(*S*)-Pyrrolidin-2-ylmethyl-1,2,3-triazolium Salts – Ionic Liquid Supported Organocatalysts for Enantioselective Michael Additions to β-Nitrostyrenes

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Abstract: (*S*)-Pyrrolidin-2-ylmethyl-1,2,3-triazolium salts were synthesized as new task-specific ionic liquids via click reaction and alkylation. They serve as excellent recyclable catalysts in enantioselective Michael additions to nitrostyrenes in excess of carbonyl compounds as reactant and as solvent providing high yields and stereoselectivities.

Key words: asymmetric organocatalysis, ionic liquids, Michael addition, task-specific ionic liquids

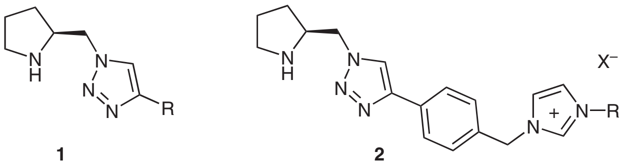

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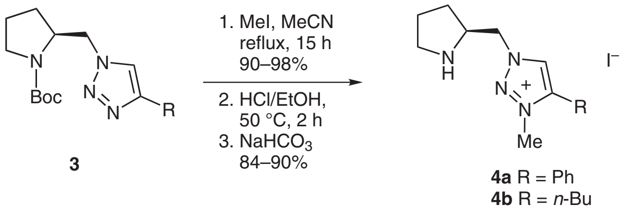
Figure 1



Scheme 1

The Michael addition of CH-acidic carbonyl compounds to nitroalkenes is the major pathway to γ-nitrocarbonyl compounds.[1] The resulting motif can serve as reactant in the synthesis of heterocycles, e.g. chiral lactones,[2] pyrrolidine carboxylic acids,[3] nitrocycloalkanes[4] or β-carbolines.[5] For direct Michael additions to nitroalkenes a number of organocatalytic systems,[6] mainly (*S*)-pyrrolidin-2-ylmethyl or proline derivatives,[3,7–21] were applied providing excellent yields and stereoselectivities. The proline-derived 1,2,3-triazoles **1** (Figure 1) were obtained by Cu(I)-mediated click reaction of (*S*)-*N*-Boc-pyrrolidin-2-ylmethyl azide and alkynes and they allowed to perform the addition of cyclohexanone to 1-nitro-2-arylethenes in water.[22,23] In order to facilitate easy catalyst recycling, Michael additions to nitroalkenes were performed in ionic liquids.[24,25] Further interesting alternative task specific ionic liquids (TSIL) were developed, where (*S*)-pyrrolidin-2-ylmethyl moieties were covalently linked to imidazolium[26,27] or pyridinium rings.[28] Amongst them the triazolylphenyl-linked imidazolium salt **2** was found.[4] Again, high yields and stereoselectivities were achieved and catalyst recycling was straightforward. Their performance was better than normal organocatalysts when dissolved in ionic liquids.

We recently disclosed a versatile novel concept for TSIL, in which 1,2,3-triazolium salts serve as the IL unit and other functions are covalently tethered in the side chains.[29] We sought to verify whether this concept could be applied in order to develop TSIL applicable in the direct asymmetric Michael addition to nitroalkenes. The (*S*)-pyrrolidin-2-ylmethyl group was chosen as chiral moiety. The synthetic route started with (*S*)-*N*-Boc-pyrrolidin-2-ylmethyltosylate, which was transferred to the corresponding azide and then submitted to a Cu(I)-catalyzed click reaction with alkynes according to a reported procedure.[22] The resulting triazoles **3** were alkylated with iodomethane and finally deprotected affording the envisaged TSIL **4**, appearing as yellowish oil **4b** and as low melting solid **4a**, with melting point of 34 °C (Scheme 1).

In comparison with the known TSIL **2** the 1,2,3-triazole ring of our compounds **4** does not only serve as a linker, but also acts as the phase tag for convenient recycling. Due to the closer proximity of the charged phase tag to the organocatalytic pyrrolidine unit, better performance can be expected in our case as is observed in analogues imidazolium compounds **2**.[27]

We checked the performance of the triazolium salts **4** as ionic liquid supported organocatalysts in Michael addition of cyclohexanone to β-nitrostyrenes (Table 1) and studied the addition to β-nitrostyrene in more detail (entries 1–7). The carbonyl component was used in excess as solvent. Excellent yields, diastereoselectivities, and enantioselectivities were obtained in the addition to β-nitrostyrene in the presence of the phenylsubstituted TSIL **4a** (entry 1).[30] The catalyst could be easily recycled by extraction of the reaction mixture with diethyl ether leaving **4a**, which was then combined with a fresh batch of reactants. In the second and third run (entries 2 and 3) slightly reduced, yet still high yields and stereoselectivities were achieved. However, after the catalyst had been recycled for the third time, the enantioselectivity dropped to 58%. Reduction of the amount of catalyst **4a** to 5 mol% continued to give excellent yield and diastereoselectivity, but a

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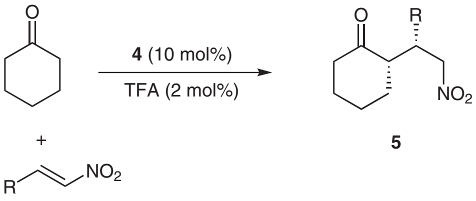
Table 1 Michael Addition of Cyclohexanone to β-Nitrostyrenes



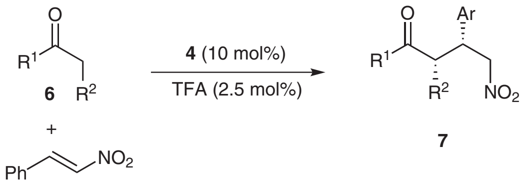
Entry	Catalyst	Product **5** R	Time (h)	Yield (%)[a]	dr[b]	ee (%)[c]
1	**4a**	Ph	24	98	99:1	99
2	**4a** (1st recycled)	Ph	24	90	94:6	90
3	**4a** (2nd recycled)	Ph	24	83	93:7	88
4	**4a** (3rd recycled)	Ph	24	74	93:7	58
5	**4a** (only 5 mol%)	Ph	40	95	97:3	82
6	**4a** (without TFA)	Ph	48	83	93:7	82
7	**4b**	Ph	24	98	99:1	99
8	**4a**	2-$O_2NC_6H_4$	20	93	99:1	83
9	**4a**	4-$MeOC_6H_4$	22	97	95:5	90
10	**4a**	4-MeC_6H_4	23	95	95:5	84

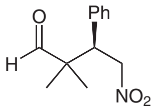
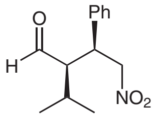
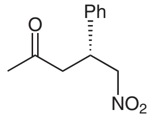
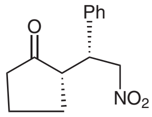
[a] Yield of isolated product, cyclohexanone, and nitrostyrene were used in a molar ratio of 20:1, the absolute configuration of the major isomer was determined by comparison with literature data.[18,19]

[b] Determined by ^{1}H NMR of the crude product.

[c] Determined by chiral HPLC (Chiralpak AD and AS, hexane–*i*-PrOH as eluent). Absolute configuration of major isomer was determined by comparison with literature data.[19,23]

Table 2 Michael Addition of Aldehydes or Acetone to β-Nitrostyrene



Entry	Catalyst	Product **7**	Time (h)	Yield (%)	dr	ee (%)
1	**4a**		24	95	–	71
2	**4a**		24	98	–	72
3	**4a**		30	84	95:5	9
4	**4b**		27	87	95:5	36
5	**4b**		17	85	–	52
6	**4b**		45	84	67:33	82

decrease of both the ee to 82% and the rate of reaction (entry 5). The same effect was notified when the reaction was conducted without trifluoroacetic acid. This confirms manifold observations in the literature underlining the importance of the presence of an acid as a co-catalyst in the reaction mixture. It seems that the substituent R in the triazolium ring of the TSIL **4** does not have an effect on the outcome of the reaction, as the butyl-substituted triazolium salt **4b** gave virtually the same result as **4a** (compare entries 1 and 7). Thus the situation is different, as compared with reported Michael additions to β-nitrostyrenes which are catalyzed by the corresponding noncharged 1,2,3-triazoles **1**, where the aryl-substituted catalysts gave higher diastereoselectivities than the alkyl-substituted. The triazolium salt **4a** was also applied as ionic liquid supported organocatalyst in reactions of β-nitrostyrenes with additional substituents in the aryl ring. In all these cases (entries 8–10) excellent yields and diastereoselectivities were achieved but with somewhat lower enantioselectivities (>83%).

We further varied the Michael donor in Michael additions to β-nitrostyrene, catalyzed by the TSIL **4** (Table 2). Isobutyraldehyde provided high yields, but the enantioselectivities were lower (71–72%) as compared with cyclohexanone. High yields and diastereoselectivities were observed with isopentanal, however, enantioselectivities were unsatisfactory (entries 3, 4). Acetone reacted comparatively fast affording high yield and an ee of 52%. Similar results were obtained by Yan et al. when the 1,2,3-triazoles **1** were used.[22] Cyclopentanone was repeatedly reported to gives more unfavorable results than cyclohexanone in organocatalyzed additions to β-nitrostyrenes. This is in line with our observation in which a low diastereoselectivity (67:33) was achieved (entry 6).

We expect that the Michael addition to β-nitrostyrenes, catalyzed by the TSIL **4** runs via a similar transition state **8** (Figure 2) as proposed for other (*S*)-pyrrolidin-2-ylmethyl-derived organocatalysts.[22] It can be assumed that the nitro group electrostatically interacts with the positively charged 1,2,3-triazolium ring and thus effectively shields the *si* face of the attacking enamine.

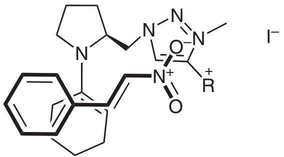


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Figure 2

In summary, we have developed novel TSIL assembled from a chiral (*S*)-pyrrolidin-2-ylmethyl moiety and a 1,2,3-triazolium salt as phase tag. The synthesis of such TSIL is straightforward and they prove as efficient and easily recyclable organocatalysts in the asymmetric Michael addition to β-nitrostyrenes. We are presently investigating further effects, such as solvents, acids, and counterions on the outcome of the Michael addition and applying these TSIL to other organocatalyzed reactions.

Acknowledgment

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(30) **Typical Procedure of Michael Addition of Cyclohexanone to Nitrostyrene**
Nitrostyrene (37 mg, 0.25 mmol) and **4** (10 mol%) were mixed with cyclohexanone (0.5 mL, 5 mmol) in the presence of TFA (0.00625 mmol, 0.2 μL) at r.t. (bulk solution of TFA in cyclohexanone was freshly prepared from 5 μL TFA in 12.5 mL of cyclohexanone). After stirring for 24 h, the homogeneous reaction mixture was diluted with Et_2O to precipitate the catalyst. The organic layer was separated and loaded onto a silica gel column to afford the Michael adduct (60 mg, 98%) as white solid; *syn*/*anti* = 99:1, 99% ee [by HPLC on a Chiralpak AD column, λ = 215 nm, eluent *i*-PrOH–hexane (10:90), flow rate = 0.8 mL min^{-1}; t_R = 10.90 (minor), 15.53 min (major)]. All the Michael addition products are known compounds.