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Novel chiral ammonium ionic liquids as efficient organocatalysts for asymmetric Michael addition of aldehydes to nitroolefins

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ABSTRACT

Two chiral ammonium ionic liquids **1a** and **1b** have been newly synthesized from commercially available (+)-*cis*-2-benzamidocyclohexanecarboxylic acid. These CILs have been demonstrated to be efficient organocatalysts for asymmetric Michael addition of aldehydes to nitroolefins with excellent yields (up to 99%), high enantioselectivities (up to 90%) and modest to high diastereoselectivities (*syn*/*anti* ratio up to 99/1).

1. Introduction

Ionic liquids (ILs) have attracted increasing interest due to their unique properties, such as non-volatility, high thermal stability, low toxicity, and reusability. Ionic liquids, also called as room temperature molten salt, entirely composed of cations and anions; cations are typically imidazolium, pyridinium or ammonium species, and anions usually include halogen anions, BF_4^-, PF_6^-, NTf_2^-. By modifying the structures of the cations or anions of ILs, their properties can be altered for desired applications. Based on the tunable feature of ILs, diverse functionalized ionic liquids (FILs) have been designed and synthesized by attachment of functional groups onto the side chains of ILs.[1] Recently, chiral ionic liquids (CILs), as one kind of FILs, have been the focus of attention due to their promising applications in chiral discrimination, asymmetric synthesis and the optical resolution of racemates.[2–8] However, only a limited number of CILs have been synthesized and used as highly efficient catalysts for asymmetric reactions up to now.

Imidazolium ionic liquids as the biggest class of ILs have been widely researched.[9] Unfortunately, the labile C2 proton limits its use in organic reactions.[10–13] In contrast, the saturated quaternary ammonium ionic liquids are more resistant against oxidation and reduction.[14] Compared to the extensive work on the chiral imidazolium ILs, chiral ammonium ILs have been explored far less. Only few chiral ammonium ILs derived from chiral pool starting materials such as amine,[15–17] natural amino acids,[18–21] and carbohydrates[22–24] have been developed (Fig. 1). Chiral ammonium ILs have been successfully used as stationary phases in gas chromatography and high-performance liquid chromatography for the resolution of racemic compounds.[25,26] However, successful application of chiral ammonium ILs for asymmetric synthesis has been rarely reported. Ephedrine-based chiral ammonium IL **I** has been used as 'chiral induction solvent' for the enantioselective photoisomerization with poor enantioselective induction (up to 12% ee).[27] Vo-Thanh group has reported a series of application of ephedrine-based ammonium ILs as chiral solvents for asymmetric

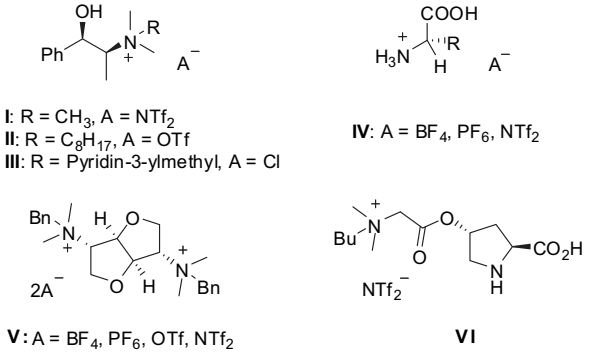

Figure 1. Known chiral ammonium ILs.

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synthesis.[28–30] The Morita/Baylis/Hillman reaction of benzaldehyde and methyl acrylate promoted by CIL **II** afforded the coupling product with up to 44% ee[28] The asymmetric aza-Diels/Alder reaction of chiral imines with Danishefsky's diene in CIL **II** provided the corresponding cycloadducts with moderate diastereoselectivity (up to 72% de).[29] Most recently, they reported the Michael reaction of diethyl-2-acetamidomalonate and enones using CIL **III** as chiral reaction media, giving moderate enantioselectivity (up to 70% ee).[30] Lombardo et al. have applied proline-derived chiral ammonium IL **VI** as a catalyst in asymmetric aldol reaction successfully, providing moderate diastereoselectivities (*anti*/*syn* ratio up to 80/20) and high enantioselectivities (up to 94% ee).[31] It is worth noting that Ni et al. have recently developed an efficient catalytic system with ammonium-based pyrrolidine organocatalyst for the asymmetric Michael addition on water.[32] Although the catalyst itself is not isolated as an ammonium ionic liquid, the aqueous solution of the ammonium-based organocatalyst can be easily recovered and reused for at least six times. The development of eco-friendly, recyclable and highly efficient chiral ammonium IL for asymmetric synthesis is still a challenging research field.

The asymmetric Michael addition reaction of nitroolefins with aldehydes is an important method for the synthesis of versatile γ-nitrocarbonyl compounds, which are useful building blocks since the nitro group can be readily converted into a variety of functional groups including amines, nitrile oxides.[33–35] More recently, the development of chiral IL organocatalysts for asymmetric Michael reaction with high stereoselectivity has received widespread attention.[36] The pyrrolidine structure is regarded as one of the 'privileged' backbones for asymmetric conjugate addition.[37] The pyrrolidine-based chiral imidazolium ILs[37–40] and pyridinium ILs[41] have been proved to be efficient catalysts for asymmetric Michael addition.

Our group has focused on the investigation of asymmetric catalysis using the derivatives of commercially available (+)-*cis*-2-benzamidocyclohexanecarboxylic acid **2**, such as chiral 1,3-aminoalcohols.[42,43] As an extension of our work, we designed and synthesized a class of novel chiral ammonium ILs, which consist of a 1,3-diamine derived from acid **2** and a chiral pyrrolidine unit. The pyrrolidine group can serve as a catalytic site, and the 1,3-diamine-derived ammonium IL can act as both a phase tag and a chirality inducing group. Herein, we report the synthesis of novel chiral ammonium ILs and their application for asymmetric Michael additions of aldehydes to nitroolefins as efficient organocatalysts.

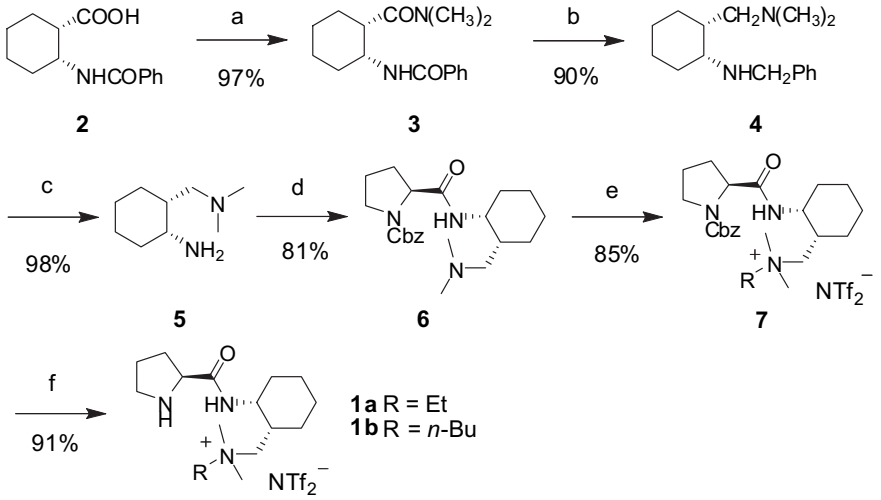
2. Results and discussion

2.1. Synthesis of chiral ionic liquids

Scheme 1 shows the synthesis of pyrrolidine-based chiral ammonium ILs **1a** and **1b**. (+)-*cis*-2-Benzamidocyclohexane-carboxylic acid **2** was activated with ethyl chloroformate and then reacted with dimethylamine to afford the corresponding *cis*-diamide **3** in 97% overall yield. Subsequent reduction and debenzylation led to *cis*-1,3-diamine **5**. The coupling reaction between *N*-Cbz-L-proline and **5** in the presence of DCC/DMAP yielded amide **6**. After quaternization with ethyl iodide or *n*-butyl iodide and anion exchange with NTf_2^-, Cbz-protected IL **7** was obtained with up to 85% overall yield. Deprotection of IL **7** with H_2 and Pd/C gave the desired CILs **1a** and **1b**. Both of the CILs are viscous liquids at room temperature and soluble in polar solvent, such as alcohols, dichloromethane and THF, but immiscible in non-polar solvents, such as diethyl ether and *n*-hexane.

2.2. Optimization of the reaction conditions

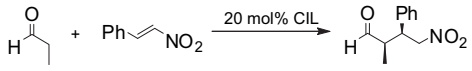
Michael addition of propanal to *trans*-β-nitrostyrene was chosen as a model reaction to determine the optimal conditions for CILs **1a** and **1b**. Initially, the solvent effect has been investigated and the representative results are presented in Table 1. It was found that the nature of the solvent has an important influence on the outcomes of this reaction. When highly polar solvents such as MeOH and IPA were used, high yields were obtained (90–92%), while IPA led to higher enantioselectivity (entries 1 and 2). Lower enantiomeric excess (46% ee) was observed in acetonitrile (entry 3). Although the reaction in dichloromethane (DCM) and 1,4-dioxane has shown higher selectivity, the reaction was retarded and resulted in comparatively lower yields (entries 5 and 7). A mixed solvent of DCM/THF (1:1, v/v) improved the diastereoisomeric ratio slightly to 72/28 (entry 8). Finally, THF was identified as the best solvent for CIL **1a** as it gave high yield (96%) and comparatively high ee (84% ee, entry 6). After the screening of solvent for CIL **1a**, three kinds of solvents (IPA, THF, and DCM) were selected for examination of CIL **1b**. Among these solvents, DCM was proved to be the most efficient solvent since the excellent yield (95%), good diastereoselectivity (78/22 dr), and high ee (89%) were obtained (entry 11). The acidic additive could promote the formation of the enamine intermediate, and thereby, improve both the reactivity and stereoselectivity.[32] It has been proved to be important to Michael addition catalyzed by



Scheme 1. Synthesis of chiral ionic liquids. Reaction conditions: (a) (1) $ClCO_2Et$, Et_3N, 0 °C-rt; (2) 50% Me_2NH Solution, rt. (b) $LiAlH_4$, dry THF, 0 °C-reflux. (c) Pd/C, H_2, EtOH, 70 °C. (d) *N*-Cbz-L-proline, DCC, DMAP, dry THF. (e) (1) RI, toluene, 90 °C. (2) $LiNTf_2$, CH_3CN/H_2O. (f) Pd/C, H_2, EtOH, 40 °C.

pyrrolidine-based organocatalyst.[39,44] The effect of other additives was also examined using CIL **1b** in DCM. The reaction without an additive or with a weak acid proceeded slowly and gave lower stereoselectivity (entries 12 and 13). Although TsOH could provide comparable diastereomeric ratio and ee, the reactivity dropped significantly, probably due to protonation of pyrrolidine nitrogen (entry 14).[45]

Table 1
Screening of solvent and additive in the Michael addition catalyzed by CILs **1a** and **1b**[a]



Entry	CIL	Additive	Solvent	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%) *syn* (*anti*)
1	**1a**	TFA	MeOH	92	65/35	63 (64)
2	**1a**	TFA	IPA	90	66/34	79 (83)
3	**1a**	TFA	CH_3CN	90	63/37	46 (52)
4	**1a**	TFA	AcOEt	94	68/32	77 (81)
5	**1a**	TFA	Dioxane	81	64/36	84 (89)
6	**1a**	TFA	THF	96	68/32	84 (81)
7	**1a**	TFA	DCM	85	64/36	90 (91)
8[e]	**1a**	TFA	DCM/THF	93	72/28	81 (81)
9	**1b**	TFA	IPA	97	74/26	78 (82)
10	**1b**	TFA	THF	95	81/19	84 (84)
11	**1b**	TFA	DCM	95	78/22	89 (89)
12	**1b**	—	DCM	52	66/34	52 (62)
13	**1b**	AcOH	DCM	66	77/23	73 (75)
14	**1b**	$TsOH{\cdot}H_2O$	DCM	70	82/18	89 (88)

[a] The reaction was conducted with β-nitrostyrene (0.1 mmol), aldehyde (0.6 mmol), and CIL (20 mol %) in 1 mL of solvent at rt for 12 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC.
[e] The ratio of DCM to THF was 1/1.

Furthermore, the catalyst loading of CILs **1a** and **1b** was tested and the results are presented in Table 2. With increasing the catalyst loading, the yield (84–96%), diastereoselectivity (66/34–71/29 dr) and enantioselectivity (82–86% ee) were enhanced slightly (entries 1–5 and 7–9). It is worth noting that no improvement of enantioselectivity (81% ee) and diastereoselectivity (67/33 dr) was observed when the reaction was conducted at 0 °C (entry 6). Finally, the preferred catalyst loading of 15 mol % and 20 mol % was chosen for CIL **1b** and **1a**, respectively.

Table 2
Catalyst loading of the Michael addition catalyzed by CILs **1a** and **1b**[a]

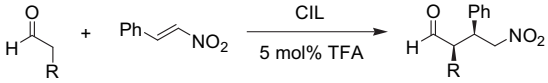
Entry	CIL (mol %)	Solvent	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%) *syn* (*anti*)
1	**1a** (10)	THF	84	66/34	82 (84)
2	**1a** (15)	THF	91	65/35	83 (84)
3	**1a** (20)	THF	96	68/32	84 (81)
4	**1a** (25)	THF	96	68/32	83 (83)
5	**1a** (30)	THF	96	71/29	86 (90)
6[e]	**1a** (20)	THF	73	67/33	81 (82)
7	**1b** (15)	DCM	95	77/23	88 (89)
8	**1b** (20)	DCM	95	78/22	89 (89)
9	**1b** (25)	DCM	98	80/20	90 (89)

[a] The reaction was conducted with β-nitrostyrene (0.1 mmol), aldehyde (0.6 mmol), CIL, and TFA (5 mol %) in 1 mL of solvent at rt for 12 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC.
[e] The reaction was conducted at 0 °C for 36 h.

2.3. Scope of substrate

The scope of substrate was explored under the optimized conditions. The results of Michael addition between aldehydes and *trans*-β-nitrostyrene are summarized in Table 3. The reaction of linear aldehydes proceeded smoothly with reaction time ranged from 12 to 36 h, and gave excellent yields (95–99%), moderate to high diastereoselectivities (67/33–90/10 dr) and enantioselectivities (72–88% ee, entries 1–6, 9, and 10). Although the reaction of branched *i*-valeraldehyde required longer reaction time, high diastereoselectivities (97/3–99/1 dr) and good enantioselectivities (77–82% ee) were obtained (entries 7 and 8). Also, it was observed that the enantioselectivity decreased slightly with the increase of carbon chain length of aldehydes, for either CIL **1a** or **1b** was used.

Table 3
Michael addition of aldehydes to *trans*-β-nitrostyrene[a]



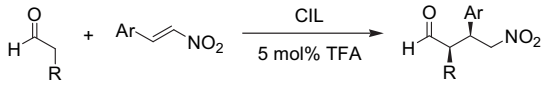
Entry	R	CIL	*T* (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%) *syn* (*anti*)	Pr.
1	Me	**1a**	12	95	68/32	84 (81)	**8a**
2		**1b**	12	95	77/23	88 (89)	
3	Et	**1a**	12	96	82/18	76 (75)	**8b**
4		**1b**	12	99	89/11	87 (82)	
5	*n*-Pr	**1a**	24	96	80/20	75 (71)	**8c**
6		**1b**	24	98	87/13	81 (78)	
7	*i*-Pr	**1a**	60	37	97/3	77	**8d**
8		**1b**	60	84	99/1	82	
9	*n*-Bu	**1a**	36	97	73/27	72 (73)	**8e**
10		**1b**	36	99	90/10	80 (77)	

[a] The reaction was conducted with β-nitrostyrene (0.1 mmol), aldehyde (0.6 mmol), and CIL **1a** (20 mol %) in 1 mL of THF or CIL **1b** (15 mol %) in 1 mL of DCM at rt.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC.

The reactions of substituted *trans*-β-nitroolefins and propanal have been studied and the results are listed in Table 4 (entries 1–10). The reaction of propanal with various substituted *trans*-β-nitroolefins gave the desired Michael products in excellent yields (up to 99%), modest diastereoselectivities (up to 77/23 dr) and high enantioselectivities (up to 90% ee, entries 1–8). The substituents on the aromatic ring of nitroolefins have almost no influence on the enantioselectivity of the corresponding adducts and show an effect on the reaction rate and diastereoselectivity. The reaction of nitroolefins bearing an electron donating group Me or MeO took long reaction time and gave higher diastereomeric ratio. On the other hand, nitroolefin with an electron withdrawing group reacted faster but gave lower diastereoselectivity (entries 1–6 vs entries 7 and 8). The reaction of (*E*)-2-(2-nitrovinyl)thiophene proceeded smoothly (entries 9 and 10) in high yields (93–97%), modest diastereoselectivities (61/39–68/32 dr) and high enantioselectivities (up to 88% ee).

As seen in Table 4 (entries 1–10), CIL **1b** exhibited higher catalytic activity and stereoselectivity than CIL **1a** for the Michael addition of aldehydes to *trans*-β-nitroolefins. Thus, using CIL **1b**, the reactions of *n*-valeraldehyde and substituted nitroolefins have been further studied (entries 11–14). The substrate of *n*-valeraldehyde gave higher diastereoselectivities (up to 90/10 dr) and a little lower enantioselectivities (up to 82% ee), compared to propanal (entries 2, 4, 6, and 8 vs entries 11–14). Moreover, it was found that high ees for both *syn*- (73–90% ee) and *anti*-diastereomers (75–89% ee) were obtained, albeit with only moderate diastereomeric ratios. In addition, the enantiomeric excess of the major *syn*-isomer is noticeably higher than that under influence of pyrrolidine-derived imidazolium ionic liquids reported by Headley et al.[39]

Table 4
Michael addition of aldehydes to substituted *trans*-β-nitroolefins[a]



Entry	R	Ar	CIL	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%) *syn* (*anti*)	Product
1	Me	4-MeOC$_6$H$_4$	**1a**	36	87	74/26	82 (85)	**8f**
2			**1b**	36	96	73/27	86 (86)	
3	Me	4-MeC$_6$H$_4$	**1a**	36	91	73/27	83	**8g**
4			**1b**	36	99	73/27	89	
5	Me	2-MeC$_6$H$_4$	**1a**	36	86	75/25	82 (81)	**8h**
6			**1b**	36	87	77/23	90 (88)	
7	Me	4-BrC$_6$H$_4$	**1a**	17	93	62/38	85	**8i**
8			**1b**	17	95	65/35	88	
9	Me	2-Thienyl	**1a**	17	93	61/39	84 (86)	**8j**
10			**1b**	17	97	68/32	88 (89)	
11	*n*-Pr	4-MeOC$_6$H$_4$	**1b**	36	94	86/14	80 (75)	**8k**
12	*n*-Pr	4-MeC$_6$H$_4$	**1b**	36	97	82/18	82 (84)	**8l**
13	*n*-Pr	2-MeC$_6$H$_4$	**1b**	36	85	90/10	79 (80)	**8m**
14	*n*-Pr	4-BrC$_6$H$_4$	**1b**	24	96	78/22	73 (76)	**8n**

[a] The reaction was conducted with β-nitroolefin (0.1 mmol), aldehyde (0.6 mmol), and CIL **1a** (20 mol %) in 1 mL of THF or CIL **1b** (15 mol %) in 1 mL of DCM at rt.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC.

2.4. Recycling studies of the CILs

The reaction of *trans*-β-nitrostyrene and propanal under the optimized reaction conditions was chosen to test the recyclability of CIL catalysts **1a** and **1b**. After the reaction was completed, the reaction mixture was concentrated and the residue was extracted three times with a mixed solvent of *n*-hexane/ether (2:1, v/v). Removal of the solvent and purification by TLC gave the Michael adduct. The precipitated CIL from the mixed solvent was dried under vacuum and reused for the next run directly. As shown in Table 5, the CIL catalysts could be efficiently reused only once. Although the catalytic activities decreased at the third run, the enantioselectivities were almost kept constant. This result is similar to the data reported by Lombardo et al.[31]

Table 5
Recycling studies of CILs **1a** and **1b** catalyzed Michael addition of propanal to *trans*-β-nitrostyrene under the optimized reaction conditions

Run	CIL	T (h)	Yield[a] (%)	dr[b] (*syn*/*anti*)	ee[c] (%) *syn* (*anti*)
1	**1a**	12	95	68/32	84 (81)
2	**1a**	18	91	67/33	80 (80)
3	**1a**	48	74	69/31	79 (79)
1	**1b**	12	95	77/23	88 (89)
2	**1b**	18	93	73/27	85 (84)
3	**1b**	48	86	68/32	86 (87)

[a] Isolated yield.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.

2.5. Mechanism of the reaction

In order to speculate the stable conformation of the catalytic intermediate, we first studied CIL **1b** by NMR spectroscopy. In the ^{1}H NMR spectrum, the signal of proton H_1 (Fig. 2) was a double doublet with coupling constants of 9.1 and 5.2 Hz. Its H–H COSY spectrum indicated that H_1 only has a weak coupling to proton H_2, but is strongly coupled to two vicinal protons, H_{6a} and H_{6e}. The large coupling constant (9.1 Hz) suggested that H_1 should be axial. It was further confirmed by spin decoupling measurement. By irradiating H_{6e}, the proton signal of H_1 turned to be a doublet with a coupling constant of 9.1 Hz. On the other hand, it was difficult to determine the orientation of H_2 due to the severely overlapped signal. To form the common chair conformation, we supposed that H_2 should be equatorial and the ammonium methylene group tend to be axial. Therefore, we suspected that the CILs take the conformation as shown in Figure 2. Furthermore, this conformation was proved to be more stable than the ring-flipped conformer by theoretical calculation using the PM3 method.

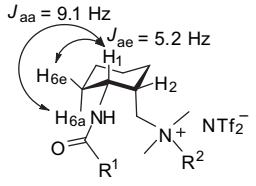


Figure 2. The stable conformation of the CILs.

Based on the experimental results, conformational analysis of CIL **1b** and the previously reported speculations on the stereochemical outcome,[35,46] we proposed that CIL-catalyzed Michael additions predominantly occur via the enamine pathway as shown in Figure 3. The bulky IL group and the hydrogen bonding between the amide NH and the nitro group of nitroolefin are considered to be important to the high catalytic activity and the stereoselectivity. In addition, the possible ionic attraction between ammonium cation and nitro group of the substrate should also contribute to stabilization of the intermediate. The enamine tends to attack from the less hindered *Si* face of the nitroolefin. Consequently, (2*R*, 3*S*) configuration of the corresponding adduct is generated preferentially (Fig. 3A). The flexible butyl side chain of ammonium group may cause moderate repulsive interaction with an aryl group of nitroolefin (Fig. 3B). The moderate diastereoselectivity of the reaction could be rationalized by considering this weak interaction.

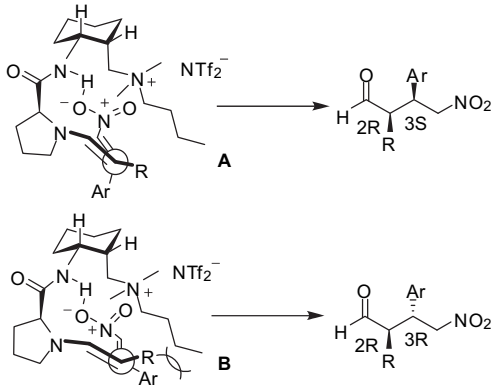


Figure 3. Proposed transition state of CIL **1b** catalyzed Michael addition.

3. Conclusion

Two novel chiral ammonium ionic liquids **1a** and **1b** have been synthesized from 'chiral pool' starting materials. Chiral ammonium IL **1b** bearing a longer butyl group was found to be superior to CIL **1a** in catalyzing Michael addition of a range of aldehydes and nitroolefins. Despite the difficulty of recycling, these CILs were proved to be efficient catalysts for the asymmetric Michael addition of aldehydes to nitrostyrenes in excellent yield, high enantioselectivity and modest to high diastereoselectivity. This study will be helpful to design and synthesize new type of chiral ammonium

ionic liquids for asymmetric catalysis. Further application of CIL **1a** and **1b** in other catalytic enantioselective reactions is currently in progress.

4. Experimental

4.1. General

All ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX 400 (400 MHz) or Bruker DPX 400 (400 MHz) spectrometers (Comprehensive Analysis Center for Science [CACS], Saitama University). Chemical shifts of ^{1}H and ^{13}C were given in parts per million relative to tetramethylsilane (TMS) as an internal standard. The coupling constant *J* was given in hertz. IR spectra were recorded on JASCO FT/IR 400. Enantiomeric excess determination was carried out using a JASCO LC 900 series HPLC consisting of a CD detector. Optical rotations were measured with a JASCO DIP-370 polarimeter. Electrospray ionization (ESI) mass measurements were performed on a Mariner (Perseptive Biosystems) mass spectrometer and a NanoFrontier eLD mass spectrometer (CACS). All commercially available substrates were used as received. All reactions unless otherwise noted were carried out directly under air. Nitroolefins were prepared according to the literature procedures.[47]

4.2. General procedures for the preparation of chiral ionic liquids 1a and 1b

*4.2.1. N-((1R,2S)-2-(Dimethylcarbamoyl)cyclo-hexyl)benzamide (**3**).* To a solution of (+)-*cis*-2-benzamidocyclohexanecarboxylic acid **2** (4.95 g, 20 mmol) and triethylamine (2.23 g, 22 mmol) in dry THF (20 mL), ethyl chloroformate (2.39 g, 22 mmol) was added dropwise at 0 °C. After stirring for 1 h, 50% aqueous solution of dimethylamine (5.41 g, 60 mmol) was added and the mixture was stirred for 48 h at room temperature. After diluting by $CHCl_3$ (20 mL), the mixture was washed with 1 M HCl (10 mL×3), saturated $NaHCO_3$ solution (10 mL×3), and then water (10 mL×3). The organic phase was dried over anhydrous Na_2SO_4 and evaporated under vacuum to give **3** (5.33 g, 97%). $[\alpha]_D^{20}$ −44.3 (*c* 2.01, $CHCl_3$); IR (neat): 3423, 3028, 2928, 1650, 1520, 1260 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, *J*=8.0 Hz, 2H), 7.49–7.40 (m, 3H), 7.10 (br, 1H), 4.27 (m, 1H), 3.11–3.08 (m, 1H), 3.05 (s, 3H), 2.91 (s, 3H), 2.45–2.43 (m, 1H), 1.65–1.59 (m, 4H), 1.48–1.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.84, 166.90, 134.82, 131.30,128.52, 127.03, 47.62, 40.90, 37.48, 35.61, 29.25, 26.04, 22.99, 22.56; HRMS (ESI+) *m*/*z* calcd for $[C_{16}H_{22}N_2O_2Na]^+$: 297.1574, found: 297.1557.

*4.2.2. (1R,2R)-N-Benzyl-2-((dimethylamino)methyl)-cyclohexanamine (**4**).* To a suspension of $LiAlH_4$ (1.06 g, 27.93 mmol) in dry THF (15 mL) was added a solution of **3** (1.53 g, 5.58 mmol) in THF (5 mL) slowly at 0 °C. After refluxing for 36 h, the reaction was quenched by cautious addition of saturated aqueous solution of Na_2SO_4 (10 mL) and 10% aqueous NaOH solution (5 mL) and the mixture was filtered through Celite. The filtrate was dried over anhydrous Na_2SO_4 and concentrated, and then purified by silica gel column chromatography ($CHCl_3$/MeOH=5/1) to afford **4** (1.24 g, 90%) as a colorless liquid. $[\alpha]_D^{20}$ −5.88 (*c* 0.18, $CHCl_3$); IR (neat): 3334, 3026, 2926, 1455, 1261, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.23 (m, 5H), 3.82 (d, *J*=13.1 Hz, 1H), 3.72 (d, *J*=13.1 Hz, 1H), 2.82–2.80 (br, 1H), 2.34–2.22 (m, 2H), 2.20 (s, 6H), 1.80 (br, 1H), 1.69 (br, 1H), 1.57–1.48 (m, 2H), 1.39–1.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.58, 128.40, 128.24, 126.81, 60.94, 55.68, 51.71, 46.35, 37.80, 29.15, 26.83, 24.19, 22.39; HRMS (ESI$^+$) *m*/*z* calcd for $[C_{16}H_{27}N_2]^+$: 247.2169, found: 247.2145.

*4.2.3. (1R,2R)-2-((Dimethylamino)methyl)cyclo-hexanamine (**5**).* A mixture of **4** (1.72 g, 6.98 mmol) and 10% Pd/C (0.09 g) in EtOH (20 mL) was stirred under hydrogen atmosphere at 70 °C for 12 h. After completion of the reaction, the catalyst was removed by filtration through a Celite pad, which was then washed with 10 mL of EtOH. The combined filtrate was concentrated, and dried in vacuo to afford **5** (1.07 g, 98%). $[\alpha]_D^{20}$ −8.1 (*c* 1.0, MeOH); IR (neat): 3368, 3292, 2928, 1574, 1383, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.98 (br, 2H), 3.48–3.32 (m, 1H), 2.75 (t, *J*=10.4 Hz, 1H), 2.26 (s, 6H), 2.12–2.07 (m, 2H), 1.91 (br, 1H), 1.70–1.67 (m, 2H), 1.46–1.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 61.14, 51.21, 45.88, 34.18, 29.23, 27.16, 23.06, 22.30; HRMS (ESI$^+$) *m*/*z* calcd for $[C_9H_{21}N_2]^+$: 157.1699, found: 157.1718.

*4.2.4. Synthesis of amide (**6**).* To a stirred solution of DCC (0.48 g, 2.32 mmol), DMAP (0.02 g, 0.19 mmol), and *N*-Cbz-L-proline (0.48 g, 1.94 mmol) in dry THF (15 mL) was added THF (5 mL) solution of **5** (0.33 g, 2.13 mmol) at 0 °C under N_2 atmosphere. After stirring for 30 min, the reaction mixture was warmed up to room temperature and stirred for 36 h. The precipitate was filtered off and washed with THF. After concentrating the combined filtrate, 1 N HCl (10 mL) was added to the residue and washed with $CHCl_3$ (5 mL×3). To the aqueous layer, saturated aqueous Na_2CO_3 was added until pH 9 was achieved and the mixture was extracted with $CHCl_3$ (10 mL×3), washed with brine (5 mL×3), dried over anhydrous Na_2SO_4, and then the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=5/1) to afford **6** (0.61 g, 81%) as a colorless oil. $[\alpha]_D^{20}$ −58.1 (*c* 5.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.34 (br, 1H), 7.35–7.31 (m, 5H), 5.20 (d, *J*=12.3 Hz, 1H), 5.06 (d, *J*=12.1 Hz, 1H), 4.34–4.29 (br, 1H), 3.97–3.84 (m, 1H), 3.49 (br, 2H), 2.90–2.84 (m, 1H), 2.13 (s, 6H), 2.01–1.71 (m, 7H), 1.58–1.36 (m, 6H), 1.15–1.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.63, 154.93, 136.43, 128.36, 128.07, 127.99, 127.93, 66.89, 61.25, 60.96, 58.44, 51.50, 47.37, 45.61, 32.52, 31.21, 30.13, 26.96, 24.81, 23.43, 20.69, 18.43; IR (neat): 3328, 3209, 3033, 1708, 1662, 1528, 1258, 1115, 1030 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for $[C_{22}H_{33}N_3O_3Na^+]$: 410.2414, found: 410.2474.

*4.2.5. Synthesis of **7a** and **7b**.* Ethyl iodide (0.57 g, 3.60 mmol) was added to a stirred solution of **6** (0.47 g, 1.20 mmol) in toluene, and stirred at 90 °C for 24 h. After reaction mixture was concentrated under reduced pressure, the residue was washed with 1,1,1-trichloroethane (5 mL×2), and then dried under vacuum to afford white solid, which was used for the next step directly. After adding a mixed solvent of CH_3CN/H_2O (1:1, v/v, 2 mL) and $LiNTf_2$ (0.36 g, 1.27 mmol), the mixture was stirred for 48 h and concentrated. To the residue, DCM was added, and then washed with H_2O (10 mL×3), dried over anhydrous Na_2SO_4, concentrated to give **7a** (0.68 g, 81%). $[\alpha]_D^{20}$ −6.31 (*c* 1.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.31 (m, 5H), 6.83 (d, *J*=7.6 Hz, 1H), 5.14–5.05 (m, 1H), 4.23 (br, 1H), 3.60–3.1 (m, 2H), 3.42–3.29 (m, 3H), 2.93 (s, 6H), 2.81–2.74 (m, 2H), 2.23 (br, 1H), 2.15–1.93 (m, 4H), 1.66–1.49 (m, 8H), 1.29 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.84, 155.40, 136.78, 128.55, 128.01, 127.30, 121.37, 118.18, 66.79, 65.82, 60.85, 60.54, 50.01, 49.67, 48.41, 47.11, 34.23, 29.64, 29.11, 28.43, 24.64, 23.29, 21.29, 8.17; IR (neat): 3379, 1697, 1678, 1534, 1196, 1135, 1057 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for $[C_{24}H_{38}N_3O_3]^+$:416.2908, found: 416.2914.

Compound **7b** was prepared by a similar method as described above in a yield of 85%. $[\alpha]_D^{20}$ −8.57 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.31 (m, 5H), 6.86 (d, *J*=8.4 Hz, 1H), 5.10 (dd, J_1=16.8 Hz, J_2=12.0 Hz, 2H), 4.24 (br, 1H), 4.16 (br, 1H), 3.39–3.64 (m, 2H), 3.17–3.15 (m, 1H), 2.95 (d, *J*=12.8 Hz, 6H), 2.89–2.76 (m, 1H), 2.23 (br, 1H), 2.15–2.11 (m, 2H), 1.97–1.89 (m, 2H), 1.60–1.49 (m, 8H), 1.39–1.25 (m, 4H), 0.97 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.80, 155.48, 136.75, 128.58, 128.06, 127.42, 121.42, 118.23, 66.88, 66.23, 65.69, 60.55, 50.53, 50.33,

48.50, 47.15, 34.30, 29.58, 29.14, 28.48, 24.57, 21.33, 19.51, 13.52; IR (neat): 3381, 1697, 1534, 1196, 1136, 1058 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $[C_{26}H_{42}N_3O_3]^+$:444.3221, found: 444.3231.

*4.2.6. Synthesis of CIL **1a** and **1b**.* A mixture of **7a** (0.57 g, 0.82 mmol) and 10% Pd/C (56.9 mg) in EtOH (8 mL) was stirred under hydrogen atmosphere at 40 °C for 12 h. The catalyst was filtered off and washed with EtOH (3 mL×3). The combined filtrate was concentrated and purified by alumina column chromatography ($CHCl_3$/MeOH=30/1 to 10/1) to give CIL **1a** (0.38 g, 83%). $[\alpha]_D^{20}$ −20.3 (*c* 0.34, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.16 (d, *J*=6.4 Hz, 1H), 4.15–4.12(m, 1H), 3.66 (dd, J_1=9.2 Hz, J_2=5.2 Hz, 1H), 3.34–3.24 (m, 2H), 3.17 (dd, J_1=13.6 Hz, J_2=4.4 Hz, 1H), 3.02–2.99 (m, 1H), 2.96 (s, 6H), 2.88–2.80 (m, 2H), 2.28 (br, 1H), 2.18–2.04 (m, 1H), 1.97–1.95 (m, 1H), 1.81–1.58 (m, 8H), 1.48–1.39 (m, 2H), 1.31–1.27 (m, 4H); ^{13}C NMR (100 MHz, CD_3CN) *δ*: 175.62, 121.51, 118.33, 66.28, 60.69, 50.04, 49.42, 47.05, 46.95, 34.64, 30.62, 29.94, 27.98, 26.02, 24.33, 20.14, 7.60; IR (neat): 3371, 3307, 1659, 1514, 1227, 1197, 1138, 1057 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $[C_{16}H_{32}N_3O]^+$: 282.2540, found: 282.2542; HRMS (ESI^-) *m/z* calcd for $[N(SO_2CF_3)_2]^-$: 279.9178, found: 279.9187.

CIL **1b** was prepared by a similar method as described above in a yield of 91%. $[\alpha]_D^{20}$ −14.2 (*c* 1.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.22 (d, *J*=8.9 Hz, 1H), 4.19 (d, *J*=4.9 Hz, 1H), 3.75 (dd, J_1=9.1 Hz, J_2=5.2 Hz, 1H), 3.38–3.19 (m, 3H), 3.09 (d, *J*=4.4 Hz, 6H), 3.06–3.04 (m, 1H), 2.96–2.88 (m, 2H), 2.27–2.09 (m, 2H), 1.91(br, 1H), 1.86–1.59 (m, 10H), 1.57–1.25 (m, 5H), 0.99 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 176.56, 121.56, 118.36, 67.23, 66.08, 60.79, 51.10, 50.01, 47.51, 35.74, 31.31, 28.29, 26.55, 24.74, 20.39, 19.59, 13.61; IR (neat): 3372, 3307, 1659, 1513, 1226, 1195, 1138, 1057 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $[C_{18}H_{36}N_3O]^+$: 310.2853, found: 310.2857; HRMS (ESI^-) *m/z* calcd for $[N(SO_2CF_3)_2]^-$: 279.9178, found: 279.9182. Anal. Calcd for $C_{20}H_{36}N_4F_6O_5S_2$: C, 40.67; H, 6.14; N, 9.49; found: C, 40.87; H, 6.27; N, 9.30.

4.3. General procedures for the asymmetric Michael addition reaction

To a stirred solution of catalyst **1b** (0.015 mmol) in DCM (1 mL), aldehyde (0.6 mmol), TFA solution of DCM (38 μL, 0.015 mg/μL, 5 mol %), and nitroolefin (0.1 mmol) were added at room temperature. The reaction mixture was stirred for an appropriate time by monitoring on TLC. After completion of the reaction, the solvent was removed and the residue was extracted with diethyl ether (2 mL×3) and purified by preparative TLC (*n*-hexane/ethyl acetate=4/1) to give the Michael adduct as a colorless oil. The relative (*syn*) and absolute configuration of most products have been determined by comparison with the known ^1H NMR data and HPLC data. The relative (*syn*) and absolute configurations of **8h** and **8m** have been accordingly tentatively assigned.

*4.3.1. (2R,3S)-2-Methyl-4-nitro-3-phenylbutanal (**8a**)*[34,48]. ^1H NMR (400 MHz, $CDCl_3$) *δ*: 9.72 (d, *J*=1.6 Hz, 1H), 7.36–7.15 (m, 5H), 4.82–4.66 (m, 2H), 3.84–3.80 (m, 1H), 2.81–2.76 (m, 1H), 1.01 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 202.42, 136.81, 129.12, 129.09, 128.16, 128.14, 128.06, 78.11, 48.42, 44.00, 12.15. HPLC (Daicel Chiralpak OD-H, *i*-PrOH/hexane=20/80, *λ*=254 nm, flow rate 1.0 mL/min), *syn*-isomer: t_{minor} 18.8 min and t_{major} 27.1 min; *anti*-isomer: t_{minor} 23.7 min and t_{major} 32.3 min.

*4.3.2. (2R,3S)-2-Ethyl-4-nitro-3-phenylbutanal (**8b**)*[34,48]. ^1H NMR (400 MHz, $CDCl_3$) *δ*: 9.72 (d, *J*=2.4 Hz, 1H), 7.36–7.28 (m, 3H), 7.19–7.17 (m, 2H), 4.80–4.60 (m, 2H), 3.82–3.76 (m, 1H), 2.70–2.67 (m, 1H), 1.74–1.65 (m, 1H), 1.53–1.49 (m, 1H), 0.83 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 203.25, 136.75, 129.15, 129.13, 128.24, 128.17, 128.01, 78.58, 54.98, 42.66, 20.37, 11.53. HPLC (Daicel Chiralpak OD-H, *i*-PrOH/hexane=20/80, *λ*=254 nm, flow rate 0.8 mL/min), *syn*-isomer: t_{minor} 18.4 min and t_{major} 22.4 min; *anti*-isomer: t_{minor} 19.8 min and t_{major} 35.2 min.

*4.3.3. (R)-2-((S)-2-Nitro-1-phenylethyl)pentanal (**8c**)*[34,49,50]. ^1H NMR (400 MHz, $CDCl_3$) *δ*: 9.76 (d, *J*=2.4 Hz, 1H), 7.36–7.29 (m, 3H), 7.18–7.16 (m, 2H), 4.72–4.62 (m, 2H), 3.80–3.75 (m, 1H), 2.72–2.68 (m, 1H), 1.50–1.47 (m, 1H), 1.37–1.34 (m, 2H), 1.20–1.17 (m, 1H), 0.80 (t, *J*=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 203.26, 136.71, 129.12, 127.97, 78.42, 53.78, 43.11, 29.46, 19.75, 13.95. HPLC (Daicel Chiralpak OD-H, *i*-PrOH/hexane=10/90, *λ*=254 nm, flow rate 1.0 mL/min), *syn*-isomer: t_{minor} 21.0 min and t_{major} 29.5 min; *anti*-isomer: t_{minor} 25.8 min and t_{major} 46.2 min.

*4.3.4. (2R,3S)-2-Isopropyl-4-nitro-3-phenylbutanal (**8d**)*[34,51]. ^1H NMR (400 MHz, $CDCl_3$) *δ*: 9.93 (d, *J*=2.0 Hz, 1H), 7.37–7.29 (m, 3H), 7.20–7.18 (m, 2H), 4.69–4.54 (m, 2H), 3.93–3.87 (m, 1H), 2.78 (d, *J*=10.8 Hz, 1H), 1.75–1.69 (m, 1H), 1.10 (d, *J*=7.2 Hz, 3H), 0.88 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 204.46, 137.03, 129.18, 128.12, 127.97, 79.03, 58.71, 41.91, 27.94, 21.70, 16.96. HPLC (Daicel Chiralpak AD-H, *i*-PrOH/hexane=2/98, *λ*=254 nm, flow rate 0.5 mL/min), *syn*-isomer: t_{minor} 34.1 min and t_{major} 28.5 min.

*4.3.5. (R)-2-((S)-2-Nitro-1-phenylethyl)hexanal (**8e**)*[33,49]. ^1H NMR (400 MHz, $CDCl_3$) *δ*: 9.71 (d, *J*=2.8 Hz, 1H), 7.35–7.29 (m, 3H), 7.18–7.16 (m, 2H), 4.79–4.64 (m, 2H), 3.80–3.77 (m, 1H), 1.55–1.14 (m, 6H), 0.78 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 203.37, 136.81, 129.13, 128.24, 128.17, 128.01, 78.44, 53.91, 43.16, 28.55, 27.05, 22.49, 13.65. HPLC (Daicel Chiralpak OD-H, *i*-PrOH/hexane=10/90, *λ*=254 nm, flow rate 1.0 mL/min), *syn*-isomer: t_{minor} 18.8 min and t_{major} 24.4 min; *anti*-isomer: t_{minor} 21.1 min and t_{major} 37.4 min.

*4.3.6. (2R,3S)-3-(4-Methoxyphenyl)-2-methyl-4-nitrobutanal (**8f**)*[52,53]. ^1H NMR (400 MHz, $CDCl_3$) *δ*: 9.71 (s, 1H), 7.13–7.07 (m, 2H), 6.87–6.85 (m, 2H), 4.79–4.61 (m, 2H), 3.79 (s, 3H), 2.79–2.71 (m, 1H), 1.01 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 202.51, 159.25, 129.18, 129.12, 128.26, 114.47, 114.43, 78.35, 55.26, 48.74, 44.30, 12.08. HPLC (Daicel Chiralpak OD-H, *i*-PrOH/hexane=10/90, *λ*=254 nm, flow rate 1.0 mL/min), *syn*-isomer: t_{minor} 34.4 min and t_{major} 38.6 min; *anti*-isomer: t_{minor} 41.8 min and t_{major} 46.9 min.

*4.3.7. (2R,3S)-2-Methyl-3-(4-methylphenyl)-4-nitrobutanal (**8g**)*[52]. ^1H NMR (400 MHz, $CDCl_3$) *δ*: 9.71 (d, 1H, *J*=1.6 Hz), 7.15–7.03 (m, 4H), 4.79–4.63 (m, 2H), 3.80–3.74 (m, 1H), 2.78–2.73 (m, 1H), 2.32 (s, 3H), 1.00 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 202.69, 138.10, 133.81, 129.96, 129.90, 128.05, 78.37, 48.85, 43.85, 21.20, 12.22. HPLC (Daicel Chiralpak OD-H, *i*-PrOH/hexane=8/92, *λ*=254 nm, flow rate 0.5 mL/min), *syn*-isomer: t_{minor} 54.7 min and t_{major} 72.2 min; *anti*-isomer: t_{minor} 91.1 min and t_{major} 95.1 min.

*4.3.8. (2R,3S)-2-Methyl-3-(2-methylphenyl)-4-nitrobutanal (**8h**).* ^1H NMR (400 MHz, $CDCl_3$) *δ*: 9.73 (d, 1H, *J*=1.2 Hz), 7.18–7.09 (m, 4H), 4.82–4.63 (m, 2H), 4.23–4.08 (m, 1H), 2.84–2.73 (m, 1H), 2.40 (s, 3H), 0.97 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 202.56, 137.11, 135.61, 131.38, 127.82, 126.84, 125.91, 78.12, 49.29, 39.00, 19.90, 12.27. HPLC (Daicel Chiralpak OD-H, *i*-PrOH/hexane=20/80, *λ*=254 nm, flow rate 0.8 mL/min), *syn*-isomer: t_{minor} 20.2 min and t_{major} 23.7 min; *anti*-isomer: t_{minor} 28.8 min and t_{major} 38.1 min.

*4.3.9. (2R,3S)-3-(4-Bromophenyl)-2-methyl-4-nitrobutanal (**8i**)*[34,53]. ^1H NMR (400 MHz, $CDCl_3$) *δ*: 9.70 (s, 1H), 7.49–7.46 (m, 2H), 7.11–7.05 (m, 2H), 4.82–4.62 (m, 2H), 3.81–3.77 (m, 1H), 2.81–2.73 (m, 1H), 1.01 (d, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ: 201.92, 135.95, 132.27, 129.84, 122.20, 77.83, 48.61, 43.46, 12.23. HPLC (Daicel Chiralpak OD-H, *i*-PrOH/hexane=8/92, λ=230 nm, flow rate 0.8 mL/min), *syn*-isomer: t_{minor} 50.7 min and t_{major} 57.3 min; *anti*-isomer: t_{minor} 65.8 min and t_{major} 68.6 min.

*4.3.10. (2R,3S)-2-Methyl-4-nitro-3-(thien-2-yl)-butanal (**8j**)*[52,53]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.70 (s, 1H), 7.26–7.24 (m, 2H), 6.97–6.90 (m, 2H), 4.80–4.69 (m, 2H), 4.27–4.17 (m, 1H), 2.86–2.75 (m, 1H), 1.14 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.04, 139.16, 127.19, 126.82, 125.45, 78.41, 48.98, 40.09, 11.81. HPLC (Daicel Chiralpak OD-H, *i*-PrOH/hexane=10/90, λ=254 nm, flow rate 0.7 mL/min), *syn*-isomer: t_{minor} 44.4 min and t_{major} 51.2 min; *anti*-isomer: t_{minor} 47.9 min and t_{major} 54.7 min.

*4.3.11. (R)-2-((S)-1-(4-Methoxyphenyl)-2-nitroethyl)pentanal (**8k**)*[33,54,55]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.70 (d, *J*=2.8 Hz, 1H), 7.09–7.07 (m, 2H), 6.88–6.83 (m, 2H), 4.69–4.56 (m, 2H), 3.79 (s, 3H), 3.75–3.63 (m, 1H), 2.67–2.64 (m, 1H), 1.49–1.55 (m, 4H), 0.81 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.43, 159.21, 129.01, 128.44, 114.45, 78.66, 55.23, 53.95, 42.43, 29.43, 19.76, 13.97. HPLC (Daicel Chiralpak OD-H, *i*-PrOH/hexane=10/90, λ=254 nm, flow rate 0.8 mL/min), *syn*-isomer: t_{minor} 32.0 min and t_{major} 35.2 min; *anti*-isomer: t_{minor} 39.0 min and t_{major} 50.8 min.

*4.3.12. (R)-2-((S)-1-(4-Methylphenyl)-2-nitroethyl)pentanal (**8l**)*[38,39]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.69 (d, *J*=2.8 Hz, 1H), 7.15–7.39 (m, 4H), 4.69–4.58 (m, 2H), 4.13–4.07 (m, 1H), 3.76–3.70 (m, 1H), 2.69–2.65 (m, 1H), 2.33 (s, 3H), 1.49–1.15 (m, 4H), 0.80 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.43, 137.88, 133.53, 129.79, 127.80, 78.55, 53.86, 42.81, 29.43, 21.10, 19.78, 13.95. HPLC (Daicel Chiralpak OD-H, *i*-PrOH/hexane=10/90, λ=254 nm, flow rate 0.8 mL/min), *syn*-isomer: t_{minor} 23.4 min and t_{major} 31.7 min; *anti*-isomer: t_{minor} 29.4 min and t_{major} 49.3 min.

*4.3.13. (R)-2-((S)-1-(2-Methylphenyl)-2-nitroethyl)pentanal (**8m**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.72 (d, *J*=3.2 Hz, 1H), 7.22–7.18 (m, 3H), 7.12–7.10 (m, 1H), 4.66 (d, *J*=3.2 Hz, 2H), 4.13–4.07 (m, 1H), 2.71–2.66 (m, 1H), 2.39 (s, 3H), 1.57–1.26 (m, 4H), 0.79 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.55, 136.97, 135.31, 131.22, 127.71, 126.85, 125.89, 78.20, 54.51, 37.90, 29.48, 20.12, 19.79, 13.91. HPLC (Daicel Chiralpak OD-H, *i*-PrOH/hexane=20/80, λ=254 nm, flow rate 0.8 mL/min), *syn*-isomer: t_{minor} 22.2 min and t_{major} 25.1 min; *anti*-isomer: t_{minor} 36.0 min and t_{major} 45.3 min.

*4.3.14. (R)-2-((S)-1-(4-Bromophenyl)-2-nitroethyl)pentanal (**8n**)*[39]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.70 (d, *J*=2.4 Hz, 1H), 7.49–7.45 (m, 2H), 7.07–7.05 (m, 2H), 4.72–4.61 (m, 2H), 3.78–3.73 (m, 1H), 2.71–2.66 (m, 1H), 1.48–1.15 (m, 4H), 0.82 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.74, 135.88, 132.32, 129.67, 122.17, 78.12, 53.50, 42.55, 29.48, 19.67, 13.94. HPLC (Daicel Chiralpak OD-H, *i*-PrOH/hexane=10/90, λ=240 nm, flow rate 0.5 mL/min), *syn*-isomer: t_{minor} 60.2 min and t_{major} 65.8 min; *anti*-isomer: t_{minor} 76.9 min and t_{major} 98.6 min.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.05.030. These data include MOL files and InChiKeys of the most important compounds described in this article.

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