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Asymmetric S_N1 α-Alkylation of Cyclic Ketones Catalyzed by Functionalized Chiral Ionic Liquid (FCIL) Organocatalysts

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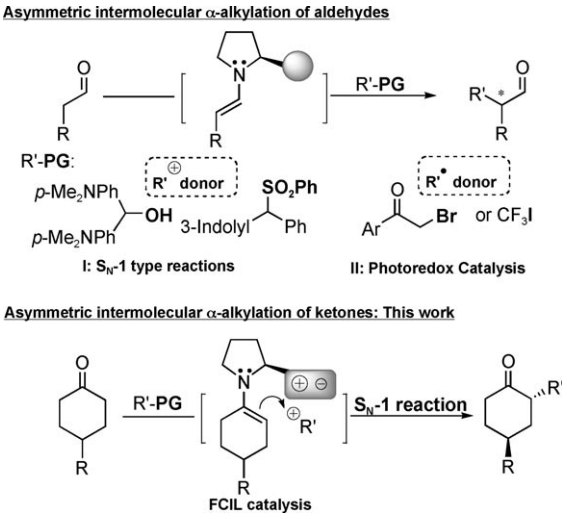
Echoed with the sustainable chemistry concept, the developments of highly efficient and practical asymmetric catalysts have been and continue to be the fore of organic synthesis. Functionalized chiral ionic liquids (FCILs), which combine the green credential of ionic liquids[1] and the catalytic principles of modern asymmetric catalysis, have recently appeared as such a type of asymmetric catalyst. Following the initial work of Howarth[2] and Seddon;[3] the applications of FCILs have moved beyond the use as chiral additives, chiral reagents, or chiral inducing reaction media,[4] and now have reached the stage of asymmetric catalysts.[5] However, the promising potentials of FCILs as asymmetric catalysts still remain largely underdeveloped at present and the current successes have been primarily confined to the reactions like Michael additions and aldol reactions. As such, in our continuing efforts in exploring this type of catalysis,[5d–f,n] we have sought new reaction development by taking advantage of the intrinsic properties of ionic liquids. Herein, we report the first FCIL-catalyzed enantioselective S_N1 type alkylation of cyclic ketones, in which the ionic liquid moieties are found to be critical for both the catalytic activity and stereocontrol.

The catalytic asymmetric direct α-alkylation reaction of carbonyl compounds has long been a daunting challenge in asymmetric catalysis and synthesis. Before the renaissance of organocatalysis, particularly the enamine-based aminocatalysis, asymmetric phase-transfer catalysis was the only successful approach to this end and it was mostly used in the synthesis of α-amino acids through alkylation of glycine derivatives.[6] In 2004, Vignola and List reported the first catalytic intramolecular nucleophilic α-alkylation of aldehydes by means of enamine activation.[7] Later on, several cascade reactions including an intramolecular α-alkylation of aldehydes as the key step were also reported.[8] However, the intermolecular α-alkylation of aldehydes or ketones are still a challenging task due to the depletion of catalytic activity through the *N*-alkylation of the aminocatalysts and various competing bypaths therewith.

The past few years have witnessed notable breakthroughs in the development of asymmetric intermolecular α-alkylations of carbonyl compounds, specifically of aldehydes. Melchiorre and Cozzi have independently reported S_N1 type α-alkylation of aldehydes by enamine catalysis.[9,10] This novel approach was based on alkyl donors endowed with suitable leaving groups (Scheme 1, I), which can generate a stabi-



Scheme 1. Organocatalytic strategies for asymmetric intermolecular alkylation of carbonyl compounds.

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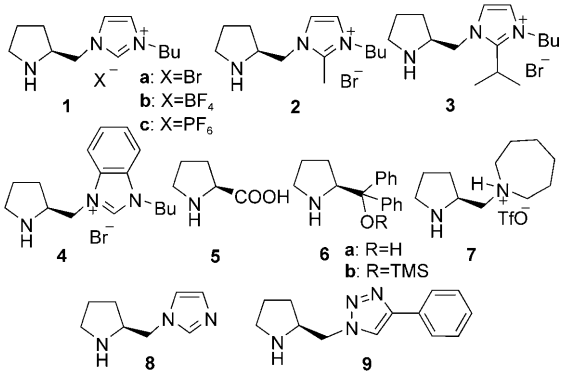
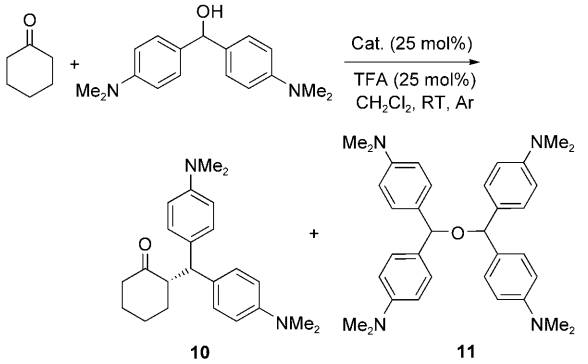
lized carbocation in situ and immediately intercept the enamine intermediate. In another notable advance, MacMillan and co-workers developed an enamine-based photoredox catalysis, wherein the enamine was intercepted with the photogenerated stabilized alkyl radical (Scheme 1, II).[11] Despite these advances, organocatalytic asymmetric intermolecular α-alkylation of ketones has not been achieved to date. Only chiral transition-metal catalysts have been reported to promote asymmetric direct α-alkylations of ketones, but these reactions were limited to allylation or vinylation reactions.[12,13] Our previous work, as well as that of others, have shown that FCILs, such as **1**, are effective enamine catalysts, particularly for the reactions of cyclic ketones.[5] Bearing in mind the highly polar and ionic features of ionic liquids, it is envisaged that FCILs might provide a favorable catalytic sphere for direct α-alkylation of ketones, in which ionic intermediates/transition states, such as carbocations (Scheme 1), are involved. Our preliminary efforts along this line indicate that such a reaction is indeed possible with FCIL catalysis and the first asymmetric S_N1 alkylation of cyclic ketones is realized. Notably, the FCIL catalyst has also enabled unprecedentedly highly stereoselective desymmetrization of *para*-substituted cyclic ketones by asymmetric S_N1 alkylation. These results are presented in this communication.

The direct α-alkylation reaction of cyclohexanone with bis(4-dimethylaminophenyl)methanol, which can form a stabilized carbocation under acidic conditions,[14] was selected as the model reaction. To our delight, our initial try with FCIL **1a** led to a smooth reactions affording the desired α-



alkylated product **10** in 65% yield with 72% *ee* in 48 h together with a minor by-product **11** (Table 1, entry 1). The FCIL catalysts with different ionic liquid moieties were further probed in order to improve both the yield and enantioselectivity. Swapping the bromide ion (**1a**) for BF_4^- (**1b**) and PF_6^- (**1c**) gave solely the desired alkylation product, but the enantioselectivity was seriously eroded in these cases (Table 1, entries 2 and 3). Meanwhile, though the use of FCILs **2** and **3**, which bear more bulkier groups at the imidazolium ring, did not gave results superior to that of FCIL **1a** (Table 1, entries 4 and 5), the catalysis of FCIL **4**

Table 1. Optimization studies.[a]



	Cat.	*t* [h]	Yield of **10** [%][b]	Yield of **11** [%][b]	*ee* [%][c]
1	**1a**	48	65	13	72
2	**1b**	48	64	–	54
3	**1c**	48	80	–	38
4	**2**	48	48	19	69
5	**3**	48	62	8	64
6	**4**	48	51	27	79
7	**5**	12	70	–	16
8	**6a**	20	–	77	–
9	**6b**	20	–	99	–
10	**7**	7	83	–	57
11	**8**	40	72	23	66
12	**9**	12	88	–	66
13[d]	**4**	20	86	–	82
14[e]	**4**	7	80	–	82

[a] Reaction conditions: The reactions were carried out at room temperature on a 0.1 mmol scale using 3 equiv of ketones and 25 mol% catalyst under argon. [b] Isolated as a mixture of **10** and **11**, the yield was calculated based on the ratio of **10**/**11** determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC analysis. [d] Using 37.5% mol% phthalic acid as acid additive. [e] The reaction was conducted in 1,2-dichloroethane using 37.5 mol% phthalic acid as additive.

with a benzoimidazolium cation was found to give much improved enantioselectivity (79% *ee*, Table 1, entry 6). With FCIL **4** as the desired catalyst, the reaction was further optimized by screening different acidic additives and solvents. The use of phthalic acid as an additive in 1,2-dichloroethane was found to give the optimal results (Table 1, entries 13 and 14). Under these conditions, the formation of by-product **11** was completely inhibited and the desired alkylation product was obtained in 80% yield with 82% *ee* in 7 h (Table 1, entry 14).

For comparison, typical aminocatalysts, such as **5–7** and **9**, FCIL precursor catalyst **8**, as well as some primary amine catalysts (see Supporting Information) were also examined in the current reaction. In all these cases, the reactions led to either low activity, mainly by-products or lower *ee* (Table 1, entries 7–12), highlighting the beneficial features of the FCIL catalysis for this reaction.

Under the optimal conditions, the scope of the present reactions was examined with a series of cyclic ketones and alcohols. As illustrated in Table 2, the reaction worked well with cyclohexanones. For example, the reactions of 4-oxa- and 4-thio-cyclohexanone (**D4**, **D5**, Table 2, entries 8 and 9)

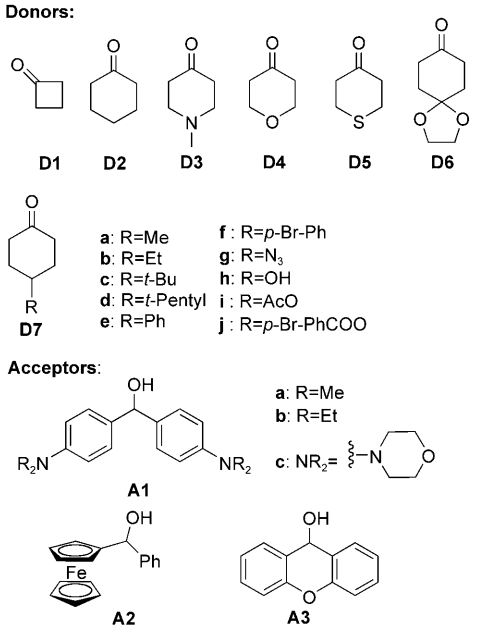
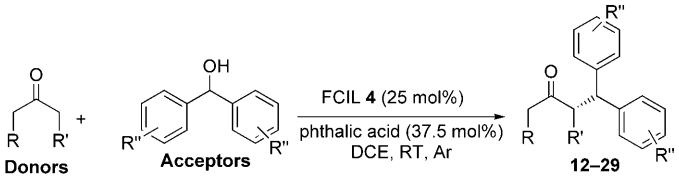


Table 2. Substrate scopes.[a]



	Donor	Acceptor	t [h]	Yield [%][b]	d.r. (*trans/cis*)[c]	*ee* [%][d]
1	**D1**	**A1a**	7	**12**/69	–	44
2	**D2**	**A1a**	7	**10**/80	–	82
3	**D2**	**A1b**	12	**13**/57	–	71
4	**D2**	**A1c**	12	**14**/56	–	68
5[e]	**D2**	**A2**	40	**15**/43	2:1	8 (major) 18 (minor)
6	**D2**	**A3**	12	trace	–	–
7	**D3**	**A1a**	18	**16**/60	–	32
8	**D4**	**A1a**	7	**17**/93	–	80
9	**D5**	**A1a**	18	**18**/82	–	77
10	**D6**	**A1a**	18	**19**/66	–	57
11	**D7a**	**A1a**	12	**20**/94	>99:1	85
12	**D7b**	**A1a**	12	**21**/82	>99:1	80
13	**D7c**	**A1a**	12	**22**/89	>99:1	81
14	**D7d**	**A1a**	12	**23**/90	>99:1	87
15	**D7e**	**A1a**	12	**24**/89	>99:1	82
16	**D7f**	**A1a**	18	**25**/99	>99:1	80
17	**D7g**	**A1a**	12	**26**/99	90:10	85
18	**D7h**	**A1a**	12	**27**/99	>99:1	72
19	**D7i**	**A1a**	18	**28**/98	84:16	77
20	**D7j**	**A1a**	24	**29**/86	87:13	78
21	**D7d**	**A1a**	12	**10**/90	>99:1	83
22	**D7d**	**A1a**	12	**10**/86	>99:1	80
23	**D7d**	**A1a**	20	**10**/74	>99:1	72

[a] Reaction conditions: The reactions were carried out at room temperature on a 0.1 mmol scale using 3 equiv of ketones under argon, 25 mol% catalyst **4** and 37.5 mol% phthalic acid as additive were used. [b] Isolated yield. [c] Determined by ^{1}H NMR or chiral HPLC analysis. [d] Determined by chiral HPLC analysis. [e] 25% TFA was used as acid additive. The absolute configuration of the major product was not determined.

gave the desired products in moderate to excellent yields with high *ee*. 4-Aza-cyclohexanone (**D3**) and 1,4-cyclohexanedione monoketal (**D6**) were also workable substrates producing the desired products with reasonable yields but low enantioselectivity (Table 2, entries 7 and 10). Notably, cyclobutanone (**D1**), among many other cyclic ketones examined, worked well in the present reaction to give the desired product **12** in 69% yield with moderate *ee* (Table 2, entry 1). A brief survey of alcohol acceptors (the carbocation precursors **A**) revealed a reactivity trend in accordance with Mayr's electrophilic scale (E).[14b] The alcohols that form more stabilized carbocations (with more negative E value) performed relatively better with higher yield of the desired product and higher *ee* (e.g., $E=-7.02$ for the cation from **A1a**, $E=-5.53$ for the cation from **A1c**, Table 2, entries 2–4). Following this trend, alcohols that form unstable carbocations (with E values close to 0) such as **A2** ($E=-2.64$) and **A3** ($E=-0.99$)[14d] are not compatible substrates in the current reactions and demonstrate very low reactivity (Table 2, entries 5 and 6). Similar reactivity trend has also been reported in Cozzi's studies.[10a]

In the course of further extending its synthetic applicability, we were delight to find that the reactions worked extremely well with *para*-substituted cyclohexanones, featuring an unprecedented stereoselective desymmetrization process (Table 2, entries 11–20). In most cases, the S_N1 alkylation reactions of *para*-substituted cyclohexanones generally produced one single diastereoisomer (>99:1 d.r.) in excellent yields (up to 99%) and good *ee* (72–87% *ee*), except in the cases of **D7g**, **D7i**, and **D7j**, for which slightly lower diastereoselectivity but good enantioselectivity were still obtained (Table 2, entries 17, 19 and 20).[15]

The FCIL catalyst used in this reaction could be recycled by precipitation with diethyl ether. The recovered catalyst could be used directly in the next run and demonstrated similar activity, diastereoselectivity, and enantioselectivity. Diminishing activity and selectivity were found in the fourth recycle, but good yields and *ee* values still remained (Table 2, entries 21–23).

The major isomer of **29** in the reaction of **D7j** and **A1a** has the (2*S*,4*S*) absolute configuration as determined by X-ray crystallographic analysis of the compound (Figure 1).[16] Other products were therefore determined by analogy. A

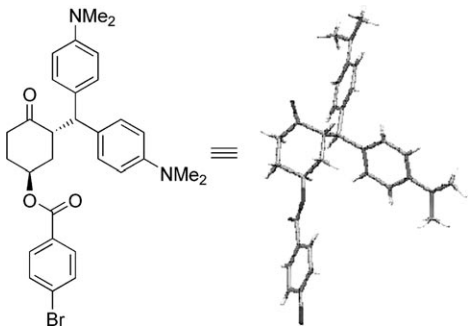
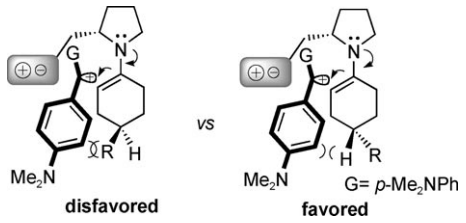


Figure 1. Crystal structure of **29**

plausible transition state was accordingly proposed to account for the observed diastereoselectivity and enantioselectivity (Scheme 2). In this model, the *Si*-face blockage of the



Scheme 2. Proposed transition state.

enamine by the ionic liquid moiety as well as the steric repulsion between the incoming carbocation and the *para*-substitution group are assumed to be the key factors influencing stereoselectivity. Besides the steric effect, the electrostatic interaction might also play an important role in the stereocontrol. The observed inefficiency of non-ionic-liquid-type catalysts (e.g., the FCIL precursor **8** and triazole-type organocatalyst **9**) in the reactions is in line with this hypothesis.

In summary, we have developed the first asymmetric catalytic direct α-alkylation of cyclic ketones catalyzed by functionalized chiral ionic liquids. An unprecedented desymmetric α-alkylation of *para*-substituted cyclohexanones was realized with up to 99% yield, >99:1 diastereoselectivity and up to 87% enantioselectivity. Further applications of FCILs in asymmetric α-alkylation of carbonyl compounds are underway in our laboratory.

Experimental Section

Typical catalytic procedure: Catalyst **4** (8.5 mg, 25 mol%) and phthalic acid (6.3 mg, 37.5 mol%) were dissolved in 1,2-dichloroethane (0.2 mL) in a glass vial. To this solution, bis(4-dimethylaminophenyl)methanol (27 mg, 0.1 mmol) and cyclohexanone (31 μL, 3 equiv) were then added. The reaction mixture was stirred at room temperature under argon for 7 h. The solvent was removed under reduced pressure and the residue was extracted with diethyl ether (5 mL×4). The combined organic layer were concentrated and loaded directly onto a silica gel for purification. The desired product **10** was isolated as a white solid (28 mg, 80% yield): 82% *ee* (by HPLC analysis on a chiralpak AD-H column, $\lambda = 254$ nm, eluent *i*PrOH/*n*-hexane (15:85), flow rate = 0.7 mL min^{-1}; $t_R = 9.48$ min (minor), 10.23 min (major). The recovered catalyst was reused directly in the next run after removal of the residue solvents.

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Keywords: alkylation · asymmetric catalysis · carbocations · chirality · ionic liquids

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[16] CCDC-743753 contains the supplementary crystallographic data for compound **29** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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