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Development of new asymmetric two-center catalysts in phase-transfer reactions

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Abstract—A new asymmetric two-center phase-transfer catalyst was designed and a catalyst library containing more than 40 new two-center catalysts was constructed. The catalysts were applied in phase-transfer alkylations and Michael additions to afford the corresponding products in up to 93% ee and 82% ee, respectively.

Phase-transfer catalysis (PTC) is one of the most important and useful methods in synthetic organic reactions because of its simple reaction procedure, mild conditions, inexpensive and environmentally friendly reagents, and the ease in scaling-up the reaction.[1] An asymmetric version of PTC utilizing chiral phase-transfer catalysts, however, has not been extensively studied as compared to general asymmetric catalysis. The pioneering studies of O'Donnell and co-workers in 1989 led to the development of a highly practical enantioselective alkylation of a prochiral protected glycine derivative using *Cinchona* alkaloid ammonium salts to produce chiral α-amino acids.[2] Later, Corey[3] and Lygo[4] independently greatly improved this catalyst system.[5] Although many types of phase-transfer catalysts have been used as chiral catalysts in PTC, *Cinchona* alkaloid derivatives give more impressive enantioselectivity for a range of reactions than do other catalysts, with few exceptions.[6] The major drawback of these catalysts is the difficulty in modifying the catalyst structure to further improve selectivity or reactivity. To address this issue, we developed a new versatile asymmetric phase-transfer catalyst. In the course of our development of new asymmetric catalyses using bifunctional complexes,[7] we designed a new asymmetric two-center phase-transfer catalyst **1**, in which the substrate could be activated and fixed in a chiral environment by a two-cationic moiety (Fig. 1). We report the design and synthesis of a variety of new asymmetric two-center catalysts **1** and their application in phase-transfer alkylations and Michael additions. The newly constructed catalyst library is very effective for screening for the best catalyst. Using the same catalyst, the alkylations and the Michael additions have opposite enantiofacial selectivity.

To design a two-center catalyst, we first performed molecular mechanics simulation using the Monte Carlo method. The results suggested that the Schiff base of *tert*-butyl glycinate **2** is fixed between both ammonium cations, as we expected (Fig. 1).[8] We then started syntheses of a variety of catalysts **1**. From the viewpoint of catalyst accessibility and versatility, our catalysts **1** have a great advantage, because both enantiomers can be easily synthesized from commercially available and relatively inexpensive[9] L- or D-tartrate with a variety of ketal moieties (R^1 and R^2) and aromatic parts (Ar).[10] Scheme 1 summarizes the five-step preparation of the catalysts **1** using only common and inexpensive reagents. Dimethyl ketal derivative **4aa** ($R^1 = R^2 = Me$, Ar = Ph) had low reactivity in the methylation step (step **e**), resulting in the formation of

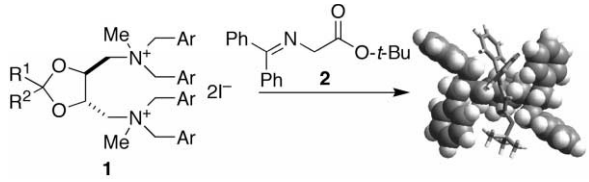

Figure 1. Structure of new two-center asymmetric catalysts **1** (left) and the result of molecular mechanics simulation (right).

Keywords: phase-transfer catalysis; asymmetric two-center catalyst; alkylation; Michael addition.

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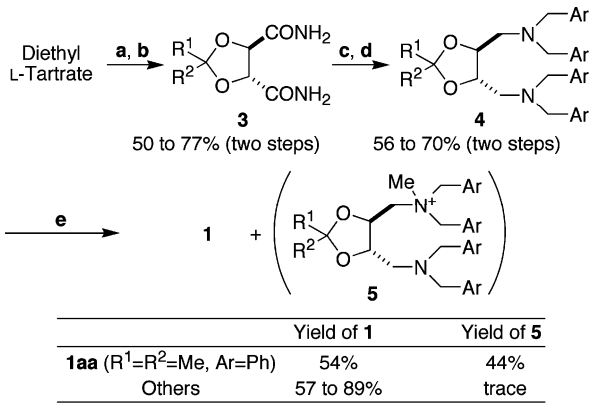


	Yield of **1**	Yield of **5**
1aa (R^1=R^2=Me, Ar=Ph)	54%	44%
Others	57 to 89%	trace

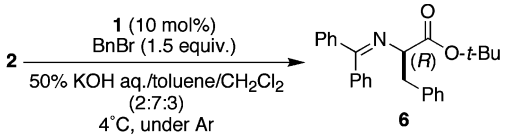
Scheme 1. *Reagents and conditions*: (a) ketone (1.2 equiv.), $HC(OMe)_3$ (1.5 equiv.), cat. $TsOH·H_2O$, MeOH, 70°C, then diethyl L-tartrate, toluene, 110°C; (b) NH_3 gas, MeOH, 4°C; (c) LAH (3.5 mol equiv.), THF, rt to reflux; (d) $ArCH_2Cl$ (7.0 mol equiv.), *i*-Pr_2NEt (7.2 mol equiv.), MeCN, rt; (e) MeI (40 mol equiv.), rt.

a mixture of mono-ammonium salt **5aa** and the desired bis-ammonium salt **1aa**, even after refluxing. In contrast, other ketal derivatives (Tables 1 and 2) were smoothly converted to bis-ammonium salts **1** in reasonable yields (57–89%).

As a preliminary study, we evaluated **1aa** and **5aa** for phase-transfer alkylation of **2** with benzyl bromide. The bis-ammonium salt **1aa** promoted the reaction approximately twice as fast as the mono-ammonium salt **5aa** with higher enantiomeric excess (42% ee compared with 12% ee). Although bis- and tris-*Cinchona* alkaloid ammonium salt catalysts were reported,[11] similar reactivity and selectivity were observed, compared with ordinal *Cinchona* alkaloid catalysts even with the same catalyst loading. Thus, our finding indicated that the two-cationic moiety simultaneously activated and fixed the substrate **2** in the chiral environment.

We then examined a variety of catalysts **1** (>40) in phase-transfer alkylations and Michael additions for catalyst screening.[12] Selected results are shown in Tables 1 and 2, respectively. All reactions were performed under an argon atmosphere[13] due to the partial decomposition of **2** under aerobic conditions (entries 1 and 2, in Tables 1 and 2).[6d] First, we examined the effect of a ketal moiety. In the case of alkylations, better results were obtained when un-C_2-symmetric catalysts were used as a catalyst (Table 1, entries 8–12 and 20). Among them, *tert*-butyl methyl ketal had the highest selectivity (entry 12). Screening of the aromatic part revealed that **1kf** (Ar = 4-methoxyphenyl) was the best catalyst for the alkylation (92% yield and 70% ee, entry 17). In all entries, the absolute configurations were *R*.[14] On the other hand, C_2-symmetric catalysts gave better results in Michael additions (Table 2, entries 1–13). In this reaction, 4-methylphenyl was the best aromatic substituent and **1cb** (entry 5), **1db** (entry

Table 1. Catalytic asymmetric phase-transfer alkylations



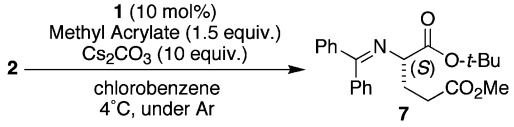
Entry	R^1	R^2	Ar	**1**	Time (h)	Yield (%)[a]	Ee (%)[b]
1[c]	Me	Me	-C_6H_5	**1aa**	4.0	67	47
2	Me	Me	-C_6H_5	**1aa**	2.0	87	47
3	Et	Et	-C_6H_5	**1ba**	2.0	94	37
4	Pr	Pr	-C_6H_5	**1ca**	2.5	92	40
5	Bu	Bu	-C_6H_4-4-OMe	**1df**	4.0	91	38
6	*i*-Bu	*i*-Bu	-C_6H_4-4-OMe	**1ef**	4.0	87	39
7	-$(CH_2)_5$-		-C_6H_5	**1fa**	2.5	92	38
8	*t*-Bu	H	-C_6H_5	**1ga**	2.0	90	48
9	*i*-Pr	Me	-C_6H_4-4-OMe	**1hf**	2.0	92	57
10	Bu	Me	-C_6H_4-4-OMe	**1if**	2.0	94	57
11	*i*-Bu	Me	-C_6H_4-4-OMe	**1jf**	2.0	91	54
12	*t*-Bu	Me	-C_6H_5	**1ka**	2.0	89	52
13	*t*-Bu	Me	-C_6H_4-4-Me	**1kb**	2.0	92	63
14	*t*-Bu	Me	-C_6H_4-4-*i*-Pr	**1kc**	2.0	89	67
15	*t*-Bu	Me	-C_6H_4-4-*t*-Bu	**1kd**	2.0	87	62
16	*t*-Bu	Me	2-Naphthyl	**1ke**	2.0	84	49
17	*t*-Bu	Me	-C_6H_4-4-OMe	**1kf**	2.0	92	70
18	*t*-Bu	Me	-C_6H_4-4-OEt	**1kg**	1.5	93	67
19	*t*-Bu	Me	-C_6H_4-4-OPr	**1kh**	1.5	89	68
20	$C_{14}H_{29}$	Me	-C_6H_4-4-OMe	**1lf**	2.5	92	60

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The reaction was performed under aerobic conditions.

12), and **1eb** (entry 13) gave the highest enantiomeric excess (64% ee). The obtained Michael products **7** had an *S* configuration in all entries.[14]

Using the best catalyst (**1kf** for alkylations, **1cb** for Michael additions), we examined the scope and limitations of different electrophiles under optimized conditions (Tables 3 and 4). When 10 mol% of **1kf** was used with cesium hydroxide, all phase-transfer alkylations of **2** with benzyl (entries 1–4), allyl (entries 5–7) and propargyl (entry 8) reagents proceeded at −70°C and gave higher enantiomeric excess (93% ee, entry 1, Table 3 compared with 70% ee, entry 17, Table 1). In addition, the reaction with 4-bromobenzyl bromide (entry 4), allyl bromide (entry 5) and methallyl bromide (entry 6) afforded the corresponding protected unnatural α-amino acids **10**–**12**, which can be a versatile intermediate of various unnatural α-amino acids, in 91% ee. The enantiomeric excess of Michael adducts was also improved (75% ee, entry 1, Table 4 compared with 64% ee, entry 5, Table 2) when the reaction was performed at −30°C.[15] Further improvement of the enantiomeric excess of the Michael product was obtained using ethyl acrylate as an electrophile (82% ee, entry 2). Moreover, all alkylations gave the *R*-configuration and all Michael additions gave the *S*-configuration. These results suggested that the bis-ammonium cation moiety in catalysts **1** functions as a bifunctional catalyst that activates and fixes nucleophiles as well as electrophiles in Michael additions.

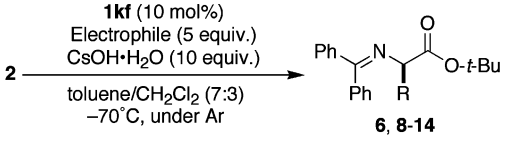
Table 2. Catalytic asymmetric phase-transfer Michael additions



Entry	R^1	R^2	Ar	**1**	Time (h)	Yield (%)[a]	Ee (%)[b]
1[c]	Me	Me	-C_6H_5	**1aa**	20	70	37
2	Me	Me	-C_6H_5	**1aa**	12	91	39
3	Et	Et	-C_6H_5	**1ba**	19	78	49
4	Pr	Pr	-C_6H_5	**1ca**	12	92	59
5	Pr	Pr	-C_6H_4-4-Me	**1cb**	9	94	64
6	Pr	Pr	-C_6H_4-4-*i*-Pr	**1cc**	11	87	59
7	Pr	Pr	-C_6H_4-4-*t*-Bu	**1cd**	12	87	62
8	Pr	Pr	2-Naphthyl	**1ce**	12	89	47
9	Pr	Pr	-C_6H_4-4-OMe	**1cf**	9	93	54
10	Pr	Pr	-C_6H_4-4-OEt	**1cg**	8	89	58
11	Pr	Pr	-C_6H_4-4-OPr	**1ch**	12	87	57
12	Bu	Bu	-C_6H_4-4-Me	**1db**	14	89	64
13	*i*-Bu	*i*-Bu	-C_6H_4-4-Me	**1eb**	12	88	64
14	*t*-Bu	H	-C_6H_4-4-Me	**1gb**	20	89	23
15	*t*-Bu	Me	-C_6H_4-4-Me	**1kb**	20	67	40

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The reaction was performed under aerobic conditions.

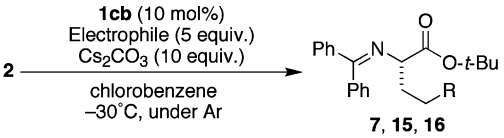
Table 3. Catalytic asymmetric phase-transfer alkylations



Entry	Electrophile	Product	Time (h)	Yield (%)[a]	Ee (%)[b]
1	Benzyl bromide	**6**	60	87	93 (*R*)
2	4-Methylbenzyl bromide	**8**	72	85	90 (*R*)
3	4-*t*-Butylbenzyl bromide	**9**	72	81	89 (*R*)
4	4-Bromobenzyl bromide	**10**	72	71	91 (*R*)
5	Allyl bromide	**11**	22	79	91 (*R*)
6	Methallyl bromide	**12**	72	82	91 (*R*)
7	Cinnamyl bromide	**13**	72	92	80 (*R*)
8	Propargyl bromide	**14**	60	73	81 (*R*)

[a] Isolated yield.
[b] Determined by HPLC analysis.

Table 4. Catalytic asymmetric phase-transfer Michael additions



7, 15, 16

Entry	Electrophile	Product	Time (h)	Yield (%)[a]	Ee (%)[b]
1	Methyl acrylate	**7**	20	86	75(*S*)
2	Ethyl acrylate	**15**	26	88	82(*S*)
3	Butyl acrylate	**16**	22	79	78(*S*)

[a] Isolated yield.
[b] Determined by HPLC analysis.

In conclusion, we designed a new versatile asymmetric two-center catalyst and constructed a catalyst library. More than 40 catalysts **1** were easily synthesized from diethyl L-tartrate[16] and applied in phase-transfer alkylations and Michael additions. Starting from the initial catalyst **1aa**, the enantiomeric excess of both alkylated products and Michael adducts was greatly improved (up to 93% ee and 82% ee, respectively) by screening the ketal moiety and the aromatic moiety in the catalyst **1**. These findings validate the usefulness of catalyst tuning for optimization. Moreover, comparing absolute configurations of alkylated products and Michael adducts led us to consider the possibility that the two-center catalysts act as bifunctional catalysts in Michael additions. Further studies on catalyst tuning, reaction mechanisms, application to other phase-transfer reactions by rational design of the catalyst based on mechanistic studies, and the development of new types of bifunctional organocatalysts are currently in progress.

Acknowledgements

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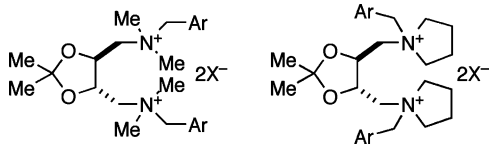
8. Computational simulation was performed with Cerius[2] (Accelrys Inc., San Diego, CA and Cambridge, UK). The conformation depicted in Fig. 1 was obtained using a random conformational search, the so-called Monte Carlo method, followed by a molecular mechanics minimization calculation (Universal Force Field v.1.02, see: Rappe, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard, W. A.; Skiff, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 10024).
9. For example, (Sigma-Aldrich Co., St. Louis, MO), L-tartaric acid: 100 g, 4100 yen (ca. 33 US$), diethyl L-tartrate: 100 g, 8600 yen (ca. 70 US$), quinine: 100 g, 78000 yen (ca. 640 US$) and (*R*)-BINOL: 100 g, 783000 yen (ca. 6420 US$).

10. In preliminary studies, *N*,*N*,*N*′*N*′-tetraalkyl-*N*,*N*′-dibenzyl type bis-ammonium salts were not effective catalysts in terms of enantioselectivity.



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12. For the purpose of catalyst screening, the described reaction conditions were selected based on reaction time. In preliminary studies, we found that toluene gave the best selectivity and CH_2Cl_2 gave the best reactivity in phase-transfer alkylations. Finally, we found that addition of CH_2Cl_2 to toluene (toluene/CH_2Cl_2 = 7:3) enhanced reactivity efficiently without any loss of selectivity. In the case of phase-transfer Michael additions, halobenzenes showed better selectivity than do other aromatic solvents, such as benzene and toluene. Although 1,2,4-trichlorobenzene gave the best selectivity, we eventually selected chlorobenzene based on reactivity.
13. Degassed conditions did not improve the results. Thus, the reaction atmosphere was simply replaced with flowing argon.
14. Absolute configurations of the products shown in Tables 1–4 were determined based on the previous reports, see: Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. *Chem. Commun.* **2001**, 245. See also Ref. 3a.
15. Because of the relatively high melting point of chlorobenzene (–45°C), –30°C should be the lowest temperature used in this system. Other solvents, such as toluene, had worse selectivity.
16. Recently, spiro-type phase-transfer catalyst derived from L-tartrate was synthesized by Arai, S., Tsuji, R. and Nishida, A. (private communication).