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Polymeric Cinchona Alkaloids as Catalysts in the Enantioselective *2,2*-Cycloaddition Reaction of Ketene and Chloral

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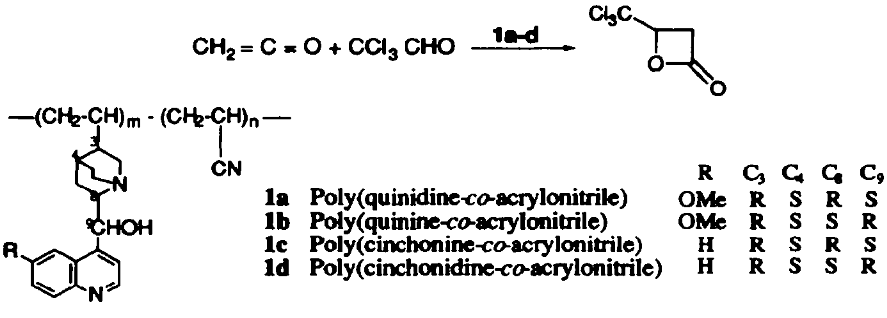
Abstract: Poly(cinchona alkaloid-*co*-acrylonitrile) **1a-d** and poly(cinchona alkaloid acrylate) **2a-b** catalyze the enantioselective cycloaddition of ketene to chloral for the preparation of (*R*)- and (*S*)-β-(trichloromethyl)-β-propiolactone. Copolymers **1a-d** showed relatively lower catalytic activity with moderate enatioselectivity (22-59% *e.e.*), while homopolymers **2a-b** gave similar catalytic activity and enatioselectivity (60-94% *e.e.*) compared to those of their monomeric alkaloids as catalysts. The polymeric effect was observed with poly(acryloyl quinidine) **2a** as catalyst to get the best enantioselectivity of 94% *e.e.* at the temperature -30°C.

Chiral 4-substituted-2-oxetanones (β-lactones) are useful starting materials for the synthesis of optically active β-functionalized carboxylic acid derivatives[1] and optically active stereoregular polyesters.[2] Optically active β-lactones have been obtained in high chemical and optical yield from the reaction of ketene with an activated aldehyde (or ketone) such as chloral in the presence of cinchona alkaloids as catalysts.[3] Thus we tried to find polymeric cinchona alkaloids, which could reveal a catalytic efficiency over monomeric alkaloids with ease of recycling. To retain the catalytic reactivity and stereoselectivity in the polymer matrix, the reactive site should have some degree of freedom and mobility and the reaction environment of reactive site in the polymer should be similiar with those of monomeric alkaloids. Preparation of such polymeric alkaloids utilizing the vinyl group of the cinchona alkaloids as the connecting site to polymers was not successful because cinchona alkaloids are quite resistant to homo-polymerization. Trials to copolymerize cinchona alkaloids with some non-polar vinyl monomers such as styrene also have failed. Thus we decided to use the known poly(cinchona alkaloid-*co*-acrylonitrile) **1a-d**[4,5], as catalysts, in which alkaloids were copolymerized using their vinyl group with acrylonitrile. Poly(cinchona alkaloid-*co*-acrylonitrile) **1a-d** catalyzed the enantioselective *2,2*-cycloaddition of ketene and chloral at -50°C in toluene.

Table 1. Enantioselective 2,2-cycloaddition reaction of ketene and chloral catalyzed by poly(cinchona alkaloid-*co*-acrylonitrile) **1a-d**[a]



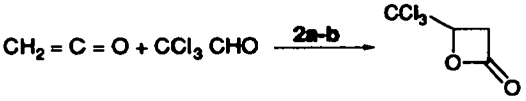
		R	C_3	C_4	C_8	C_9
1a	Poly(quinidine-*co*-acrylonitrile)	OMe	R	S	R	S
1b	Poly(quinine-*co*-acrylonitrile)	OMe	R	S	S	R
1c	Poly(cinchonine-*co*-acrylonitrile)	H	R	S	R	S
1d	Poly(cinchonidine-*co*-acrylonitrile)	H	R	S	S	R

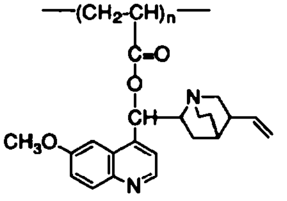
	4-trichloromethyl-2-oxetanone			
Catalyst	yield %	$[\alpha]_D$	*e.e.*% [b]	configuration [c]
1a	73	-8.9	59	*R*
1b	71	+3.8	25	*S*
1c	66	-4.0	27	*R*
1d	60	+3.2	22	*S*

a) The reactions were carried out by using 12 mmol of the catalyst, 30 mmol of chloral 30 mmol of ketene and 150ml of toluene at -50°C. b) Based on the reported value of optical rotation $[\alpha]_D$ =+15 (c=1 in cyclohexane) from Aldrich catalog. c) Preferred configuration.

Copolymer catalysts **1a-d** gave relatively lower catalytic activity and enantioselectivity (22-59% *e.e.*) compared to those[6] of monomeric alkaloid catalysts. To obtain similar chemical yields we had to use about 0.4 molar equivalent of alkaloid content. The low catalytic reactivity of **1a-d** could be explained by low accessibility of the substrate to the catalytic moiety because of a low degree of swelling of the copolymer catalysts in toluene. In the reaction medium, polymers may exist as tightly contracted coil conformers in which reactive sites are sterically crowded. Moreover, the highly polar reaction environment of the resin phase in the copolymers could effect the low enantioselectivity. The acrylonitrile part in copolymers could make the reaction environment of the resin phase polar. The optical yield of ketene with aldehyde in a polar solvent such as acetonitrile is very low.[7] Thus, we decided to use the known poly(acryloyl quinidine)**2a** and poly(acryloyl quinine)**2b**[8,9] as catalysts, in which monomeric portions have the same structures as those of the *O*-acetyl alkaloids, active homogeneous catalysts. Polymers **2a-b** were prepared by homo-polymerization of *O*-acryloyl cinchona alkaloids using AIBN as an initiator in dry benzene according to the literature procedure.[8] Enantioselective 2,2-cycloaddition of ketene to chloral using **2a-b** as catalysts affords β-(trichloromethyl)-β-propiolactone in high chemical and optical yields. The results are summarized in Table 2.

Table 2. Enantioselective 2,2-cycloaddition reaction of ketene and chloral catalyzed by poly(cinchona alkaloid acrylate) **2a-b**[a)]





		4-trichloromethyl-2-oxetanone			
catalyst	reac. temp. °C	yield %	$[\alpha]_D$	*e.e.*%[b)]	configuration [c)]
2a	-50	75	-10.3	68	*R*
	-30	70	-14.1	94	*R*
	-10	72	-11.5	76	*R*
2b	-50	77	+9.1	60	*S*
	-30	74	+9.5	63	*S*
	-10	71	+9.8	65	*S*

a) The reactions were carried out by using 0.9 mmol of the catalyst, 30 mmol of chloral 30 mmol of ketene and 150ml of toluene at the specified temperature. b) Based on the reported value of optical rotation $[\alpha]_D$=+15 (c=1 in cyclohexane) from Aldrich catalog. c) Preferred configuration.

Chiral homopolymers **2a-b** gave similar catalytic activity and enantioselectivity(60-94% *e.e.*) to those[6] of their monomeric alkaloids. The higher enantioselectivity (94% *e.e.*) with polymer **2a** at the reaction temperature -30°C rather than at -50°C (68% *e.e.*) can be explained by the polymeric effect.[10] In toluene the polymers **2a-b** exist as a quasi-dissolved gel state. Generally a highly compatible solvent will give rise to an expanded coil conformation. In this state the chain segments of polymers are nearly in continous motion. Through the motion the gel-coil undergoes a constant intensive blending action. This can explain why polymers **2a-b** are catalytically very active. The high enantioselectivity of **2a-b** could be also explained by the great freedom of movement of the polymer chain in the expanded coil conformation and similar polarity of the reaction environment with those of monomeric catalysts. But at the low reaction temperature the polymer coils can be to some degree contracted and therefore the catalytic function is sterically hindered. This can be one of the reasons why poly(acryloyl quinidine) **2a** is more enantioselective at -30°C than at -50°C.

General reaction procedure with polymer **2a-b** as catalysts : Through the suspension of 0.340g of polymeric alkaloid **2a-b** (0.9mmol) in 150ml toluene, ketene was bubbled at the temperature specified in table 2 with stirring while 2.9ml(30mmol) of anhydrous chloral in 40ml toluene was added dropwise during 1-1.2hr. Excess of ketene should be avoided to minimize formation of diketene. Stirring was continued at the same temperature for 1.5hr, then the reaction mixture was poured into 100ml ether. The polymer was filtered off and filtrate was washed with saturated NaCl solution. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by distillation to give pure product (120°C/0.5mmHg).

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5. The ^{1}H NMR and IR spectra of this copolymers **1a-d** were found to be identical with those of the literature.[4] The molar ratio of the corresponding cinchona alkaloid and acrylonitrile in the copolymer **1a-d** was calculated on the basis of the elementary analysis. **1a**: 8.1 mol% of quinidine, $[\alpha]^{25}_D$+33.3 (c 1.0, DMF), **1b**: 5.2 mol% of quinine, $[\alpha]^{25}_D$-20.5 (c 1.0, DMF), **1c**: 1.5 mol% of cinchonine, $[\alpha]^{25}_D$+7.8 (c 1.0, DMF), **1d**: 3.9 mol% of cinchonidine, $[\alpha]^{25}_D$-14.1 (c 1.0, DMF).
6. H. Wynberg and co-worker conducted the same reaction in toluene using 4 mol% monomeric alkaloids as catalysts at -50°C. The reported ee's are 98% (quinidine catalyst), 76% (quinine catalyst), 68% (acetyl quinine catalyst), 84% (cinchonine catalyst) and 67% (cinchonidine catalyst). : See ref. 3a.
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9. Satisfactory analytical data for **2a-b** were obtained. **2a** : $[\alpha]^{25}_D$ +4.9 (c 1.0, $CHCl_3$); **2b**(Mw(THF) 174,000) : $[\alpha]^{25}_D$ -14.8 (c 1.0, $CHCl_3$), [lit : $[\alpha]^{25}_D$-14.7 (c 1.0, $CHCl_3$).[8a]].
10. Polymeric cinchona alkaloids showed the polymeric effect with regard to stereoselectivity on the asymmetric addition reaction of methanol to phenylmethylketene : See ref. 8.

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