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Highly Enantioselective Asymmetric Darzens Reactions with a Phase Transfer Catalyst†

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Abstract

A class of easily accessible and readily tunable chiral phase transfer catalysts based on 6'-OH cinchonium salts was found to efficiently catalyze an unprecedented highly enantioselective Darzens reaction of α -chloro ketones and aldehydes, which directly produces optically active chiral epoxides from readily available carbonyl compounds.

Introduction

The Darzens reaction employs α -halogenated carbonyl compounds and aldehydes or ketones to form α,β -epoxy carbonyl compounds.¹ By directly converting accessible carbonyl compounds into epoxides, the Darzens reaction provides a non-oxidative method for the preparation of epoxides. Consequently, it constitutes a valuable alternative method to olefin epoxidations by its unique ability to tolerate oxidation sensitive functionalities. However, a side product of the Darzens reaction is a strongly acidic hydrogen halide, which could catalyze a racemic background reaction or diminish a base-catalyzed asymmetric Darzens reaction by neutralizing the catalyst (Eq. 1, Scheme1). This presents a significant challenge to the development of a catalytic enantioselective variant of the Darzens reaction by homogeneous chiral acid or base catalysis. Indeed, to our knowledge, the chiral metal complex-promoted reaction of diazoacetamide with aldehydes represents the only example of a highly enantioselective Darzens-type reaction in the literature.² On the other hand, chiral phase transfer catalysis, which typically involves an excess amount of inorganic base, appears to be particularly suitable for the development of a catalytic asymmetric Darzens reaction (Eq 2, Scheme 1).

The benefit of having the presence of an aliphatic alcohol in a chiral ammonium salt-based chiral phase transfer catalyst has been documented with those derived from cinchona alkaloids,³ the BINAP skeleton,⁴ ephedrine⁵ and chiral crown ethers.⁶ The role played by the aliphatic alcohol in these existing successful phase transfer catalysts have been postulated to either provide a secondary interacting point to more effectively control the orientation of the nucleophile (**I**, Figure 1) or to activate the electrophiles (**II**, Figure 1). Nonetheless, pioneering studies by Arai and Shiori documented that the 9-OH cinchona alkaloid-derived phase transfer catalyst afforded only moderate enantioselectivity in the reactions of α -chloro ketones or sulfones with aldehydes.⁷ Even with an improved 9-OH

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cinchona alkaloid-derived phase transfer catalyst, Jeong and coworkers documented enantiomeric excess of over 90% for reactions between a highly limited range of aromatic aldehydes and a single nucleophile, α -chloromethyl phenyl sulfone.⁸ Thus, the development of a highly enantioselective Darzens reaction of substantial scope remains a significant challenge.

Recent explorations of cinchona alkaloids bearing hydrogen bond donors other than aliphatic alcohols have led to great strides in chiral acid-base cooperative catalysis.^{9,10} In principle, the corresponding chiral *N*-alkylated ammonium salts of these cinchona alkaloid derivatives could potentially serve as effective chiral phase transfer catalysts. However, earlier attempts by the Berkessel¹¹ and the Fernandez and Lassaletta¹² groups have documented only moderate to good enantioselectivity for epoxidations of enones and conjugate addition of cyanide to nitroalkenes, respectively. In this paper, we describe the development of cuperidium salts **2** as an effective phase transfer catalyst for an unprecedented highly enantioselective Darzens reaction between α -chloroketones and aldehydes.

Results and Discussions

As outlined in Scheme 2, we have established an *N*-alkylation procedure that transforms the readily available 6'-OH cinchona alkaloids¹⁰ **1** into the corresponding ammonium salts bearing various *N*-alkyl groups. Specifically, the phase transfer catalysts **2** are easily prepared by stirring **1** with the appropriate alkyl bromide in a chloroform/ethanol mixture providing yields ranging from 45–85%.

Our investigations of the capacity of phase transfer catalysts (PTC) **2** for the promotion of asymmetric Darzens reactions began with a model reaction between α -chloro ketone **5A** and aldehyde **6a** in dichloromethane. Our screening studies began with catalyst **2a**, an *N*-benzyl cinchonium salt bearing a 9-O-benzyl group. The reaction proceeded smoothly at room temperature, providing the *trans*-epoxide **7Aa** in 19% ee after 5 hours (entry 1, Table 1). By tuning the *N*-alkyl group, the enantioselectivity was improved to 25% with the 3,4,5-trifluorobenzyl ammonium salt **2c** (entries 2–5, Table 1). The enantioselectivity could be further improved by modifying the 9-substituent in **2** (entries 6–8, Table 1). PTC **2h**, with a 9-phenanthracenyl ether (Table 1, entry 8), emerged as the optimal catalyst among those examined affording a complete reaction to produce **7Aa** in 86% ee.

To assess the consequence of removing the 6'-OH group from **2h**, the same reaction with the corresponding 6'-OMe analogue **4** was examined, which was found to occur in very poor conversion and enantioselectivity (entry 8 vs entry 10, Table 1). In another control experiment, PTC **2h** was found to be more effective than the 9-OH cinchona alkaloid-derived PTC **3** (entries 8 vs. entry 9, Table 1). The dramatically lower activity and enantioselectivity by the 6'-OMe analogue **4** vs **2h**, indicates that the 6'-OH in **2h** plays a critical role in the enhanced activity and enantioselectivity by **2h**. These experimental results support the notion that, in addition to interacting with the anionic nucleophile through an ion-pair interaction, catalyst **2h** also activates the electrophile through hydrogen bonding (Figure 1).

The reaction was investigated in a range of solvents at room temperature. Other chlorinated solvents, such as dichloroethane (DCE) and chloroform, afforded **6a** in slightly lower selectivities than dichloromethane (entries 11 and 12 vs 8, Table 1). In THF or toluene a significant decrease of enantioselectivity was observed (entries 13 and 14 vs. 8, Table 1). We suspect that the poor solubility of **2h** in these solvents could be the cause of this deterioration in catalyst enantioselectivity. In protic solvent such as methanol, both the

catalytic activity and selectivity suffered, a result could be attributed to the disruption of hydrogen bonding interactions between catalyst **2h** and the substrates by the solvent. Overall, dichloromethane was found to be the optimal solvent in which an excellent enantioselectivity could be attained with **2h** by cooling the reaction to 0°C (entry 16, Table 1).

Under the optimized reaction conditions, the **2h**-catalyzed Darzens reaction with various aromatic aldehydes bearing either an electron withdrawing or electron donating substituent afforded the corresponding epoxides in high yields with excellent enantioselectivities (entries 2–5, Table 2). In addition, the catalyst also tolerated changes in the position of the substituent on the aromatic ring (entry 2 vs. 3 and 6 vs 7, Table 2). We also investigated reactions of various α -chloro ketones **5A–C** with aldehyde **6g** and found the enantioselectivity to be excellent in these reactions (entries 7, 9–10, Table 2). An aliphatic aldehyde was also investigated in the asymmetric Darzens reaction and gave the corresponding epoxide in high yield and useful enantioselectivity (entry 8, Table 2). On the other hand, chloroacetone, an alkyl α -chloro ketone bearing a much more basic α -hydrogen, was found to be inactive for this reaction.

To our knowledge, no example of greater than 90% ee has been documented with the sterically more hindered α -substituted α -chloro ketones in a catalytic asymmetric Darzens reaction. On the other hand, efficient enantioselective Darzens reactions with these more challenging substrates should provide a valuable alternative method for the asymmetric synthesis of optically active trisubstituted epoxides.^{4a} We were pleased to find that the high enantioselectivity afforded by **2h** could be extended to Darzens reactions with α -substituted α -chloro ketones **8**. As summarized in Table 3, in the presence of **2h**, reactions of aromatic aldehydes and α -chloro ketone **8A** proceeded in a highly enantioselective manner to produce exclusively the *trans*-epoxide **9** in good yields (entries 1–7, Table 3). It is noteworthy that the enantioselectivity remained high with aliphatic aldehydes (entries 9 and 10, Table 3).

Conclusions

In summary, we have demonstrated that cuperidium salts **2** are highly enantioselective chiral phase transfer catalysts for the Darzens reaction. To our knowledge, these results constitute the first documentation of a highly enantioselective Darzens reaction of both aliphatic and aromatic aldehydes as well as providing access to both di- and trisubstituted epoxides. It is also noteworthy that our studies demonstrated, for the first time, that the variations of the 9-substituent of these cinchonium salts provide an effective handle for productive catalyst tuning. Studies to explore these phase transfer catalysts for other asymmetric transformations and to delineate their mode of action are underway in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure. 1.
Proposed modes of activation by the bifunctional phase transfer catalysts.

Scheme 1.

(1) Homogenous acid or base catalyzed Darzens reaction. (2) Phase transfer catalyzed Darzens reaction

Scheme 2.
 Synthesis of the Bifunctional Phase Transfer Catalysts

Table 1

Darzens Reaction of **5A** and **6a** with PTC **2**^a

entry	catalyst	solvent	t (°C)	conv (%) ^b	ee (%) ^c
1	2a	CH ₂ Cl ₂	20	>99	19
2	2b	CH ₂ Cl ₂	20	>99	13
3	2c	CH ₂ Cl ₂	20	>99	25
4	2d	CH ₂ Cl ₂	20	>99	17
5	2e	CH ₂ Cl ₂	20	>99	9
6	2f	CH ₂ Cl ₂	20	>99	17
7	2g	CH ₂ Cl ₂	20	>99	4
8	2h	CH ₂ Cl ₂	20	>99	86
9	3	CH ₂ Cl ₂	20	42	32
10	4	CH ₂ Cl ₂	20	14	6
11	2h	ClCH ₂ CH ₂ Cl	20	>99	77
12	2h	CHCl ₃	20	>99	85
13	2h	THF	20	>99	22
14	2h	Toluene	20	65	38
15	2h	MeOH	20	45	4
16 ^d	2h	CH ₂ Cl ₂	0	>99	96

^a See Supporting Information (SI) for details.^b Conversion was determined by ¹H NMR.

^cThe ee was determined by chiral HPLC (Column OJ-H).

^d₂₄ hr reaction time.

Table 2

Darzens Reaction of **5** and **6** with PTC **2h**.^a

$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{Cl} \\ \mathbf{5} \end{array} + \begin{array}{c} \text{O} \\ \parallel \\ \text{R}'-\text{C}-\text{H} \\ \mathbf{6} \end{array} \xrightarrow[\text{LiOH}\cdot\text{H}_2\text{O}(4\text{eq}), 24 \text{ hrs}]{\mathbf{2h} (5 \text{ mol\%}), \text{CH}_2\text{Cl}_2, 0^\circ\text{C}}$		$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}'-\text{C}-\text{CH} \\ \mathbf{7} \end{array}$	
entry	R	R'	yield (%) ^b ee (%) ^c
1	C ₆ H ₅ (5A)	C ₆ H ₅ (6a)	7Aa 94 96
2	C ₆ H ₅ (5A)	4-ClC ₆ H ₄ (6b)	7Ab 96 96
3	C ₆ H ₅ (5A)	3-ClC ₆ H ₄ (6c)	7Ac 92 90
4	C ₆ H ₅ (5A)	4-BrC ₆ H ₄ (6d)	7Ad 90 95
5	C ₆ H ₅ (5A)	4-MeC ₆ H ₄ (6e)	7Ae 95 91
6	C ₆ H ₅ (5A)	1-Nap (6f)	7Af 96 91
7	C ₆ H ₅ (5A)	2-Nap (6g)	7Ag 93 98
8 ^d	C ₆ H ₅ (5A)	<i>n</i> -C ₃ H ₇ (6h)	7Ah 93 81
9	4-FC ₆ H ₄ (5B)	2-Nap (6g)	7Bg 93 97
10	4-ClC ₆ H ₄ (5C)	2-Nap (6g)	7Cg 96 99

^a See Supporting Information (SI) for details. Reactions were carried out at a substrate concentration of 0.1 M for 24 h, **5:6** = 0.2 mmol : 0.24 mmol, 0 °C;

^b Isolated yield;

^c Ee was determined by chiral HPLC column.

^d The reaction was carried out at -20 °C for 72 hrs.

Table 3

Darzens Reaction of **8** and **6** with PTC **2h**^a

entry	R	R'	9	yield(%) ^b	ee(%) ^c
1	H (8A)	C ₆ H ₅ (6a)	9Aa	92	90
2	H (8A)	4-ClC ₆ H ₄ (6b)	9Ab	91	93
3	H (8A)	3-ClC ₆ H ₄ (6c)	9Ac	95	91
4	H (8A)	2-ClC ₆ H ₄ (6i)	9Ai	96	94
5	H (8A)	2-Nap (6e)	9Ae	96	97
6	H (8A)	1-Nap (6f)	9Af	90	93
7	H (8A)	2-MeC ₆ H ₄ (6j)	9Aj	92	90
8	4-OMe (8B)	2-Nap (6e)	9Be	76	94
9 ^d	H (8A)	<i>n</i> -C ₃ H ₇ (6h)	9Ah	95	80
10 ^d	H (8A)	<i>n</i> -C ₇ H ₁₅ (6K)	9Ak	92	87

^a See Supporting Information (SI) for details. Reactions were carried out at a substrate concentration of 0.2 M for 72 h, **8:6** = 0.2 mmol : 0.4 mmol, 0°C;

^b Isolated yield;

^c Ee was determined by chiral HPLC column.

^d The reaction was carried out at -20°C for 72 hrs.