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New polymer-supported chiral phase-transfer catalysts in the asymmetric synthesis of α-amino acids: the role of a spacer

Baptiste Thierry, Jean-Christophe Plaquevent and Dominique Cahard*

Université de Rouen, UPRES-A 6014 de l'Institut de Recherche en Chimie Organique Fine (IRCOF), Rue Tesnière 76821 Mont Saint Aignan Cedex, France

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Abstract—Polymer-supported cinchona alkaloid salts with different spacers were used as phase-transfer catalysts in the asymmetric *C*-alkylation of *N*-diphenyl methylene glycine *tert*-butyl ester. Various catalysts and alkylation conditions were studied, the best result being 81% e.e. with cinchoninium iodide bound to polystyrene with a four-carbon spacer.

The asymmetric synthesis of α-amino acids remains a major challenge in organic chemistry.[1] An attractive method, first introduced by O'Donnell in 1989,[2] used the liquid/liquid phase-transfer catalysed asymmetric alkylation of *N*-diphenyl methylene glycine *tert*-butyl ester with the aid of *N*-benzyl cinchona alkaloid salts as phase-transfer catalysts (first generation, vide infra). Two further generations of catalysts derived from cinchona alkaloids were subsequently developed (Fig. 1). The second generation of catalysts, i.e. the *N*-alkyl *O*-alkyl cinchona alkaloid salts was reported in 1994,[3] also by O'Donnell et al. Finally, the third generation of catalysts was described independently by Lygo et al.[4] and Corey et al.[5] in 1997 in which a 9-anthracenylmethyl group was introduced as an effective unit for masking the nitrogen face, leading to substantially improved e.e.s. A further useful development in this field would be the immobilisation of the catalyst on an insoluble polymeric support. This strategy presents several practical advantages over the use of the same catalyst in solution, including greatly simplified product purification, the easy recovery of catalyst by simple filtration and potential recycling. Few examples of polymer-supported phase-transfer catalysts (PS–PTC) have been reported in the literature.[6] When we initiated the project, the best reported result on enantioselective alkylation of *N*-diphenyl methylene glycine *tert*-butyl ester was 27% e.e., using cinchona alkaloids grafted on Merrifield resins at the quinuclidinium nitrogen atom (Fig. 1, polymer-supported first generation).[7] We decided to investigate the role of a flexible spacer between the quaternary ammonium and the polymer backbone, since we considered that distancing the chiral moiety from the matrix could enhance asymmetric induction. During the course of this work, Najera reported improved e.e.s of up to 58%, using the first generation of supported cinchona alkaloids on alkylation of *N*-diphenyl methylene glycine *tert*-butyl ester, and an e.e. of 90% in the alkylation of the *iso*-propyl derivative.[8] We report herein the synthesis of polystyrene supported cinchona alkaloids possessing a spacer and an evaluation of their catalytic asymmetric behaviour in the phase-transfer alkylation of glycine derivatives.

On poly(styrene-co-divinylbenzene) (200–400 mesh, 1% cross-linked), we performed lithiation by means of the complex butyllithium/TMEDA which gives a 2/1 mixture of *m*-/*p*-regioisomers.[9] Next, the lithiated polymer was allowed to react with a bromochloro- or a dibromoalkane spacer. It is worth noting that this polymethylene spacer does not contain any functionality which could interfere with the alkylation reaction. For reasons of reactivity, we substituted the terminal halogen for iodine to allow easier substitution of the alkaloid. We focused our strategy on three spacer lengths, four, six and eight carbon atoms (Scheme 1).

The four alkaloids, cinchonine (CN), cinchonidine (CD), quinine (QN), and quinidine (QD), were grafted giving 12 new chiral polymers. These catalysts were first evaluated in the enantioselective liquid/liquid/solid phase-transfer alkylation of *N*-diphenyl methylene

* Corresponding author. Fax: +33-2 35 52 29 71; e-mail: dominique.cahard@univ-rouen.fr

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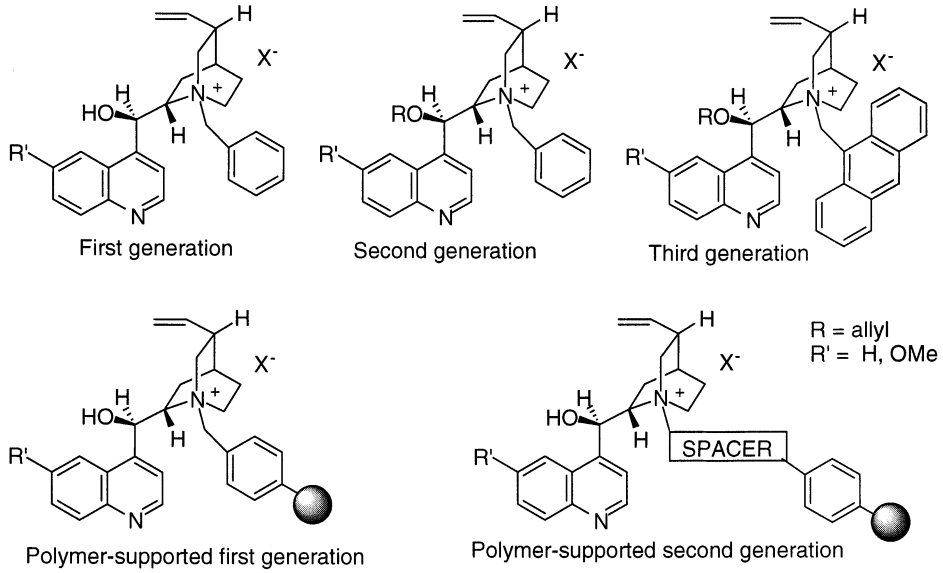
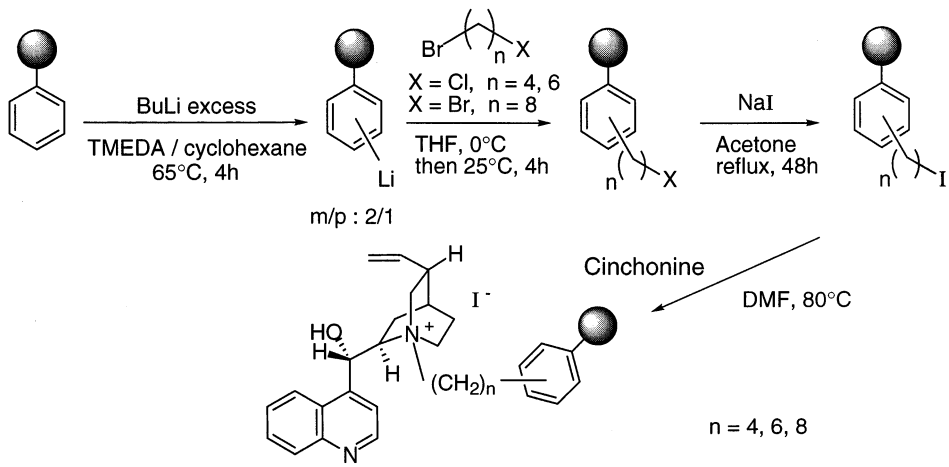


Figure 1. The generations of cinchona alkaloid phase-transfer catalysts.

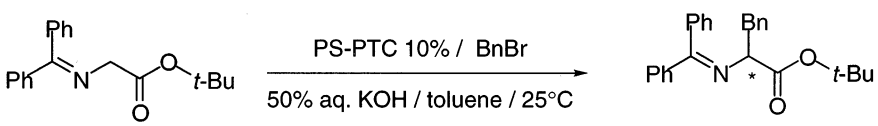


Scheme 1. Preparation of polymer-supported cinchonine.

glycine *tert*-butyl ester (Scheme 2). Toluene was preferred to dichloromethane, giving higher enantioselectivity.

After screening of the alkaloid and the spacer length under identical conditions, the enantioselectivity was found to be strongly dependent on the alkaloid and moderately altered by the length of the spacer (Table 1). Thus, quinine and quinidine were discarded, and cinchonine preferred to cinchonidine.

To our surprise, the same major enantiomer was always obtained irrespective of the catalyst used and even though cinchonine and cinchonidine are known to behave as pseudoenantiomers[10] (in that the two families normally give rise to opposite enantiomers in phase-transfer catalysed reactions). This implies that the hydroxy group in the catalyst is not involved to any significant extent in the enantiotopic differentiation of the reaction. By inference, the stereogenic centres of the quinuclidinium species that remain invariant through the series must be responsible for the observed asymmetric induction in this case.[11] Indeed, in comparison to unsupported catalysts derived from cinchona alkaloids having a benzyl or anthracenylmethyl group, the quinuclidinium nitrogen in polymer-supported catalysts bearing the spacer is not as sterically hindered.



Scheme 2. Enantioselective alkylation of *N*-diphenyl methylene glycine *tert*-butyl ester.

Table 1. Alkaloid and spacer effects

PS–PTC		Time (h)[a]	Product		
n	Alkaloid		Yield (%)[b]	E.e. (%)[c]	Abs. conf. [d]
4	CN	12	63	63	*R*
4	CD	48	57	6	*R*
4	QN	48	43	8	*R*
4	QD	48	39	4	*R*
6	CN	40	61	54	*R*
6	CD	96	48	29	*R*
6	QN	72	26	6	*R*
6	QD	72	33	9	*R*
8	CN	19	74	70	*R*
8	CD	65	62	27	*R*
8	QN	41	68	6	*R*
8	QD	40	61	10	*R*

[a] The reaction was followed by TLC and quenched when no further conversion was observed.
[b] Purification by column chromatography over silica gel (eluent: dichloromethane/triethylamine, 99:1).
[c] Determined by HPLC (Chiralcel OD, 2-propanol/heptane, 0.5:99.5, 1 mL/min, 23°C, $\lambda = 254$ nm) and polarimetry.
[d] See Ref. 5.

In conclusion from this first set of experiments, catalysts bearing cinchonine gave substantially higher e.e.s (54–70%). Next, we optimised the reaction to reach still higher e.e.s with cinchonine anchored to the matrix through the three lengths of carbon spacers. A number of conditions of the reaction (temperature, base and alkylating reagent) were also investigated (Table 2).

By cooling the reaction mixture to 0°C, we obtained higher enantioselectivity for the three catalysts used (entries 1–3), with our best e.e. to date (81%) for the four methylene spacer. However, a lower temperature (−20°C) did not produce any positive effect since the product was isolated in only 69% e.e. (entry 4). Other aqueous bases were tested (entries 5–7) as well as a liquid/solid/solid approach using CsOH solid (entry 8), but in this study on base effects, the e.e.s were not improved. The reaction with other electrophiles, reactive alkylating agents and simple alkyl halides, was found to be moderately enantioselective (entries 9–11).

The results described herein (e.e.s of up to 81%) are much more promising than those obtained with the first generation of supported catalysts (e.e. 27%[7] and e.e. 58%[8]) for the model reaction studied and better than those obtained with comparable unsupported first generation catalysts (66%).[2] These data indicate the importance of the spacer between the alkaloid residue and the matrix. Indeed, when applied to the *iso*-propyl ester derivative, our best catalysts (4-CN and 4-CD PS–PTC) were less efficient than those described by Najera[8] (46 versus 90% e.e.), indicating a substrate-dependent reaction. These observations incite us to further study the polymer-supported catalysts in order to improve enantioselectivity and to gain insights into the mechanism of the asymmetric induction.

Table 2. Optimisation of the enantioselectivity

Entry	PS–PTC		R-X	Reaction conditions			Product		
	n	Alkaloid		Base	*T* (°C)	*t* (h)	Yield[a] (%)	E.e. (%)[b]	Abs. conf.[c]
1	4	CN	BnBr	50% aq. KOH	0	15	60	81	*R*
2	6	CN	BnBr	50% aq. KOH	0	48	73	75	*R*
3	8	CN	BnBr	50% aq. KOH	0	15	52	73	*R*
4	4	CN	BnBr	50% aq. KOH	−20	65	72	69	*R*
5	4	CN	BnBr	50% aq. LiOH	0	48	23	47	*R*
6	4	CN	BnBr	50% aq. NaOH	0	18	58	64	*R*
7	4	CN	BnBr	50% aq. CsOH	0	24	64	33	*R*
8	4	CN	BnBr	CsOH solid	0	6	48	67	*R*
9	4	CN	2-MeNaph*t*Br	50% aq. KOH	0	16	74	57	Nd[d]
10	4	CN	EtI	50% aq. KOH	0	24	80	51	*R*
11	4	CN	AllylBr	50% aq. KOH	0	24	76	37	*R*

[a] Purification by column chromatography over silica gel (eluent: dichloromethane/triethylamine, 99:1).
[b] Determined by HPLC and polarimetry. Entries 1–8: Chiralcel OD, propan-2-ol/heptane, 0.5:99.5, 1 mL/min, $\lambda = 254$ nm, entry 10: Chiralcel OD, 2-propanol/heptane, 0.5:99.5, 0.5 mL/min, $\lambda = 254$ nm, entry 11: Regis Whelk-01, propan-2-ol/heptane, 5:95, 1 mL/min, $\lambda = 254$ nm.
[c] See Ref. 5.
[d] Not determined.

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