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Asymmetric Michael addition reactions of aldehydes with nitrostyrenes catalyzed by functionalized chiral ionic liquids

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ABSTRACT

A new class of pyrrolidine-based functionalized chiral ionic liquids (FCILs) has been developed and shown to be effective and reusable catalysts for the asymmetric Michael addition reactions. For the Michael addition reaction involving various aldehydes and nitrostyrenes, FCIL **6**, in combination with trifluoroacetic acid as an additive, was found to be a very effective catalyst, compared to FCIL **3**, which varied slightly in structure. Excellent yields (up to 99%), good enantioselectivities (up to 85% ee), and high diastereoselectivities (*syn*/*anti* ratio up to 97:3) were obtained for these reactions. The FCIL catalysts were easily recycled and reused for at least five times without significantly losing their ability to affect the outcome of the asymmetric reactions.

1. Introduction

There has been considerable interest in the use of room temperature ionic liquids (RTILs) as a new type of media for organic synthesis,[1] electrochemistry,[2] material science,[3] and green chemistry[4] due to their unique properties. Most ionic liquids are thermally stable over a wide temperature range, lack measurable vapor pressure, incombustibility, and exhibit high ionic conductivity.[5] One of the attractive properties of ionic liquids is their 'tunable' feature. Ionic liquids can be modified by varying the structure of either the cation or the anion in order to make them easier to separate from organic phases, as well as aqueous media. Recently, such ionic liquids have been used as soluble supports for reagents,[6] catalysts,[7] and for the synthesis of small molecules[8] and bio-oligomers.[9] Ionic liquids that contain tethered specialized groups are known as functionalized ionic liquids (FILs), and they have been used successfully to catalyze various organic reactions;[7] in addition, they are also recyclable. Recently, chiral ionic liquids that are also FILs have been the focus of attention, especially their effect on asymmetric reactions.[10,11] To date, there are only a few of such functionalized chiral ionic liquids (FCILs) that have been designed, synthesized, and used effectively as catalysts for asymmetric reactions; these include hydrogenation reactions,[11a–c] the Michael additons,[11d–f] aldol reactions,[11g,h] and borane reductions.[11i] This 'designer' feature of ionic liquids opens up new areas of research for their design and use for asymmetric reaction.

Michael addition reactions of nitrostyrenes with aldehydes and ketones have emerged as one of the most important and efficient methods for the preparation of γ-nitrocarbonyl compounds. These compounds are versatile synthetic building blocks since the nitro and carbonyl groups can be easily transformed into other useful functional groups.[12] In recent years, research into finding simple organocatalysts for asymmetric Michael addition reactions that do not contain metals has intensified.[13] Proline and its derivatives have proven to be a very promising group of organocatalysts for various reactions,[14,15] and pyrrolidine catalysts have been used successfully for direct asymmetric Michael addition reactions.[15] A major drawback in the use of these catalysts is that they are typically used in substantial quantity, and their efficient recovery and reuse have become a major concern. Therefore, there is an urgent need to develop a new group of catalysts that are easily recyclable and possess enhanced catalytic abilities. FCILs[11] that contain specific functionalities should be ideal compounds to serve as effective recyclable catalysts.

In our preliminary communication,[11e] we reported that FCIL **3** served as a recyclable catalyst for Michael addition reactions of β-nitrostyrenes and aldehydes with good enantioselectivities (up to 82%) and high diastereoselectivities (*syn*/*anti* ratio up to 97:3) via an enamine intermediate. Based on the mechanism proposed, the acidic N–H of the FCIL **3** is believed to stabilize the transition state via a hydrogen bond. Therefore, a new FCIL that is more acidic should be a more efficient catalyst for the Michael reaction. Thus, we have developed a new FCIL, in which the electron-withdrawing group, the imidazolium cation, is separated from the sulfonyl group by a methylene unit. FCIL **6**, which contains a more acidic N–H as well as more steric bulk closer to the catalytic site, should exhibit the enhanced catalytic activity and selectivity for the Michael

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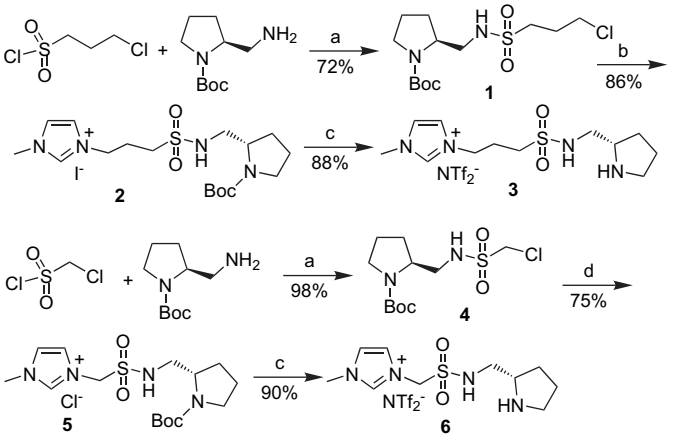
reaction. Herein, we report the results of the effect of our newly designed catalyst, FCIL **6**, on the Michael addition reaction, compared to that of FCIL **3**.

2. Results and discussion

2.1. Synthesis of the pyrrolidine-based FCILs 3 and 6

The pyrrolidine-based FCILs **3** and **6** were synthesized using the 'chiral pool' strategy from commercially available starting material (*S*)-2-amino-1-*N*-Boc-pyrrolidine and sulfonyl chloride (Scheme 1). The reaction of 3-chloropropanesulfonyl chloride with (*S*)-2-amino-1-*N*-Boc-pyrrolidine provided **1**, which was converted to imidazolium iodide **2** in 86% overall yield via two steps involving iodination with NaI and alkylation of the corresponding pyrrolidine sulfonamide with 1-methylimidazole in CH_3CN. The final chiral ionic liquid **3** was obtained by deprotecting to Boc group followed by anion exchange with NTf_2 in 88% overall yield. Using a method analogous to that for the synthesis of FCIL **3**, chiral ionic liquid **6** was obtained in 66% overall yield from (*S*)-2-amino-1-*N*-Boc-pyrrolidine and chloromethanesulfonyl chloride (Scheme 1). These two FCILs are viscous liquids at room temperature. FCIL **3** was found to be very soluble in common solvents, such as CH_2Cl_2, $CHCl_3$, EtOAc, alcohol, DMF, and DMSO, but was immiscible in Et_2O and hexane. FCIL **6** was only soluble in more polar solvents, such as alcohol, DMF, and DMSO, and was immiscible in CH_2Cl_2, $CHCl_3$, EtOAc, Et_2O, and Hexane.



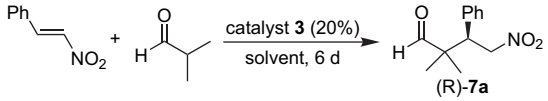
Reaction conditions: (a) Et_3N, CH_2Cl_2; (b) (1) NaI, acetone; (2) 1-methylimidazole, CH_3CN; (c) (1) CF_3COOH, CH_2Cl_2; (2) $LiNTf_2$, H_2O; (d) 1-methylimidazole, neat.

Scheme 1. Synthesis of pyrrolidine-based chiral ionic liquids.

2.2. Optimization of the reaction conditions

Once synthesized, FCILs **3** and **6** were tested as catalysts utilizing the Michael reaction of isobutyraldehyde and *trans*-β-nitrostyrene in various solvents, and the results are shown in Tables 1 and 2. Using FCIL **3** as catalyst, the reaction proceeds smoothly to give the desired Michael adduct **7a** in good yields (62–80%) and enantioselectivities (66–67%) in polar solvents, such as MeOH and *i*-PrOH (Table 1, entries 1 and 3), but the addition of 5 mol % TFA resulted in very poor yields (entry 2). This observation indicates that the acidity plays a role in catalytic efficiency. Using CH_3CN as the solvent also resulted in low yield, but similar enantioselectivity as that obtained in MeOH (entry 4). Higher enantioselectivities (74–78%) were observed in a solvent-free medium or in THF and CH_2Cl_2 as solvents, but the yields were poor (entries 5–7). The addition of

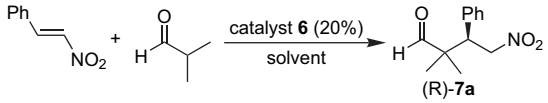
Table 1
Optimization of the reaction conditions



Entry	Solvent	Additive	*T*	Yield[a] (%)	ee[b] (%)
1	MeOH	—	rt	80	67
2	MeOH	5% TFA	rt	<5	[c]
3	*i*-PrOH	—	rt	62	66
4	CH_3CN	—	rt	22	68
5	Neat	—	rt	22	74
6	THF	—	rt	17	75
7	DCM	—	rt	34	77
8	THF	5% TsOH	rt	<10	[c]
9	DCM	5% TsOH	rt	<10	[c]
10	EtOAc	—	rt	<5	[c]
11	Et_2O	—	rt	52	78
12	$CHCl_3$	—	rt	43	76
13[d]	Et_2O	—	rt	20	77
14	**Et_2O**	—	**4 °C**	**58**	**82**

[a] Yield of isolated product.
[b] Determined by chiral HPLC analysis (Chiralpak AS-H).
[c] Not determined.
[d] The reaction was carried for 7 d using 10 mol % of catalyst **3**.

Table 2
Optimization of the reaction conditions for catalyst **6**



Entry	Solvent	Additive	*T*	*t* (d)	Yield[a] (%)	ee[b] (%)
1	CH_3CN	—	rt	6	<5	[c]
2	MeOH	—	rt	6	86	79
3	*i*-PrOH	—	rt	6	84	79
4	DCM/MeOH	—	rt	6	80	81
5	**MeOH**	**5% TFA**	**rt**	**3**	**90**	**84**
6	MeOH	5% TFA	4 °C	6	<10	[c]
7	MeOH	10% TFA	rt	6	81	79
8	MeOH	5% AcOH	rt	3	80	77

[a] Yield of isolated product.
[b] Determined by chiral HPLC analysis (Chiralpak AS-H).
[c] Not determined.

catalytic amounts of an organic acid or using ethyl acetate as solvent does not result in enhanced yields (entries 8–10). However, when the less polar solvents, such as Et_2O or $CHCl_3$, are used in conjunction with IL **3**, the Michael adduct was afforded in moderate yields (43–52%) and good enantioselectivities (76–78%) (entries 11 and 12). When the loading of catalyst **3** was minimized to 10 mol %, the reaction only gave 20% yield (entry 13). Finally, optimal results were obtained at a lower temperature (4 °C) with 82% ee and 58% yield using Et_2O as solvent (entry 14). The absolute configuration of **7a** was determined to be *R*, by comparing the specific rotation of **7a** with that reported elsewhere.[15b]

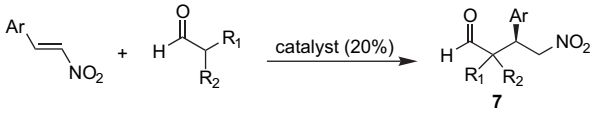
In the presence of 20 mol % FCIL **6** as catalyst, the reaction of isobutyraldehyde with *trans*-β-nitrostyrene was examined under different conditions. As can be seen from the results shown in Table 2, when using CH_3CN as solvent, only a trace amount of the desired adduct **7a** was observed (entry 1); on the other hand, in the more polar solvents MeOH and *i*-PrOH, FCIL **6** promoted the addition with a good enantioselectivity of 79% and good yields of 84–86% (entries 2 and 3). Noteworthy, catalyst **6** exhibited superior enantiocontrol, compared to catalyst **3** in MeOH and *i*-PrOH (Table 1, entries 1 and 3 vs Table 2, entries 2 and 3). The introduction of the electron-withdrawing imidazolium cation in close proximity to the NH in catalyst **6** increases the strength of hydrogen bond

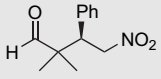
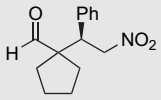
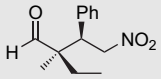
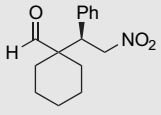
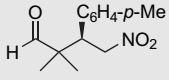
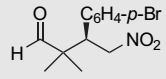
interaction in the transition state, which results in enhanced stereochemical control. A solvent mixture of CH_2Cl_2/MeOH resulted in a slightly enhanced enantioselectivity of 81% (Table 2, entry 4). Interestingly, the addition of a catalytic amount of the organic acid, TFA, dramatically increased the reaction rate, along with an improvement in the enantioselectivity of 84% with MeOH as the solvent (Table 2, entry 5). This observation indicates that acidic additives in the reaction accelerate the formation of the enamine intermediate and promote the catalytic cycle. Interestingly, catalyst **3**, which is similar to catalyst **6**, in combination with TFA as acidic additive provided poorer yield, compared to that obtained for catalyst **6** (Table 2, entry 5 vs Table 1, entry 2). It was also observed that lowering the reaction temperature to 4 °C from room temperature, only a trace amount of adduct **7a** resulted (Table 2, entry 6). Increasing the amount of TFA or replacing to organic acid TFA with AcOH provided no further improvement in the enantioselectivity (Table 2, entries 7 and 8).

2.3. Study of the scope of substrates

Based on the results summarized in Tables 1 and 2, the reaction conditions of entry 14 (Table 1) for catalyst **3** and entry 5 (Table 2) for catalyst **6** were chosen to study the scope of the Michael reactions using a series of aldehydes and nitrostyrenes, and the results are summarized in Tables 3 and 4. The scope of the reaction included a variety of α,α-disubstituted aldehyde donors and nitrostyrene acceptors, and as shown in Table 3, all α,α-disubstituted aldehydes, except cyclohexanecarboxaldehyde, reacted efficiently with nitrostyrenes of variable electronic characteristics in the presence of catalyst **6** with moderate to high yields (33–90%) and high enantioselectivities (up to 85%). Catalyst **3** however, was found to exhibit low reactivity for the α,α-disubstituted aldehydes and nitrostyrene acceptors except for the reaction of isobutyraldehyde and *trans*-β-nitrostyrene (entry 1). From the results in Table 3, catalyst **6** exhibits greater reactivity and selectivity, compared to catalyst **3** for the Michael reaction of α,α-disubstituted aldehydes and nitrostyrenes.

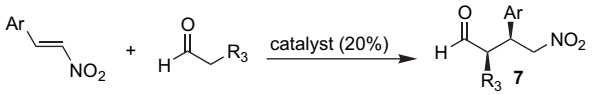
Table 3
Michael reactions of α,α-disubstituted aldehydes to *trans*-nitrostyrenes catalyzed by **3** and **6**

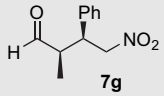
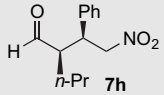
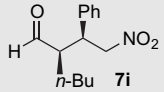
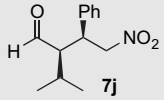
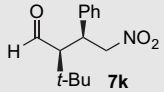
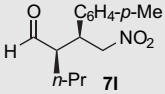
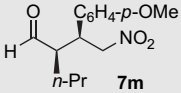
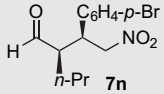
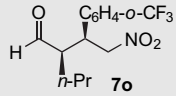


Entry	Product	Catalyst[a]	*t* (d)	Yield[b] (%)	ee[c] (%)	dr[d] (*syn*/*anti*)
1		**3**	6	58	82	—
2		**6**	3	90	84	—
	7a					
3		**3**	6	<10	[e]	—
4		**6**	6	82	85	—
	7b					
5		**3**	6	<10	[e]	—
6		**6**	6	54	63 (*syn*); 71 (*anti*)	56:44
	7c					
7		**3**	6	<10	[e]	—
8		**6**	6	<10	[e]	—
	7d					
9		**3**	6	<10	[e]	—
10		**6**	6	43 (89)[f]	80	—
	7e					
11		**3**	6	<10	[e]	—
12		**6**	6	33 (85)[f]	83	—
	7f					

[a] Reaction conditions: catalyst **3** was carried out in Et_2O at 4 °C, **6** was carried out in MeOH at room temperature with 5% TFA.
[b] Yield of isolated product.
[c] The ee values were determined by HPLC analysis on a chiral column.
[d] Determined by ^1H NMR spectroscopy (400 MHz).
[e] Not determined.
[f] Yield based on recovered starting material.

Table 4
Michael reactions of α-monosubstituted aldehydes to *trans*-nitrostyrenes catalyzed by **3** and **6**

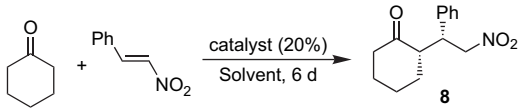


Entry	Product	Catalyst[a]	*t* (d)	Yield[b] (%)	ee[c] (%)	dr[d] (*syn*/*anti*)
1		**3**	6	70	54	91:9
2		**6**	2	99	45	94:6
	7g					
3		**3**	6	49 (87)[f]	64	89:11
4		**6**	2	99	45	93:7
	n-Pr **7h**					
5		**3**	6	64	68	97:3
6		**6**	2	99	46	78:22
	n-Bu **7i**					
7		**3**	6	53	66	96:4
8		**6**	2	99	33	91:9
	7j					
9		**3**	6	<5	[e]	[e]
10		**6**	6	<5	[e]	[e]
	t-Bu **7k**					
11		**3**	6	38 (90)[f]	68	96:4
12		**6**	2	98	44	93:7
	n-Pr **7l**					
13		**3**	6	29 (85)[f]	67	92:8
14		**6**	2	91	44	92:8
	n-Pr **7m**					
15		**3**	6	<5	[e]	[e]
16		**6**	2	91	41	92:8
	n-Pr **7n**					
17		**3**	6	<5	[e]	[e]
18		**6**	2	98	41	93:7
	n-Pr **7o**					

[a] Reaction conditions: catalyst **3** was carried out in Et_2O at 4 °C, **6** was carried out in MeOH at room temperature with 5% TFA.
[b] Yield of isolated product.
[c] The ee values were determined by HPLC analysis on a chiral column.
[d] Determined by ^1H NMR spectroscopy (400 MHz).
[e] Not determined.
[f] Yield based on recovered starting material.

Based on these results, we examined the Michael reactions, in which a variety of α-monosubstituted aldehydes and nitrostyrenes were used in conjunction with FCIL **3** and FCIL **6**/TFA catalysts, respectively (Table 4). The Michael reactions involving aldehydes with *trans*-β-nitrostyrene in the presence of 20 mol % of catalyst **3** in Et_2O at 4 °C gave the corresponding Michael adducts **7g–j** in moderate yields (49–70%), good enantioselectivities (54–68% ee), and high diastereoselectivities (*syn*/*anti* ratio up to 97:3).[16] However, in the presence of catalyst **6** with 5 mol % of TFA in MeOH, these reactions gave Michael adducts **7g–j** in nearly quantitative yields, but the enantioselectivities are relatively low (entries 1–8). For the reaction involving the branched aldehyde, 3,3-dimethylbutyraldehyde, only a trace amount of the desired adduct **7k** resulted when both catalysts **3** and **6** (entries 9 and 10), respectively, are used. The reaction of substituted nitrostyrenes and linear aldehyde *n*-pentanal was studied. It was observed that reactions involving nitrostyrenes bearing electron-donating substituents Me and MeO groups with the catalyst **3** gave the desired adducts **7l**,**m** with moderate yields (29–38%), good enantioselectivities (67–68%), and high diastereoselectivities (*syn*/*anti* ratio up to 96:4) (entries 11 and 13); whereas, reactions involving nitrostyrenes bearing electron-withdrawing substituents Br and CF_3 groups with the catalyst **3** only produced a trace amount of adducts **7l**,**m** (entries 15 and 17). On the other hand, when catalyst **6** was used for the reactions of nitrostyrenes, bearing both electron-donating and electron-withdrawing substituents, excellent yields (91–98%), moderate enantioselectivities (41–44%), and high stereoselectivities (*syn*/*anti* ratio up to 93:7) resulted (entries 12, 14, 16, and 18). From the results depicted in Table 4, it can be concluded that FCIL **6** results in higher reactivity and in a broader spectrum of substrates than FCIL **3** in the catalysis of Michael reaction of α-monosubstituted aldehydes and nitrostyrenes, even though lower enantioselectivities result with FCIL **6**.

The asymmetric addition of cyclohexanone to *trans*-β-nitrostyrene using **3** and **6** as catalyst, respectively, was also investigated and the results are shown in Scheme 2. It was observed that cyclohexanone gave the desired product **8** in moderate yields (38–40%), high enantioselectivities (88–90%), and high diastereoselectivities (*syn*/*anti* up to 95:5). The absolute configuration of **8** was determined to be 2*S*,3*R* by comparison with the optical rotation of that reported elsewhere.[15k] In this case, catalysts **3** and **6** showed comparable reactivity and selectivity.



Catalyst (additive)	solvent	yield(%)	ee (%)	dr (*syn*/*anti*)
FCIL **3**	CH_3CN	38 (88)[a]	88	95/5
FCIL **6** (TFA)	MeOH	40 (91)[a]	90	94/6

[a] Yield based on recovered starting material.

Scheme 2. The Michael addition of cyclohexanone to *trans*-β-nitrostyrene catalyzed by **3** and **6**.

2.4. Recyclability of the FCIL catalysts

The reaction of *trans*-β-nitrostyrene and isobutyraldehyde under standard reaction conditions was chosen as the model to examine the recyclability of catalysts FCILs **3** and **6**. After the reaction was completed, the reaction mixture was concentrated and the residue extracted twice with ether. Removal of the solvent and purification by chromatography column gave the Michael adduct **7a**. Since catalysts **3** and **6** were insoluble in ether, they could be easily isolated. Each catalyst was dried and reused for the next run of the reaction. As shown in Table 5, catalysts **3** and **6** could be recycled and reused for at least five times without significant loss of activity.

Table 5
Recycling studies of FCILs **3** and **6** catalyzed Michael addition reaction between *trans*-β-nitrostyrene and isobutyraldehyde under standard reaction conditions

Run	*t* (d)	Catalyst	Yield (%)	ee (%)
1	6	**3**	58	82
2	6	**3**	57	81
3	6	**3**	55	82
4	6	**3**	50	80
5	7	**3**	45	77
1	3	**6**	90	84
2	3	**6**	87	82
3	3	**6**	85	83
4	3	**6**	83	81
5	4	**6**	80	78

2.5. Mechanism of the reactions

Based on the results summarized in Tables 1–4, a possible mechanism of catalysts **3** and **6** catalyzed Michael reaction of aldehydes with nitrostyrene should be similar to aldol reactions catalyzed by L-proline in which the enamine intermediate is formed.[17,13a,15k] As shown in Figure 1, it is obvious that the N–H acidic hydrogen plays an important role in the reaction by forming hydrogen bonds to the nitrostyrene substrate in a manner that the C–C bond formation would take place by the preferential enamine addition to the less hindered *Si*-face of the nitrostyrene generating 2*R*,3*S* configuration of products (Fig. 1, mode **A**). For the cyclohexanone substrate, we speculate that the ketone-derived enamine attacked the nitrostyrene from the less hindered *Re*-face to afford the 2*S*,3*R* configuration of product due to the steric hindrance induced by the ketone side chain (Fig. 1, mode **B**). In addition, from FCILs **3** and **6**, being bifunctional catalysts, it is expected that they should stabilize the transition state, possibly resulting in increased selectivity for the reaction.

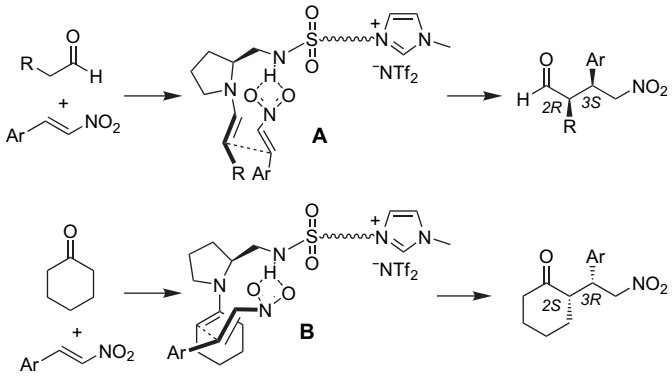


Figure 1. Mechanism for the Michael addition using catalysts **3** and **6**.

3. Conclusion

A new class of recyclable pyrrolidine-based functionalized chiral ionic liquids (FCILs) has been developed for the asymmetric Michael addition reactions. These catalysts result in high yields (up to 99%), good enantioselectivities (up to 85%), and high diastereoselectivities (*syn*/*anti* ratio up to 97:3). FCIL **6**, in combination with trifluoroacetic acid as additive, was found to be more effective than FCIL **3** in influencing the enantioselective outcome of the Michael

addition reactions of α,α-disubstituted aldehydes and nitrostyrenes to provide the Michael adducts with one quaternary carbon center. On the other hand, FCIL **3** was found to be superior in enantioselectivities for reactions involving α-monosubstituted aldehydes, while FCIL **6** was observed to be more effective because of the higher yields and reactivity. These FCIL catalysts were easily recycled and reused up to five times without significant loss of their ability to influence the reactivities and enantioselectivities of the Michael reactions.

4. Experimental section

4.1. Synthesis of compound 1

To a solution of *N*-Boc-(*S*)-2-aminomethylpyrrolidine (1.00 g, 5.0 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (0.7 mL, 5.5 mmol), the solution was cooled to 0 °C and 3-chloropropanesulfonyl chloride (0.89 g, 5.0 mmol) was added. Following the addition, the reaction mixture was warmed to room temperature while stirring for 17 h. The solution was diluted with CH_2Cl_2 (60 mL) and washed with 0.5 M HCl (15 mL), saturated aqueous $NaHCO_3$ (15 mL), and then brine (15 mL); the organic phase was dried with Na_2SO_4 and purified by flash chromatography on silica gel (hexane/ethyl acetate=2:1) to afford the product **1** (1.22 g, 72%). $[\alpha]_D^{20}$ −24.4 (*c* 0.55, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33–6.18 (br, 1H), 4.02–3.85 (br, 1H), 3.66 (t, *J*=6.0 Hz, 2H), 3.50–3.05 (m, 6H), 2.35–2.20 (m, 2H), 2.08–1.97 (m, 1H), 1.92–1.76 (m, 2H), 1.74–1.62 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 80.4, 57.0, 49.1, 48.5, 47.3, 42.9, 29.5, 28.4, 26.9, 23.8; IR (neat) ν=2976, 1670, 1397, 1148, 1111 cm^{-1}; HRMS (ESI) *m*/*z* (%) calcd for $C_{13}H_{26}ClN_2O_4S$ (MH^+): 341.1296, found: 341.1286.

4.2. Synthesis of compound 2

To a solution of compound **1** (1.22 g, 3.58 mmol) in acetone (15 mL), NaI (5.3 g, 35.3 mmol) was added under N_2 atmosphere. The reaction mixture was stirred at reflux for 24 h and the solvent removed; the concentrate was diluted with CH_2Cl_2 (60 mL) then washed with water followed by brine. The organic phase was dried over Na_2SO_4, filtrated, and concentrated to give the crude iodine product (1.45 g, 96%), which was used for the next step directly without further characterization.

The above iodine compound (1.45 g, 3.36 mmol) and 1-methylimidazole (0.30 g, 3.69 mmol) were dissolved in CH_3CN (2 mL) and the solution was stirred for 14 h at 65 °C, followed by removal of the solvent under reduced pressure. The residue was washed with Et_2O (2×5 mL) and dried to give the compound **2** (1.55 g, 90%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.69 (d, *J*=1.6 Hz, 1H), 7.59 (d, *J*=1.6 Hz, 1H), 4.43 (t, *J*=7.2 Hz, 2H), 3.94 (s, 3H), 3.87–3.79 (m, 1H), 3.37–3.23 (m, 3H), 3.15 (t, *J*=7.2 Hz, 2H), 3.11–3.02 (m, 1H), 2.36 (dt, *J*=14.4 and 7.2 Hz, 2H), 2.00–1.77 (m, 4H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 156.7, 156.3, 138.0, 125.2, 123.6, 81.2, 80.9, 58.8, 58.5, 45.9, 36.9, 29.6, 29.2, 28.8, 25.9, 24.4, 23.6. This compound was used for the next step without further characterization.

4.3. Synthesis of compound 3

Compound **2** (1.55 g, 3.02 mmol) was dissolved in a 1:1 mixture of trifluoroacetic acid and dichloromethane (10 mL) and the solution was stirred for 2 h at room temperature, at which time the solvent was evaporated under reduced pressure. The pH was adjusted to 8 with aqueous $NaHCO_3$, and $LiNTf_2$ (0.87 g, 3.02 mmol) was added and the mixture was stirred for 1 h at room temperature, extracted with CH_2Cl_2 (3×20 mL) and the organic phase was dried over $NaSO_4$ and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH=10:1) to afford the product **3** (1.51 g, 88% for two steps). $[\alpha]_D^{20}$ +0.42 (*c* 0.71, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.85 (s, 1H), 7.62 (t, *J*=1.6 Hz, 1H), 7.57 (t, *J*=1.6 Hz, 1H), 4.40 (t, *J*=7.2 Hz, 2H), 3.93 (s, 3H), 3.72–3.65 (m, 1H), 3.45 (dd, *J*=15.2 and 4.4 Hz, 1H), 3.40–3.25 (m, 3H), 3.21 (t, *J*=7.2 Hz, 2H), 2.38 (dt, *J*=14.4 and 7.2 Hz, 2H), 2.23–2.00 (m, 3H), 1.80–1.70 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 138.1, 125.3, 123.6, 121.2 (q, *J*=319.2 Hz, 2C), 62.0, 46.6, 44.6, 44.3, 36.6, 28.1, 25.6, 23.9; IR (neat) ν=1568, 1347, 1187, 1133, 1056 cm^{-1}; HRMS (ESI +) *m*/*z* (%) calcd for $[C_{12}H_{23}N_4OS]^+$: 287.1542, found: 287.1536; HRMS (ESI−) *m*/*z* (%) calcd for $[N(SO_2CF_3)_2]^-$: 279.9173, found: 279.9202.

4.4. Synthesis of compound 4

N-Boc-(*S*)-2-aminomethylpyrrolidine (0.5 g, 2.5 mmol) and Et_3N (0.46 mL, 3.3 mmol) in CH_2Cl_2 (15 mL) were reacted with 3-Chloromethanesulfonyl chloride (0.45 g, 3.0 mmol) according to the procedure described for the preparation of **1** to give product **4** (0.77 g, 98%) as a white solid. Mp: 86–88 °C; $[\alpha]_D^{20}$ −31.0 (*c* 1.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87–6.75 (br, 1H), 4.49 (s, 2H), 4.17–3.96 (m, 1H), 3.50–3.17 (m, 4H), 2.12–2.02 (m, 1H), 1.92–1.80 (m, 3H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 80.5, 57.0, 55.2, 49.5, 47.3, 29.6, 28.4, 23.9; IR (neat) ν=1645, 1414, 1159 cm^{-1}; HRMS (ESI) *m*/*z* (%) calcd for $C_{11}H_{21}ClN_2O_4S$ (MNa^+): 335.0803, found: 335.0813.

4.5. Synthesis of compound 5

To a solution of compound **4** (2.4 g, 7.58 mmol) and 1-methylimidazole (0.62 g, 7.58 mmol) in toluene (2 mL), which was refluxed under N_2 for 3 d, was added ethyl acetate to precipitate the solid, which was collected to give the compound **5** (2.24 g, 75%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.16 (s, 1H), 7.72 (s, 1H), 7.68 (s, 1H), 5.59 (s, 2H), 3.99 (s, 3H), 3.87–3.78 (br, 1H), 3.37–3.24 (m, 3H), 3.08 (dd, *J*=13.6 and 7.6 Hz, 1H), 2.00–1.70 (m, 4H), 1.45 (s, 9H). This compound was used for the next step without further characterization.

4.6. Synthesis of compound 6

Compound **5** (2.24 g, 5.69 mmol) reacted with 1:1 mixture of trifluoroacetic acid and dichloromethane (20 mL) according to the procedure described for the preparation of **3** to give product **6** (2.80 g, 90% for two steps). $[\alpha]_D^{20}$ −2.88 (*c* 1.25, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.95 (s, 1H), 7.69 (d, *J*=2.0 Hz, 1H), 7.66 (d, *J*=2.0 Hz, 1H), 5.64 (s, 2H), 3.98 (s, 3H), 3.68–3.60 (m, 1H), 3.50 (dd, *J*=15.2 and 4.4 Hz, 1H), 3.42–3.23 (m, 3H), 2.23–2.14 (m, 1H), 2.10–1.98 (m, 2H), 1.77–1.66 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 138.1, 125.4, 124.9, 121.1 (q, *J*=319.3 Hz, 2C), 63.6, 62.0, 46.7, 44.5, 37.0, 28.2, 23.7; IR (neat) ν=1346, 1187, 1054 cm^{-1}; HRMS (ESI+) *m*/*z* (%) calcd for $[C_{10}H_{19}N_4OS]^+$: 259.1229, found: 259.1222; HRMS (ESI−) *m*/*z* (%) calcd for $[N(SO_2CF_3)_2]^-$: 279.9173, found: 279.9179.

4.7. Typical experimental procedure for Michael addition reaction. Synthesis of (*R*)-2,2-dimethyl-4-nitrophenylbutanal 7a[15b]

To a solution of catalyst FCIL **6** (23 mg, 0.04 mmol) in MeOH (1 mL) were added trifluoroacetic acid solution of MeOH (16 μL, 14 μL/mg, 5 mol %) and isobutyraldehyde (87 mg, 1.2 mmol). After stirring for 10 min at room temperature, and *trans*-β-nitrostyrene (30 mg, 0.2 mmol) was added and the reaction mixture was stirred at room temperature for 3 d. The reaction mixture was concentrated and the residue was extracted with ether for two times. Removal of the solvent and purification by silica gel column (eluent: hexane/ethyl acetate=4:1) gave the Michael adduct (40 mg, 90%) as a colorless oil. The residue was ether insoluble catalyst FCIL **6**, which was dried under vacuum for 1 h and used directly for the

next run. $[\alpha]_D^{20}$ −15.0 (*c* 0.01, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.40–7.15 (m, 5H), 4.83 (dd, *J*=13.0 and 11.4 Hz, 1H), 4.67 (dd, *J*=13.0 and 4.0 Hz, 1H), 3.76 (dd, *J*=11.4 and 4.0 Hz, 1H), 1.11 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 135.3, 129.0, 128.7, 128.1, 76.3, 48.4, 48.2, 21.6, 18.8; HPLC (Chiralpak AS-H, *i*-propanol/hexane=5:95, flow rate 0.5 mL/min, λ=238 nm): t_{minor}=33.1 min, t_{major}=34.5 min; ee=84%.

4.8. 1-((*R*)-2-Nitro-1-phenylethyl)cyclopentanecarbaldehyde 7b[15d]

$[\alpha]_D^{20}$ −12.7 (*c* 0.28, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.33–7.19 (m, 5H), 4.96 (dd, *J*=13.8 and 11.6 Hz, 1H), 4.70 (dd, *J*=13.8 and 3.2 Hz, 1H), 3.71 (dd, *J*=11.2 and 3.6 Hz, 1H), 2.10–2.00 (m, 1H), 1.94–1.84 (m, 1H), 1.74–1.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 136.3, 128.8, 128.1, 60.2, 49.3, 32.6, 31.5, 24.8, 24.6; HPLC (Chiralcel OD-H, *i*-propanol/hexane=20:89, flow rate 1 mL/min, λ=254 nm): t_{minor}=14.7 min, t_{major}=10.7 min; ee=85%.

4.9. (2*R*,3*S*)-2-Ethyl-2-methyl-4-nitro-3-phenylbutanal 7c[15b]

$[\alpha]_D^{20}$ +4.0 (*c* 0.15, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (*syn*) and 9.52 (*anti*) (s, 1H), 7.38–7.27 (m, 3H), 7.24–7.15 (m, 2H), 4.90–4.60 (m, 2H), 3.78 (dt, *J*=11.2 and 4.0 Hz, 1H), 1.78–1.24 (m, 2H), 1.11 (s, 3H), 0.89 (*anti*) and 0.82 (*syn*) (t, *J*=7.2 Hz, 3H); HPLC (Chiralcel OD-H, *i*-propanol/hexane=10:90, flow rate 1 mL/min, λ=254 nm): t_{major}=13.4 min (*anti*), t_{major}=15.9 min (*syn*), t_{minor}=17.5 min (*anti*), t_{minor}=23.8 min (*syn*); ee=63% (*syn*), ee=71% (*anti*).

4.10. (*R*)-2,2-Dimethyl-4-nitro-3-p-tolylbutanal 7e[15k]

Mp: 54–56 °C; $[\alpha]_D^{20}$ +1.7 (*c* 0.18, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.13 (d, *J*=8.0 Hz, 2H), 7.08 (d, *J*=8.0 Hz, 2H), 4.83 (dd, *J*=13.2 and 11.6 Hz, 1H), 4.67 (dd, *J*=13.2 and 4.4 Hz, 1H), 3.74 (dd, *J*=10.8 and 4.0 Hz, 1H), 2.32 (s, 3H), 1.13 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 137.9, 132.1, 129.4, 128.9, 76.4, 48.2, 21.6, 21.0, 18.9; HPLC (Chiralcel OD-H, *i*-propanol/hexane=20:80, flow rate 1 mL/min, λ=254 nm): t_{minor}=14.1 min, t_{major}=10.1 min; ee=80%.

4.11. (3*S*)-(4-Bromo-phenyl)-2,2-dimethyl-4-nitrobutanal 7f[18]

$[\alpha]_D^{20}$ +11.4 (*c* 0.09, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.48 (d, *J*=2.0 Hz, 2H), 7.46 (d, *J*=2.0 Hz, 2H), 4.82 (dd, *J*=13.2 and 11.2 Hz, 1H), 4.67 (dd, *J*=13.2 and 4 Hz, 1H), 3.75 (dd, *J*=11.2 and 4.0 Hz, 1H), 1.12 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 134.5, 131.9, 130.7, 122.3, 76.1, 48.1, 48.0, 21.8, 18.9; HPLC (Chiralpak AS-H, *i*-propanol/hexane=10:90, flow rate 0.7 mL/min, λ=220 nm): t_{minor}=21.4 min, t_{major}=23.1 min; ee=83%.

4.12. (2*R*,3*S*)-2-Methyl-4-nitro-3-phenylbutanal 7g[14i]

$[\alpha]_D^{20}$ −2.7 (*c* 0.47, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.36–7.15 (m, 5H), 4.80 (dd, *J*=12.8 and 5.6 Hz, 1H), 4.68 (dd, *J*=12.8 and 9.2 Hz, 1H), 3.81 (dt, *J*=9.2 and 5.6 Hz, 1H), 2.81–2.73 (m, 1H), 1.00 (d, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 136.5, 129.1, 128.1, 128.0, 78.1, 48.4, 44.0, 12.1; HPLC (Chiralcel OD-H, *i*-propanol/hexane=9:91, flow rate 1 mL/min, λ=237 nm): t_{minor}=24.5 min, t_{major}=33.4 min; ee=45%.

4.13. (*R*)-2-[(*S*)-2-Nitro-1-phenylethyl]pentanal 7h[15d]

$[\alpha]_D^{20}$ −13.3 (*c* 0.15, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J*=2.8 Hz, 1H), 7.38–7.15 (m, 5H), 4.75–4.61 (m, 2H), 3.77 (dt, *J*=9.6 and 4.2 Hz, 1H), 2.75–2.67 (m, 1H), 1.53–1.10 (m, 4H), 0.80 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 137.8, 129.1, 128.2, 128.1, 128.0, 78.4, 53.8, 43.2, 29.5, 19.8, 13.9; HPLC (Chiralcel OD-H, *i*-propanol/hexane=20:80, flow rate 1 mL/min, λ=254 nm): t_{minor}=11.9 min, t_{major}=15.5 min; ee=64%.

4.14. (*R*)-2-[(*S*)-2-Nitro-1-phenylethyl]hexanal 7i[14i]

$[\alpha]_D^{20}$ −5.5 (*c* 0.22, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J*=2.8 Hz, 1H), 7.38–7.15 (m, 5H), 4.73–4.62 (m, 2H), 3.78 (dt, *J*=9.6 and 5.2 Hz, 1H), 2.73–2.67 (m, 1H), 1.53–1.11 (m, 6H), 0.78 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 136.8, 129.1, 128.1, 128.0, 78.4, 53.9, 43.1, 28.5, 27.0, 22.4, 13.6; HPLC (Chiralcel OD-H, *i*-propanol/hexane=15:85, flow rate 1 mL/min, λ=254 nm): t_{minor}=12.8 min, t_{major}=16.0 min; ee=68%.

4.15. (2*R*,3*S*)-2-(Methylethyl)-4-nitro-3-phenylbutanal 7j[14i]

$[\alpha]_D^{20}$ +32.7 (*c* 0.15, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.93 (d, *J*=2.4 Hz, 1H), 7.40–7.13 (m, 5H), 4.70–4.53 (m, 2H), 3.90 (dt, *J*=10.4 and 4.4 Hz, 1H), 2.80–2.73 (m, 1H), 1.75–1.67 (m, 1H), 1.10 (d, *J*=7.2 Hz, 3H), 0.89 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 137.1, 129.1, 128.1, 127.9, 79.0, 58.8, 41.9, 27.9, 21.6, 17.0; HPLC (Chiralpak AS-H, *i*-propanol/hexane=5/95, flow rate 0.5 mL/min, λ=254 nm): t_{minor}=30.3 min, t_{major}=31.8 min; ee=66%.

4.16. (*R*)-2-[(*S*)-1-(4-Methylphenyl)-2-nitroethyl]-pentanal 7l[11e]

$[\alpha]_D^{20}$ +41.8 (*c* 0.11, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J*=2.8 Hz, 1H), 7.14 (d, *J*=8.0 Hz, 2H), 7.05 (d, *J*=8.0 Hz, 2H), 4.68 (dd, *J*=12.8 and 5.6 Hz, 1H), 4.61 (d, *J*=12.8 and 9.6 Hz, 1H), 3.73 (dt, *J*=9.6 and 5.2 Hz, 1H), 2.70–2.64 (m, 1H), 2.33 (s, 3H), 1.60–1.10 (m, 4H), 0.81 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 137.9, 133.6, 129.8, 127.8, 78.5, 53.9, 42.9, 29.4, 21.1, 19.8, 13.9; HPLC (Chiralcel OD-H, *i*-propanol/hexane=20:80, flow rate 1 mL/min, λ=254 nm): t_{minor}=10.4 min, t_{major}=12.6 min; ee=68%.

4.17. (*R*)-2-[(*S*)-1-(4-Methoxyphenyl)-2-nitroethyl]-pentanal 7m[15j]

$[\alpha]_D^{20}$ +29.2 (*c* 0.12, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J*=2.8 Hz, 1H), 7.08 (d, *J*=8.8 Hz, 2H), 6.87 (d, *J*=8.8 Hz, 2H), 4.70–4.55 (m, 2H), 3.80–3.69 (m, 1H), 2.70–2.60 (m, 1H), 1.60–1.10 (m, 4H), 0.81 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 159.3, 129.0, 128.5, 114.5, 78.6, 55.2, 54.0, 42.5, 29.4, 19.8, 13.9; HPLC (Chiralcel OD-H, *i*-propanol/hexane=10:90, flow rate 1 mL/min, λ=254 nm): t_{minor}=20.5 min, t_{major}=22.4 min; ee=67%.

4.18. (*R*)-2-[(*S*)-1-(4-Bromophenyl)-2-nitroethyl]pentanal 7n

$[\alpha]_D^{20}$ +3.47 (*c* 0.38, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J*=2.4 Hz, 1H), 7.48 (d, *J*=6.8 Hz, 2H), 7.07 (d, *J*=6.8 Hz, 2H), 4.72–4.58 (m, 2H), 3.75 (dt, *J*=10.0 and 5.2 Hz, 1H), 2.72–2.66 (m, 1H), 1.52–1.14 (m, 4H), 0.82 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 135.9, 132.3, 129.7, 122.1, 78.1, 53.5, 42.5, 29.5, 19.7, 13.9; HRMS (ESI) *m*/*z* (%) calcd for [$C_{13}H_{16}BrNO_3$+H^+]: 314.0386, found: 314.0372; HPLC (Chiralcel OD-H, *i*-propanol/hexane=10:90, flow rate 1 mL/min, λ=254 nm): t_{minor}=20.1 min, t_{major}=21.8 min; ee=44%.

4.19. (*R*)-2-[(*S*)-1-(2-Trifluoromethylphenyl)-2-nitroethyl]pentanal 7o[15k]

$[\alpha]_D^{20}$ +7.7 (*c* 0.71, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, *J*=2.8 Hz, 1H), 7.73 (d, *J*=7.6 Hz, 1H), 7.59 (d, *J*=8.0 Hz, 1H), 7.44 (t, *J*=7.6 Hz, 1H), 7.36 (d, *J*=8.0 Hz, 1H), 4.83–4.73 (m, 1H), 4.65 (dd, *J*=13.2 and 5.2 Hz, 1H), 4.19–4.14 (m, 1H), 2.97–2.92 (m, 1H),

1.62–1.18 (m, 4H), 0.82 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 136.3, 132.6, 129.4 (q), 128.0, 126.9, 125.4, 122.7, 77.8, 54.0, 38.6, 30.3, 20.1, 13.9; HPLC (Chiralcel OD-H, *i*-propanol/hexane=20:80, flow rate 1 mL/min, λ=254 nm): t_{minor}=10.1 min, t_{major}=8.9 min; ee=41%.

4.20. (*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclohexanone 8[15k]

$[\alpha]_D^{20}$ −28.0 (*c* 0.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.23 (m, 3H), 7.17 (d, J=6.8 Hz, 2H), 4.94 (dd, J=12.4 and 4.4 Hz, 1H), 4.63 (dd, J=12.4 and 10.0 Hz, 1H), 3.76 (dt, J=10.0 and 4.8 Hz, 1H), 2.72–2.65 (m, 1H), 2.52–2.34 (m, 2H), 2.13–2.04 (m, 1H), 1.83–1.50 (m, 4H), 1.30–1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 137.7, 128.9, 128.2, 127.8, 78.9, 52.5, 43.9, 42.7, 33.2, 28.5, 25.0; HPLC (Chiralpak AS-H, *i*-propanol/hexane=10:90, flow rate 0.7 mL/min, λ=238 nm): t_{minor}=22.8 min, t_{major}=34.5 min; ee=88%.

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