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Review Aricle

Synthesis of New Chiral Phase Transfer Catalysts and their Application in the Asymmetric Alkylation of Glycine Derivatives

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Abstract

A new type of chiral phase transfer catalysts were synthesized and applied in the asymmetric alkylation of glycine derivatives with high yields and moderate to high ees (58-88%).

Keywords: Chiral phase transfer catalysts; Asymmetric alkylation; Glycine derivatives

Chiral unnatural amino acids play an important role in pharmaceutical industry and the synthesis of them are of great importance. The asymmetric alkylation of glycine derivatives with chiral phase transfer catalysts is one of the most important methods to prepare the chiral unnatural amino acids [1]. In recent years, chiral phase transfer catalysts derived from cinchona alkaloids have been a hotspot in asymmetric catalysis. Up to date, such kind catalysts can be divided into three generations [2-5]. As is shown in Figure 1: the first generation: R=H, Ar=Phenyl; the second generation: R=Allyl, Ar=Phenyl; and the third generation: R=Alkyl, Ar=Anthracyl. Deng et al. reported that the second generation of the catalysts could catalyze the asymmetric Darzens reaction with high yield and excellent enantioselectivity [6], Waser et al. reviewed the catalyzed asymmetric reactions catalyzed by the bifunctional ammonium catalysts [7], Maruoka et al. reviewed the asymmetric phase transfer catalysis with choral ammonium catalysts derived from cinchona and choral C_2-type ammonium catalysts [8].

According to E.J. Corey's theory about the chiral phase transfer catalysts derived from cinchona alkaloids, if the bridgehead nitrogen of a cinchona alkaloid quaternary salt is taken to be at the center of a tetrahedron, the 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^+ Figure 2.

The natural chiral carbon atoms of cinchona alkaloids are essential for their enantioselectivity. The hydroxyl group and bridgehead nitrogen of cinchona alkaloids parent nucleus are two key groups, and the modification of them would directly affect the enantioselectivity based on Corey's theory. And till now all modification were on the two groups respectively, only few papers [9] reported the modification on both two groups with one single reagent at the same time. We tried to realize the modification on the two groups at the same time with some simple methods, for example, the two groups could be combined together with one reagent to form a new cycle. Such structure would be more stable to shield the three faces of the tetrahedron, and the stereoselectivity would be enhanced. Herein we designed a new series of chiral phase transfer catalysts (1,2,3,4) based on the imagination. Those catalysts all had a six-member rigid ring structure, which would be more stable and their asymmetric induction would be better. We expected that the enantioselectivity would be increased by the formation of the rigid ring of those catalysts Figure 3.

A new series of chiral phase transfer catalysts were derived from cinchona alkaloids with 2-bromo-1-(4-(trifluoromethyl) phenyl)

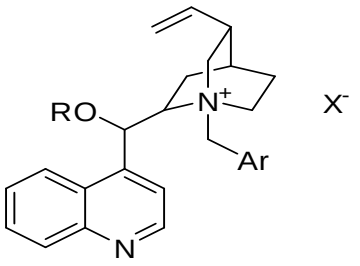

Figure 1:

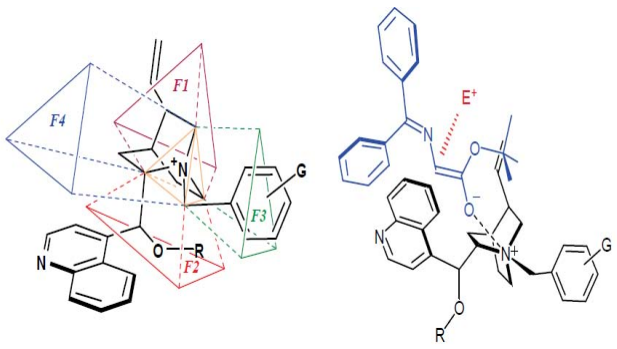

Figure 2:

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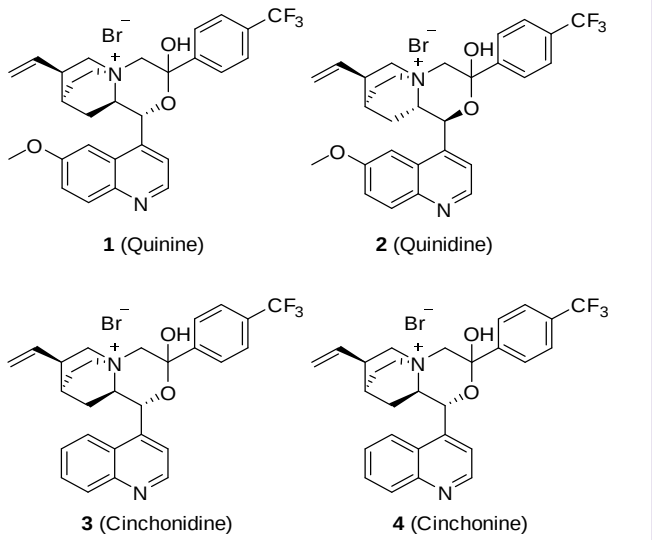


Figure 3:

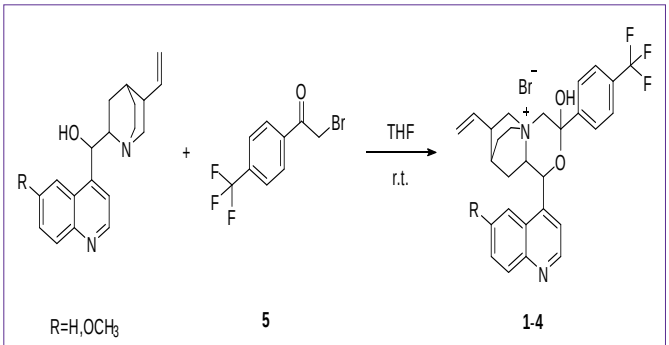
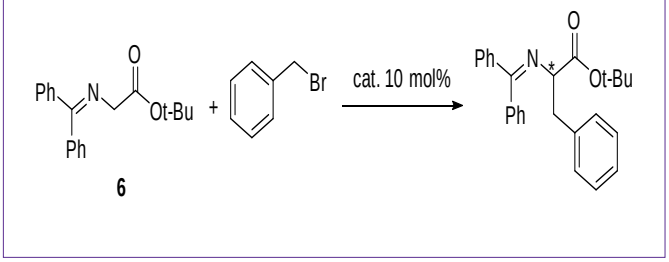


Figure 4:

Table 1: The asymmetric catalytic benzylation of glycine derivatives with different catalysts under different reaction conditions.



Entry	Catalyst	Tempe-rature	Base	Solvent	Yield(%)[b]	ee(%)[c]	Configuration[d]
1	1	10°C	50%KOH	Toluene	80	67	S
2	2	10°C	50%KOH	Toluene	76	44	R
3	3	10°C	50%KOH	Toluene	88	88	S
4	3	4°C	50%KOH	Toluene	60	72	S
5	3	20°C	50%KOH	Toluene	73	76	S
6	3	10°C	50%NaOH	Toluene	50	73	S
7	3	10°C	$CsOH·H_2O$	Toluene	40	82	S
8	3	10°C	50%KOH	CH_2Cl_2	70	55	S

ethan-1-one. First, Chem-3D was used to simulate Three-Dimensional of the designed catalysts in order to determine the feasibility of this kind of compounds and their minimum energy state. As shown in the note [10], all the four isomers of cinchona alkaloids could form the imagined conformation of six-member ring structure, and their energy was close to each other, wandering about 65kcal/mol. In accordance to the reference 9, only one anomer was formed in the condensation of the α-halogen ketone with cinchona alkaloids. Then the catalysts were synthesized, the 2-bromo-1-(4-(trifluoromethyl) phenyl)ethan-1-one (**5**) was prepared by 1-(4-(trifluoromethyl) phenyl)-ethan-1-one and bromine [11], then the four isomers were stirred with 5 in THF for 8 hours Figure 4, and only 1, 2, and 3 could be achieved in 97-99% yields [12], while 4 could not be achieved with cinchonine as starting material, as cinchonine was insoluble in THF.

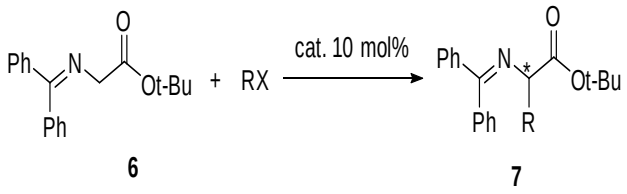
Then all the three catalysts were applied in the asymmetric alkylation of glycine derivatives to evaluate their catalytic efficiency and enantioselectivity. The asymmetric benzylation of glycine derivatives (**6**) was used as a model reaction to optimize the reaction condition [13] and the results were list in Table 1.

- 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.
- Isolated yields.
- Enantiopurity was determined by HPLC analysis of benzylated imine using a chiral colume (DAICEl Chiralcel OD-H) with hexanes/ *i*-PrOH (volume ratio = 99.5:0.5) as a solvent.
- The absolute configuration was determined by comparison of the optical rotation with references [4,14].

As shown in Table.1, of all the catalysts investigated, catalyst **3** was the best one with the highest yield and best ee value. The absolute configurations of the products were the same with catalyst 1 and 3 as their chiral carbon atoms were also consistent, but the absolute configuration of the product with 2 as catalyst was opposite. The enantioselectivities did not change much as temperature changed, and 10°C was the best temperature. Different bases were also investigated, and 50% of the aqueous potassium was better than aqueous sodium hydroxide and solid cesium hydroxide. Of all the solvents investigated, toluene gave the best enantioselectivity. So the optimized reaction condition was with 3 as catalyst, with 50% aqueous of KOH as base, with toluene as the solvent and at 10°C. Having found the optimized reaction conditions, we tried to investigate the other alkylation reagents and the results were listed in

- Reaction was carried out with 1.1 equiv. of alkyl halides and 20.0 equiv. of 50% aqueous KOH in the presence of 10 mol% 3 in toluene under the given conditions.
- Isolated yields.
- Enantiopurity was determined by HPLC analysis of benzylated imine using a chiral colume (DAICEl Chiralcel OD-H) with hexanes/ *i*-PrOH (volume ratio = 99.5:0.5) as a solvent.

Table 2: Catalytic asymmetric alkylation of glycine derivatives with catalyst **3**[a].



6 7

Entry	Product	RX	Times(h)	Yield(%)	ee(%)
1	**7a**	CH_3I	18	65	58
2	**7b**	CH_3CH_2I	48	55	62
3	**7c**	$CH{\equiv}CCH_2Br$	36	66	71
4	**7d**	$CH_2{=}CHCH_2Br$	24	64	66
5	**7e**	$4\text{-}FC_6H_4CH_2Br$	18	80	78
6	**7f**	BnBr	18	88	88

- The absolute configuration was determined by comparison of the optical rotation with references [4,14].

As was shown in Table 2, the ees of the asymmetric alkylation with aromatic alkylation reagents was around 80%, while the ees with aliphatic alkylation reagents were only in the medium level. The yields with the aliphatic alkylation reagents were also not so good.

In conclusion, we designed and synthesized a series of new chiral phase transfer catalysts(1-3) derived from cinchona alkaloids and their applications in the asymmetric alkylation of glycine derivatives were also investigated, and mediate to high yields and mediate to high ees were achieved with 3 as catalyst. Further work is under to under the mechanism of the reaction and to increase the enantioselectivity.

Acknowledgment

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