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Catalytic, asymmetric cyanohydrin synthesis in propylene carbonate

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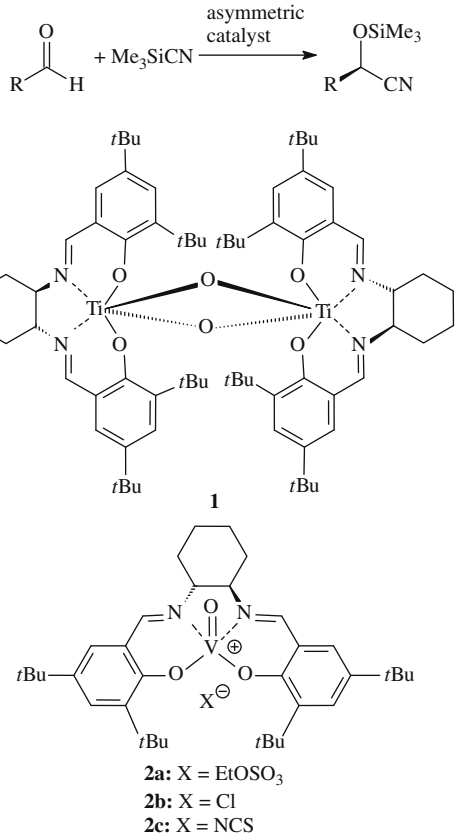
ABSTRACT

Propylene carbonate can be used as a green solvent for asymmetric cyanohydrin synthesis catalyzed by VO(salen)NCS. A range of 10 aromatic and aliphatic aldehydes gave high enantioselectivities (up to 93%) and conversions (up to 100%) in reactions carried out at or near room temperature with reaction times of 24 h or less.

The asymmetric addition of trimethylsilyl cyanide to aldehydes[1] is a 100% atom economical reaction[2] which produces a product which contains a stereocenter and two functional groups, one of which is conveniently protected (Scheme 1). In recent years, a large number of synthetic catalysts have been developed for this reaction[1] including bimetallic titanium(salen) complex[3] **1** and vanadium(salen) complexes[4] **2a–c**. Reactions catalyzed by complexes **1** and **2** have been commercialized,[5] and have a number of green credentials including high substrate to catalyst ratios (1000:1) and optimal activity at room temperature.[6] However, catalysts **1** and **2** (along with most other catalysts for this reaction[7]) have only been found to be effective in chlorinated organic solvents, preferably dichloromethane. Use of ethereal, alcoholic, hydrocarbon, aromatic, or traditional polar aprotic solvents were all found to be severely detrimental to the level of asymmetric induction, though the use of ionic liquids did give good levels of asymmetric induction at higher catalyst loadings.[8]

Propylene carbonate **3** is starting to attract interest as a green solvent for synthetic transformations.[9] It can be prepared by the 100% atom economical reaction between carbon dioxide and propylene oxide (Scheme 2).[10] The green credentials of propylene carbonate have recently been enhanced by the commercialization of a low temperature route for the synthesis of propylene oxide from propene and hydrogen peroxide;[11] by the development of a greener synthesis of hydrogen peroxide[12] and by the combination of these processes into a one-pot synthesis of propylene oxide from propene, hydrogen, and oxygen.[13] In addition, it has recently been demonstrated,[14] that in the presence of an appropriate catalyst, the reaction between propylene oxide and carbon dioxide can be achieved at atmospheric pressure and room temperature, thus facilitating the use of waste carbon dioxide in this process.

Therefore, we decided to investigate the use of propylene carbonate as a replacement for dichloromethane in asymmetric cyanohydrin synthesis catalyzed by complexes **1** and **2c**.[15]



Scheme 1. Asymmetric cyanohydrin synthesis.

A standard set of conditions were initially adopted in which all reactions were carried out at room temperature for 2 h using 0.1 mol % of catalyst at a substrate concentration of 0.56 M in either dichloromethane or propylene carbonate. The extent of conversion of aldehyde into cyanohydrin trimethylsilyl ether was

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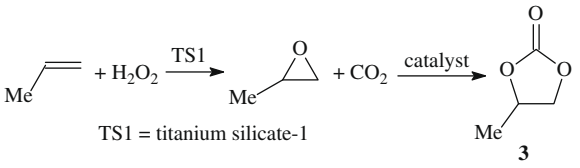
determined by ^{1}H NMR spectroscopy, and the asymmetric induction was determined by chiral GC after conversion of the cyanohydrin trimethylsilyl ether into the corresponding cyanohydrin acetate as previously reported.[16] Initial results using catalyst **1** were not encouraging as detailed in Table 1. In each case, use of propylene carbonate as solvent significantly lowered the enantioselectivity of the reaction, and for aromatic substrates the conversion was also reduced substantially. Interestingly however, nonanal gave a higher conversion in propylene carbonate than in dichloromethane. The reason for the generally lower reactivity and enantioselectivity observed in propylene carbonate is probably related to the dissociation of bimetallic catalyst **1** into monometallic units in the more polar solvent.[3]

In contrast, reactions catalyzed by vanadium-based catalyst **2c** were far less affected by the change in solvent. Table 2 details the results obtained with 10 different aldehydes. Whilst aromatic aldehydes again gave lower conversions in propylene carbonate, the decrease was nowhere near as dramatic as that observed for catalyst **1**. Aliphatic aldehydes in contrast gave conversions in propylene carbonate which were comparable to, or higher than those obtained in dichloromethane. The enantioselectivities obtained in propylene carbonate were in the range of 62–93%, which, whilst lower than those obtained using catalyst **2** in dichloromethane, were much higher than those obtained using catalyst **1** in propylene carbonate.

The kinetics of the addition of trimethylsilyl cyanide to benzaldehyde catalyzed by complex **2c** (0.2 mol %) were determined at 0 °C as previously described.[3,4] The reaction was shown to follow overall second-order kinetics (first order in both benzaldehyde and trimethylsilyl cyanide) to at least 74% conversion (Fig. 1). This is the same kinetic profile as previously determined in dichloromethane[4] which suggests that the mechanism of catalysis is the same in both solvents. In addition, the kinetics showed no evidence of catalyst deactivation which indicates that the lower conversions observed in propylene carbonate are due to an intrinsically slower reaction rather than to catalyst decomposition. This was also supported by the kinetics analysis which showed that the second-order rate constant in dichloromethane was five times greater than that in propylene carbonate.

To optimize the reaction conditions for the use of catalyst **2c** in propylene carbonate, the effects of varying the reaction temperature, reaction time and amount of catalyst were determined. As the results shown in Table 3 illustrate, for benzaldehyde, increasing the reaction time to 24 h at room temperature increased the conversion to >90% whilst retaining a high level of asymmetric induction. Increasing the amount of catalyst to 0.2 mol % had a



Scheme 2. Synthesis of propylene carbonate.

Table 1
Synthesis of cyanohydrin trimethylsilyl ethers using catalyst **1**

Aldehyde	Propylene carbonate		Dichloromethane	
	Conversion[a]	ee[b]	Conversion[a]	ee[b]
PhCHO	33	40 (*S*)	95	80 (*S*)
4-FC_6H_4CHO	24	35 (*S*)	40	78 (*S*)
4-ClC_6H_4CHO	20	25 (*S*)	98	83 (*S*)
2-MeC_6H_4CHO	47	43 (*S*)	76	76 (*S*)
3-MeC_6H_4CHO	30	61 (*S*)	95	97 (*S*)
4-MeC_6H_4CHO	16	49 (*S*)	82	69 (*S*)
$Me(CH_2)_7CHO$	98	45 (*S*)	71	73 (*S*)
Me_3CCHO	100	10 (*S*)	93	47 (*S*)

[a] Conversions were determined by ^{1}H NMR spectroscopy.
[b] Enantioselectivities were determined by chiral GC analysis after conversion of the cyanohydrin trimethylsilyl ethers into the corresponding cyanohydrin acetates.

Table 2
Synthesis of cyanohydrin trimethylsilyl ethers using catalyst **2c**

Aldehyde	Propylene carbonate		Dichloromethane	
	Conversion[a]	ee[b]	Conversion[a]	ee[b]
PhCHO	73	81 (*S*)	100	86 (*S*)
4-FC_6H_4CHO	67	77 (*S*)	81	91 (*S*)
3-ClC_6H_4CHO	56	64 (*S*)	83	89 (*S*)
4-ClC_6H_4CHO	73	76 (*S*)	90	93 (*S*)
2-MeC_6H_4CHO	78	62 (*S*)	81	97 (*S*)
3-MeC_6H_4CHO	67	93 (*S*)	100	98 (*S*)
4-MeC_6H_4CHO	56	86 (*S*)	86	87 (*S*)
$Me(CH_2)_7CHO$	96	66 (*S*)	88	92 (*S*)
CyCHO	97	67 (*S*)	100	88 (*S*)
Me_3CCHO	99	72 (*S*)	100	86 (*S*)

[a] Conversions were determined by ^{1}H NMR spectroscopy.
[b] Enantioselectivities were determined by chiral GC analysis after conversion of the cyanohydrin trimethylsilyl ethers into the corresponding cyanohydrin acetates.

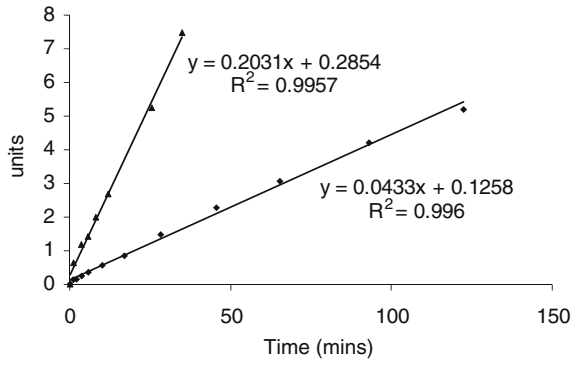


Figure 1. Second-order kinetics plot for the addition of trimethylsilyl cyanide to benzaldehyde at 0 °C catalyzed by complex **2c** (0.2 mol %) in dichloromethane (triangles) and propylene carbonate (diamonds). The units for the vertical scale are: $\ln[(B_oA_t)/(B_tA_o)]/(A_o - B_o)$ where: A = [PhCHO], B = [Me_3SiCN] and the subscripts o and t refer to initial concentrations and concentrations at time *t*, respectively.

Table 3
Optimization of the synthesis of cyanohydrin trimethylsilyl ethers using catalyst **2c** in propylene carbonate

Aldehyde	Temperature	Time	Catalyst mol %	Conversion[a]	ee[b]
PhCHO	rt	4 h	0.1	83	83 (*S*)
PhCHO	rt	24 h	0.1	92	85 (*S*)
PhCHO	rt	2 h	0.2	86	85 (*S*)
PhCHO	0 °C	18 h	0.1	73	86 (*S*)
4-MeC_6H_4CHO	0 °C	18 h	0.1	63	91 (*S*)
$Me(CH_2)_7CHO$	0 °C	18 h	0.1	100	72 (*S*)
CyCHO	0 °C	18 h	0.1	92	78 (*S*)
Me_3CCHO	0 °C	18 h	0.1	100	80 (*S*)
$Me(CH_2)_7CHO$	−20 °C	24 h	0.1	98	79 (*S*)
CyCHO	−20 °C	24 h	0.1	88	81 (*S*)
Me_3CCHO	−20 °C	24 h	0.1	100	82 (*S*)
4-FC_6H_4CHO	0 °C	24 h	0.1	88	88 (*S*)
3-ClC_6H_4CHO	0 °C	24 h	0.1	89	80 (*S*)
4-ClC_6H_4CHO	0 °C	24 h	0.1	86	83 (*S*)
2-MeC_6H_4CHO	rt	24 h	0.1	100	86 (*S*)
3-MeC_6H_4CHO	rt	24 h	0.1	93	90 (*S*)
4-MeC_6H_4CHO	rt	24 h	0.1	90	85 (*S*)

[a] Conversions were determined by ^{1}H NMR spectroscopy.
[b] Enantioselectivities were determined by chiral GC analysis after conversion of the cyanohydrin trimethylsilyl ethers into the corresponding cyanohydrin acetates.

similar effect after a reaction time of just 2 h. For a range of five aldehydes, reducing the reaction temperature to 0 °C enhanced the enantioselectivities, in the case of aromatic aldehydes, to a level comparable with or better than those obtained in dichloromethane at room temperature. However, these reactions did require an extended reaction time (18 h) to give conversions which were comparable to those obtained in 2 h at room temperature.

On the basis of the above results, the aldehydes were grouped into three classes each of which had its own optimal reaction temperature to obtain high conversions and enantioselectivities after a reaction time of 24 h. Aliphatic aldehydes gave high conversions even at reduced reaction temperatures, so the optimal conditions involved carrying out reactions at −20 °C to maximize the asymmetric induction (Table 3), though these were only slightly better than the enantioselectivities obtained at 0 °C. For electron-deficient aromatic aldehydes, the optimal reaction temperature was 0 °C, whilst electron-rich aromatic aldehydes only gave high conversions at room temperature (Table 3).

It was not possible to directly isolate the cyanohydrin trimethylsilyl ether from reactions carried out in propylene carbonate as they codistilled with the solvent and decomposed when purification was attempted by chromatography. However, one of the main applications of cyanohydrins is in the preparation of α-hydroxy acids[5] and it was possible to obtain (*S*)-mandelic acid in 60% isolated yield simply by refluxing the mixture of propylene carbonate and mandelonitrile trimethylsilyl ether (81% ee) with 12 N hydrochloric acid for 6 h followed by crystallization from ether/hexane. That no racemization occurred during this process was demonstrated by conversion of the mandelic acid into methyl mandelate followed by chiral HPLC (Chirasil OD column; 80% hexane, 20% propan-2-ol; flow rate 1 mL per minute) which gave an enantiomeric excess of 87%.

In conclusion, we have shown that vanadium complex **2c** is an active catalyst for asymmetric cyanohydrin synthesis in propylene carbonate using low catalyst loadings at or near to room temperature.

Acknowledgements

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15. *Typical experimental procedure*: The aldehyde (0.98 mmol) was added to a solution of catalyst **1** or **2c** (0.98 μmol, 0.1 mol %) in propylene carbonate (1.75 mL) at the specified temperature. Trimethylsilyl cyanide (1.12 mmol, 0.15 mL) was then added and the reaction mixture was stirred for the specified time. The solution was then passed through a short silica plug eluting with CH_2Cl_2. The eluent was evaporated in vacuo to remove the CH_2Cl_2, and the residue was analyzed by ^1H NMR spectroscopy to determine the conversion. To determine the enantiomeric excess, acetic anhydride (2.0 mmol, 0.15 mL) and $Sc(OTf)_3$ (5 mg, 0.01 mmol) were added to the stirred residue. After 20 min, the reaction mixture was passed through a short silica plug eluting with MeCN. The resulting solution was analyzed by chiral GC using a Supelco Gamma DEX 120 fused silica capillary column (30 m × 0.25 mm) with hydrogen as a carrier gas. *Synthesis of mandelic acid*: To a solution of mandelonitrile trimethylsilyl ether in propylene carbonate obtained as above, was added 12 N HCl (10 mL). The mixture was heated at reflux for 6 h, cooled to rt and made basic using 10% aqueous NaOH solution. The aqueous solution was extracted with ether (3 × 10 mL), acidified with 12 N HCl, and extracted again with ether (3 × 10 mL). The last three ethereal extracts were combined, dried (Na_2CO_3), and evaporated in vacuo to give a yellow solid which was recrystallized at 4 °C from ether/hexane and the resulting solid was washed with hexane to give mandelic acid (91 mg, 60%) as white crystals.
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