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Phase-transfer-catalyzed asymmetric Darzens reaction using a new chiral ammonium salt

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Abstract—Catalytic asymmetric Darzens reaction of haloamides is described. A new and easily-prepared bis-ammonium salt derived from BINOL acts as an effective phase-transfer catalyst and efficiently promotes the reaction to give the desired epoxides under quite mild conditions with up to 70% ee.

Phase-transfer catalysts (PTCs) are some of the most powerful reagents in chemical transformation because they are easy to use, economical and environmentally benign.[1] In particular, chiral onium salts, as PTCs, have attracted considerable attraction as potential tools for asymmetric synthesis because they are easy to prepare and structurally diverse. Many potential applications of chiral PTCs derived from natural and synthetic compounds have been investigated over the past few decades[2] since the first independent reports of successful asymmetric alkylations by Dolling[3] and O'Donnell.[4] We have also developed a variety of PTC-promoted asymmetric reactions and recently reported a new and efficient PTC derived from L-tartrate.[5] While the Darzens reaction,[6] which gives very important synthetic intermediates, is one of the most powerful and challenging chemical transformations, there have been few reports on its successful application to asymmetric synthesis (not *catalytic*).[7] In general, a stoichiometric amount of strong base is required to effectively promote the reaction. To achieve a catalytic asymmetric Darzens sequence, onium salts as PTCs would be expected to be useful agents because they can be regenerated by reacting with an inorganic base to establish a catalytic cycle.

For example, metal reagents act as a base and can easily abstract an α-proton to be converted into the unreusable side product (MX) during C–C and C–O bond formation. Ammonium halides, however, react with an enolate to provide active species and give the desired epoxides catalytically. Thus, regeneration of chiral QX could provide a catalytic asymmetric protocol, as shown in Figure 1. Based on this strategy, we have developed catalytic asymmetric Darzens reactions of α-chloro acyclic[8a,b] and cyclic[8c] ketones and a sulfone[9] using cinchona alkaloid derivatives as PTCs. To the best of our knowledge, there have been no reports of a successful phase-transfer-catalyzed asymmetric Darzens reaction to give glycidic acid derivatives. The products of this asymmetric transformation are expected to have rich and useful functionality, and therefore its further development is an important goal in organic synthesis. In this communication, we report the results of the first successful asymmetric synthesis of glycidic amides via a catalytic Darzens strategy.[10]

Initially, a new chiral PTC was designed by modifying quaternary ammonium salts derived from cinchona alkaloids. Their rigid structures prevent the synthesis of derivatives, which reduces the generality of possible substrates in each asymmetric transformation. Moreover, it has been reported that the substituents on the quinuclidine nitrogen greatly affect the enantioselectivity due to steric and electronic effects. Therefore, simplification and modification of the catalyst would be expected to overcome these problems, and an easily prepared new PTC in which a chiral source is directly introduced to the quinuclidine nitrogen was examined (Fig. 2). Furthermore, a large twist angle between two naphthyl moieties would be expected due to both steric and dipole repulsion between bulky bis-ammonium

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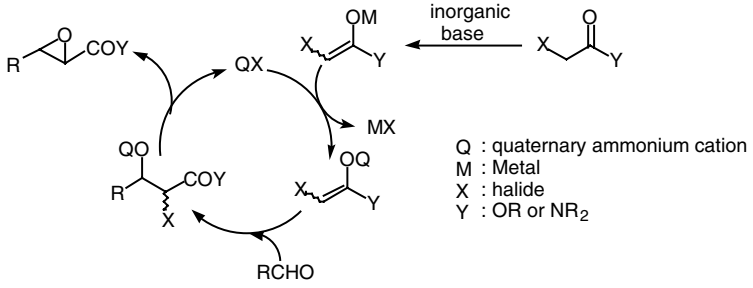


Figure 1. Proposed catalytic cycle in the Darzens reaction.

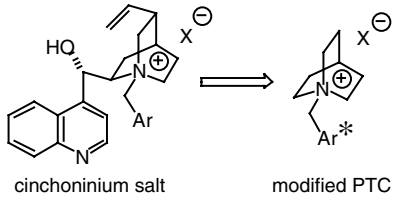
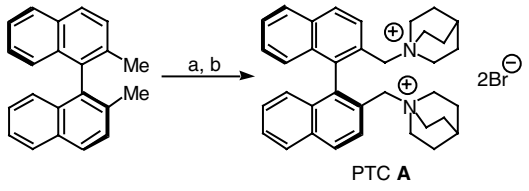


Figure 2. Simplification of chiral quaternary salt.

units and it would affect enantioselectivity. PTC **A** was prepared in quantitative yield by bromination of (*R*)-2,2′-dimethyl-1,1′-binaphthyl, which is readily available from (*S*)-BINOL,[11] and subsequent condensation with quinuclidine (2 equiv) under reflux conditions, as outlined in Scheme 1.[12]

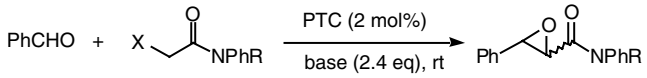


Scheme 1. Synthesis of PTC. Reagents and conditions: (a) NBS, $(BzO)_2$, cyclohexane, 64%; (b) quinuclidine, THF, reflux, quant.

Next, we investigated the asymmetric Darzens reaction using PTC **A**. α-Protons of benzylamide **2a** were acidic enough to be abstracted by an inorganic base (KOH) and the reaction proceeded smoothly to give the desired epoxide **3a** in good yield in both the presence and absence of an achiral PTC (THAB, 10 mol%), as shown in Table 1 (entries 1 and 2). Moreover, PTC **A** (2 mol%) was found to be effective in the reaction of THF to give an ee value of up to 20% (entry 3). Solvent screening using **2a** showed that dichloromethane gave the best results, with up to 37% ee (entry 4). Unfortunately, other attempts using *N*,*N*-dialkylamides as nucleophiles gave unsuccessful results. *N*,*N*-Diphenylamides were found to be the best substrates, and the enantioselectivity of both *cis* and *trans* **3b** improved to 51% and 52% ee, respectively, with reasonable yields (entry 5). Moreover, rubidium hydroxide monohydrate gave a better result with regard to diastereoselectivity (43% de) and α-bromo amide **2c** underwent rapid transformation to the corresponding epoxide **3b** within 6.5 h with 58% ee (*cis*) and 63% ee (*trans*), respectively (entries 6 and 7). These results are summarized in Table 1.

Encouraged by these results, we next investigated the scope and limitations of PTC **A** in this asymmetric process. PTC **A** effectively promoted the reaction with various aldehydes, as summarized in Table 2.[13] For example, aromatic aldehydes such as **1b–e** were

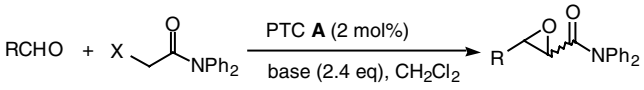
Table 1. Phase-transfer-catalyzed asymmetric Darzens reaction of α-haloamides **2**



Entry	Amide	PTC	Base	Conditions	Product	Yield (%)	*cis*/*trans*	Ee of *cis* (%)	Ee of *trans* (%)
1	**2a**	None	KOH	THF, 12 h	**3a**: R = Bn	61	0.71	—	—
2	**2a**	THAB[a]	KOH	THF, 12 h	**3a**: R = Bn	69	1.2	—	—
3	**2a**	PTC **A**	KOH	THF, 6 h	**3a**: R = Bn	66	1.2	12	20
4	**2a**	PTC **A**	KOH	CH_2Cl_2, 12 h	**3a**: R = Bn	82	1.0	27	37
5	**2b**	PTC **A**	KOH	CH_2Cl_2, 4 h	**3b**: R = Ph	87	2.5	51	52
6	**2b**	PTC **A**	RbOH·H_2O	CH_2Cl_2, 31 h	**3b**: R = Ph	81	3.5	52	51
7	**2c**	PTC **A**	RbOH·H_2O	CH_2Cl_2, 6.5 h	**3b**: R = Ph	81	2.3	58	63

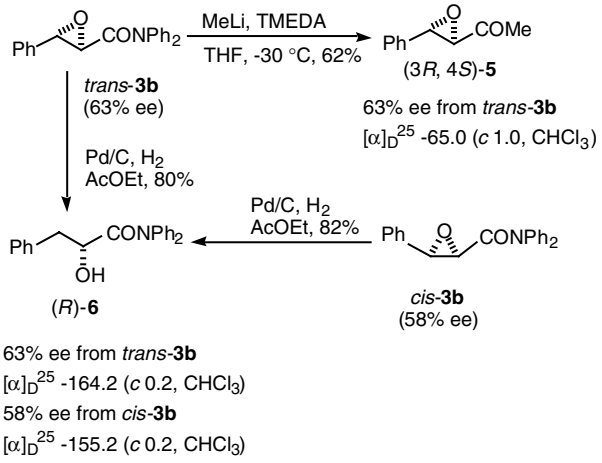
THAB: tetrahexylammonium bromide.
[a] THAB (10 mol%) was used.

Table 2. Catalytic asymmetric Darzens reaction using various aldehydes



1 **2b** or **2c** **4**

Entry	Aldehyde	Amide	Base	Conditions	Yield (%)	*cis*/*trans*	Ee of *cis* (%)	Ee of *trans* (%)
1	**1b**: R = 3-Br-Ph	**2c**	$RbOH{\cdot}H_2O$	rt, 14 h	**4b**: 93	2.4	51	60
2	**1c**: R = 4-MeO-Ph	**2c**	$RbOH{\cdot}H_2O$	rt, 24 h	**4c**: 82	8.1	62	60
3	**1d**: R = 2-MeO-Ph	**2c**	$RbOH{\cdot}H_2O$	−10 °C, 132 h	**4d**: quant	2.2	57	67
4	**1e**: R = 2-Me-Ph	**2c**	$RbOH{\cdot}H_2O$	−30 °C, 137 h	**4e**: 77	2.0	64	70
5	**1f**: R = 4-*t*-Bu-Ph	**2c**	$RbOH{\cdot}H_2O$	rt, 34 h	**4f**: 70	2.8	63	64
6	**1g**: R = *i*-Pr	**2b**	Cs_2CO_3	rt, 70 h	**4g**: 77	4.4	57	40
7	**1h**: R = *c*-Hex	**2b**	Cs_2CO_3	rt, 70 h	**4h**: 61	5.0	60	48



Scheme 2. Determination of the absolute stereochemistry of **3b**.

smoothly converted into the corresponding epoxides **4b–e** with good enantioselectivity in excellent yield (entries 1–4). Especially, *trans*-**4e** was obtained with 70% ee (entry 4). In the case of aliphatic aldehydes **1g** and **h**, a weaker base such as Cs_2CO_3 with **2b** was found to be the most effective and products **4g** were obtained with 57% ee for *cis* and 40% ee for *trans*, while **4h** was obtained with 60% ee for *cis* and 48% ee for *trans*, respectively (entries 6 and 7).[14]

The absolute configurations of **3b** were determined by comparison to the literature to be 2*R*,3*S* after *trans*-**3b** was converted to the corresponding methyl ketone **5**.[15] *Cis* and *trans*-**3b** were converted to (2*R*)-α-hydroxyamide **6** by hydrogenation without racemization, and the absolute stereochemistry of the *cis*-isomer was assigned by optical rotation to be 2*R*,3*R*, as outlined in Scheme 2.

In conclusion, we have developed a catalytic asymmetric Darzens reaction using α-haloamides promoted by a new chiral PTC. As described above, both aromatic and aliphatic aldehydes can be used with quite low catalyst loading (2 mol %) to give the desired epoxides with up to 70% ee. However, the diastereo- and enantiocontrol are still unsatisfactory, and further modification and optimization of the catalyst are now under investigation.

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12. (*S*)-2,2′-Bis(quinuclidiniomethyl)-1,1′-binaphthyl dibromide (PTC **A**): white solid; mp 218 °C (decomposed); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.69 (br, 6H), 1.95 (br, 1H),

3.04 (br, 3H), 3.53 (br, 3H), 4.08 (d, $J = 13.2$ Hz, 1H), 5.51 (d, $J = 13.2$ Hz,1H), 7.30–7.36 (m, 2H), 7.53–7.60 (m, 1H), 8.03 (d, $J = 8.1$ Hz, 1H), 8.17–8.21 (m, 1H), 8.39 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (CD_3OD, 67.8 MHz) δ 19.3, 23.9, 55.1, 65.5, 125.4, 127.2, 127.6, 129.2, 130.0, 132.3, 132.4, 133.8, 137.3; IR (KBr) ν 2942, 2886, 1464 cm^{-1}; MS (FAB) m/z 581 (M^+-Br), 470, 391, 307, 154; HRMS (FAB) calcd for $C_{36}H_{42}$ $^{79}BrN_2$: 581.2531. Found 581.2535; $[\alpha]_D^{25}$ +132.6° (c 0.5, $CHCl_3$). PTC **A** is a quite air-stable compound and can be stored at rt over 6 months. And it shows enough solubility in CH_2Cl_2, $CHCl_3$ and MeOH however toluene and THF are not easy to be dissolved.

13. Representative experimental procedure for a catalytic asymmetric Darzens reaction; synthesis of **3b** (Table 1, entry 7): To a solution of benzaldehyde **1a** (20 μL, 0.20 mmol), bromoamide **2c** (69 mg, 0.24 mmol) and catalyst (2.6 mg, 0.004 mmol, 2 mol%) in dichloromethane (1.0 mL) was added $RbOH{\cdot}H_2O$ (58 mg, 0.48 mmol) at rt. After being stirred for 6.5 h, the reaction was quenched with 1 N HCl (1.0 mL) and the resulting organic layer was extracted with AcOEt (2.0 mL × 3), washed with brine and dried over Na_2SO_4. After the solvents were removed in vacuo, the crude product was purified by flash column chromatography (hexane/AcOEt = 3:1) to give the desired products as a white amorphous (for *trans*: 15 mg, 24% and *cis*: 36 mg, 56%). Both enantiomeric excesses were determined by chiral HPLC analysis. For *trans*-**3b** (63% ee, $[\alpha]_D^{25}$ +44.2° (c 1.0, $CHCl_3$): Daicel Chiralpak AD, 254 nm, flow rate: 1.0 mL/min, hexane/*i*-PrOH = 4:1, t_R: 17.6 min (major) and 25.0 min (minor). For *cis*-**3b** (58% ee, $[\alpha]_D^{25}$ +142.0° (c 1.0, $CHCl_3$)): Daicel Chiralpak AD, 254 nm, flow rate: 1.0 mL/min, hexane/*i*-PrOH = 4:1, t_R: 10.3 min (major) and 12.5 min (minor), respectively.
14. However derivatives of PTC A were investigated, any attempts to introduce substituents on aromatic rings and quaternary ammonium moieties gave unsatisfactory results in enantiomeric excess.
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