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Functionalized Chiral Ionic Liquid Catalyzed Enantioselective Desymmetrizations of Prochiral Ketones via Asymmetric Michael Addition Reaction

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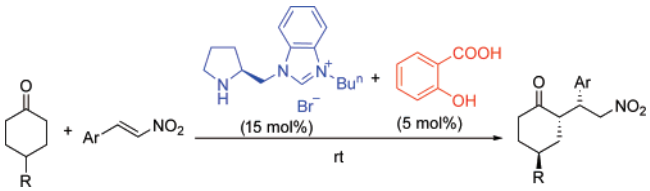

Functionalized chiral ionic liquids were found to be highly effective and reusable organocatalysts for asymmetric Michael additions of 4-substituted cyclohexanones. The desymmetrization reaction afforded the desired Michael adducts bearing three carbon stereocenters with up to 99% ee.

Asymmetric Michael addition to nitroalkenes represents one of the fundamental transformations that have wide applications in organic synthesis.[1] Among the variants of this reaction, the Michael additions of carbonyl compounds to nitroalkenes normally generate versatile bis-functionalized compounds with two consecutive stereocenters. Considerable research efforts have been made toward developing efficient asymmetric catalysts, especially environment-friendly nonmetallic organocatalysts.[2] In this vein, aminocatalysis, especially that of chiral pyrrolidinyl derivatives, has proved to be the most powerful strategy, leading to a range of effective organocatalysts with high activity and excellent diastereoselectivity and enantioselectivity.[3] For example, since the seminal work with proline catalysis by List, Barbas, and Enders,[4] proline derivatives such as aminomethyl pyrrolidine,[5a−d,n] pyrrolidine-pyridine,[5p] and 2,2′-bipyrrolidine,[5e−g] as well as some hydrogen-bonding donor containing chiral amines[5h,i,l,m,q−u] have been shown to serve as useful asymmetric catalysts for Michael addition of ketones or aldehydes.[5] In this context, our group has developed functionalized chiral ionic liquids (FCILs) as reusable organocatalysts for Michael addition of ketones and aldehydes to nitroalkenes.[6] The chiral ionic liquid type of catalyst comprises a chiral pyrrolidine covalently connected with an imidazolium ionic liquid moiety, wherein the former serves as a catalytic site and the latter as both a phase tag and a chiral inducing group.

To further explore the utility of FCILs, prochiral 4-substituted cyclohexanones were next selected as the Michael donors. The Michael reactions of prochiral cyclohexanones leads principally to chiral adducts with the formation of three carbon stereocenters. Despite the numerous numbers of organocatalytic processes for Michael additions of carbonyl compounds to nitroolefines,[2−6] catalytically stereoselective versions involving prochiral ketones are rare. Only Cordova reported a single example of 4-methylcyclohexanone, but with moderate diastereoselectivity.[5k] On the other hand, enantioselective desymmetrizations of *meso* or prochiral compounds using asymmetric catalysis are powerful ways to generate chiral products with multiple stereogenic centers.[7] Although asymmetric transition metal catalysts[7a] and enzymes[7b] have been applied in desymmetrization of *meso* or prochiral ketones, the examples using asymmetric organocatalysts are rare, especially for intermolecular reactions.[8]

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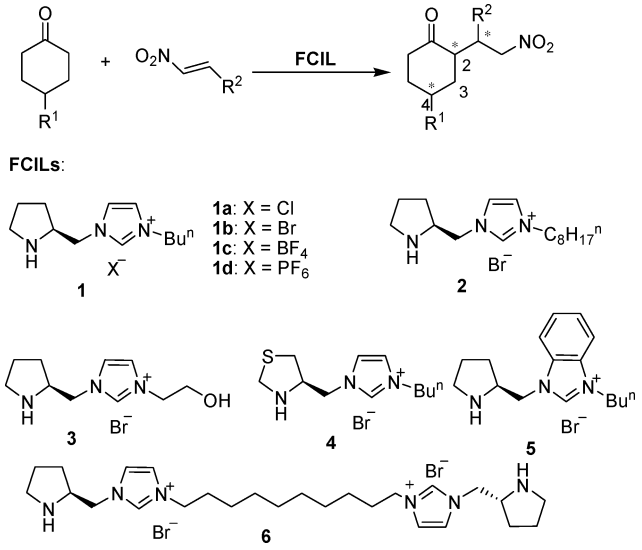
SCHEME 1. Desymmetrization of Prochiral Ketones via Michael Addition to Nitroolefins

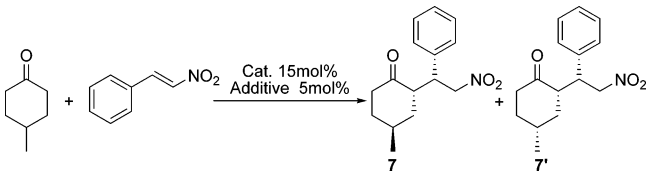


We reported herein FCIL-catalyzed desymmetrizations of prochiral ketones via asymmetric Michael addition reactions. In this reaction, challenges mainly come from the difficulties in simultaneously controlling the dia- and enantio-stereoselectivities of C_2 and the remote C_4. We envisaged that the "designer" properties of chiral ionic liquids[9] might provide promising solutions as both of the cations and anions are easily tuned to affect the stereocontrol. Indeed, one of the FCILs was identified in this work to catalyze the desymmetrization reaction with high dia- and enantio-stereoselectivity.

The FCILs were synthesized following our previous procedures (Scheme 1).[6a,b] An initial test of FCIL **1a** in the model reaction of 4-methyl cyclohexanone and nitrostyrene gave mainly two diastereoisomers that were characterized as **7** and **7′** in a ratio of 4.5:1 (Table 1, entry 1). The major isomer **7** has 95% ee. Other diastereoisomers are detected only in trace amounts.

A series of FCILs were then examined, and the screening results are listed in Table 1. As revealed in Table 1, the structural variations of cations have significant impact on the catalytic outcome. Whereas pyrrolidine-containing FCILs demonstrated good catalytic activity, the thiazolidine-containing FCIL **4** was totally inactive in the reaction (Table 1, entry 7). The side chains of FCIL cation also influenced the catalytic activity, with longer or protic-group-containing chains giving lower yields (Table 1, entries 5 and 6). Unexpectedly, a bis-cation FCIL **6** was inert for catalysis, though it showed good catalytic activity in direct aldol reactions (Table 1, entry 9).[6d] By screening different cations, we reached the optimal FCIL catalyst **5**, which catalyzed

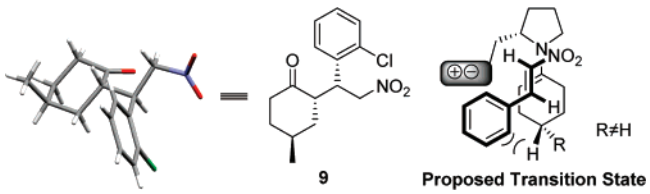
TABLE 1. Screening of Functionalized Chiral Ionic Liquids[a]



entry	catalyst	additive	*T* (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	TFA	12	50	4.5:1	95
2	**1b**	TFA	12	64	3.1:1	93
3	**1c**	TFA	12	99	4.7:1	95
4	**1d**	TFA	12	79	5.1:1	94
5	**2**	TFA	12	63	3.7:1	92
6	**3**	TFA	12	46	4.7:1	94
7	**4**	TFA	12	NR		
8	**5**	TFA	**12**	**90**	**6.1:1**	**97**
9	**6**	TFA	12	trace		
10	**5**	salicylic acid	**10**	**90**	**6.2:1**	**97**
11	**5**	PhCOOH	10	68	3.6:1	96
12	**5**	AcOH	10	64	7.6:1	97
13	**5**	$ClCH_2COOH$	10	86	5.7:1	97
14	**5**	TfOH	10	trace		

[a] 0.25 mmol of nitrostyrene, 2.5 mmol 4-methyl cyclohexanone without the use of solvent. [b] Isolated yields. [c] Ratio of **7**:**7′**, determined by ^{1}H NMR of the crude products. [d] Determined by chiral HPLC.

SCHEME 2. X-ray Crystal Structure of 9 (left) and the Proposed Transition State (right)



the model reaction smoothly to afford the desired Michael adduct with 90% yield, 6.1:1 dr and 97% ee (Table 1, entry 8). As for the anions, the swap of halide anions to BF_4^- and PF_6^- leads to comparable results with enhanced catalytic activity (Table 1, entries 1−4).

With the identified FCIL **5**, the reaction was further optimized by screening different acidic additives. Among a series of Brønsted acids (selected results are listed in Table 1, entries 10−14), salicylic acid was found to give the optimal results in terms of both activity and stereoselectivity. In this case, the reaction went to completion in 10 h, affording 90% yield, 6.2:1 dr, and 97% ee (Table 1, entry 10). Acidic additives have been frequently shown to enhance the catalytic activity in Michael additions reactions via assisting the enamine catalytic cycle;[5b,c,i,m,p,6a] however, the detailed mechanism remains to be disclosed.

The major isomer in the reaction of 4-methyl cyclohexanone and *o*-chloronitrostyrene has the (2′*R*,2*S*,4*S*) absolute configuration as determined by X-ray crystallographic analysis of product **9** (Scheme 2, left).[10] Other products were therefore determined by analogy. A plausible transition state was then proposed to account for the observed stereochemistry (Scheme

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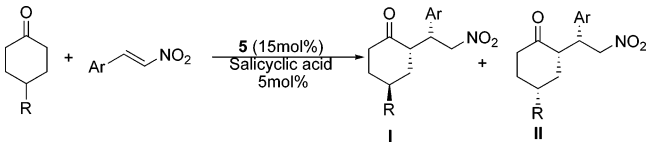
(10) Crystal data for **9**: $C_{15}H_{18}ClNO_3 \cdot H_2O$, colorless block, $M_r = 311.75$ (the hydrogen atoms on the water can not be determined), crystal size 0.50 × 0.15 × 0.08 mm^3, hexagonal, space group *P*6(5), $a = 17.250(2)$ Å, $b = 17.250(2)$ Å, $c = 9.5313(19)$ Å, $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 120.00°$, $V = 2456.3(7)$ Å^3, $Z = 6$, $\rho_{calc} = 1.265$ g cm^{-3}, $T = 293(2)$ K. A total of 3671 reflections and 1117 parameters were used for the full matrix, least-squares refinement on *F*2. $R_1 = 0.0349$ [$I > 2\sigma(I)$], $R_1 = 0.1400$ (all data), $wR_2 = 0.0569$ [$I > 2\sigma(I)$], $wR_2 = 0.0719$ (all data).

TABLE 2. Substrates Scope[a]



entry	R	Ar	*T* (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	Me	Ph	10	89 (**7**)	6.2:1	97
2	Me	4-ClPh	10	89 (**8**)	6.1:1	99
3	Me	2-ClPh	10	99 (**9**)	>10:1	97
4	Me	4-MePh	16	89 (**10**)	7.0:1	98
5	Me	4-PhPh	12	92 (**11**)	6.0:1	94
6	Me	4-MeOPh	21	94 (**12**)	7.6:1	97
7	Me	4-NO_2Ph	3	88 (**13**)	5.0:1	98
8	Me	2-NO_2Ph	3	93 (**14**)	4.4:1	97
9[e]	Me	2-NO_2Ph	4	99 (**14**)	4.8:1	97
10[e]	Me	2-NO_2Ph	12	94 (**14**)	5.1:1	93
11[e]	Me	2-NO_2Ph	24	78 (**14**)	6.3:1	96
12	Me	3-NO_2Ph	12	80 (**15**)	4.0:1	98
13	Me	1-Naph	24	99 (**16**)	8.1:1	97
14	Me	Piperal	24	95 (**17**)	6.8:1	96
15	Et	Ph	10	81 (**18**)	6.5:1	97
16	*t*-Bu	Ph	12	88 (**19**)	7.9:1	98
17	Ph	Ph	10	63 (**20**)	12:1	96
18	N_3	Ph	20	61 (**21**)	>5:1	93
19	SAc	Ph	24	65 (**22**)	>5:1	93
20	OH	Ph	24	trace		
21	Br	Ph	24	trace		
22	CN	Ph	24	NR		

[a] Entries 1−15: 0.25 mmol of nitrostyrene and 10 equiv of cyclohexanone without the use of solvent. Entries 16−22: 0.25 mmol of nitrostyrene and 0.5 mmol of cyclohexanone in 100 μL of dioxane. [b] Isolated yields. [c] Ratio of **I**:**II**, determined by ^{1}H NMR of the crude products. [d] Determined by chiral HPLC. [e] Second−fourth reuse of the catalyst used in entry 8.

2, right). In this model, the ionic-liquid moiety would effectively shield one face of the enamine. At this stage, factors affecting remote C_4 stereochemistry remain unclear; the orientation of the C_4-substitute relative to the incoming nitrostyrene as well as the ionic liquid would play an important role.

The scope of the desymmetrization was next explored under the optimized conditions. A range of nitrostyrenes bearing either electron-withdrawing or electron-donating substitutes were applicable in the reaction with 4-methylcyclohexanone (Table 2, entries 1−14). In all of these cases, the major product was isolated with excellent enantioselectivities (93−99% ee). The diastereoselectivities (i.e., I:II) are in the range of 4.0:1 to 10:1. Other 4-substituted cyclohexanones have also been examined.

(11) Other solvents have also been tried in the reaction of 4-*tert*-butyl cyclohexanone and nitrostyrene: $CHCl_3$, 69% yield, 4.2:1 dr, 97% ee; CH_3OH, 86% yield, 3.5:1 dr, 95% ee; CH_2Cl_2, 69% yield, 3:1 dr, 97% ee; CH_3CN, 86% yield, 3.8:1 dr, 98% ee; THF, 77% yield, 5.3:1 dr, 97% ee. Dioxane was selected as the solvent of choice to assist the reactions of solid cyclohexanones.[11] Substitutes on C_4 demonstrate dramatic effect on the reactivity. 4-Hydroxyl, 4-bromo, and 4-cyano-cyclohexanones were shown to be totally inert substrates in the reactions (Table 2, entries 20−22). In contrast, the reactions work smoothly with 4-ethyl, 4-*tert*-butyl, 4-phenyl, 4-azido, and 4-acetyl mercapto-cyclohexanones, affording the desired Michael adducts with excellent enantioselectivities (93−98% ee, entries 15−19).

The recyclability and reusability of FCIL **5** was briefly tested. After reaction, the catalyst could be easily recycled by precipitation with ethyl ether and reused directly in the next run. FCIL **5** could be recycled and reused for four times, maintaining similar stereoselectivities (Table 2, entries 8−11). Loss of activity was observed in the third and fourth reuse.

In conclusion, we have developed functionalized chiral ionic liquid catalyzed asymmetric Michael reactions of 4-substituted cyclohexanones. To the best of our knowledge, this represents the first successful example of asymmetric intermolecular desymmetrizations via organocatalytic Michael additions. FCIL **5** was identified as the optimal catalyst, with high activities (61−99% yield, good diastereoselectivities (4.0:1->10:1 dr) and excellent enantioselectivities (93−99% ee). FCIL **5** accommodates a range of 4-substituted cyclohexanones and nitrostyrenes and could be recycled and reused for four times.

Experimental Section

General Procedure for Michael Reaction. Nitrostyrene (37 mg, 0.25 mmol), FCIL **5** (12.7 mg, 15 mol %), and salicylic acid (1.7 mg, 5 mol %) were mixed with *p*-methyl cyclohexanone (0.3 mL, 2.5 mmol) at room temperature. The homogeneous reaction mixture was stirred at room temperature for 10 h. The reaction mixture was diluted with ether to precipitate the catalyst. The organic layer was separated and loaded onto silica gel column to afford the Michael product (58 mg, 90%) as a yellow oil: dr = 6.2:1, 97% ee (by HPLC on a chiralpak OD-H column, 254 nm, ^{i}PrOH/hexane = 10:90, 0.5 mL·min^{-1}; t_R = 27.2 min (minor), 30.4 min (major)). The catalyst was used directly for the next run after removing the residue solvents.

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Supporting Information Available: Experimental details and characterizations of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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