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Construction of a Chiral Quaternary Carbon Center by Catalytic Asymmetric Alkylation of 2-Arylcyclohexanones under Phase-Transfer Conditions

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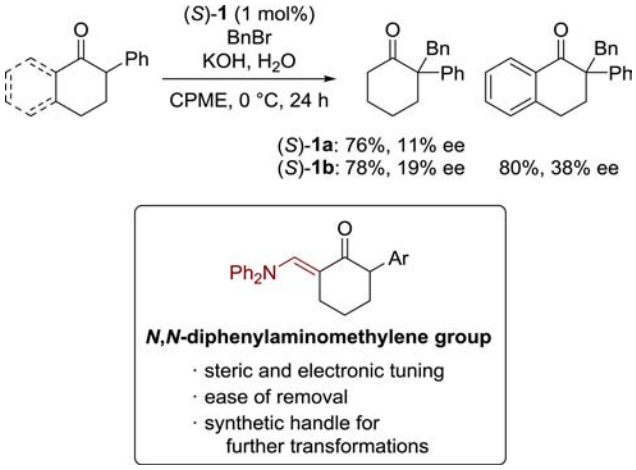
Supporting Information

ABSTRACT: In this paper, we present an asymmetric alkylation of modified 2-arylcyclohexanones that employs a novel chiral ammonium bromide as a phase-transfer catalyst and an achiral auxiliary as a controller to improve the enantioselectivity to afford optically enriched products having a chiral quaternary carbon center.

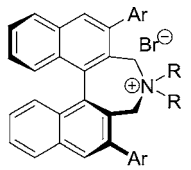
Cyclohexane rings containing a chiral quaternary carbon center are frequently found in natural products and are considered as important and useful building blocks in organic synthesis.[1−4] Among them, 1-alkyl-1-arylcyclohexanes represent an attractive structural motif that constitutes the core structure of biologically active compounds exemplified by morphine and strychnine.[5] Asymmetric alkylation of 2-arylcyclohexanones is a simple and direct method for constructing such chiral quaternary carbon centers;[5a] however, only a few reports on the catalytic asymmetric synthesis of 2-alkyl-2-arylcyclohexanones have appeared to date with limited success (e.g., Mukaiyama aldol reaction, Pd-catalyzed allylation and arylation).[5,6] In contrast to the previous attempts, phase-transfer-catalyzed asymmetric alkylation is undoubtedly one of the most reliable methods for introducing alkyl substituents in an enantioselective fashion, though such an approach has not reached to a synthetically useful level.[7,8] Here we disclose our initial results on this study.

The reaction between 2-phenylcyclohexanone and benzyl bromide under phase-transfer conditions gave the benzylated product with low enantioselectivity (Scheme 1), and a chiral phase-transfer catalyst, (*S*)-**1**, was found to be unsuitable for relatively small substrates such as 2-phenylcyclohexanone, probably because of the difficulty of enantioface discrimination. On the other hand, asymmetric benzylation of 2-phenyltetralone with a fused benzene ring gave the product with somewhat higher enantioselectivity (Scheme 1). On the basis of these results, we installed *N*,*N*-diphenylaminomethylene as a tunable achiral auxiliary at the 6-position of 2-phenylcyclohexanone with the expectation that the structural modification in the cyclic ketone would result in efficient enantioface discrimination, leading to higher enantioselectivity (Scheme 1).[9,10] Indeed, a significant improvement in the enantioselectivity was observed in the reaction of modified 2-phenylcyclohexanone **2a** (Table 1, entry 3). We then tuned the structure of the catalyst and found that replacing the butyl groups on the quaternary nitrogen with isobutyl groups was effective in achieving high enantioselectivity (entry 4).[11] Fine-

Scheme 1. 2-Arylcyclohexanone Modified with a *N*,*N*-Diphenylaminomethylene Group



tuning of the catalyst and lowering the reaction temperature to −10 °C led to a slight increase in enantioselectivity, while a longer reaction time was required (entries 5 and 6). It should be noted that even with the optimized catalyst (*S*)-**1d**, the reaction between 2-phenylcyclohexanone and benzyl bromide under similar conditions gave the benzylated product with low enantioselectivity, indicating the importance of the achiral auxiliary for the high asymmetric induction (entry 7).



(*S*)-**1a** (Ar = 3,4,5-F_3-C_6H_2, R = butyl)
(*S*)-**1b** (Ar = 3,5-(3,4,5-F_3-C_6H_2)$_2$-C_6H_3, R = butyl)
(*S*)-**1c** (Ar = 3,5-(3,4,5-F_3-C_6H_2)$_2$-C_6H_3, R = *i*-butyl)
(*S*)-**1d** (Ar = 3,5-(3,5-F_2-C_6H_3)$_2$-C_6H_3, R = *i*-butyl)

With the optimized conditions in hand, we examined the substrate scope, and the results are shown in Table 2. In the presence of 1 mol % (*S*)-**1d**, the reactions of **2a** with various alkyl bromides gave the corresponding products in good yields and enantioselectivities (entries 1−6). Use of a propargyl

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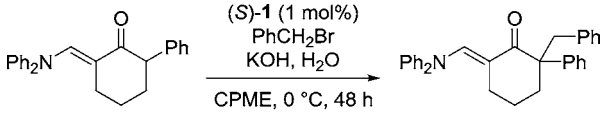
Table 1. Asymmetric Benzylation of Modified 2-Phenylcyclohexanone 2a[a]



2a 3a

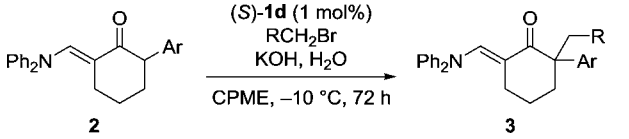
entry	catalyst	temp (°C)	yield (%)[b]	ee (%)[c]
1[d]	(*S*)-**1a**	0	80	−3
2[d]	(*S*)-**1b**	0	99	67
3	(*S*)-**1b**	0	85	67
4	(*S*)-**1c**	0	90	87
5	(*S*)-**1d**	0	89	89
6[e]	(*S*)-**1d**	−10	91 (90)	92
7[f]	(*S*)-**1d**	0	50	9

[a]The reaction of **2a** (0.10 mmol) with benzyl bromide (0.12 mmol) was carried out in the presence of a catalyst (0.001 mmol), KOH (0.50 mmol), and H_2O (0.10 mmol) in cyclopentyl methyl ether (CPME) (1.0 mL) at room temperature for 48 h. [b]Conversion yield based on the **3a**/**2a** ratio as determined by ^{1}H NMR analysis. The value in parentheses is the isolated yield. [c]Determined by HPLC using a chiral column. [d]The reaction was performed in *t*-BuOMe for 24 h. [e]The reaction was performed for 72 h. [f]Under similar conditions, the reaction of 2-phenylcyclohexanone instead of **2a** was carried out for 24 h.

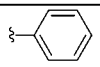
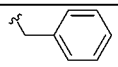
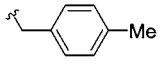
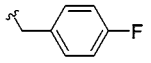
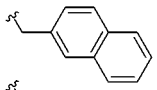
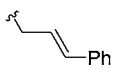
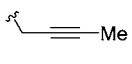
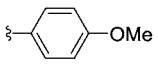
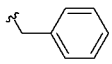
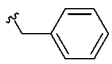
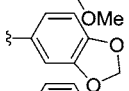
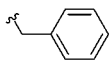
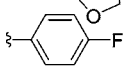
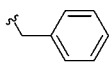
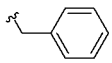
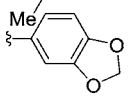
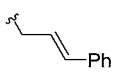
bromide, 1-bromo-2-butyne, resulted in a decrease in both yield and enantioselectivity (entry 7). We then tested the scope of the reaction by varying the substituents on the phenyl ring of the modified 2-arylcyclohexanone (entries 8−12). While para and/or meta substituents did not significantly affect the enantioselectivity (entries 8−11), ortho substitution resulted in no conversion (entry 12). The electronic nature of the aryl group has some effect on the reaction rate and yield. Since an electron-withdrawing group on the phenyl ring significantly slowed the reaction, a large excess of benzyl bromide was required for completion of the reaction (entry 11). Unfortunately, the reaction of **2a** with ethyl iodide as an unactivated alkyl halide did not afford the desired product. When 2-phenylcyclopentanone having the *N*,*N*-diphenylaminomethylene moiety at the 5-position was used instead of **2a**, a significant decrease in enantioselectivity was observed (93% yield, 38% ee).

The introduction of an *N*-methylanilinomethylene group is a well-known method for blocking the α-position of a ketone.[9] This blocking group can be removed by hydrolysis with aqueous HCl followed by a retro-Claisen reaction of the formylated ketone under basic conditions. Accordingly, we applied this procedure to remove the *N*,*N*-diphenylaminomethylene group in **3a** after the asymmetric alkylation. However, a significant amount of the starting material **3a** was recovered after the acidic hydrolysis. Fortunately, treatment of **3a** with 1 M KOH in 1,4-dioxane under reflux afforded 2-benzyl-2-phenylcyclohexanone **4a** directly in quantitative yield without loss of enantiopurity (Scheme 2). On the other hand, ozonolysis of **3a** gave the corresponding enol **5a** as a useful building block that is amenable to further transformation. The absolute configuration of the allylation product **3b** was determined to be *S* by conversion to 2-allyl-2-phenylcyclohexanone (**4b**) and comparison of its optical rotation to the literature value (Scheme 3):[5b] the alkylating agent (allyl bromide) should approach from the *Si* face of the enolate anion generated from modified 2-phenylcyclohexanone **2a** under the influence of the chiral phase-transfer catalyst (*S*)-**1d**, as shown in Figure 1.

Table 2. Asymmetric Alkylation of 2-Arylcyclohexanones 2[a]

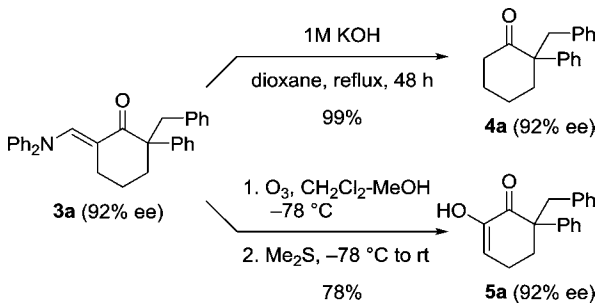


2 3

entry	Ar	RCH_2	yield (%)[b]	ee (%)[c]
1			90	92
2			85	92
3			94	93
4			85	90
5			78	91
6			94	95
7			67	80
8			92	96
9			80	92
10			95	92
11[d]			92	91
12			0	-
13			64	93

[a]The reaction of **2** (0.10 mmol) with alkyl bromide (0.12 mmol) was carried out in the presence of (*S*)-**1d** (0.001 mmol), KOH (0.50 mmol), and H_2O (0.10 mmol) in CPME (1.0 mL) at −10 °C for 72 h. [b]Isolated yields. [c]Determined by HPLC using a chiral column. [d]Using 5 equiv of benzyl bromide.

Scheme 2. Removal of the *N*,*N*-Diphenylaminomethylene Group



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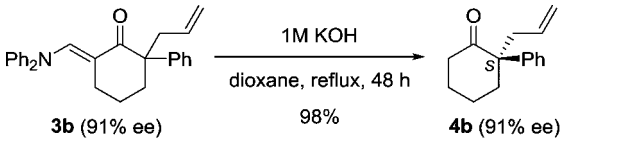
Scheme 3. Determination of the Absolute Configuration



$[\alpha]_D^{27}$ = 234.50 (*c* 1.50, CH_2Cl_2, 91% ee (*S*))
Lit. $[\alpha]_D^{23}$ = –222.31 (*c* 1.23, CH_2Cl_2, 88% ee (*R*))

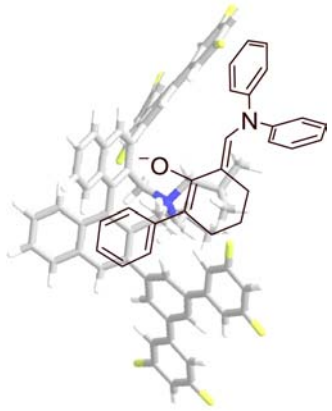
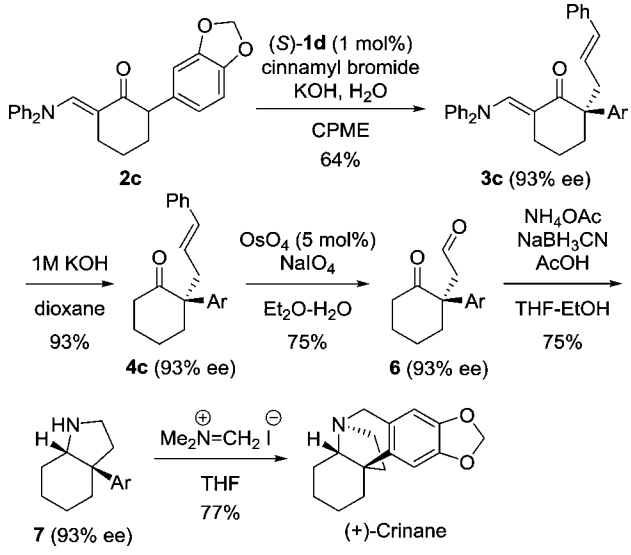


Figure 1. Plausible transition state model.

The further synthetic utility of the present asymmetric alkylation was successfully demonstrated in the synthesis of an Amaryllidaceae alkaloid, crinane,[12] as shown in Scheme 4.

Scheme 4. Asymmetric Synthesis of (+)-Crinane



Optically enriched cyclohexanone **4c** was prepared by the asymmetric alkylation of **2c** with cinnamyl bromide followed by removal of the *N*,*N*-diphenylaminomethylene group. The styryl group of **4c** was converted to a formyl group using OsO_4 and $NaIO_4$. Reductive amination of γ-keto aldehyde **6** afforded octahydroindole **7**, which was treated with Eschenmoser's salt to give (+)-crinane according to the literature procedure.[12b]

In summary, we have realized a highly enantioselective alkylation of 2-arylcyclohexanones by installing an achiral auxiliary, the *N*,*N*-diphenylaminomethylene group, at the 6-position of the cyclohexanones. The auxiliary was readily removed from the alkylation product by simple basic hydrolysis. This methodology certainly expands the synthetic utility of chiral phase-transfer-catalyzed alkylation and provides a practical entry to the construction of chiral quaternary carbon centers in organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(11) Chiral phase-transfer catalysts having other *N*-alkyl groups such as isopropyl, neopentyl, cyclohexylmethyl, and isopentyl showed lower enantioselectivities (less than 75% ee).

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