

Review Article

The Asymmetric Darzens Reaction Catalyzed by the Novel Chiral Phase Transfer Catalysts Derived from Cinchona Alkaloids

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Abstract

Herein a series of asymmetric Darzens reactions catalyzed by the novel chiral phase transfer catalysts derived from cinchona alkaloids were reported with moderate to high diastereoselectivity and with moderate enantioselectivity.

Keywords: Chiral phase transfer catalysts; Cinchona alkaloid; Darzens reaction; Diastereoselectivity; Enantioselectivity

Introduction

The development of asymmetric phase transfer catalysis has become more and more significant in both economic and environmental fields [1,2,3]. Until recently, there have been three main generations of the catalysts derived from cinchona alkaloids. The first generation: R=H, Ar= Phenyl; the second generation: R=Allyl, Ar=Phenyl; and the third generation: R=Alkyl, Ar=Anthracyl. The first generation of catalysts were developed by Dolling's group in 1984 [4,5], which were successfully applied in the asymmetric alkylation of glycine Schiff base by O'Donnell's group with good enantioselectivity [6,7]. The second generation of the catalysts was applied by Deng et al. in the asymmetric Darzens reaction with high yield and good enantioselectivity [8]. The third generation of the catalysts were developed by E.J. Corey's group (Figure 1) [9]. Until recently, only few chiral phase transfer catalysts have been reported to be applied in the asymmetric Darzens reaction. Deng et al. reported that the second generation of the catalysts derived from cinchona alkaloids could catalyze the asymmetric Darzens reaction with high yield and good enantioselectivity [8]. Shioiri's group reported the diastereoselective Darzens reaction catalyzed by tetrahexylammonium bromide [10]. Macromolecular phase transfer catalysts were reported by Wang's group and were applied in diastereoselective Darzens reaction (Figure 2) [11]. Jonczyk's group and Murugan's group also reported the asymmetric Darzens reaction with different kinds of chiral phase transfer catalysts [12,13].

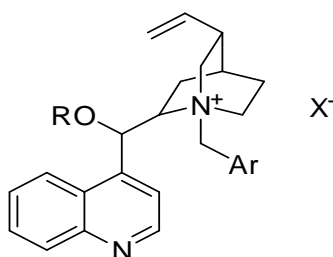


Figure 1: Three main generations of cinchona alkaloid based catalysts.

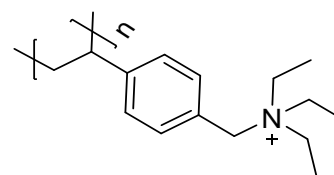


Figure 2: The catalyst synthesized by Wang's group.

Till now, we have reported three novel chiral phase transfer catalysts derived from cinchona alkaloids with cycle structure (Figure 3). The asymmetric alkylation reaction and sulfenylation reactions of glycine derivatives catalyzed by these catalysts were also investigated with high yields and moderate to good ee values (44-88%) [14]. In continuation of our studies on the asymmetric phase transfer catalysis, herein we report the asymmetric Darzens reaction with the novel chiral phase transfer catalysts 4a to 4c. We began our investigation with non-chiral phase transfer catalyst, we tried TEBAC (triethyl benzyl ammonium chloride) and TBAB (tetrabutyl ammonium bromide) in the Darzens reaction between benzaldehyde and chloroacetonitrile in THF and we found only TBAB could catalyze the Darzens reaction, then we applied the reaction to different aldehydes and chloroacetonitrile in THF (Figure 4) and the results were listed in Table 1.

As was shown in Table 1, the rates between cis-product and trans-product were nearly 1:1. Only poor diastereoselectivity of the normal non-chiral phase transfer catalyst of TBAB was achieved and further work should be done to enhance the diastereoselectivity.

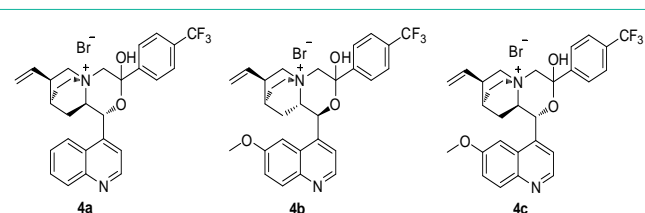


Figure 3: Three novel cinchona alkaloids based catalysts [14].

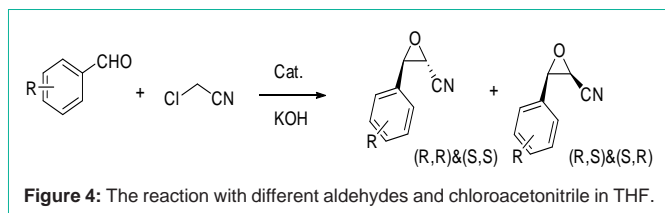


Table 1: The Darzens reaction between aldehydes and chloroacetonitrile under non-chiral phase transfer catalyst.

Entry	R	Catalyst	Time(h)	Yield ^a	cis:trans
1	H	TBAB	23	70%	1.2:1
2	p-Cl	TBAB	24	13%	1.4:1
3	p-Br	TBAB	12	30%	1.4:1
4	p-Me	TBAB	12	20%	0.9:1
5	m-Me	TBAB	12	31%	0.8:1

a. Isolated yields including cis-product and trans-product.

Having realized the non-chiral Darzens reaction between aldehydes and chloroacetonitrile, we turned our attention to its asymmetric version. We tried to investigate the novel chiral phase transfer catalysts 4a to 4c developed by our group in the asymmetric Darzens reaction. Firstly, we chose the Darzens reaction between benzaldehyde and chloroacetonitrile as the model reaction and different reaction conditions were investigated and the results were listed in Table 2 [15].

In Table 2, we found that 4a was the best catalyst and could give the best result both in cis/trans value and ee value, while catalyst 4b and 4c gave relatively lower cis/trans value and lower ee values. Of all the solvents we investigated, THF gave the best yield, cis/trans value and ee value, the more dipolar solvent gave out a better yield but very low cis/trans rate and enantioselectivity (entry 5), the less polar solvent toluene gave no product whether with the solid or aqueous solution of KOH as the base (entry 6 and 7). Of all the bases we investigated, solid KOH gave the best yield, the cis/trans rate and the best enantioselectivity. So the optimal reaction condition was with 4a as the catalyst, with THF as the solvent, and with solid KOH as the base (entry 1). Under the optimal reaction condition, the Darzens reaction between different aldehydes and chloroacetonitrile were investigated, and the results were collected in Table 3.

Table 2: The asymmetric Darzens reaction between benzaldehyde and chloroacetonitrile under different reaction conditions.

Entry	Catalyst	Solvent	Base	Yield ^a	Cis:trans	Ee of major ^b
1	4a	THF	KOH	67%	2.1:1	60%
2	4b	THF	KOH	60%	2.1:1	51%
3	4c	THF	KOH	56%	1.5:1	45%
4	4a	toluene	KOH	0%	n.d.	n.d.
5	4a	DMSO	KOH	76%	1.4:1	50%
6	4a	toluene	KOH (50% in water)	0%	n.d.	n.d.
7	4a	THF	NaOH	50%	1.5:1	54%
8	4a	THF	CsOH	53%	1.4:1	55%

a. Isolated yields including cis-product and trans-product.

b. Enantiopurity was determined by HPLC analysis using chiral column (DAICEL Chiralcel OD-H) with hexanes/ *i*-PrOH as a solvent.

Table 3: The asymmetric Darzens reaction between different aldehydes and chloroacetonitrile.

Entry	R	Yield ^a	cis:trans	ee of major ^b
1	H	67%	2.2:1	60%
2	p-Cl	63%	3.8:1	35%
3	p-Br	66%	4.1:1	50%
4	p-Me	68%	5.8:1	17%
5	m-Me	55%	6.9:1	30%

a. Isolated yields including cis-product and trans-product.

b. Enantiopurity was determined by HPLC analysis using chiral column (DAICEL Chiralcel OD-H) with hexanes/ *i*-PrOH as a solvent.

As was shown in Table 3, the reaction catalyzed by 4a was much faster than common non-chiral phase transfer catalysts such as TBAB and higher diastereoselectivities were also achieved. The highest rate (cis:trans) was achieved as 6.9:1 with 3-methylbenzaldehyde as the substrate (entry 5). For the reactions catalyzed by 4a, low to moderate ee values were also achieved, and the highest ee value was achieved to be 60% with benzaldehyde as the substrate (Entry 1).

In all, we successfully applied the newly-designed chiral phase transfer catalysts 4a to 4c in the asymmetric Darzens reactions and satisfying and interesting results were achieved. Further work is under way to understand the mechanism and improve the diastereoselectivity and the enantioselectivity of the reaction.

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16. Typical procedure of the asymmetric Darzens reactions: To a mixture of benzaldehyde (0.106 g, 1 mmol), chloroacetonitrile (0.091 g, 1.2 mmol) and THF (5 ml), 4a (0.035 g, 0.1 mmol) was added and stirred for 20minutes. Solid KOH (0.067 g, 1.2 mmol) was added and stirring continued for 16 hours. The mixture was filtered and purified by TLC (PE: EA = 50:1) to give the cis-product (0.067 g) and trans-product (0.03 g) as colorless oil. Cis-product 1H NMR (500 MHz, CDCl₃):7.408–7.388(3H, m), 7.282–7.263(2H, m), 4.278–4.275(1H, m), 3.410–3.405(1H, m) [α]_D²⁵ = 36° (major product). Trans-product 1H NMR (500 MHz, CDCl₃):7.245–7.260(5H, m), 4.248–4.237(1H, m), 3.778–3.766(1H, m).