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The asymmetric alkylation reaction of glycine derivatives catalyzed by the novel chiral phase transfer catalysts

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ABSTRACT

Herein a new series of chiral phase transfer catalysts derived from the cinchona alkaloids were synthesized and applied in the asymmetric alkylation of glycine derivatives with high yields and moderate to excellent ee values (39.5–99.7%).

The development of the chiral phase transfer catalysts derived from the structure of cinchona alkaloids is becoming an area of growing importance.[1] From the points of economical and environmental views, catalytic use of these kinds of catalysts is very promising.[2–4] Until recently, there have been three main generations of these catalysts derived from cinchona alkaloids (Fig. 1). 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,[5,6] which were successfully applied in the asymmetric alkylation of glycine Schiff base by O'Donnell's group with good enantioselectivity.[7,8] Deng and co-workers reported that the second generation of the catalysts could catalyze the asymmetric Darzens reaction with high yields and excellent enantioselectivity.[9] The third generation of catalysts were developed by Corey's group.[10] Recently Waser and co-workers reviewed the catalyzed asymmetric reactions catalyzed by the bifunctional ammonium catalysts,[11] and Hashimoto and Maruoka also reviewed the asymmetric phase transfer catalysis with chiral ammonium catalysts derived from cinchona alkaloids and chiral C_2-type ammonium catalysts.[12]

According to the theory stated by Corey, the chiral phase transfer catalyst should be structured so as to provide steric screening which prevents close approach of the counter-ion to three of the faces of this tetrahedron, while the fourth face should be sufficiently open to allow close contact between the substrate counter-ion and N^+ (Fig. 2).[13] There should also be a nearby binding surface for attractive van der Waal's interaction.[10] In continuation of our research on the asymmetric phase transfer catalysis,[14] herein we wish to report a series of novel chiral phase transfer catalysts derived from cinchona alkaloids.

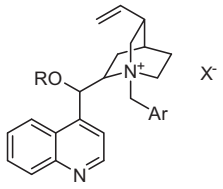

Figure 1. Three generations of chiral phase transfer catalysts derived from cinchona alkaloids.

The natural chiral carbon atoms of cinchona alkaloids are essential for their enantioselectivity. The hydroxyl group and bridgehead nitrogen are two key groups of cinchona alkaloid parent nucleus. Till now a method of modification of the two groups at the same time has not been reported yet. Herein we wish to report the first modification on both groups at the same time with an easy reaction. Through the reaction, a circular structure containing oxygen and nitrogen can be brought into the new catalysts to bring the better screen to the bridgehead nitrogen. Firstly, we designed a series of catalysts with a six-member cycle as **3a** (Fig. 3) derived from cinchona alkaloids and 1,2-dibromoethane. But when the experiment was processed, we found it was unsuccessful and no desired product was achieved. The potential reason was that this

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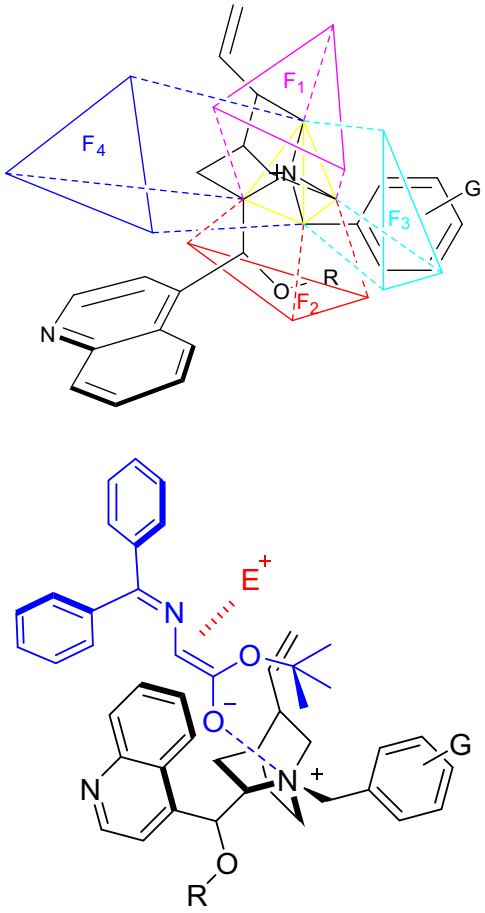
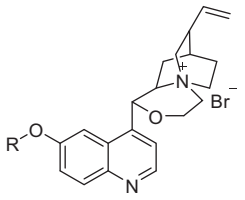
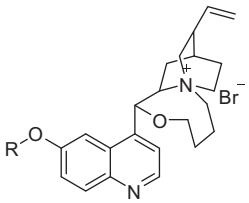


Figure 2. Model of the theory stated by Corey.



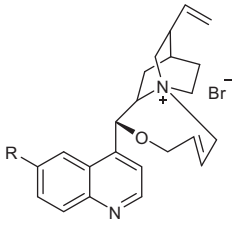
3a: R=H, CH3



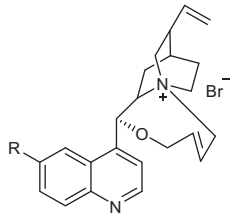
3b: R=H, CH3

Figure 3. Some catalyst we tried to synthesize but did not achieve.

six-member cycle has an exaggerated steric hindrance to prevent the generation of the circular structure. According to this potential reason, the new structure with eight-member cycle was designed as **3b**. We tried to synthesize this compound with cinchona alkaloids and 1,4-dibromobutane, but it was also not successful and no desired product was achieved probably due to the low reactivity of 1,4-dibromobutane.



4a: R=H
4b: R=OCH$_3$



4c: R=OCH3
4d: R=H

Figure 4. Structure of catalysts **4a**–**4d**.

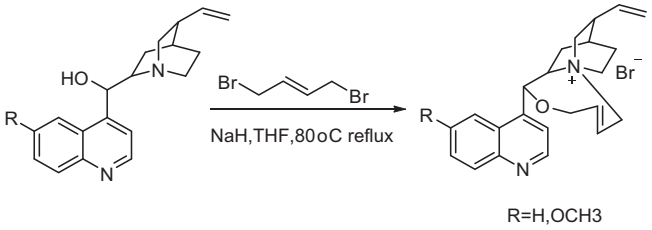


Figure 5. Synthesis of catalysts **4a** to **4d**.

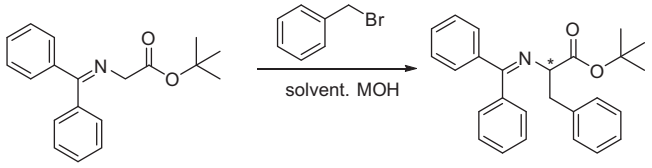


Figure 6. Asymmetric benzylation of glycine derivative reaction under different conditions.

Concerning the better activity of 1,4-dibromobut-2-ene, it was considered to replace 1,4-dibromobutane. So herein we designed and synthesized a series of chiral catalysts as **4a**–**4d** (Fig. 4). As shown in Figure 4, the structure of eight-member cycle can play an important role in these catalysts. It could provide satisfying steric screening with the structure of the *endo*-cycle which can prevent close approach of the counter-ion to three of the faces of this tetrahedron. With the potential advantage of the circular structure, especially the great flexibility of the eight-member cyclic structure, the catalysts should have a better enantioselectivity.

The catalysts **4a**–**4d** were synthesized by the reaction of (*E*)-1,4-dibromobut-2-ene and cinchona alkaloids with sodium hydride as base, the reactions were all carried out at 80 °C, with THF as the solvent, with the yield between 60% and 70% (Fig. 5).[16]

With the catalysts from **4a** to **4d** in hand, we applied them in the asymmetric alkylation of glycine derivatives. The asymmetric benzylation was chosen as a model reaction (Fig. 6), several

Table 1
Asymmetric benzylation of glycine derivative under different reaction conditions[a]

Entry	Catalyst	Temperature (°C)	Base	Solvent	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	**4a**	10	50% KOH	Toluene	87	99.7	*S*
2	**4b**	10	50% KOH	Toluene	75	80.1	*S*
3	**4c**	10	50% KOH	Toluene	77	17.8	*R*
4	**4d**	10	50% KOH	Toluene	80	60.7	*R*
5	**4a**	4	50% KOH	Toluene	60	88.4	*S*
6	**4a**	20	50% KOH	Toluene	71	90.1	*S*
7	**4a**	10	50% NaOH	Toluene	70	90.3	*S*
8	**4a**	10	50% CsOH	Toluene	74	91.2	*S*
9	**4a**	10	KOH(s)	Toluene	85	85.6	*S*
10	**4a**	10	50% KOH	CH_2Cl_2	76	45.6	*S*
11	**4a**	10	KOH(s)	THF	90	39.3	*S*
12	**4a**	10	50% KOH	Cyclohexane	78	83.7	*S*

[a] The reaction was carried out with 1.1 equiv of benzyl bromide and 20.0 equiv of 50% alkaline solution in the presence of 10 mol % 1–3 in different organic agents under the given conditions.
[b] Isolated yields.
[c] Enantiopurity was determined by HPLC analysis of benzylated imine using a chiral column (DAICEl Chiralcel OD-H) with hexanes/*i*-PrOH (volume ratio = 99.5:0.5) as an eluent.
[d] The absolute configuration was determined by comparison of the optical rotation with Refs. 10,15.

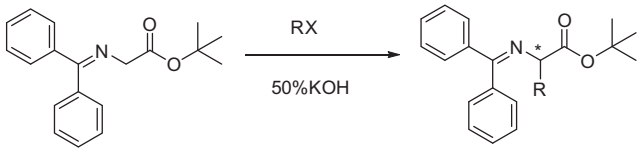


Figure 7. Asymmetric alkylation reactions of glycine derivative under optimal reaction condition.

different reaction conditions were investigated and the results are listed in Table 1.[17]

As shown in Table 1, of all the catalysts we investigated, **4a** gave the best enantioselectivity (entry 1) while catalysts **4b**, **4c**, and **4d** gave poor to moderate enantioselectivity and catalyst **4c** gave an amazing low enantioselectivity (entry 3), while there was no credible explanation till now and further research will be continued in this field in the future. Of all the solvents we investigated, toluene gave the best enantioselectivity while more dipolar THF and CH_2Cl_2 gave poor enantioselectivity. Different kinds of bases were also investigated, 50% of aqueous KOH was found to be the best base, which gave the best ee value, while the bases of 50% NaOH and 50% CsOH gave the relatively low enantioselectivity. Decrease of the temperature did not give the better enantioselectivity but lowered the yield (entry 5) as more of the starting material was observed to be decomposed under lower temperature. So the optimal condition was with **4a** as the catalyst, with 50% KOH as the base and toluene as the solvent at 10 °C (entry 1). Under the optimal reaction condition, several other alkylation reagents were also applied in the asymmetric alkylation of the glycine derivative (Fig. 7) and the results are listed in Table 2.[17]

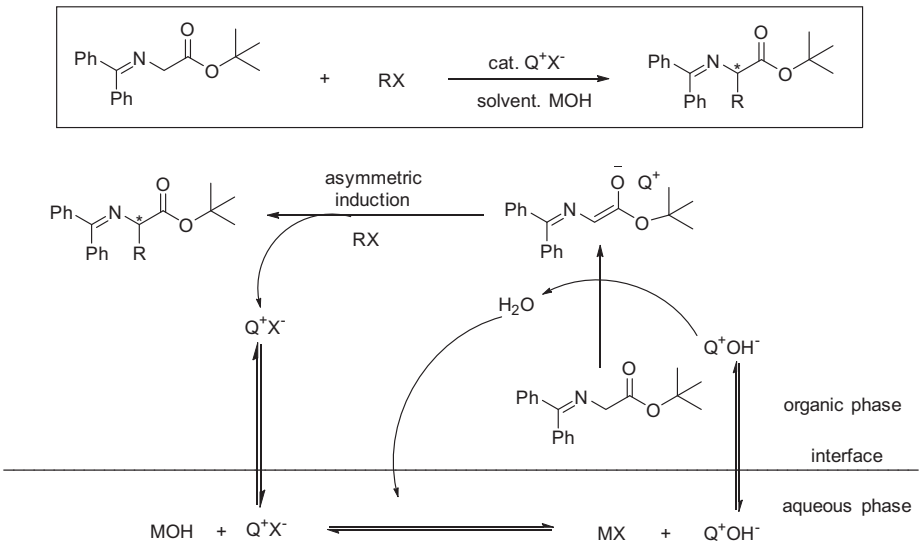
As shown in Table 2, the asymmetric alkylation reactions of glycine derivative were smooth at 10 °C with high yields and moderate to excellent ee value. Relatively high enantioselectivity was achieved with the aromatic alkylation reagents and relatively low enantioselectivity was achieved with aliphatic alkylation reagents, and for the aromatic alkylation reagents, a lower enantioselectivity was achieved with the electron-withdrawing group on the aromatic ring, and of all the alkylation reagents, the highest ee value achieved was 99.7% with benzyl bromide as the alkylation reagent (entry 1).

The possible work model is listed in Scheme 1, the catalysts could transfer between the organic phase and the aqueous phase. In the aqueous phase, the catalysts Q^+X^- could exchange the anion with the base MOH and the new organic base Q^+OH^- was obtained. The organic base Q^+OH^- was then transferred to the organic phase and the active α-H of the glycine Schiff base was deprived. The Schiff Base thus formed the chiral ion-pair together with Q^+ and the ion-pair could shield one face of the enolate of the Schiff base effectively, then the asymmetric induction was realized and the asymmetric alkylation was also realized with desired product

Table 2
Asymmetric alkylation of glycine derivative under optimal reaction condition

Entry	RX	Cat.	Yield[a] (%)	ee[b] (%)
1	Benzyl bromide	**4a**	87	99.7
2	4-Trifluoromethylbenzyl bromide	**4a**	82	63
3	4-Fluorobenzyl bromide	**4a**	86	80
4	Iodomethane	**4a**	77	71
5	Iodoethane	**4a**	69	67
6	3-Bromoprop-1-yne	**4a**	75	87
7	(Bromomethyl)cyclopropane	**4a**	65	57
8	3-Bromoprop-1-ene	**4a**	76	53
9	Benzyl bromide	**4b**	75	80.1
10	4-Trifluoromethylbenzyl bromide	**4b**	68	40.3
11	4-Fluorobenzyl bromide	**4b**	65	54.5

[a] Isolated yield.
[b] The enantiomeric excess was determined by HPLC analysis with a chiral column (DAICEl Chiralcel OD-H) with hexanes/*i*-PrOH (volume ratio = 99.5:0.5) as eluent.



Scheme 1. Possible mechanism of asymmetric alkylation of glycine Schiff base.

formed and the catalysts Q^+X^- were reformed and re-transferred to the aqueous layer to form the catalytic cycle.

We successfully designed and synthesized a series of new chiral phase-transfer catalysts with the structure of 8-atom cycle derived from cinchona alkaloids. These new catalysts were applied in the asymmetric alkylation of glycine derivatives with high yields and moderate to excellent enantioselectivity. Further work is under way to understand the mechanism and improve the enantioselectivity.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.063.

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16. Typical procedure of the synthesis of the catalysts **4a** to **4d**:
(1S,7R,10S,E)-1-(Quinolin-4-yl)-9-vinyl-1,3,6,8,9,10,11,11a-octahydro-7,10-ethanopyrido[2,1-c][1,4]oxazocin-7-ium bromide (**4a**): Cinchonidine (0.294 g, 1 mmol) was dissolved in THF (5 ml), and sodium hydride (0.048 g, 2 mmol) was added. The reaction mixture was stirred and heated to 80 °C and refluxed for 1 h, then (*E*)-1,4-dibromo-2-butene (0.321 g, 1.5 mmol) was added. The reaction mixture was further refluxed for 12 h and the reaction was monitored by TLC. After the completion of the reaction, the solvent was evaporated and the residue was purified with silica gel (chloroform/methanol = 30:1) to give the product (0.24 g, 70% yield).
^{1}H NMR (500 MHz, $CDCl_3$): 8.9188–8.9043 (m, 1H), 8.2234–8.1656 (m, 2H), 7.7959–7.6351 (m, 2H), 7.4242–7.4097 (m, 1H), 6.4735–6.4328 (m, 1H), 6.1463–6.0199 (m,1H), 5.8805 (s, 1H), 5.7594–5.6443 (m, 2H), 5.0114–4, 9213 (m, 3H), 4.8283–4.7940 (m, 1H), 3.4942–3.4170 (m, 1H), 3.2820–3.1826 (m, 2H), 2.8837–2.7382 (m, 2H), 2.3971 (s, 1H), 1.9077–1.8730 (m, 3H),1.6735–1.5299 (m, 2H) ^{13}C NMR (500 MHz, $CDCl_3$): 150.0278, 147.9949, 146.0408, 142.1767, 133.1039, 129.8867, 129.0374, 126.5786, 125.8792, 123.8068, 119.5861, 114.1071, 111.9291, 109.5361, 107.8249, 82.5908, 81.2770, 60.2081, 55.8686, 41.6474, 27.2226, 24.6763.
ES-MS: 347.2 (M); $[\alpha]_D^{22}$ +95.5° (*c* 0.2, CH_2Cl_2) elemental analysis: calculated: C, 79.5; H, 7.8; N, 8.1. Found: C, 79.39; H, 7.89; N, 7.95.
(1R,7R,10S,E)-1-(6-Methoxyquinolin-4-yl)-9-vinyl-1,3,6,8,9,10,11,11a-octahydro-7,10-ethanopyrido[2,1-c][1,4]oxazocin-7-ium bromide (**4b**): 63% yield, ^{1}H NMR (500 MHz, $CDCl_3$): 8.7290–8.7204 (m,1H), 8.0506–8.0238 (m,1H), 7.3945–7.3349 (m,2H), 7.2528–7.2218 (m,1H), 6.4336–6.4090 (m, 1H), 6.0792–6.0454 (m, 1H), 5.7119–5.6122 (m, 2H), 5.5391–5.5336 (m,1H), 4.9527–4.8838 (m, 2H), 4.7799–4.7595 (m, 1H), 3.9461–3.9340 (m, 3H), 3.3115 (s, 1H), 3.1652–3.0853 (m, 2H), 2.7290–2.6179 (m, 2H), 2.2770 (s, 1H), 2.1537 (s, 2H), 1.8751–1.7688 (m, 4H), 1.5377–1.5175 (m, 3H), 1.2454–1.2100 (m, 1H) ^{13}C NMR (500 MHz, $CDCl_3$): 157.8505, 148.6980, 147.3576, 143.9983, 141.5296, 139.6108, 138.8185, 132.7581, 129.2598, 126.1965, 121.9891, 119.2893, 102.0956, 78.5066, 76.8134, 65.8451, 58.7737, 56.7155, 54.0146, 42.7227, 37.3716, 26.7743, 24.7174, 20.4527, 18.0087 ES-MS: 377.2 (M); $[\alpha]_D^{22}$ +100° (*c* 0.2, CH_2Cl_2) elemental analysis: calculated: C, 76.4; H, 7.7; N, 7.4; found: C, 76.28; H, 7.92; N, 7.58.
(1S,7R,10S,E)-1-(6-Methoxyquinolin-4-yl)-9-vinyl-1,3,6,8,9,10,11,11a-octahydro-7,10-ethanopyrido[2,1-c][1,4]oxazocin-7-ium bromide (**4c**): 53.1% yield, ^{1}H NMR (500 MHz, $CDCl_3$): 8.7204–8.7193 (m,1H), 8.0601–8.0294 (m, 1H), 7.4040–7.3413 (m, 2H), 7.2626–7.2166 (m,1H), 6.4454–6.4046 (m, 1H), 6.1093–6.0400 (m, 2H), 5.6780–5.5472 (m, 2H), 5.1599–5.0716 (m, 2H), 4.9482–4.8920 (m, 1H), 4.7891–4.7547 (m, 1H), 3.9442–3.9328 (m, 3H), 3.1868–3.1019 (m, 2H), 2.9826–2.7679 (m, 4H), 2.2706–2.2463 (m,1H), 1.7724 (s, 1H), 1.5069–1.4824 (m, 3H), 1.2527–1.1816 (m, 2H), 0.9454–0.8975 (m, 1H) ^{13}C NMR (500 MHz, $CDCl_3$): 157.1687, 150.1687, 147.3799, 145.8176, 144.0027, 140.8254, 133.1505, 131.2325, 129.6808, 126.9962, 121.2880, 119.2112, 102.2112, 82.2055, 80.6039, 60.2081, 55.4593, 49.9428, 49.0488, 48.3823, 39.6256, 27.7150, 25.9084, 24.6867 ES-MS: 377.2 (M); $[\alpha]_D^{22}$ −14° (*c* 0.2, CH_2Cl_2) elemental analysis: calculated: C, 76.4; H, 7.7; N, 7.4; found: C, 76.6; H, 7.45; N, 7.57.
(1R,7R,10S,E)-1-(Quinolin-4-yl)-9-vinyl-1,3,6,8,9,10,11,11a-octahydro-7,10-ethanopyrido[2,1-c][1,4]oxazocin-7-ium bromide (**4d**): 56.9% yield, ^{1}H NMR (500 MHz, $CDCl_3$): 8.9185–8.9043 (m, 1H), 8.1907–8.1148 (m, 2H), 7.7660–7.6210 (m,2H), 7.4260–7.4120 (m, 1H), 6.4651–6.4240 (m, 1H), 6.1454–6.0176 (m, 2H), 5.9080–5.8020 (m,1H), 5.7185–5.6410 (m, 1H), 5.1782–5.0697 (m, 2H), 4.9745–4.9180 (m,1H), 4.8213–4.7874 (m,1H), 3.2700–3.1762 (m, 3H), 3.0660–2.9939 (m,2H), 2.8654 (s, 1H), 2.3483–2.1630 (m, 3H), 1.8380 (s, 2H), 0.9761–0.8701 (m, 2H) ^{13}C NMR (500 MHz, $CDCl_3$): 149.9942, 147.9244, 145.8366, 140.6015, 133.0530, 129.8156, 129.0673, 126.6098, 125.8520, 123.8260, 119.3837, 118.8478, 82.0510, 80.6292, 68.2785, 59.9805, 49.0344, 48.1538, 27.6099, 25.6839, 24.5560, 23.5513 ES-MS: 347.2 (M); $[\alpha]_D^{22}$ +6° (*c* 0.2, CH_2Cl_2) elemental analysis: calculated: C, 79.5; H, 7.8; N, 8.1; found: C, 79.63; H, 7.31; N, 8.35.

17. Typical procedure of the asymmetric alkylation of glycine derivative:
To a mixture of *tert*-butyl 2-((diphenylmethylene)amino)acetate (0.148 g, 5 mmol) and catalyst **4a** (10% mol, 20 mg) in 5 ml toluene were added benzyl bromide (1.1 equiv) and KOH (20 equiv, 50% aqueous) at 10 °C. The reaction mixture was stirred vigorously at the same temperature for 18 h. Then water (5 ml) was added, the organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 twice. The organic layer was combined, washed with brine, dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified with preparative TLC (PE/EA = 50:1) to give the product (0.168 g) as oil.
^{1}H NMR (500 MHz, $CDCl_3$): 7.82–7.81 (m, 2H), 7.38–7.28 (m, 6H), 7.25–7.14 (m, 3H), 7.08–7.06 (m, 2H), 6.64–6.62 (m, 2H), 4.15–4.11 (m, 1H), 3.27–3.15 (m, 2H), 1.45 (s, 9H). $[\alpha]_D^{22}$ −210° (*c* = 0.2, CH_2Cl_2). HPLC analysis retention time: 10.72 min, 13.41 min (major) (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 99.5:0.5, flow rate = 0.5 ml/min).