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Communications

Organocatalytic Enantioselective α-Alkylation of Cyclic Ketones by S_N1-Type Reaction of Alcohols

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The α-alkylation of carbonyl compounds is one of the fundamental C-C bond forming transformations in synthetic organic chemistry.[1] In 2004, List presented the first catalytic asymmetric intramolecular α-alkylation of aldehydes using chiral secondary amines as catalysts.[2] Melchiorre and Cozzi have independently reported S_N1-type α-alkylation of aldehydes with stable carbocations generated in situ from diarylmethanol and sulfonylindole derivatives as alkyl donors to proceed through enamine catalysis.[3] More recently, Luo reported the direct asymmetric intermolecular α-alkylation of ketones using pyrrolidene-derived functionalized ionic liquids.[4] However, a highly enantioselective α-alkylation of ketones through enamine catalysis remains elusive.

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[5] we recently reported the catalytic α-alkylation of active methines with high enantioselectivities promoted by chiral phase transfer catalysts.[6] Herein, we wish to describe the direct enantioselective α-alkylation of cyclohexanone derivatives with bis(4-dimethylaminophenyl)methanol, which can form stabilized carbocation under acidic condition.[7]

To determine suitable reaction conditions for the catalytic enantioselective α-alkylation of cyclic ketones, we initially investigated the reaction system with cyclohexanone (**1a**) with bis(4-dimethylaminophenyl)methanol (**2**) in the presence of 20 mol % of chiral primary amine organocatalyst and TFA (30 mol %) in diethyl ether at room temperature. We first examined the impact of the structure of catalysts **I**-**VII** (Fig. 1) on enantioselectivity (Table 1, entries 1-7). The best results have been obtained with catalyst **V** (Table 1, entry 5). A survey of the reaction media indicated that many

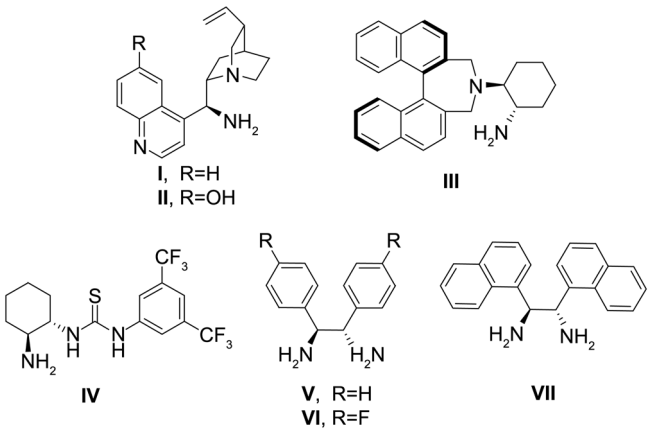
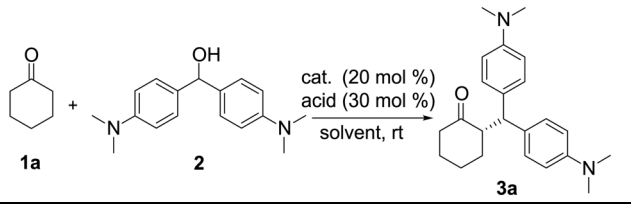


Figure 1. Structure of chiral primary amine catalysts.

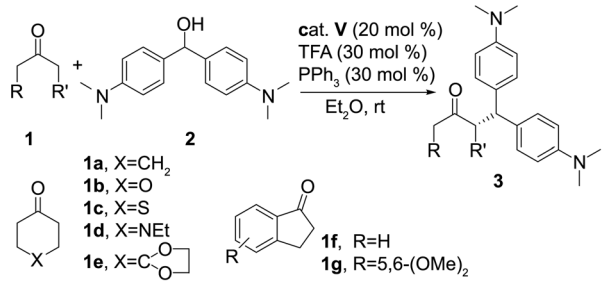
Table 1. Optimazation of the reaction conditions



Entry	Cat.	Solvent	Acid	Time (h)	Yield[a] (%)	ee[b] (%)
1	**I**	Et_2O	TFA	13	91	51
2	**II**	Et_2O	TFA	22	70	61
3	**III**	Et_2O	TFA	22	26	11
4	**IV**	Et_2O	TFA	5 d	60	5
5	**V**	Et_2O	TFA	10	90	81
6	**VI**	Et_2O	TFA	20	90	53
7	**VII**	Et_2O	TFA	20	85	53
8	**V**	THF	TFA	24	84	80
9	**V**	PhMe	TFA	24	90	79
10	**V**	DCM	TFA	24	90	64
11	**V**	MeCN	TFA	24	85	37
12	**V**	MeOH	THF	24	95	43
13	**V**	Et_2O	(+)-CSA	3 d	70	55
14	**V**	Et_2O	(−)-CSA	3 d	50	45
15	**V**	Et_2O	fumaric acid	48	60	43
16	**V**	Et_2O	maleic acid	20	90	75
17	**V**	Et_2O	oxalic acid	4 d	20	10
18	**V**	Et_2O	picric acid	4 d	20	10
19	**V**	Et_2O	DNBS	3 d	80	35
20[c]	**V**	Et_2O	TFA	10	90	90

[a]Isolated yield of **3a**. [b]Enantiomeric excess was determined by HPLC analysis using a Chiralpak AD-H column. [c]PPh_3 (30 mol %) was added as co-additive.

Table 2. Variation of the ketone derivatives



Entry	1	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1a**	15	**3a**, 90	90
2	**1b**	15	**3b**, 89	79
3	**1c**	15	**3c**, 90	67
4	**1d**	24	**3d**, 80	69
5[a]	**1e**	24	**3e**, 95	73
6	**1f**	24	**3f**, 75	71
7	**1g**	24	**3g**, 78	65

[a]Isolated yield. [b]Enantiomeric excess was determined by HPLC analysis using chiral columns (Chiralpak AD-H for **3a**, **3c**, **3f**, IB for **3b**, **3e**, IA for **3d**).

common solvents, such as THF, toluene, dichloromethane, MeCN, and MeOH (Table 1, entries 5 and 8-12), were well tolerated in this α-alkylation reaction with moderate to high enantioselectivities. The best results (90% yield and 81% ee) were achieved when the reaction was conducted in diethyl ether (Table 1, entry 5). We examined our investigations by examining the reactivity and selectivity with organocatalyst **V** in diethyl ether in the presence of different acids, such as TFA, camphorsulfonic acid, fumaric acid, maleic acid, oxalic acid, picric acid, and 2,4-dinitrobenzoic acid as additives (Table 1, entries 5 and 13-20). The best results (90% yield and 90% ee) were achieved when the reaction was conducted in 30 mol % of TFA with 30 mol % of PPh_3 (Table 1, entry 20).

We then explored the possibility of using wide range of cyclic ketones **1** with bis(4-dimethylaminophenyl)methanol (**2**) under the optimized reaction condition.[8] As it can be seen by the results summarized in Table 2, the corresponding α-alkylated ketones **3a-g** were obtained in excellent yields and high enantioselectivities. The cyclic ketones **1a-e** and indanone derivatives **1f-g** reacted with bis(4-dimethylamino-phenyl)methanol (**2**) to give the corresponding α-aminated ketones **3a-g** in 75-95% yields and 65-90 ee (Table 2). The stereochemistry of **3** was determined by comparing chiral HPLC, optical rotation, and ^{1}H NMR data with literature value.[4]

In conclusion, we have developed an efficient catalytic enantioselective α-alkylation of ketones with bis(4-dimethyl-aminophenyl)methanol using (1*S*,2*S*)-1,2-diphenyl-1,2-eth-anediamine. The desired α-alkylated ketones were obtained in high yields and high enantioselectivities (65-90% ee) for various substrates. Further details and application of this asymmetric α-alkylation of ketones with stable carbocations will be presented in due course.

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8. General procedure for the organocatalytic α-alkylation of cyclic ketones **1**: To a stirred solution of bis(4-dimethylaminophenyl)-methanol (**2**, 81.9 mg, 0.3 mmol), catalyst **V** (12.6 mg, 0.06 mmol), triphenyl phosphine (23.4 mg, 0.09 mmol), and TFA (6.6 mL, 0.09 mmol) in diethyl ether (1.2 mL) was added ketones **1** (1.5 mmol) at room temperature. Reaction mixture was stirred for 15-24 h at room temperature, concentrated, and purified by flash column chromatography (EtOAc/hexane: 1/3) to afford the alkylated product **3**.