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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 265–268

Enantioselective cyanoformylation of aldehydes using a recyclable dimeric cinchonidine ammonium salt as an organocatalyst

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Received 5 December 2007; accepted 10 January 2008

Abstract—A dimeric anthracenyldimethyl-derived cinchonidine ammonium salt is used as a chiral organocatalyst in the enantioselective addition of alkyl cyanoformates to aldehydes in the presence of substoichiometric amounts of triethylamine. Quantitative yields and enantioselectivities up to 88% ee for the corresponding (*R*)-*O*-methoxycarbonyl cyanohydrins are obtained using only 1 mol % organocatalyst loading and working at 10 °C. The organocatalyst can be almost quantitatively recovered by precipitation and reused.

1. Introduction

The preparation of optically active cyanohydrins by the enantioselective cyanation of prochiral carbonyl compounds has aroused great interest in recent years[1] because of the synthetic versatility of cyanohydrins when transferring their functionality in the preparation of bioactive and natural products. In particular, procedures allowing the direct access to *O*-protected non-racemic cyanohydrins are interesting to avoid reversibility of the cyanide addition and therefore a decrease in the final enantioselection. Thus, methodologies for the direct enantioselective preparation of *O*-silylated, *O*-phosphorylated, *O*-acylated and *O*-formylated cyanohydrins from aldehydes and ketones have been developed.[1] Among these *O*-protected cyanohydrins, cyanohydrin carbonates show a series of advantages. They are configurationally stable and significantly less prone to decomposition than others, such as the most popular cyanohydrin trimethylsilyl ethers, and can be prepared using inexpensive and less toxic reagents. Cyanocarbonates have shown excellent configurational stability towards chemioselective hydrolysis in acidic media,[2] in reduction processes affording β-aminoalcohols,[2] and in palladium-catalyzed nucleophilic substitutions.[1g,3]

The direct synthesis of enantiomerically enriched *O*-formylated cyanohydrins has been mainly achieved by the addition of alkyl cyanoformates (ROCOCN) to aldehydes in the presence of catalytic amounts of a chiral metal complex. Thus, titanium(salen) bimetallic[4] and *N*,*N*′-dioxide titanium[5] complexes have been used as chiral catalysts, as well as self-assembled,[6] multicomponent titanium catalysts[7] and heterobimetallic titanium–vanadium complexes.[8] In addition, the enantioselective cyanoformylation of aldehydes has been performed using chiral binaphthyl-containing monometallic bifunctional aluminium catalysts,[2] as well as a cinchonine-containing heterobimetallic aluminium lithium bis(binaphthoxide) complex.[9] Moreover, a lithium tris(binaphthoxide) yttrium complex has been used in the asymmetric cyanoethoxycarbonylation of aldehydes.[10]

Although these chiral catalysts have generally achieved a high enantioselection in the addition of alkyl cyanoformates to aldehydes, there are inherent disadvantages associated with the use of these types of metal complexes which hamper its use on a large scale. Most of them are air and moisture sensitive, which makes necessary the use of careful and rather strict reaction conditions. They are not recoverable and large amounts (5–20 mol %) of chiral ligands are frequently required as well as the presence of some additives. Thus, the development of efficient metal-free enantioselective cyanoformylation of carbonyl compounds would be desirable.

The organocatalyzed enantioselective addition of alkyl cyanoformates to carbonyl compounds is a field where few examples can be found. Thus, Deng used a dimeric

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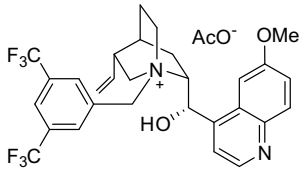
doi:10.1016/j.tetasy.2008.01.011

dihydroquinidine derivative to catalyze the asymmetric addition of ethyl cyanoformate to ketones with up to 97% ee, although the reaction required 10–30 mol % of the catalyst and long reaction times up to 7 d.[11] Recently, Feng reported the enantioselective formylation of aldehydes catalyzed by a chiral quaternary ammonium salt from quinidine **1** (10 mol %) in the presence of triethylamine, achieving moderate enantioselectivities (61–72% ee) in reaction times ranging from ca. 1 to 6 d and working at −78 °C.[12]



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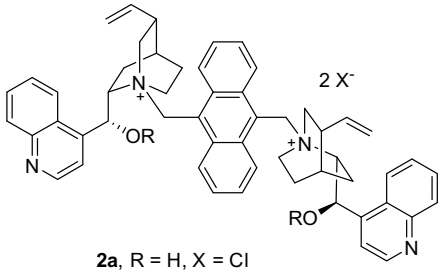
We have developed a series of dimeric anthracenyldimethyl-derived ammonium salts from Cinchona alkaloids, such as the cinchonidine-derived quats **2**, as recoverable chiral phase-transfer catalysts for asymmetric alkylation[13] and Michael addition[14] reactions of glycinate Schiff bases for the enantioselective synthesis of α-amino acids.[15] Herein, we report the behaviour of the dimeric ammonium salts **2** as organocatalysts in the direct enantioselective formylation of aldehydes.

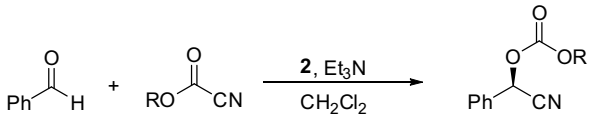


2a, R = H, X = Cl
2b, R = allyl, X = Br
2c, R = H, X = BF_4

2. Results and discussion

The cyanoformylation of benzaldehyde as a model substrate with methyl cyanoformate **3a** using cinchonidine-derived salt **2a** as organocatalyst was performed under reaction conditions similar to Feng's.[12] A 10 mol % of organocatalyst loading was used in the presence of triethylamine (20 mol %) in dichloromethane as solvent at room temperature. Under these conditions, a 60% ee of the (*R*)-O-formylated cyanohydrin **4aa** was obtained in quantitative yield after 2 h reaction time (Table 1, entry 1). The (*R*)-stereochemistry for **4aa** was assigned according to the relative reported retention times in chiral HPLC.[2b,12] This result was very promising, as only 44% ee of the corresponding protected cyanohydrin was reported using **1** as organocatalyst and working at −15 °C.[12] However, when the O-allylated cinchonidine-derived dimeric ammonium salt **2b** was used as an organocatalyst, no enantioselection for product **4aa** was obtained (Table 1, entry 2). This result showed the importance of the presence of the free OH group in the organocatalyst. In addition, exchanging the chloride counteranion in **2a** by the tetrafluoroborate anion affording the dimeric salt **2c**, something favourable when dealing with enantioselective PTC reactions using these dimeric catalysts,[13b,14] gave rise to a lower enantioselection for **4aa** (44% ee) (Table 1, entry 3). Therefore, ammonium salt **2a** was used in subsequent reactions.

Table 1. Organocatalytic addition of alkyl cyanoformates to benzaldehyde



3a, R = Me
3b, R = Et
3c, R = Bn

4aa
4ba
4ca

Entry	**2** (mol %)	**3**	Et_3N (mol %)	*T* (°C)	*t* (h)	No.	Yield[a] (%)	ee[b] (%)
1	**2a** (10)	**3a**	20	25	2	**4aa**	99	60
2	**2b** (10)	**3a**	20	25	2	**4aa**	99	0
3	**2c** (10)	**3a**	20	25	2	**4aa**	99	44
4	**2a** (5)	**3a**	20	25	2	**4aa**	99	60
5	**2a** (1)	**3a**	20	25	2	**4aa**	99	69
6	**2a** (1)	**3b**	20	25	3	**4ba**	99	56
7	**2a** (1)	**3c**	20	25	3	**4ca**	99	65
8	**2a** (1)	**3a**	20	10	3	**4aa**	99	80
9	**2a** (1)	**3a**	20	0	6	**4aa**	99	75
10	**2a** (1)	**3a**	20	−20	15	**4aa**	99	61
11	**2a** (1)	**3a**	10	10	8	**4aa**	88[c]	74
12	**2a** (1)	**3a**	5	10	9	**4aa**	85[c]	63

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).

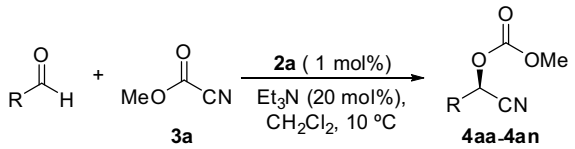
Once the appropriate organocatalyst was established, the next step was to determine if the catalyst loading could be lowered while keeping its asymmetry-inducing properties. Thus, the amount of **2a** was reduced to 5 mol % observing no influence in the final enantioselectivity for **4aa** (Table 1, entry 4). Interestingly, when the loading of **2a** was lowered to only 1 mol %, a quantitative yield of **4aa** in 69% ee was obtained in the same reaction time (Table 1, entry 5). When other alkyl cyanoformates, such as ethyl cyanoformate **3b** and benzyl cyanoformate **3c**, were used as cyanide sources under these reaction conditions and catalyst loading, slightly lower enantioselectivities for the corresponding formylated products **4ba** and **4ca**, respectively, were obtained (Table 1, entries 6 and 7).

We subsequently wondered if the enantioselectivity of the reaction could be improved by lowering the reaction temperature. Thus, when the temperature was lowered to 10 °C, the reaction took 3 h instead of 2 h and compound **4aa** was obtained quantitatively in 80% ee (Table 1, compare entries 5 and 8). This result can be considered quite good, when compared to the 67% ee reported using ammonium salt **1** as a catalyst working at −78 °C.[12] However, when the reaction temperature was lowered to 0 °C, a 75% ee for compound **4aa** was obtained in 6 h, this

decrease in the enantioselectivity was even more noticeable when working at −20 °C where only a 61% ee was obtained in 15 h reaction time (Table 1, entries 9 and 10). In addition, we also lowered the amount of triethylamine present in the reaction, observing a lower enantioselectivity and yield, as well as longer reaction times, when using 10 or 5 mol % of triethylamine (Table 1, entries 11 and 12). Other attempted bases, such as dicyclohexylmethylamine or pyridine gave almost a racemic **4aa**.

With the optimized reaction conditions for the model reaction (1 mol % loading of **2a**, 20 mol % Et_3N, CH_2Cl_2, 10 °C), we investigated the enantioselectivity of the reaction for a series of aldehydes (Table 2, entry 1 included for comparison).[16,17] All the obtained (*R*)-*O*-methoxycarbonyl cyanohydrins **4a**[18] were isolated generally as pure crude products (see footnote in Table 2) after only 2–4 h reaction times.

Table 2. Enantioselective cyanoformylation of aldehydes using **2a** as organocatalyst (Ref. 16)



Entry	Aldehyde	*t* (h)	No.	Yield[a] (%)	ee[b] (%)
1	Benzaldehyde	3	**4aa**	99	80
2	4-Methylbenzaldehyde	3	**4ab**	99	83
3	4-Methoxybenzaldehyde	3	**4ac**	99	88
4	3,4,5-Trimethoxybenzaldehyde	3	**4ad**	99	80
5	Heliotropin	2	**4ae**	99	83
6	4-Chlorobenzaldehyde	3(8)[c]	**4af**	99	41(71)[c]
7	4-Nitrobenzaldehyde	4	**4ag**	99	75
8	1-Naphthaldehyde	3	**4ah**	99	78
9	2-Naphthaldehyde	3	**4ai**	99	75
10	Nicotinaldehyde	3	**4aj**	99	0
11	Furfural	3	**4ak**	99	81
12	(*E*)-Crotonaldehyde	3	**4al**	97[d]	60[e]
13	(*E*)-Oct-2-enal	3	**4am**	88[d]	46[e]
14	Cyclohexanecarbaldehyde	3	**4an**	86[d]	40[e]

[a] Isolated as pure crude products according to ^1H NMR (300 MHz) and with >95% purity according to GLC.
[b] Determined by chiral HPLC (Ref. 17).
[c] In parenthesis, result when performed at −20 °C.
[d] Determined by ^1H NMR (300 MHz).
[e] Determined by chiral GLC (Ref. 17).

The presence of a 4-methyl group in the aromatic ring of benzaldehyde produced higher enantioselectivity for the corresponding formylated cyanohydrin **4ab** (Table 2, compare entry 1 with entry 2). When a more powerful electron-donating group was present, as in the case of 4-methoxybenzaldehyde, the corresponding O-protected cyanohydrin **4ac** was isolated in 88% ee (Table 2, entry 3). This result is remarkable, as only a 65% of **4ac** in 70% ee has been reported after 160 h reaction time at −78 °C when a quinidine-derived ammonium salt as been used as an organocatalyst.[12] The presence of other electron rich groups, as in the case of the 3,4,5-trimethoxybenzaldehyde or heliotropin (benzo[*d*][1,3]dioxole-5-carbaldehyde), gave rise to the corresponding products **4ad** and **4ae** in 80% and 83% ee, respectively (Table 2, entries 4 and 5).

When the electron-poor 4-chlorobenzaldehyde was cyanoformylated, the final enantioselectivity was lower, affording product **4af** in only 41% ee (Table 2, entry 6). In this case, lowering the reaction temperature to −20 °C was beneficial and the enantioselectivity improved to 71% ee (Table 2, entry 6). However, when a more powerful electron-withdrawing group was present, as in the case of 4-nitrobenzaldehyde, product **4ag** was obtained in 75% ee under the typical reaction conditions (Table 2, entry 7). This result is interesting, as this substrate has given rise to low enantioselections when using chiral aluminium complexes in the synthesis of other *O*-protected systems such as cyanohydrin *O*-phosphates, probably due to competing coordination of the nitro group to the metal.[19] In addition, other aromatic aldehydes, such as 1- and 2-naphthaldehyde, afforded final enantioselections of 78% and 75% for **4ah** and **4ai**, respectively (Table 2, entries 8 and 9).

The use of a heteroaromatic aldehyde with a basic character such as nicotinaldehyde gave racemic product **4aj** (Table 2, entry 10). This result was expected, due to the competing properties of a stoichiometric amount of a pyridine-containing system with the triethylamine when activating the cyanation reagent. However, when other heteroaromatic aldehyde such as furfural was employed, the corresponding cyanoformate **4ak** was isolated quantitatively in 81% ee (Table 2, entry 11). In addition, α,β-unsaturated aldehydes gave lower enantioselectivities than aromatic aldehydes, as shown in the formylation of (*E*)-crotonaldehyde and (*E*)-oct-2-enal, which gave the corresponding products **4al** and **4am** in 60% and 46% ee, respectively (Table 2, entries 12 and 13). An aliphatic aldehyde such as cyclohexanecarbaldehyde gave poor enantioselectivity (Table 2, entry 14).

As the dimeric cinchonidine ammonium salt **2a** has been previously used as a phase-transfer catalyst recoverable by precipitation in ether,[13] its recuperation was studied by performing the cyanoformylation reaction of benzaldehyde on a 4 mmol scale with a slight change in the final workup.[16] Thus, the dichloromethane was evaporated after the reaction completion and the crude was dissolved in ether. Filtering the precipitate allowed the almost quantitative (94%) recovery of the organocatalyst **2a**, which could be reused without any loss of activity. The final yield and enantioselectivity for **4aa** in this scaled reaction resulted also similar to when performed at smaller scale (Table 2, entry 1), also proving the scalability of the procedure.

The mechanism operating in this enantioselective transformation is still unclear. As the presence of a free hydroxyl group in the catalysts is crucial, probably a hydrogen bond between this group and the carbonyl of the aldehyde is possibly created in a preliminary substrate-catalyst interaction. In addition, the higher enantioselectivities obtained using aromatic aldehydes as substrates would suggest a π-stacking between both species. How the cyanide anion approaches the carbonyl group in the nucleophilic attack

remains unknown. Perhaps a preliminary cyanide anion interaction takes place with the positively charged ammonium cation, leaving the cyanide close to the activated carbonyl. This cyanide anion would arise after the formation of an acyl triethylammonium species by reaction of the alkylcyanoformate reagent with triethylamine.[2,11] In addition, the (*R*)-enantioselectivity of this process is unexpected, considering that (*R*)-cyanoformates have also been obtained when using the quinidine-derived catalyst **1** which contains an apparent *pseudoenantiomeric* chiral environment. Additional investigation would be necessary to clarify these points.

3. Conclusion

We can conclude that dimeric cinchonidine-derived ammonium salt **2a** can be used as an efficient and recoverable organocatalyst in the direct enantioselective cyanoformylation of aldehydes using methyl cyanoformate as the cyanide source in the presence of triethylamine. The final enantiomerically enriched methyl cyanoformates are obtained quantitatively in short reaction times without requiring very low temperatures or anhydrous conditions and with the lowest catalyst loading employed up to date for this type of reaction. Further experiments are currently underway in our laboratory order to determine the origin of the enantioselection of this reaction.

Acknowledgements

We thank the financial support from the Spanish Ministerio de Educación y Ciencia (projects CTQ 2004-00808/BQU and Consolider Ingenio 2010, CSD2007-00006), the Generalitat Valenciana (projects CTIOIB/2002/320, GRUPOS03/134 and GV05/144) and the University of Alicante. F.J.O. thanks the University of Alicante for a pre-doctoral fellowship.

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16. *Typical cyanoformylation procedure*: A solution of the corresponding aldehyde (0.2 mmol), catalyst **2a** (0.002 mmol, 1.7 mg) and Et_3N (0.04 mmol, 5.5 μL) dissolved in CH_2Cl_2 (2 mL) was cooled to 10 °C. 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 ^1H NMR (300 MHz) spectroscopy.
17. *Chiral HPLC*: Chiralcel OD-H, $\lambda = 210$ nm, hexane–2-propanol 99:1, 1.0 mL/min; Chiralcel OG, $\lambda = 210$ nm, hexane–2-propanol 99:1, 1.0 mL/min; Chiralpak AD, $\lambda = 210$ nm, hexane–2-propanol 99:1, 1.0 mL/min. Chiral GLC: Cyclosil-B, initial temperature 105 °C, flow rate 2.0 °C/min, 9 psi. Racemic samples were prepared in the absence of **2a**: Baeza, A.; Nájera, C.; de Gracia Retamosa, M.; Sansano, J. M. *Synlett* **2005**, 2787–2797.
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