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Stereoselective *Michael* Addition of Carbonyl Compounds to (*E*)-*β*-Nitrostyrene Catalysed by *N*-Toluensulfonyl-L-proline Amide in Ionic Liquids

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Summary. *N*-Toluensulfonyl-L-prolin amide was tested as catalyst in the enantioselective *Michael* addition of carbonyl compounds to (*E*)-*β*-nitrostyrene in nine ionic liquids under different reaction conditions. The reaction rates and enantioselectivities were strongly dependent on the ionic liquids. Change of enantioselectivity was observed too and it is attributed to both the cation and the anion of ionic liquid. The best yields (up to 98%) and enantioselectivity (70% *ee*) of product were obtained in a basic ionic liquid [*bmim*]BF_4 at room temperature.

Keywords. Ionic liquids; *Michael* addition; Enantioselectivity; Organocatalysis.

Introduction

The asymmetric transformations of carbonyl compounds by chiral amines as are *α*-amino acids, especially L-proline and its derivatives as organocatalysts are well known. The crucial intermediate is an enamine formed from the ketone. Enamine catalysis has been applied to both intramolecular and intermolecular aldol reactions, *Mannich* reactions, addition to azodicarboxylates as well as to nitrosobenzene, *Michael* additions, *α*-alkylations of aldehydes, *etc*. Using the *MacMillan*'s chiral amines as the organocatalysts the crucial intermediate is an minimum salt. Such catalysis has been used for highly enantioselective *Diels-Alder* reactions, 1,3-dipolar cycloadditions, epoxidations, cyclopropanations, *etc*. [1].

L-Proline is a very attractive and useful organocatalyst. It is nontoxic, inexpensive, no stringent to special reaction conditions (temperature, inert atmosphere . . .), and it is available in both enantiomeric forms. On the other hand, fine-tuning of its catalytic properties by derivatization is difficult. *N*-Sulfonylation of proline amide has resulted in an organocatalyst having comparable NH acidity as L-proline. The advantage of such a sulfonamide catalyst is the possibility of electronic and steric fine-tuning of the catalyst by variation of substituents on the aryl residue [2].

N-Arylsulfonyl derivatives of L-proline amide have been applied to enantioselective aldol reactions of aromatic aldehydes with acetone in *DMSO*. Compared to L-proline, the enantioselectivity was improved while maintaining high activity at low catalyst loadings [2]. Both the chemical yields and the enantioselectivities of the aldol reactions catalysed by *N*-toluenesulfonyl-L-proline amide in 1-butyl-3-methylimidazolium hexafluorophosphate and 1-butyl-1-methylpyrrolidinium tris(pentafluoroethyl) trifluorophosphate ionic liquids were comparable to those in *DMSO*. The undoubted advantage is that the ionic liquid containing the catalyst is recyclable and the chemical yield as well as the enantiopurity of the product remained at a comparable level as in the case of fresh catalyst [3].

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Michael addition of carbonyl compounds to (*E*)-β-nitrostyrene catalysed by chiral amines in classical organic solvents are well known [4–10]. Additions have been performed with high diastereoselectivity (*syn*/*anti* up to 95/5), but with very different enantioselectivity (20–99% *ee*). Stereoselectivity of the additions was strongly dependent on the catalyst as well as on the solvent. The best results have been obtained with polar nonprotic solvents, such as *DMF* and *NMP* [9].

Michael additions of different carbonyl compounds to (*E*)-β-nitrostyrene and 2-(β-nitrovinyl)-thiophene catalysed by various organocatalysts in ionic liquids were described for the first time by *Kotrusz et al.* [11]. The ionic liquids were shown to be good solvents for additions of various donors to (β-nitrovinyl)arenes. L-Proline was found to be the best among seven catalysts tested. Just 5 mol% of this catalyst were necessary to reach reasonable to high yields. Aldehydes proved to be much better donors than ketones.

The good solubility of L-proline in ionic liquids could be likely the reason for better enantioselectivity than that obtained in classical organic solvents. The catalytic activity of L-proline was strongly dependent on the nature of the ionic liquids. The structure of ionic liquids influenced the yield and selectivity of the process [12].

The main aim of this work was to examine the course of the *Michael* addition of carbonyl compounds to (*E*)-β-nitrostyrene catalysed by *N*-toluenesulfonyl-L-proline amide in various ionic liquids.

Results and Discussion

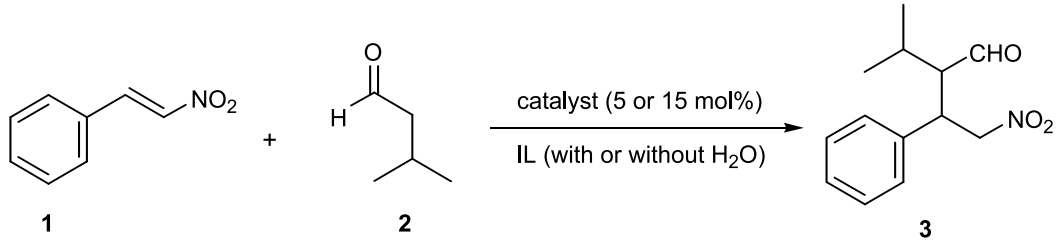
We started our work with a study of *Michael* addition of 3-methylbutanal (**2**) to (*E*)-β-nitrostyrene (**1**) catalysed by *N*-toluenesulfonyl-L-proline amide (Fig. 1) (5 mol%) in **IL4** under different reaction conditions (Scheme 1). The results are given in Table 1.

Since the addition of 3-methylbutanal (**2**) to (*E*)-β-nitrostyrene (**1**) in **IL4** was sluggish and after five day reaction at room temperature we isolated only 40% of the product **3**, we tried to improve the reaction course by increasing the reaction temperature. Reaction performed at 60°C gave after 1 day 44% of **3** and the enantioselectivity did not change (Entries 1 and 2). This observation is in accordance with those observed at organocatalytic enantioselective aziridination of α,β-unsaturated aldehydes [13] and asymmetric α-aminomethylation of cyclohexanones [14], which were thermally accelerated, but the enantioselectivity did not drop.

Increasing the *Michael* donor amount from 1.5 equiv. to 5 equiv. resulted in slight rate enhancement, but the enantioselectivity dropped from 32 to 20% *ee* (Entry 3).

The beneficial effect of water addition in proline-catalyzed aldol reactions is well known. Water might help to increase the solubility of the catalyst in reaction media and it might also assist in the hydrolysis of the oxazolidinones that might be forming from carbonyl compounds and catalyst [15]. Addition of 5 equiv. of water to the reaction mixture of **1** and **2** in **IL4** accelerated the reaction. We isolated 64% of **3** after 2 days instead of 40% after 5 days, when the reaction proceeded without water. On the other hand the enantioselectivity dropped from 32 to 18% *ee* (Entry 4). Increasing the amount of water to 10 equiv. resulted in further acceleration, 83% of **3** was isolated after one day reaction. The enantioselectivity slightly increased to 24% *ee* (Entry 5). Addition of 20 equiv. water slowed down the reaction rate as well as the enantioselectivity. The product **3** was isolated after 2 days in 41% yield with 12% *ee* (Entry 7). This observation was probably due to formation of a two-phase reaction system after addition of 20 equiv. of water.

Organocatalysts in ionic liquids can be reused in several reaction cycles without significant changes of the reaction course [11]. Therefore we tried to



Scheme 1

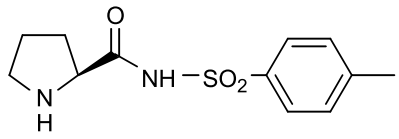


Fig. 1. Structure of the catalyst *N*-toluenesulfonyl-L-proline amide

perform the addition of 3-methylbutanal (**2**) to (*E*)-β-nitrostyrene (**1**) in the recycled catalyst in **IL4** with 10 equiv. of water (Entry 6). Yield of **3** obtained in the recycled IL-water-catalyst reaction system dropped from 83% to 70%, while the enantioselectivity remained unchanged (24%).

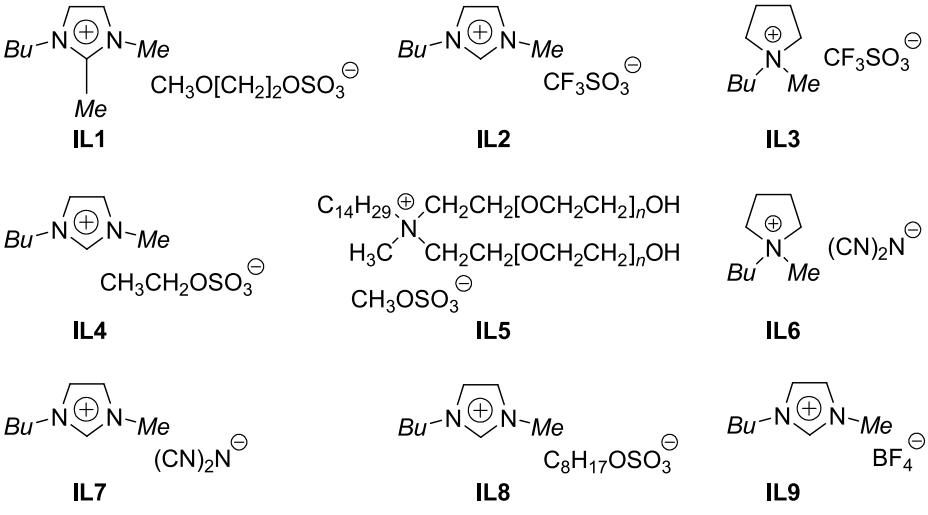
It has been described [9] that the stereoselectivity of additions of ketones to (*E*)-β-nitrostyrene catalyzed by 1,2-amino-alcohol-derived prolineamides were strongly dependent on the solvent. The catalysts exhibited the highest activity in polar aprotic solvents such as *DMF* and *NMP*. These literature data inspired us to study the *Michael* addition of 3-methylbutanal to (*E*)-β-nitrostyrene catalysed by *N*-toluenesulfonyl-L-proline amide in various ionic liquids (Fig. 2).

Table 1. Results of *Michael* addition of **2** to **1** catalysed by *N*-toluenesulfonyl-L-proline amide in **IL4** under different reaction conditions

Entry	Water/ eq.	Time/ days	Temp./ °C	Yield[c]/ %	*ee*[d]/ % ([e])
1	0	5	20	40	32 (−)
2	0	1	60	44	34 (−)
3	0[a]	4	20	65	20 (−)
4	5	2	20	64	18 (−)
5	10	1	20	83	24 (−)
6	10[b]	1	20	70	24 (−)
7	20	2	20	41	12 (−)

[a] Reaction was performed with 5 equiv. **2**
[b] Reaction was performed in recycled IL-catalyst system
[c] *dr* (*syn*/*anti*) values (90/10–95/5) were determined using ^{1}H NMR spectra
[d] *ee* values were determined by HPLC
[e] Sign of optical rotation

Ionic liquids are known to be not only solvents, but they can play also a role as catalyst. Many reactions in acidic and basic ionic liquids as reaction media with catalytic activity have been described [16]. Such



IL1 1-Butyl-2,3-dimethylimidazolium ethylenglykolmonomethylethersulfate
IL2 1-Butyl-3-methylimidazolium trifluoromethanesulfonate
IL3 1-Butyl-1-methylpyrrolidinium trifluoromethanesulfonate
IL4 1-Ethyl-3-methylimidazolium ethylsulfate
IL5 *Peg*-5 cocomonium methylsulfate (ECOENG^{TM}500)
IL6 1-Butyl-1-methylpyrrolidinium dicyanamid
IL7 1-Butyl-3-methylimidazolium dicyanamid
IL8 1-Butyl-3-methylimidazolium octylsulfate (ECOENG^{TM}418)
IL9 1-Butyl-3-methylimidazolium tetrafluoroborate

Fig. 2. Structures of ionic liquids

Table 2. Results of *Michael* addition of **2** to **1** in various ionic liquids under different conditions

IL	*pH* IL	Water/eq.	Catalyst/mol%	Time/days	Yield[a]/%	*ee*[b]/% ([c])
IL1	1.58 (22.8°C)	0	5	7	traces	–
		10	5	7	traces	–
IL2	2.58 (23.2°C)	0	5	6	traces	–
		10	5	6	50	18 (−)
		0	15	6	68	36 (−)[d]
IL3	3.09 (22.9°C)	0	5	7	traces	–
		10	5	5	38	20 (−)
		0	15	6	62	36 (−)
IL4	4.33 (22.2°C)	0	5	5	40	32 (−)
		10	5	1	83	42 (−)
		0	15	2	80	38 (−)
IL5	7.01 (22.7°C)	0	5	1	traces	–
		10	5	1	95	28 (+)
		0	15	1	92	30 (+)
IL6	7.09 (23.1°C)	0	5	2	94	34 (+)
		10	5	1	89	20 (+)
		0	15	2	96	42 (+)
IL7	7.09 (23.1°C)	0	15	1	98	28 (+)
IL8	7.89 (22.8°C)	0	5	2	95	18 (+)
		10	5	1	86	30 (+)[e]
		0	15	1	98	42 (+)
IL9	8.32 (22.8°C)	0	5	1	98	32 (+)
		10	5	1	98	70 (+)

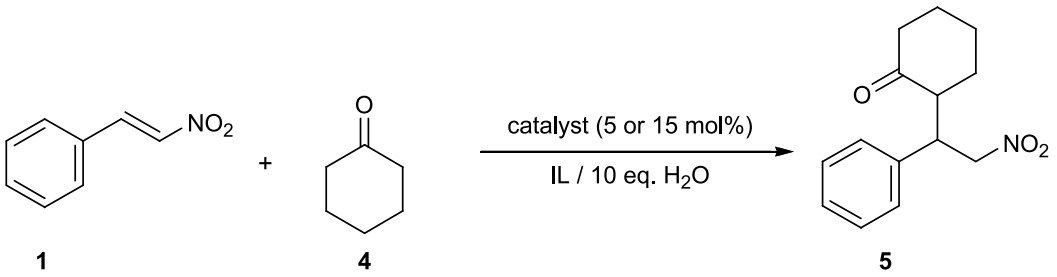
[a] *dr* (*syn*/*anti*) values (90/10–95/5) were determined using ^{1}H NMR spectra
[b] *ee* values were determined by HPLC
[c] Sign of optical rotation
[d] $[\alpha]_D = -15.2\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.77$, $CHCl_3$, $ee = 36\%$)
[e] $[\alpha]_D = +16.5\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.77$, $CHCl_3$, $ee = 30\%$)

ionic liquids usually have a basic or acidic function attached to the alkyl chain. Some non-functionalized ionic liquids are claimed to be acidic or basic, but no *pH* values for them are available. We decided therefore to estimate the *pH* values of ionic liquids used in this paper (**IL1**–**IL7**) as from their 10 vol% solution in water. From the data given in Table 2 it is possible to see that the *pH* values of used ionic liquids varied under these conditions from 1.58 to 8.32.

The diastereoselectivities of all reactions described in this work have been very high. For the *syn*/*anti* ratio values of 90/10–95/5 were achieved.

Results of *Michael* addition of 3-methylbutanal to (*E*)-β-nitrostyrene catalysed by *N*-toluenesulfonyl-L-proline amide in various ionic liquids are given in Table 2. *Michael* addition of **2** to **1** did not proceed in acidic **IL1** (*pH* 1.58) not even after addition of 10 equiv. water to the reaction mixture. Only traces of the product **3** were detected in the reaction mixture (TLC) after 7 days. In ionic liquids **IL2** (*pH* 2.58) and **IL3** (*pH* 3.09) reaction did not proceed using 5 mol% of the catalyst without water. Addition of 10 equiv. of water improved the reaction course and 50% (**IL2**) or 38% (**IL3**) of the product **3** were isolated. Performing the reaction with 15 mol% of the catalyst improved the chemical yield to 50% in **IL2** and to 62% in **IL3**. The enantioselectivity increased to 36% for both **IL2** and **IL3**.

Reaction in **IL4** (*pH* 4.33) with 5 mol% of catalyst without water gave after 5 days 40% of the product **3** with 32% *ee*. Addition of water enhanced the rate, yield, and enantioselectivity. Product **3** was isolated in 83% yield with 42% *ee* after 1 day at room temperature. Very similar results were obtained when the addition of **2** to **1** was performed with 15 mol% of the catalyst for 2 days. Product **3** was isolated in 80% yield with 38% *ee*. A positive effect of water on the addition of **2** to **1** was observed also in the neutral **IL5** (*pH* 7.01). When the reaction was performed for 1 day with 5 mol% of the catalyst with 10 equiv. of



Scheme 2

water, we obtained **3** in 95% yield with 28% *ee*. The same results were achieved when the reaction was performed with 15 mol% of the catalyst without water. On the other hand, the reaction did not proceed with 5 mol% of the catalyst, but without water.

Reaction rate as well as enantioselectivity of the addition of **2** to **1** catalysed by *N*-toluenesulfonyl-L-proline amide were the best in basic ionic liquids. Very similar results were achieved in **IL6** (*pH* 7.09) and **IL8** (*pH* 7.89). Using 5 mol% of the catalyst without water we obtained product **3** after 2 days in 94% yield with 34% *ee* (**IL6**) and 95% yield with 18% *ee* (**IL8**), respectively. Addition of water decreased the enantioselectivity in **IL6** from 34 to 20% *ee* and on the other hand, increased the enantioselectivity in **IL8** from 18 to 30% *ee*. Enantioselectivity of the process increased to 42% (**IL6**) and 48% (**IL8**), respectively, when 15 mol% of the catalyst were used in the reaction. Quantitative yield of **3** with 28% *ee* was obtained in **IL7** (*pH* 7.09) when the addition was performed with 15 mol% of the catalyst. The highest enantioselectivity was achieved when the studied reaction was performed in **IL9** (*pH* 8.32). Addition of water to the reaction mixture improved the enantioselectivity to 70%. Without water we obtained the product **3** with only 32% *ee*.

From the results given in Table 2 it follows, that ionic liquids play an active role in organocatalyzed *Michael* addition of **2** to **1**. Very different reaction rates and yields were achieved in various ionic liquids, but interestingly the enantioselectivity was reversed in the reactions in acidic and neutral and basic ionic liquids. While (2*R*,3*S*)-(+)-2-isopropyl-4-nitro-3-phenylbutanal was the major enantiomer isolated from neutral and basic ionic liquids, (2*S*,3*R*)-(−)-2-isopropyl-4-nitro-3-phenylbutanal was isolated as the mayor enantiomer from acidic ionic liquids. Similar results described *Dere et al.* [17]. They observed reversal of enantioselectivity of *Michael* addition of dimethyl malonate to chalkone in [*bmim*]PF_6, [*bmim*]BF_4 (−), and [*bpy*]BF_4 (+). According to this study, the reversal of the enantioselectivity might be attributed to the cation associated with the anion of the ionic liquid.

We also studied the *Michael* addition of cyclohexanone (**4**) to (*E*)-β-nitrostyrene (**1**) in three different ionic liquids with 10 equiv. of water (Scheme 2). As it follows from Table 3 the reactions proceeded with moderate yields. The reaction rate was lower in acidic ionic liquid **IL4** (*pH* 4.33) than in **IL6** (*pH* 7.09) and **IL8** (*pH* 7.89). On the other hand, the highest enantioselectivity was observed in **IL4**. Product **3** was isolated from **IL4** after 2 days in 44% yield with 60% *ee*. The best yield (63%) was achieved in **IL8**, but only 16% *ee* was determined. Product **3** was isolated after 1 day from **IL6** in 53% yield, but no enantioselectivity was observed.

In contrast to addition of 3-methylbutanal, *Michael* addition of **4** to **1** gave (2*S*,1′*R*)-(−)-2-(1-phenyl-2-nitroethyl)cyclohexanone as the major enantiomer both in acidic and basic ionic liquids.

Michael addition of different carbonyl compounds to (*E*)-β-nitrostyrene catalysed by *N*-arylsulfonyl-L-proline amide in ionic liquids is under investigation

Table 3. Results of *Michael* addition of **4** to **1** catalysed by 5 mol% of *N*-toluenesulfonyl-L-proline amide in various ionic liquids with 10 equiv. of water

IL	*pH* IL	Time/days	Yield[a]/%	*ee*[b]/% ([c])
IL4	4.33 (22.2°C)	2	44	60 (−)
IL6	7.09 (22.8°C)	1	53	2 (n.d.)
IL8	7.89 (22.8°C)	1	63	16 (−)

[a] *dr* (*syn*/*anti*) values (90/10–95/5) were determined using ^{1}H NMR spectra

[b] *ee* values were determined by HPLC

[c] Sign of optical rotation

in our laboratory. The change of the stereoselectivity by acidity of the ionic liquids will be scrutinized also.

Experimental

Starting materials, that is (*E*)-β-nitrostyrene and carbonyl compounds were commercially available (Aldrich, Fluka, Acros) and purified by standard methods. Ionic liquids were obtained from Merck (**IL2**, **IL6**, **IL7**, **IL9**) and Solvent Innovation (**IL1**, **IL3**, **IL4**, **IL5**, **IL8**). The catalyst *N*-toluenesulfonyl-L-proline amide was prepared according to the procedure described in Ref. [2]. Column chromatography was performed on Merck silica gel 65/40. Thin-layer chromatography was performed on Merck TLC-plates silica gel 60, F-254. ^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini spectrometer in $CDCl_3$ with *TMS* as an internal standard. The *pH* of ionic liquids (10% aq. solutions) were measured on a WTW inoLab *pH* 720 instrument using a SenTix 81 electrode. Optical rotations were measured on a Perkin-Elmer 241 instrument. Enantiomeric excesses were determined by HPLC using a Chiralpac AD-H (Daicel Chemical Industries) column with *n*-hexane/*i*-propanol (70/30) as a mobile phase and detection by UV-detector at 254 nm.

General Procedure for Michael Addition of Carbonyl Compounds to (E)-β-nitrostyrene

N-Toluenesulfonyl-L-proline amide catalyst (40.25 mg, 5 mol% or 120.75 mg, 15 mol%) was suspended in 3 cm^3 ionic liquid. In some cases, water (5–20 equiv.) was added to the ionic liquids. This mixture was stirred at room temperature for 15 min, then 4.5 mmol carbonyl compounds were added and the reaction mixture was stirred for another 15 min. At the end 450 mg **1** (3 mmol) were added and the reaction mixture was intensively stirred at r.t. for the time given in the Tables and monitored by TLC. The solution was extracted with 15×3 cm^3 ether. The combined organic extracts were concentrated and the residue purified by column chromatography (SiO_2, *n*-hexane/*t*-butyl methyl ether 5/1). The enantiomeric excess was determined by HPLC.

(2R,3S)-(+)-2-Isopropyl-4-nitro-3-phenylbutanal (**3**)

^{1}H NMR data were found to be identical with the data described in Ref. [5]. $[\alpha]_D = +16.5\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.77$, $CHCl_3$, $ee = 30\%$) (Ref. [18] $[\alpha]_D = +53.1\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.77$, $CHCl_3$, $ee = 99\%$) Retention time of the major enantiomer was 7.0 min (HPLC, Daicel Chiralpac AD-H, *n*-hexane/*iPr*OH 70/30, 0.75 cm^3/min, 3.8 MPa).

(2S,3R)-(−)-2-Isopropyl-4-nitro-3-phenylbutanal (**3**)

^{1}H NMR data were found to be identical with the data described in Ref. [5]. $[\alpha]_D = -15.2\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.77$, $CHCl_3$, $ee = 36\%$). Retention time of the major enantiomer was 7.5 min (HPLC, Daicel Chiralpac AD-H, *n*-hexane/*iPr*OH 70/30, 0.75 cm^3/min, 3.8 MPa).

(2S,1′R)-(−)-2-(1-Phenyl-2-nitroethyl)cyclohexanone (**5**)

^{1}H NMR data were found to be identical with the data described in Ref. [19]. $[\alpha]_D = -12.5\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.77$, $CHCl_3$, $ee = 60\%$) (Ref. [19] $[\alpha]_D = +26.8\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1$, $CHCl_3$)) Retention time of the major enantiomer was 9.5 min, retention time of the minor enantiomer was 8.2 min (HPLC, Daicel Chiralpac AD-H, *n*-hexane/*iPr*OH 70/30, 0.75 cm^3/min, 3.8 MPa).

Acknowledgements

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