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Asymmetric Michael addition promoted by (*R,R*)-*trans*-1,2-diaminocyclohexane in ionic liquids

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Abstract

In tetrafluoroborate based ionic liquids fair yields and enantiomeric excesses up to 91% were obtained in the Michael addition of ethyl cyclohexanone-2-carboxylate to methyl vinyl ketone, using (*R,R*)-*trans*-1,2-diaminocyclohexane as chiral auxiliary (37% mol/mol with respect to the donor). The presence of catalytic amounts of metal sources [$Ni(OAc)_2 \cdot 4H_2O$, $Co(acac)_2$, $FeCl_3 \cdot 6H_2O$, $LaCl_3$, $Cu(OAc)_2 \cdot H_2O$] did not improve the activity, and, in some instances, caused a drop of enantioselectivity. Reactions carried out in the absence of any metal and with a Michael donor/diamine molar ratio of 20 allowed us to ascertain that the reaction can be performed catalytically.

Keywords: Michael additions; Chiral auxiliary; Ionic liquids; Enantioselectivity

1. Introduction

The Michael addition of 1,3-dicarbonyl compounds to activated olefins is an extremely versatile C–C bond forming tool [1]. In particular, asymmetric Michael addition has provided an easy access to chiral precursors of many functional compounds [2]. The asymmetric induction has been achieved either using chiral metal complexes as catalysts, or by means of classic chiral auxiliaries [3]. Among the metal containing systems [4], heterobimetallic chiral complexes based on alkali metal and lanthanides [5] revealed to be highly selective catalysts for asymmetric addition of β-keto esters to cyclic 2-enones, while chiral copper complexes derived from natural aminoacids [6] and nickel(II) acetate in presence of (*R,R*)-*trans*-1,2-diaminocyclohexane [7] showed high enantioselectivity in the reaction between cyclic β-keto esters and methyl vinyl ketone. Recent examples of chiral auxiliaries [8] applied to enantioselective Michael additions include, among the others [9], proline [10] and pyrrolidines [11].

Ionic liquids (ILs) have emerged as potentially useful reaction media in catalysis because of their peculiar physical and chemical properties. The latest efforts of the scientific community have been addressed towards finding new, possibly recyclable, catalytic systems that exhibit higher activity than those obtainable with classic solvents [12]. We were the first to study metal catalysed Michael additions in ILs showing that the catalytic system based on nickel(II) acetylacetonate in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) is very efficient in the addition of acetylacetone to methyl vinyl ketone and can be easily recycled several times without loss of activity [13]. ILs have been reported as

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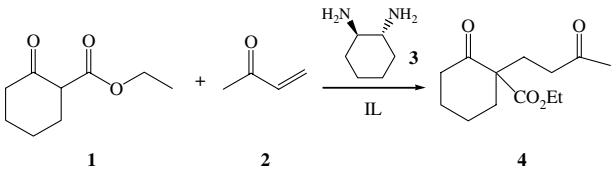


Scheme 1.

suitable solvents also for asymmetric Michael additions using aminoacids as chiral auxiliaries [14], quininium bromide as phase transfer catalyst [15] or cationic palladium complexes in the presence of BINAP derivatives [16] as catalysts.

This paper deals with the asymmetric Michael addition of ethyl cyclohexanone-2-carboxylate (**1**) to methyl vinyl ketone (**2**) in ionic liquids (Scheme 1) facilitated by (*R,R*)-*trans*-1,2-diaminocyclohexane (**3**), a chiral auxiliary successfully used for the first time in the absence of any metal source.

2. Results and discussion

Table 1 collects selected results obtained in the reaction of Scheme 1.

The slow addition of **2** to the mixture obtained by stirring **1** and **3** in [bmim]BF_4 at 25 °C gave the adduct **4** with enantiomeric excess that depended on the time of stirring of **1** and **3**. When the stirring lasted 3 h, a 40% isolated yield in **4** and 58% ee after 24 h was obtained (entry 1), whereas an 82% ee was achieved after 24 h when the stirring lasted 16 h (entry 2). These experimental conditions (stirring of **1** and **3** for 16 h, then addition of **2**) were followed for all reactions (except entry 1) reported in Table 1.

The yields in Michael adduct obtained in [bmmim]BF_4 (bmmim: 1-*n*-butyl-2,3-dimethylimidazolium) or [bupy]BF_4 (bupy: *n*-butylpyridinium) were lower than that achieved in [bmim]BF_4, while the enantioselectivity remained unaltered. The reaction in [bmmim]BF_4 resulted in a 50% yield and an 80% ee (entry 3), while using [bupy]BF_4 a 34% yield was achieved (entry 4). Employing the diamine *R*-(+)-2,2′-diamino-1,1′-binaphthalene (**5**), L-hystidine and L-proline as potential chiral auxiliaries in [bmim]BF_4, gave no reaction (entries 5–7).

When the reaction with **3** in [bmim]BF_4 was carried out at 0 °C an increase of enantioselectivity was registered (92% ee, entry 8).

In principle, **3** can facilitate the Michael addition of Scheme 1 through two different pathways. It can abstract the proton in the α position of the donor, thus, triggering a basic catalysis leading to a racemic mixture of the product. In alternative, the diamine can react with **1** forming a composite mixture of isomers **6a–c** in prototropic equilibrium (Fig. 1).

Among the compounds depicted in Fig. 1, the enaminoesters **6b–c** are able to attack methyl vinyl ketone giving the corresponding Michael adduct.

The observed enantioselectivity, together with the detection of variable amounts of the diastereomeric (di)imines of the product [17] strongly supports the mechanism via enamine. According to this hypothesis, the relative abundance of active isomers **6b–c** has to be responsible for the observed enantioselectivity. This can also account for the different ee values registered varying the time of stirring of **1** and **3**. In fact, allowing the system to reach the thermodynamic equilibrium (16 h of stirring) gave higher ee values compared with those obtained after only 3 h stirring, a time presumably insufficient to reach the equilibrium [18]. GC–MS analyses of mixtures of **1** and **3** revealed that the condensation reaction is already complete after 3 h, but prolonging the stirring up to 16 h, the relative amount of the isomers **6a–c** changes. In particular, after 3 h stirring the reaction mixture contains nearly equimolar amounts of **6a–c**, whereas after 16 h their ratio changes and one of them becomes clearly predominant. ^1H, $^{13}C\{^1H\}$, ^1H–^{13}C HSQC and ^1H–^1H COSY NMR spectra of the isomeric mixture obtained after 16 h stirring indicate that the major isomer present is **6c**, the species presumably responsible for good enantioselectivity.

The lack of reactivity observed with the aromatic diamine **5** or with the aminoacids (entries 5–7 of Table 1) can be ascribed to the lack of imine formation (as confirmed by GLC analysis).

Previous work carried out by Christoffers et al. on $Ni(OAc)_2 \cdot 4H_2O$ catalysed Michael reaction performed in chloroform and in presence of **3** [7] showed that the isolated yield of the products did not exceed the amount of applied chiral diamine. In particular, the reaction between **1** and **2** gave a 37% yield using 37% (in mol with respect to **1**) of **3**. Noteworthy, neither the nickel salt nor the chiral ligand catalysed the reaction when used separately.

Table 1
Screening of ILs and auxiliaries

Entry	Auxiliary	Ionic liquid	Isolated yield (%)	ee (%)
1[a]	**3**	[bmim]BF_4	40	58
2	**3**	[bmim]BF_4	64	82
3	**3**	[bmmim]BF_4	50	80
4	**3**	[bupy]BF_4	34	81
5	**5**	[bmim]BF_4	–	–
6	L-hystidine	[bmim]BF_4	–	–
7	L-proline	[bmim]BF_4	–	–
8[b]	**3**	[bmim]BF_4	34	92

Reaction conditions: solvent mass: 1.2 g, molal concentration of **3** = 0.31 mol/kg, molal concentration of **1** = 0.83 mol/kg, **2/1** = 1.4 mol/mol, T = 25 °C, stirring of **1** and **3** for 16 h, then addition of **2**, reaction time = 24 h.

[a] Stirring of **1** and **3** for 3 h, then addition of **2**.

[b] T = 0 °C, reaction time = 48 h.

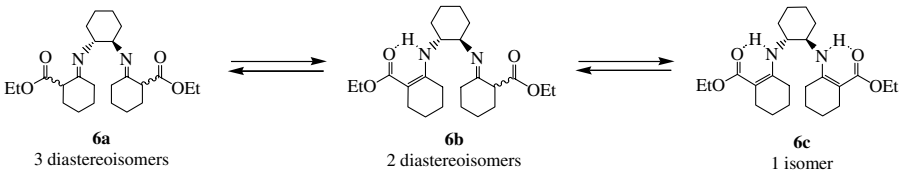


Fig. 1. Prototropic equilibria involving the adducts between **1** and **3**.

In order to exploit a possible synergic effect of a metal in conjunction with **3**, we have added several metal sources to the system comprised of **1**, **2** and **3** in [bmim]BF_4 at 25 °C. The relevant results are reported in Table 2 and show the influence of the metal (added after 16 h reaction between **1** and **3**, procedure A) on the reaction. It is apparent that a substantial retention of enantioselectivity was accompanied by a drop of activity in the cases of $Ni(OAc)_2 \cdot 4H_2O$, $Co(acac)_2$, $FeCl_3 \cdot 6H_2O$ and $LaCl_3$ (entries 1–4). No variation in activity was observed with $Cu(OAc)_2 \cdot H_2O$ (entry 5).

These results could be explained admitting that in all cases coordination of the formed enaminoester to Ni, Co, Fe or La, leads to a supposedly inactive complex and accounts for the observed lower yields. In the case of Cu, it could not be ascertained whether the enaminoester **6** coordinated to the metal preserves its activity in the Michael addition or it reacts outside the copper coordination sphere.

Further experiments were carried out by stirring **1**, **3** and the metal source in IL for 16 h before the addition of **2** (procedure B), in order to test whether a chiral complex possibly formed between metal and **3** could enantioselectively catalyse the Michael addition, avoiding at the same time the detrimental formation of metal complexes with **6a**–**b**. However, ee values reported in Table 2 and ranging from 18% to 82% indicate that metal-free reactions represent the best protocol for the title addition and that, following the experimental procedure B, an achiral metal catalysed pathway could be also operative in the cases of Ni, Co and La.

A last issue was examined: the possibility to carry out the reaction of Scheme 1 catalytically. The detection (by GC–MS) of product **4** in the mixture after reaction indicates that the donor in excess (or the water produced during the formation of enaminoesters **6a**–**c**) is able to liberate **4**, which can be isolated in up to 64% yield *without prior hydrolysis of the reaction mixture* (see Section 3). However, the relative amounts of **3** (which possesses two active NH_2 groups) and **1** employed in this study (**1**/**3** molar ratio of 2.7) did not allow us to discriminate whether the chiral auxiliary could give rise to more than one reaction cycle.

To this purpose, we have carried out the Michael addition using a **1**/**3** molar ratio of 20. The reaction went to completion within 6 days and gave 83% isolated yield of **4**, thus, demonstrating that it proceeded catalytically.

In conclusion, we have demonstrated that, in ionic liquids, **3** acts as chiral auxiliary for the addition of **1** to **2** giving enantiomeric excesses up to 91%. A possible role of the IL might be to favor the first step of the reaction, that is the enamine formation. In this regard, decreasing solvating ability towards water in the series bmim–bmmim–bupy [BF_4] [19] could be responsible for the difference in activity observed. The reaction, on which a detrimental effect of various metals has been ascertained, can be performed catalytically.

Table 2
Screening of metal sources

Entry	Catalyst	Ionic liquid	Isolated yield (%)	ee (%)[a]
1	$Ni(OAc)_2 \cdot 4H_2O$/**3**	[bmim]BF_4	38	80 (28)
2	$Co(acac)_2$/**3**	[bmim]BF_4	43	81 (18)
3	$FeCl_3 \cdot 6H_2O$/**3**	[bmim]BF_4	43	83 (80)
4	$LaCl_3$/**3**	[bmim]BF_4	42	83 (61)
5	$Cu(OAc)_2 \cdot H_2O$/**3**	[bmim]BF_4	67	84 (82)

Reaction conditions: procedure A; solvent mass: 1.2 g, molal concentration of metal = 0.042 mol/kg, molal concentration of **3** = 0.31 mol/kg, molal concentration of **1** = 0.83 mol/kg, **2**/**1** = 1.4 mol/mol, T = 25 °C, reaction time = 24 h.

[a] Values in parenthesis refer to reactions carried out with procedure B.

3. Experimental

All the manipulations were conducted under an inert atmosphere (nitrogen) using standard Schlenk techniques. All commercial reagents were used as received without further purification. Solvents were dried and distilled under nitrogen according to standard procedures; water (resistivity >17.5 MΩ cm^{-1}) was deionised with a Millipore Simplicity unit. Flash-chromatography was performed on silica gel Kieselgel 230–400 mesh. The NMR spectra were recorded with a Bruker AX400 spectrometer (400 MHz for ^1H) at 295.0 K; chemical shifts are reported in ppm referenced to $SiMe_4$ for ^1H and ^{13}C. Enantiomeric excesses were assessed by GLC analyses performed on an HP6890 instrument equipped with a Supelco BETA DEX 120 chiral column (30 m × 250 μm × 0.25 μm). The racemic mixture of **4** used in the standardisation of the analysis was prepared according to a literature procedure [20]. GC–MS analyses were performed with an HP6890-HP5973MSD instrument equipped with an HP-5MS capillary column (30 m × 250 μm × 0.25 μm). [bmim]BF_4, [bmmim]BF_4, [bupy]BF_4 were synthesised by metathesis from the relevant

chloride salts with $NaBF_4$ in dichloromethane; the resulting suspensions were filtered through Celite and washed with the minimum amount of water until the $AgNO_3$ test on the aqueous layer was negative. The solvent was then evaporated and the resulting ILs dried at 40–50 °C under vacuum for 48 h and stored under nitrogen. The ionic liquids were obtained as pale-yellow ([bupy]BF_4) or colourless liquids and characterised by multinuclear NMR spectroscopy. Their chloride content was determined in aqueous solution by a potentiometric automatic titration using a Metrohm 716 DMS Titrino (AgCl electrode, 300 mg sample, ca. 30 ml deionised water, three replicates, chloride content was lower than the detection limit of 0.38 mg/l for all ILs), while the water content was determined by the Karl–Fischer method using a Metrohm 716 DMS Titrino equipped with a 703 Titration Stand using sodium tartrate-dihydrate as standard and dry methanol as solvent (1 g sample, ca. 30 ml MeOH, three replicates, water content was lower than 460 ppm for all ILs).

3.1. Typical procedure for Michael additions promoted by **3**

A mixture of **3** (42.8 mg, 0.375 mmol) and **1** (170.0 mg, 1.000 mmol) in ionic liquid (1.2 g) was stirred for 16 h at 25 °C, then methyl vinyl ketone (98.0 mg, 1.400 mmol) was added portion-wise (10 μl/min, ca. 6 h) under magnetic stirring at the desired temperature (25 or 0 °C). After further 18 h of stirring at the same temperature, the product was extracted with diethyl ether (5 × 2 ml) and purified by preparative TLC (silica gel, Et_2O/petroleum ether 40–60 °C = 1/1, $R_f = 0.41$). The enantiomeric excess was determined after conversion of **4** into its cyclisation product ethyl bicyclo[4.4.0]dec-1-en-3-one-6-carboxylate. Compound **4** was dissolved in a threefold volume of conc. H_2SO_4 and stirred for 16 h at 50 °C. Ice was added to the mixture and the cyclisation product was extracted with diethyl ether from the resulting aqueous solution. After washing with saturated aqueous solution of $NaHCO_3$ and drying with Na_2SO_4, the product was obtained by solvent evaporation under reduced pressure.

MS (EI, 70 eV); *m/z* (%): 222 (54) $[M]^+$, 149 (100), 138 (24), 122 (52), 107 (50), 91 (46), 79 (44). Chiral GLC: isotherm elution at 120 °C, $t_1 = 248$ min, $t_2 = 264$ min.

3.2. Ethyl 2-oxo-1-(3-oxobutyl)cyclohexanecarboxylate (**4**)

MS (EI, 70 eV); *m/z* (%): 240 (1) $[M]^+$, 212 (17), 194 (35), 170 (100), 151 (72), 124 (70).

IR (film, CsI, *v*, cm^{-1}): 2940, 2867, 1741, 1448, 1368, 1299, 1245, 1219, 1189, 1169, 1137, 1096, 1080, 1063, 1021, 530.

^1H NMR ($CDCl_3$, 400 MHz, 295 K, δ, ppm): 1.26 (t, 3H, $J = 7.1$, OCH_2CH_3), 1.45 (m, 1H, CH*H*), 1.62 (m, 2H, CH_2), 1.75 (m, 1H), 1.83 (ddd, $J = 15.7$, 10.3, 5.4, 1H, CH*H*), 1.98 (m, 1H, C*H*H), 2.07 (ddd, $J = 15.4$, 10.2, 5.2, 1H, CH*H*), 2.11 (s, 3H, CH_3), 2.34 (ddd, $J = 17.7$, 10.2, 5.4, 1H, CH*H*), 2.43 (m, 2H, CH_2), 2.46 (m, 1H, C*H*H), 2.56 (ddd, $J = 17.7$, 10.3, 5.3, 1H, C*H*H), 4.18 (m, 2H, OCH_2CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz, δ, ppm): 14.1 (OCH_2CH_3), 22.5 (CH_2), 27.5 (CH_2), 28.3 (CH_2), 29.8 (CH_3), 36.6 (CH_2), 38.7 (CH_2), 40.9 (CH_2), 59.9 (C), 61.3 (OCH_2CH_3), 171.9 (CO_2Et), 207.7 (C=O), 207.9 (C=O).

3.3. Typical procedures for Michael additions promoted by **3** in the presence of metal source

Procedure A. A mixture of **3** (0.375 mmol) and **1** (1.000 mmol) in [bmim]BF_4 (1.2 g) was stirred for 16 h at 25 °C, then the metal source (0.05 mmol) was added. The mixture was magnetically stirred for further 1 h before the portion-wise addition (10 μl/min, ca. 6 h) of methyl vinyl ketone (98.0 mg, 1.400 mmol) at 25 °C. After further 18 h stirring at the same temperature, the product was extracted with diethyl ether (5 × 2 ml) and purified by preparative TLC (silica gel, Et_2O/petroleum ether 40–60 °C = 1/1, $R_f = 0.41$).

Procedure B. A mixture of the metal source (0.05 mmol), **3** (0.375 mmol) and **1** (1.000 mmol) in [bmim]BF_4 (1.2 g) was magnetically stirred for 16 h at 25 °C, then methyl vinyl ketone (98.0 mg, 1.400 mmol) was added portion-wise (10 μl/min) at 25 °C. After further 18 h stirring, the product was isolated as described above.

3.4. Adducts **6a–c**

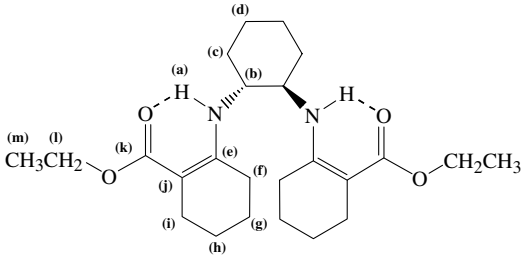
Compound **1** (340 mg, 2.00 mmol) was added to a magnetically stirred solution of **3** (86 mg, 0.75 mmol) in [bmim]BF_4 (2.4 g) at room temperature. After 16 h the adducts **6a–c** were extracted with diethyl ether (5 × 2 ml) and purified by flash chromatography (silica gel, Et_2O/petroleum ether 40–60 °C = 1/4, $R_f = 0.57$).

MS (EI, 70 eV); *m/z* (%): 372 (19) $[M - EtO - H]^+$, 344 (6) $[M - CO_2Et - H]^+$, 299 (100) $[M - CO_2Et - EtO - H]^+$, 279 (75), 204 (19) $[M - C_6H_9(CO_2Et)(NH)]^+$.

IR (film, CsI, *v*, cm^{-1}): 3265, 3162, 2977, 2933, 2857, 1744, 1716, 1643, 1596, 1454, 1425, 1403, 1362, 1298, 1257, 1225, 1180, 1163, 1125, 1101, 1080, 1061, 832, 777, 732.

NMR features of the major isomer (**6c**, see figure below): ^1H ($CDCl_3$, 400 MHz, δ, ppm): **(a)** 8.96 (d, $J = 9.2$ Hz, 1H), **(b)** 3.03 (m, 1H), **(c)** 1.23 (m, 1H) and 1.88 (m, 1H), **(d)** 1.19 (m, 1H) and 1.67 (m, 1H), **(f)**, **(g)**, **(h)**, **(i)**, 1.26 (m, 1H), 1.39 (m, 2H), 1.51 (m, 1H), 2.00 (m, 1H), 2.10 (m, 2H), 2.21 (m, 1H), **(l)** 3.97 (dq,

^2J = 10.7 Hz, ^3J = 7.2 Hz, 1H) and 4.04 (dq, ^2J = 10.7 Hz, ^3J = 7.2 Hz, 1H), **(m)** 1.16 (t, ^3J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ (101 MHz, $CDCl_3$, δ, ppm): **(b)** 57.3, **(c)** 33.5, **(d)** 25.0, **(e)**, **(k)**, 159.6, 171.0, **(j)** 89.1, **(f)**, **(g)**, **(h)**, **(i)**, 22.3, 22.4, 23.9, 26.5, **(l)** 58.4, **(m)** 14.6.



6c

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[17] TLC analysis (silica gel, Et2O/petroleum ether 40–60 °C = 1/1; R_f = 0.74) of the mixtures after reaction shows in all cases the presence of the (di)imine of **4**. In one experiment it was isolated by flash chromatography and characterised by ^1H and $^{13}C\{^1H\}$ NMR and by acidic hydrolysis which liberated **4**.
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