldehyde	10	3	**6an**	99	55
30		−78	15		99	48
31	4-Chlorobenzaldehyde	10	3	**6ao**	99	41
32		−78	16		99	86
33	4-Bromobenzaldehyde	10	3	**6ap**	99	7
34		−78	17		99	90
35	1-Naphthaldehyde	10	3	**6aq**	99	78
36		−78	16		99	79
37	2-Naphthaldehyde	10	3	**6ar**	99	75
38		−78	16		99	90
39	Anthracene-9-carbaldehyde	10	3	**6as**	99	41
40		−78	15		99	39
41		10	6	**6at**	99	74
42		−78	72		60[c]	42
43		10	3	**6au**	99	69
44		−20	14		99	80
45		−78	15		43[c]	29
46	Furfural	10	3	**6av**	99	81
47		−78	17		99	90
48	Thiophene-2-carbaldehyde	10	3	**6aw**	99	65
49		−78	16		95[c]	80

[a] Isolated as pure crude products according to ^{1}H NMR (300 MHz) and with >95% purity according to GLC.
[b] Determined by chiral HPLC (see Section 4).
[c] Determined by ^{1}H NMR (300 MHz).

enantioselectivities for the corresponding cyanoformates **6a** and **7a** than when working at a much lower scale. Evaporation of the dichloromethane and the addition of ether allowed us to precipitate the organocatalyst **4a**, which was filtered (>95% recovery) and reused without observing any loss of activity.

Considering our previous experience in the preparation and use of *Cinchona* alkaloid-resin supported species as phase-transfer organocatalysts,[14] we also investigated the possible use of cinchonidine-anchored species in order to perform an easier catalyst removal and recycling just by direct filtration, Thus, we used the

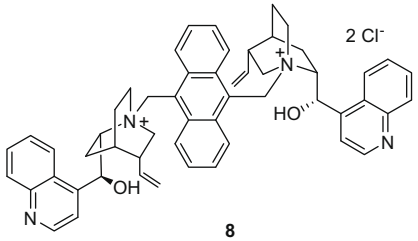
Table 3
Enantioselective cyanoformylation of alkyl and alkenyl aldehydes using **4a** as an organocatalyst



Entry	Aldehyde	*t* (h)	No.	Yield[a] (%)	ee[b] (%)
1	(*E*)-Crotonaldehyde	3	**7aa**	97[c]	60
2	(*E*)-Hex-2-enal	6	**7ab**	99	55
3	(*E*)-Oct-2-enal	3	**7ac**	88[c]	46
4	3-Methylbut-2-enal	5	**7ad**	99	36
5[d]	3-Phenylpropanal	14	**7ae**	99	40
6	Cyclohexanecarbaldehyde	3	**7af**	86[c]	40

[a] Isolated as pure crude products according to ^{1}H NMR (300 MHz) and with >95% purity according to GLC.
[b] Determined by chiral GLC (see Section 4).
[c] Determined by ^{1}H NMR (300 MHz).
[d] The reaction was performed at −78 °C.

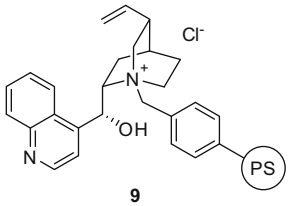
Merrifield-anchored cinchonidinium ammonium salt **9**[14a] (resin loading = 1.7 mmol g^{-1}) as a catalyst (100 mg mmol^{-1} catalyst amount) in the cyanoformylation reaction of 3,5-dimethoxybenzaldehyde under the previous successful reaction conditions (Table 2, entry 16); however, the obtained ee of **6ag** was very low (<10%), whereas other previously used supported catalysts[14b] gave null enantioselectivities. However, when the anchored cinchonidinium-derived ammonium salt incorporating a 9-anthrylmethyl moiety **10**[14b] (resin loading = 1.4 mmol g^{-1}) was employed under the same reaction conditions, **6ag** was obtained quantitatively in 14 h reaction time after filtration in an excellent 95% ee. Disappointingly, when the filtered recycled supported catalyst **10** was used in a second run, the enantioselectivity dropped down to 35%.



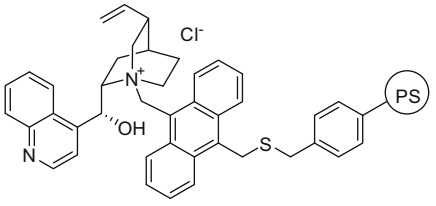
8

Related to the mechanism operating in this enantioselective process, the importance of the presence of a free OH in catalyst **4a** to achieve stereoinduction suggests a possible hydrogen bond between this group and the carbonyl of the aldehyde creating an initial substrate–catalyst interaction. In addition, π-stacking between both species could also be possible, as aromatic and heteroaromatic aldehydes give rise to higher enantioselectivities. Moreover, as it is known that cyanide-precursor reagents such as alkyl cyanoformates need the presence of a nucleophilic species, such as triethylamine, to generate cyanide in situ which adds to the carbonyl compound,[3] perhaps a preliminary cyanide anion interaction takes place with the positively charged ammonium cation of the organocatalyst leaving the cyanide close to the activated carbonyl.

In order to determine the possible influence of a close cyanide in the aldehyde–catalyst initial pair, we prepared a cinchonidine-derived cyanide salt from dichloride **4a** by an anion exchange reaction[12b] with silver cyanide in acetonitrile as a solvent. The salt obtained showed the presence of a C≡N stretching band at 2131 cm^{-1} in its infrared spectrum. However, when this salt was used in the model cyanoformylation reaction of benzaldehyde, only a 42% ee for the product **4aa** was quantitatively obtained in 3 h reaction time working at room temperature, not much differences in ee's being observed at lower temperatures.



9



10

[PS = crosslinked polystyrene]

A dynamic kinetic resolution (DKR) mechanism could not be completely discarded.[3,10,22] Thus, the stereodetermining step may not be the addition of cyanide to the prochiral aldehyde. If the mechanism involves a reversible addition of cyanide followed by irreversible protection of the initial cyanohydrin alkoxide under the influence of the chiral organocatalyst, then a DKR may occur, with the second step determining the stereochemistry of the overall reaction. In this case, the cyanide-containing reagent would not be involved in the stereodetermining step. However, in our case noticeable different enantioselectivities for **4aa** were observed when using methyl or ethyl cyanocarbonate, while no significative differences in ee for **4aa** were detected when running the model cyanoformylation reaction of benzaldehyde at short reaction times. In addition, the null stereoinduction produced with the cinchonine-derived *pseudoenantiomeric* ammonium salt **8** is difficult to explain. Perhaps not in just one, but a combination of processes controls the good enantioselectivities that can be achieved using this methodology.

3. Conclusions

We can conclude that non-supported and supported recoverable cinchonidine-derived ammonium salts can be employed as recyclable organocatalysts in the high-yielding cyanoformylation reaction of aldehydes, using methyl cyanoformate as a cyanide source and in the presence of substoichiometric amounts of triethylamine as a base. The higher enantioselectivities (up to 96% ee) can be achieved from aromatic and heteroaromatic aldehydes, using only a 1 mol % of a dimeric anthracenyldimethyl-derived cinchonidine ammonium salt as an organocatalyst, in a process where the optimum reaction temperature is highly dependent of the structure of the starting aldehyde. The results obtained using this catalyst are considerably better than those recently reported when using a quinidine-derived quaternary ammonium salt[11] in terms of higher enantioselectivities, much lower reaction times, and lower catalyst loading. In addition, the easy recyclability of this catalyst after precipitation in ether and filtration makes it very interesting when considering a scaling-up of the process.

4. Experimental

4.1. General

All the reagents and solvents employed were of the best grade available and were without further purification. Melting points are uncorrected. Optical rotations were measured using a Perkin–Elmer 341 polarimeter. IR data were collected on a Nicolet Impact 400D-FT spectrometer and only diagnostic bands are given. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 at 300 MHz and 75 MHz, respectively, using $CDCl_3$ as a solvent and TMS as an internal standard. MS (EI, 70 eV) were performed on a HP MS-GC-5973A. HRMS analyses were carried out on a Finnigan MAT 95S. Ammonium salts **4b**[12a] and **4c**[12b] have been prepared following the reported procedure. The enantiomeric excesses of products **6** were determined by chiral HPLC analyses, whereas in the case of products **7a,** these were determined by chiral GLC analyses. Chromatographic conditions for each described compound are given. Reference racemic samples were obtained by performing the cyanoformylation reaction in the absence of an organocatalyst.[23]

4.2. Preparation of cinchonidine- and cinchonine-derived ammonium salts 4a and 8

To a suspension of cinchonidine (for **4a**) or cinchonine (for **8**) (8.8 mmol, 2.36 g) in EtOH/DMF/$CHCl_3$ (5/6/2 v/v/v, 25 mL) was added 9,10-dichloromethylanthracene[12a] (4 mmol, 1.10 g), and the mixture was stirred at 100 °C overnight. The solution was allowed to cool down at rt, diluted with MeOH (25 mL), and poured over Et_2O (75 mL). The precipitate was filtered off and washed with Et_2O (3 × 20 mL), and the resulting solid was crystalized twice from MeOH/Et_2O, yielding ammonium salts **4a** (2.93 g, 85%) or **8** (2.76 g, 80%). Analytical data for these compounds have already been reported.[12]

4.3. Enantioselective cyanoformylation reaction. General procedure

A solution of the corresponding aldehyde (0.2 mmol), ammonium salt **4a** (0.002 mmol, 1.7 mg), and Et_3N (0.04 mmol, 5.5 μL) in CH_2Cl_2 (2 mL) was cooled to the selected temperature (Tables 2 and 3). Methyl cyanoformate (0.3 mmol, 24 μL) was added and the mixture was stirred vigorously. After the reaction was completed (GLC), the mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organics were dried with $MgSO_4$, filtered, and evaporated in vacuo (15 Torr) to afford crude products, which were analyzed by ^{1}H NMR (300 MHz) spectroscopy.

Scaling-up the reaction was achieved by performing the reaction similarly, but starting from 4 mmol of aldehyde. After the reaction was completed, the CH_2Cl_2 was evaporated, the residue was diluted with Et_2O (30 mL), and the precipitate was filtered off. The solution was diluted with water (40 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organics were dried ($MgSO_4$) and evaporated in vacuo (15 Torr) affording the crude products. The precipitate was washed with Et_2O and corresponded to the ammonium salt (>95% recovery), which was used in other runs without a loss in activity.

Yields of the obtained products are shown in Tables 2 and 3. Analytical data for compounds **6ab**,[23] **6ac**,[24] **6aj**,[23] **6an**,[5b] **6ap**,[24] **7ab**,[5b] **7ad**,[5b] and **7ae**[5b] have already been described, whereas data for the rest of cyanohydrins follow.

4.3.1. (*R*)-Cyano(phenyl)methyl methyl carbonate 6aa

Colorless oil; IR (film): ν 2250, 1759 cm^{-1}; ^{1}H NMR: δ_H 3.87 (3H, s, OCOOC*H*$_3$), 6.27 (1H, s, C*H*CN), 7.47 (3H, m, Ar*H*), 7.54 (2H, m, Ar*H*); ^{13}C NMR: δ_C 55.8, 66.5, 115.6, 127.8, 129.2, 130.6, 131.1, 154.0; MS (EI): *m*/*z* 191 (M$^+$, 40), 116 (100); HRMS calcd for $C_{10}H_9NO_3$: 191.0582, found 191.0559; HPLC: Chiracel OG, λ = 210 nm, *n*-hexane/2-propanol, 99/1, 1.0 mL/min, t_r (major) = 11.3 min, t_r (minor) = 12.8 min.

4.3.2. (*R*)-Cyano(*p*-tolyl)methyl methyl carbonate 6ad

Colorless oil; IR (film): ν 2356, 1762 cm^{-1}; ^{1}H NMR: δ_H 2.39 (3H, s, C*H*$_3$ArH), 3.86 (3H, s, OCOOC*H*$_3$), 6.27 (1H, s, C*H*CN), 7.26 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.42 (2H, d, *J* = 8.2 Hz, Ar*H*); ^{13}C NMR: δ_C 21.3, 55.8, 66.5, 115.8, 127.9 (2), 129.9 (2), 141.0, 153.0, 154.1; MS (EI): *m*/*z* (%) 205 (M$^+$, 33), 129 (100); HRMS calcd for $C_{11}H_{11}NO_3$: 205.0739, found 205.0712; HPLC: Chiracel OG, λ = 210 nm, *n*-hexane/2-propanol, 99/1, 1.0 mL/min, t_r (major) = 11.0 min, t_r (minor) = 12.5 min.

4.3.3. (*R*)-Cyano(4-methoxyphenyl)methyl methyl carbonate 6ae

Colorless oil; IR (film): ν 2244, 1758 cm^{-1}; ^{1}H NMR: δ_H 3.86, 3.88 (6H, 2 × s, OCOOC*H*$_3$, PhOC*H*$_3$), 6.23 (1H, s, C*H*CN), 6.98 (2H, d, *J* = 8.8 Hz, Ar*H*), 7.50 (2H, d, *J* = 8.8 Hz, Ar*H*); ^{13}C NMR: δ_C 55.3, 55.8, 66.3, 114.8, 115.8, 123.1, 129.6, 154.0, 161.3; MS (EI): *m*/*z* 221 (M$^+$, 9), 146 (100); HRMS calcd for $C_{11}H_{11}NO_4$: 221.0688, found 221.0684; HPLC: Chiracel OG, λ = 210 nm, *n*-hexane/2-propanol, 99/1, 1.0 mL/min, t_r (major) = 20.5 min, t_r (minor) = 23.9 min.

4.3.4. (*R*)-Cyano(3,4-dimethoxyphenyl)methyl methyl carbonate 6af

Colorless oil; IR (film): ν 1758, 1258 cm^{-1}; ^{1}H NMR: δ_H 3.87, 3.91, 3.92 (9H, 3 × s, OCOOC*H*$_3$, 2 × PhOC*H*$_3$), 6.21 (1H, s, C*H*CN), 6.89–6.91 (1H, m, Ar*H*), 7.02 (1H, br s, Ar*H*), 7.10–7.12 (1H, m, Ar*H*); ^{13}C NMR: δ_C 55.9, 56.1, 56.1, 66.7, 110.7, 111.2, 115.9, 121.4, 123.5, 149.6, 151.0, 154.2; MS (EI): *m*/*z* (%) 251 (M$^+$, 27), 176 (100); HRMS calcd for $C_{12}H_{13}NO_5$: 251.0794, found 251.0845; HPLC: Chiracel AD, λ = 210 nm, *n*-hexane/2-propanol, 95:5, 1.0 mL/min, t_r (minor) = 22.1 min, t_r (major) = 23.7 min.

4.3.5. (*R*)-Cyano(3,5-dimethoxyphenyl)methyl methyl carbonate 6ag

Colorless oil; IR (film): ν 1762, 1263 cm^{-1}; ^{1}H NMR: δ_H 3.81 (6H, s, 2 × PhOC*H*$_3$), 3.88 (3H, s, OCOOC*H*$_3$), 6.19 (1H, s, C*H*CN), 6.52 (1H, br s, Ar*H*), 6.65 (2H, br s, Ar*H*); ^{13}C NMR: δ_C 55.6, 56.0, 66.5, 102.5, 105.7, 115.7, 133.1, 154.1, 161.4; MS (EI): *m*/*z* (%) 251 (M$^+$, 58), 192 (100); HRMS calcd for $C_{12}H_{13}NO_5$: 251.0794, found 251.0811; HPLC: Chiracel AD, λ = 210 nm, *n*-hexane/2-propanol, 92:8, 1.0 mL/min, t_r (major) = 12.9 min, t_r (minor) = 13.9 min.

4.3.6. (*R*)-Cyano(3,4,5-trimethoxyphenyl)methyl methyl carbonate 6ah

Colorless oil; IR (film): ν 1996, 1763 cm^{-1}; ^{1}H NMR: δ_H 3.74 (3H, s, OCOOC*H*$_3$), 3.83 (9H, s, 3 × PhOC*H*$_3$), 6.43 (2H, s, Ar*H*), 6.50 (1H, s, C*H*CN); ^{13}C NMR: δ_C 55.1, 56.1 (2), 60.3, 74.8, 100.8 (2), 114.9, 129.6, 137.6, 153.0 (2), 153.3; MS (EI): *m*/*z* (%) 281 (M$^+$, 22), 206 (100); HRMS calcd for $C_{13}H_{15}NO_6$: 281.0899, found 281.0870; HPLC: Chiracel OD-H, λ = 254 nm, *n*-hexane/2-propanol, 97/3, 1.0 mL/min, t_r (major) = 29.3 min, t_r (minor) = 31.9 min.

4.3.7. (*R*)-Benzo[*d*][1,3]dioxol-5-yl(cyano)methyl methyl carbonate 6ai

Colorless oil; IR (film): ν 2204, 1759, 1251 cm^{-1}; ^{1}H NMR: δ_H 3.82 (3H, s, OCOOC*H*$_3$), 5.98 (2H, s, C*H*$_2$), 6.14 (1H, s, C*H*CN), 6.80 (1H, d, *J* = 7.9 Hz, Ar*H*), 6.96–7.00 (2H, m, Ar*H*); ^{13}C NMR: δ_C 55.7, 66.3, 101.7, 108.1, 108.5, 115.6, 122.4, 124.6, 148.3, 149.5, 153.9; MS (EI): *m*/*z* (%) 235 (M$^+$, 18), 160 (100); HRMS calcd for $C_{11}H_9NO_5$: 235.0481, found 235.0496; HPLC: Chiracel OD-H,

λ = 210 nm, *n*-hexane/2-propanol, 99/1, 1.0 mL/min, t_r (major) = 22.0 min, t_r (minor) = 30.7 min.

4.3.8. (*R*)-4-Cyano(methoxycarbonyloxy)methyl)phenyl acetate 6ak

Colorless oil; IR (film): ν 1759, 1259, 1201; ^{1}H NMR: δ_H 2.32 (3H, s, OCOC*H*$_3$), 3.87 (3H, s, OCOOC*H*$_3$), 6.27 (1H, s, C*H*CN), 7.20 (2H, d, *J* = 8.6 Hz, Ar*H*), 7.57 (2H, d, *J* = 8.7 Hz, Ar*H*); ^{13}C NMR: δ_C 21.2, 56.1, 66.0, 115.6, 122.7, 128.7, 129.4, 152.4, 154.1, 169.1; MS (EI): *m*/*z* (%) 249 (M^+, 8), 131 (100); HRMS calcd for $C_{12}H_{11}NO_5$: 249.0637, found 249.0572; HPLC: Chiracel AD, λ = 210 nm, *n*-hexane/2-propanol, 97:3, 1.0 mL/min, t_r (minor) = 28.9 min, t_r (major) = 31.2 min.

4.3.9. (*R*)-(4-(*tert*-Butyldimethylsilyloxy)phenyl)(cyano)methyl methyl carbonate 6al

Colorless oil; IR (film): ν 1759, 1254; ^{1}H NMR: δ_H 0.21 (6H, s, 2 × SiC*H*$_3$), 0.98 (9H, s, SiC(C*H*$_3$)$_3$), 3.86 (3H, s, OCOOC*H*$_3$), 6.20 (1H, s, C*H*CN), 6.89 (2H, d, *J* = 8.6 Hz, Ar*H*), 7.41 (2H, d, *J* = 8.4 Hz, Ar*H*); ^{13}C NMR: δ_C −4.3, 18.3, 25.7, 55.9, 66.5, 116.0, 120.9, 123.9, 129.8, 154.3, 158.0; MS (EI): *m*/*z* (%) 321 (M^+, 9), 89 (100); HRMS calcd for $C_{16}H_{23}NO_4Si$: 321.1396, found 321.1429; HPLC: Chiracel OG, λ = 210 nm, *n*-hexane/2-propanol, 95:5, 1.0 mL/min, t_r (major) = 5.6 min, t_r (minor) = 6.6 min.

4.3.10. (*R*)-Cyano(4-(methylthio)phenyl)methyl methyl carbonate 6am

Colorless oil; IR (film): ν 1758, 1255 cm^{-1}; ^{1}H NMR: δ_H 2.49 (3H, s, PhSC*H*$_3$), 3.86 (3H, s, OCOOC*H*$_3$), 6.22 (1H, s, C*H*CN), 7.28 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.44 (2H, d, *J* = 8.4 Hz, Ar*H*); ^{13}C NMR: δ_C 15.3, 56.0, 66.4, 115.7, 126.4, 127.5, 128.5, 142.7, 154.2; MS (EI): *m*/*z* (%) 237 (M^+, 30), 162 (100); HRMS calcd for $C_{11}H_{11}NO_3S$: 237.0460, found 237.0483; HPLC: Chiracel OD-H, λ = 210 nm, *n*-hexane/2-propanol, 90:10, 1.0 mL/min, t_r (major) = 9.9 min, t_r (minor) = 11.9 min.

4.3.11. (*R*)-(4-Chlorophenyl)(cyano)methyl methyl carbonate 6ao

Colorless oil; IR (film): ν 2247, 1767 cm^{-1}; ^{1}H NMR: δ_H 3.90 (3H, s, OCOOC*H*$_3$), 6.26 (1H, s, C*H*CN), 7.44–7.53 (4H, m, Ar*H*); ^{13}C NMR: δ_C 55.9, 65.7, 115.2, 128.1, 129.2, 129.5, 130.8, 153.8; MS (EI): *m*/*z* (%) 225 (M^+, 32), 150 (100); HRMS calcd for $C_{10}H_8ClNO_3$: 225.0192, found 225.0188; HPLC: Chiracel OG, λ = 210 nm, *n*-hexane/2-propanol, 99/1, 1.0 mL/min, t_r (major) = 15.3 min, t_r (minor) = 18.8 min.

4.3.12. (*R*)-Cyano(naphthalen-1-yl)methyl methyl carbonate 6aq

Colorless oil; IR (film): ν 2223, 1756 cm^{-1}; ^{1}H NMR: δ_H 3.74 (3H, s, OCOOC*H*$_3$), 6.53 (1H, s, C*H*CN), 7.07–7.13 (1H, m, Ar*H*), 7.41–7.45 (1H, m, Ar*H*), 7.54–7.64 (2H, m, Ar*H*), 7.73–7.78 (1H, m, Ar*H*), 8.05–8.09 (1H, m, Ar*H*), 8.15–8.21 (1H, m, Ar*H*); ^{13}C NMR: δ_C 55.1, 73.0, 114.9, 125.1, 125.8, 126.3, 126.4, 127.5, 128.9, 134.2, 140.4, 153.3; MS (EI): *m*/*z* (%) 241 (M^+, 20), 165 (100); Chiracel OG, λ = 210 nm, *n*-hexane/2-propanol, 99/1, 1.0 mL/min, t_r (major) = 16.2 min, t_r (minor) = 19.4 min.

4.3.13. (*R*)-Cyano(naphthalen-2-yl)methyl methyl carbonate 6ar

Colorless oil; IR (film) ν 2249, 1770 cm^{-1}; ^{1}H NMR: δ_H 3.89 (3H, s, OCOOC*H*$_3$), 6.44 (1H, s, C*H*CN), 7.57 (3H, m, Ar*H*), 7.90 (3H, m, Ar*H*), 8.04 (1H, s, Ar*H*); ^{13}C NMR: δ_C 55.8, 66.7, 115.6, 124.0, 127.0, 127.6, 127.7, 128.0, 128.2, 128.3, 129.4, 132.7, 133.9, 154.0; MS (EI): *m*/*z* 241 $[M]^+$; HRMS calcd for $C_{14}H_{11}NO_3$: 241.0739, found 241.0732; HPLC: Chiracel OG, λ = 210 nm, *n*-hexane/2-propanol, 99/1, 1.0 mL/min, t_r (major) = 17.3 min, t_r (minor) = 21.8 min.

4.3.14. (*R*)-Anthracen-9-yl(cyano)methyl methyl carbonate 6as

Yellow solid, mp 153–155 °C; IR (KBr) ν 1755, 1274 cm^{-1}; ^{1}H NMR: δ_H 3.83 (3H, s, OCOOC*H*$_3$), 7.50–7.54 (2H, m, Ar*H*), 7.64–7.69 (2H, m, Ar*H*), 7.85 (1H, s, C*H*CN), 8.04 (2H, d, *J* = 8.2 Hz, Ar*H*), 8.48 (2H, d, *J* = 9.0 Hz, Ar*H*), 8.59 (1H, s, Ar*H*); ^{13}C NMR: δ_C 56.1, 60.8, 116.5, 120.9, 123.2, 125.6, 128.1, 129.6, 130.2, 131.4, 132.1, 154.6; MS (EI): *m*/*z* (%) 291 (M^+, 24), 216 (100); HRMS calcd for $C_{18}H_{13}NO_3$: 291.0895, found 291.0933; HPLC: Chiracel OD-H, λ = 254 nm, *n*-hexane/2-propanol, 90:10, 1.0 mL/min, t_r (minor) = 17.5 min, t_r (major) = 29.2 min.

4.3.15. (*R*)-Cyano(1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)methyl methyl carbonate 6at

Colorless oil; IR (film): ν 1762, 1265 cm^{-1}; ^{1}H NMR: δ_H 3.88 (3H, s, OCOOC*H*$_3$), 6.34–6.36 (1H, m, Ar*H*), 6.72 (1H, s, C*H*CN), 6.83–6.84 (1H, m, Ar*H*), 7.38–7.40 (1H, m, Ar*H*), 7.51–7.56 (2H, m, Ar*H*), 7.63–7.68 (1H, m, Ar*H*), 7.81–7.84 (2H, m, Ar*H*); ^{13}C NMR: δ_C 55.9, 59.1, 112.3, 114.6, 119.6, 123.5, 126.2, 126.8, 129.6, 134.5, 138.3, 153.6; MS (EI): *m*/*z* (%) 245 (M^+-75, 11), 77 (100); HPLC: Chiracel AD, λ = 210 nm, *n*-hexane/2-propanol, 90:10, 1.0 mL/min, t_r (minor) = 18.0 min, t_r (major) = 22.3 min.

4.3.16. (*R*)-(1-Acetyl-1*H*-indol-3-yl)(cyano)methyl methyl carbonate 6au

Colorless oil; IR (film): ν 2215, 1759, 1465, 1388, 1260 cm^{-1}; ^{1}H NMR: δ_H 2.66 (3H, s, NCOC*H*$_3$), 3.88 (3H, s, OCOOC*H*$_3$), 6.54 (1H, s, C*H*CN), 7.36 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.43 (1H, t, *J* = 8.2 Hz, Ar*H*), 7.68 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.73 (1H, s, Ar*H*), 8.44 (1H, d, *J* = 8.4 Hz, Ar*H*); ^{13}C NMR: δ_C 24.0, 56.1, 59.9, 113.1, 115.1, 117.0, 119.0, 124.6, 126.3, 126.6, 126.8, 136.1, 154.2, 168.5; MS (EI): *m*/*z* (%) 272 (M^+, 14), 154 (100); HRMS calcd for $C_{14}H_{12}N_2O_4$: 272.0797, found 272.0806; HPLC: Chiracel AD, λ = 210 nm, *n*-hexane/2-propanol, 95:5, 0.9 mL/min, t_r (minor) = 33.3 min, t_r (major) = 36.5 min.

4.3.17. (*S*)-Cyano(furan-2-yl)methyl methyl carbonate 6av

Colorless oil; IR (film): ν 2254, 1763 cm^{-1}; ^{1}H NMR: δ_H 3.89 (3H, s, OCOOC*H*$_3$), 6.36 (1H, s, C*H*CN), 6.46 (1H, dd, *J* = 3.3, 1.9 Hz, OCHC*H*), 6.75 (1H, d, *J* = 3.3 Hz, OCC*H*), 7.53 (1H, d, *J* = 1.9 Hz, OC*H*CH); ^{13}C NMR: δ_C 55.9, 59.3, 111.1, 113.0, 113.6, 143.4, 145.2, 153.8; MS (EI) *m*/*z* (%) 181 (M^+, 18), 106 (100); HRMS calcd for $C_8H_7NO_4$: 181.0375, found 181.0376; HPLC: Chiralpak AD, λ = 210 nm, *n*-hexane/2-propanol, 99/1, 1.0 mL/min, t_r (major) = 13.0 min, t_r (minor) = 14.7 min.

4.3.18. (*S*)-Cyano(thiophen-2-yl)methyl methyl carbonate 6aw

Colorless oil; IR (film): ν 1759, 1261 cm^{-1}; ^{1}H NMR: δ_H 3.88 (3H, s, OCOOC*H*$_3$), 6.50 (1H, s, C*H*CN), 7.06 (1H, dd, *J* = 5.2, 3.7 Hz, SCHC*H*), 7.39 (1H, d, *J* = 3.6 Hz, SCC*H*), 7.49 (1H, d, *J* = 5.2 Hz, SC*H*CH); ^{13}C NMR: δ_C 56.1, 61.8, 115.1, 127.4, 129.6, 130.2, 132.7, 154.0; MS (EI): *m*/*z* (%) 197 (M^+, 23), 122 (100); HRMS calcd for $C_8H_7NO_3S$: 197.0147, found 197.0175; HPLC: Chiralpak AD, λ = 254 nm, *n*-hexane/2-propanol, 99:1, 1.0 mL/min, t_r (major) = 13.6 min, t_r (minor) = 14.9 min.

4.3.19. (*R*,*E*)-1-Cyanobut-2-enyl methyl carbonate 7aa

Colorless oil; IR (film): ν 2254, 1759 cm^{-1}; ^{1}H NMR: δ_H 1.83 (3H, d, *J* = 6.6 Hz, C*H*$_3$CH), 3.87 (3H, s, OCOOC*H*$_3$), 5.58–5.68 (2H, m, C*H*CN, CNCHC*H*), 6.22 (1H, m, CHCH=C*H*); ^{13}C NMR: δ_C 17.6, 55.6, 65.0, 115.2, 120.8, 136.4, 153.9; MS (EI): *m*/*z* (%) 155 (M^+, 7), 53 (100); HRMS calcd for $C_7H_9NO_3$: 155.0582, found 155.0582; GLC: Cyclosil-B, $T_{injector}$ = 250 °C, $T_{detector}$ = 260 °C, T_{column} = 105 °C (1 min) to 180 °C (2.0 °C/min), P = 120 kPa, t_r (major) = 5.1 min, t_r (minor) = 5.8 min.

4.3.20. (*R*,*E*)-1-Cyanooct-2-enyl methyl carbonate 7ac

Colorless oil; IR (film): ν 2249, 1763 cm^{-1}; ^{1}H NMR: δ_H 0.89 (3H, t, J = 6.7 Hz, CH_3CH_2), 1.25–1.30 (4H, m, 2 × CH_2), 1.40–1.45 (2H, m, CH_2), 2.13 (2H, m, CH_2CH), 3.86 (3H, s, OCOOCH_3), 5.54–5.61 (1H, m, CNCHCH), 5.66–5.68 (1H, m, CHCN), 6.20 (1H, dt, J = 14.6, 7.2 Hz, CH_2CH); ^{13}C NMR: δ_C 13.8, 22.3, 27.8, 31.1, 31.9, 55.6, 65.1, 115.2, 119.4, 141.5, 154.0; MS (EI): m/z (%) 211 (M$^+$, 2), 55 (100); HRMS calcd for $C_{11}H_{17}NO_3$: 211.1208, found 211.1212; GLC: Cyclosil-B, $T_{injector}$ = 250 °C, $T_{detector}$ = 260 °C, T_{column} = 105 °C (1 min) to 180 °C (2.0 °C/min), P = 120 kPa, t_r (major) = 22.0 min, t_r (minor) = 22.9 min.

4.3.21. (*R*)-Cyano(cyclohexyl)methyl methyl carbonate 7af

Colorless oil; IR (film): ν 2247, 1762 cm^{-1}; ^{1}H NMR: δ_H 1.18–1.23 (5H, m, cyclohexyl), 1.80–1.94 (6H, m, cyclohexyl), 3.86 (3H, s, OCOOCH_3), 5.04 (1H, d, J = 5.7 Hz, CHCN); ^{13}C NMR: δ_C 25.1, 25.1, 25.5, 27.6, 27.8, 40.0, 55.6, 69.0, 115.6, 154.3; MS (EI): m/z (%) 197 (M$^+$, 0.03), 83 (100); HRMS calcd for $C_{10}H_{15}NO_3$: 197.1052, found 197.1060; GLC: Cyclosil-B, $T_{injector}$ = 250 °C, $T_{detector}$ = 260 °C, T_{column} = 105 °C (1 min) to 180 °C (2.0 °C/min), P = 120 kPa, t_r (major) = 18.6 min, t_r (minor) = 19.2 min.

Acknowledgments

We thank the financial support from the Spanish Ministerio de Educación y Ciencia (Projects CTQ2004-00808/BQU, CTQ2007-62771/BQU and Consolider Ingenio 2010, CSD2007-00006), the Generalitat Valenciana (Project GV05/144), and the University of Alicante. F.J.O. and S.T. thank the Universidad de Alicante and the Generalitat Valenciana, respectively, for pre-doctoral fellowships.

References

1. (a) Fleming, F. F. *Nat. Prod. Rep.* **1999**, *16*, 597–606; (b) Park, D.-J.; Coats, J. R. *J. Pest. Sci.* **2005**, *30*, 99–102.
2. Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kebeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788–824.
3. North, M.; Usanov, D. L.; Young, C. *Chem. Rev.* **2008**, *108*, 5146–5226.
4. Reviews: (a) North, M. *Synlett* **1993**, 807–820; (b) Effenberg, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555–1563; (c) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649–3682; (d) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147–176; (e) Brunel, J.-M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752–2778; (f) Chen, F.-X.; Feng, X. *Curr. Org. Synth.* **2006**, *3*, 77–97; (g) Baeza, A.; Sansano, J. M.; Saá, J. M.; Nájera, C. *Pure Appl. Chem.* **2007**, *79*, 213–221; (h) Khan, N. H.; Kureshy, R. I.; Abdi, S. H. R.; Agrawal, S.; Jasra, R. V. *Coord. Chem. Rev.* **2008**, *252*, 593–623.
5. (a) Casas, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron: Asymmetry* **2003**, *14*, 197–200; (b) Baeza, A.; Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Eur. J. Org. Chem.* **2006**, 1949–1958.
6. Baeza, A.; Casas, J.; Nájera, C.; Sansano, J. M. *J. Org. Chem.* **2006**, *71*, 3837–3848.
7. Rosenthaler, L. *Biochem. Z* **1908**, *14*, 238–253.
8. Bredig, G.; Fiske, P. S. *Biochem. Z* **1913**, *46*, 7–23.
9. Reviews on organocatalysis which include enantioselective cyanohydrin synthesis: (a) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621–631; (b) Colby Davie, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812.
10. (a) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196; (b) Tian, S.-K.; Deng, L. *Tetrahedron* **2006**, *62*, 11320–11330.
11. Peng, D.; Zhou, H.; Liu, X.; Wang, L.; Chen, S.; Feng, X. *Synlett* **2007**, 2448–2450.
12. (a) Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2002**, *13*, 927–931; (b) Chinchilla, R.; Mazón, P.; Nájera, C.; Ortega, F. J. *Tetrahedron: Asymmetry* **2004**, *15*, 2603–2607.
13. Chinchilla, R.; Mazón, P.; Nájera, C.; Ortega, F. J.; Yus, M. *Arkivoc* **2005**, *vi*, 222–232.
14. (a) Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2000**, *11*, 3277–3281; (b) Chinchilla, R.; Mazón, P.; Nájera, C. *Molecules* **2004**, *9*, 349–364; (c) Chinchilla, R.; Mazón, P.; Nájera, C. *Adv. Synth. Catal.* **2004**, *346*, 1186–1194.
15. Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671.
16. Preliminary communication: Chinchilla, R.; Nájera, C.; Ortega, F. J. *Tetrahedron: Asymmetry* **2008**, *19*, 265–268.
17. The stereochemistry was assigned by the order of elution of the corresponding enantiomers in chiral chromatography according to the literature (Refs.[5b,11,17]).
18. When a new O-formylated cyanohydrin was obtained, its tentatively assigned absolute stereochemistry was confirmed by comparing the order of elution of its enantiomers with that in an optically active cyanohydrin prepared by a totally different enantioselective route involving a chiral binaphthyl-containing monometallic bifunctional aluminum catalyst (Ref.[5]).
19. Prepared by reaction of 4-hydroxybenzaldehyde with acetic anhydride in the presence of triethylamine: Papadakis, P. E. *J. Am. Chem. Soc.* **1945**, *67*, 1799–1800.
20. Prepared by the reaction of 4-hydroxybenzaldehyde with tert-butyldimethylsilyl chloride in the presence of triethylamine: Swenton, J. S.; Carpenter, K.; Chen, Y.; Kerns, M. L.; Morrow, G. W. *J. Org. Chem.* **1993**, *58*, 3308–3316.
21. (a) Crossley, R. J. *Chirality and the Biological Activity of Drugs*; CRC: Boca Raton, 1995. pp 90–92; (b) Stoschitzky, K.; Klein, W.; Lindler, W. *Trends Pharm. Sci.* **1997**, *18*, 306–307; (c) Waldeck, B. *Pharm. News* **2001**, *8*, 25–31; (d) Mehvar, R.; Brocks, D. R. *J. Pharm. Pharm. Sci.* **2001**, *4*, 185–200; (e) Davies, N. M.; Teng, X. W. *Adv. Pharm.* **2003**, *1*, 242–252; (f) Path, P. N.; Li, C.; Kumari, V.; Hieble, J. P. *Chirality* **2008**, *20*, 529–543.
22. (a) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5–26; (b) Pellisier, H. *Tetrahedron* **2008**, *64*, 1563–1601.
23. Baeza, A.; Nájera, C.; de Gracia Retamosa, M.; Sansano, J. M. *Synlett* **2005**, 2787–2797.
24. Iwakami, K.; Hinakubo, Y.; Oriyama, T. *Tetrahedron Lett.* **2005**, *46*, 5881–5883.