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Chiral Imidazolium Ionic Liquids derived from (*S*)-Prolinamine as Organocatalysts in the Asymmetric Michael Reaction and Michael-Aldol Cascade Reaction under Solvent-Free Conditions

Arturo Obregón-Zúñiga,[a] Marco Guerrero-Robles,[a] and Eusebio Juaristi*[a][b]

Abstract: The synthesis of three novel chiral imidazolium ionic liquids (prepared by the combination of one new chiral organic cation with different anions) and their application in the enantioselective Michael reaction between cyclohexanone and substituted nitrostyrenes under solvent-free conditions is described. In addition, the first asymmetric cascade Michael-Aldol reaction of cyclohexanone and benzylidenepyruvate organocatalyzed by chiral ionic liquids is reported. Recyclability of the catalyst was evaluated on both reactions observing no loss in stereoselectivity up to the third cycle.

Introduction

Ionic liquids (IL) are salts that contain both an organic cation and an organic or inorganic anion, and that present melting points below 100 °C. This property enables their use as highly polar, non-volatile solvents. Some of the most studied and versatile ionic liquids are those incorporating an imidazolium cation. These ILs have been used in many different organic transformations, with excellent results.[1]

With the emergence of asymmetric organocatalysis,[2] several chiral ionic liquids (CIL) have been developed and employed as efficient recyclable organocatalysts in enantioselective transformations.[3] Indeed, the highly polar nature of ILs facilitates their separation from crude reaction mixtures.

In this context, the asymmetric Michael addition reaction is a well-studied reaction where ionic liquids derived from (*S*)-proline and (*S*)-prolinamine have been successfully employed as organocatalysts.[4] The Michael reaction has also provided access to the synthesis of highly valuable pharmaceutical drugs,[5] owing to its versatility in the construction of C-C bonds from readily available substrates. Moreover, several asymmetric cascade reactions have a Michael addition as their starting point.[6] With this backgroud, we decided to design and synthesize chiral ionic liquids derived from (*S*)-prolinamine, which was obtained following a synthetic route previously reported by our group.[7]

[a] *Departamento de Química, Centro de Investigación y de Estudios Avanzados, Avenida Instituto Politécnico Nacional 2508, Colonia Zacatenco, 07360 Ciudad de México, México.*
E-mail: juaristi@relaq.mx

[b] *El Colegio Nacional, Donceles 104, Centro Histórico, 06020 Ciudad de México, México.*

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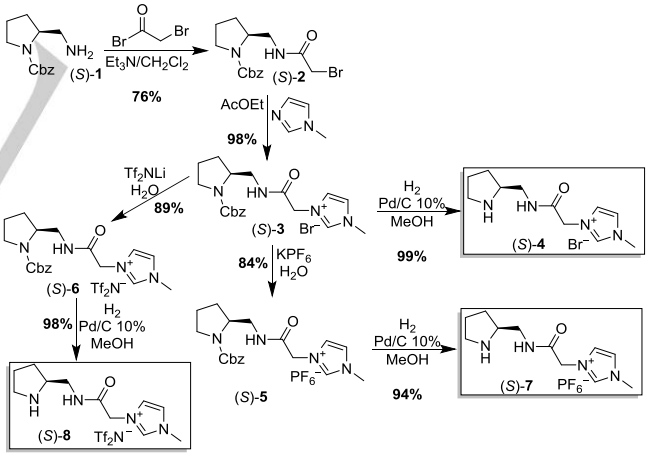
Results and Discussion

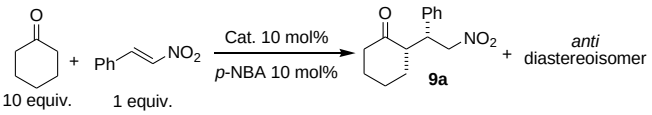
N-Cbz-protected (*S*)-prolinamine (*S*)-**1** was treated with bromoacetyl bromide to afford bromoamide (*S*)-**2** in 76% yield. Following this, a quaternization reaction with 1-methylimidazole gave imidazolium derivative (*S*)-**3** in 98% yield. Subsequently, Pd/C catalyzed hydrogenolysis effectively removed the *N*-Cbz protecting group to obtain chiral ionic liquid bromide (*S*)-**4** in 99% of yield. From chiral imidazolium salt (*S*)-**3**, anionic exchange with salts KPF_6 and Tf_2NLi provided hydrophobic chiral ionic liquids (*S*)-**5** and (*S*)-**6**, in 84% and 89% yield, respectively. Finally, hydrogenolytic *N*-Cbz group removal afforded chiral ionic liquids (*S*)-**7** and (*S*)-**8** in 94% and 98% yields, respectively (Scheme 1).



Scheme 1. Synthetic route for the preparation of chiral imidazolium ionic liquids (*S*)-**4**, (*S*)-**7**, and (*S*)-**8**.

With chiral imidazolium ionic liquids (*S*)-**4**, (*S*)-**7** and (*S*)-**8** at hand, we examined their efficiency as organocatalysts in the asymmetric Michael addition reaction between cyclohexanone and β-nitrostyrene. Bromide imidazolium salt (*S*)-**4** gave the poorest results, in terms of both yield and selectivity, even in the presence of *p*-nitrobenzoic acid (*p*-NBA) as an additive (Table 1, entries 1 and 2). On the other hand, chiral ionic liquids (*S*)-**7** and (*S*)-**8** afforded rather similarly good,results (Table 1, entries 3 and 4). In subsequent work, (*S*)-**8** was discarded owing to the high cost of Tf_2N^- anion relative to PF_6^-.

Table 1. Catalyst evaluation in the asymmetric Michael reaction between cyclohexanone and β-nitrostyrene.

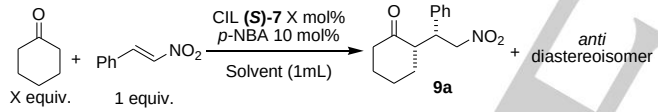


Entry	Cat.	*p*-NBA additive	Yield (%)[a]	dr (*syn*/*anti*)[b]	er (*syn*)[c]
1	(*S*)-4	No	44	70:30	87:13
2	(*S*)-4	Yes	86	70:30	86:14
3	**(*S*)-7**	**Yes**	**92**	**90:10**	**89:11**
4	(*S*)-8	Yes	95	91:9	88:12

[a] Determined after purification by flash chromatography. [b] Determined by ^{1}H NMR from the crude reaction product. [c] Determined by HPLC with chiral stationary phase.

We then screened different reaction conditions in order to optimize the reaction yield. Firstly, the effect of solvent polarity was evaluated, finding eventually that higher yields and shorter reaction times were achieved under neat conditions (Table 2, compare entries 2-8 with entry 1). Catalyst loading was also analyzed, concluding that 10 mol% corresponds to the best catalyst load. Indeed, 5 mol% and 15 mol% concentrations resulted in lower yields and/or stereoselectivities (compare entry 1 with entries 9-11 in Table 2). Finally, seeking to minimize the amount of ketone employed in the reaction it was found that 6 equivalents of cyclohexanone were sufficient to maintain a good reaction performance (compare entries 12-16 in Table 2).

Table 2. Screening of reaction conditions for the optimization of the asymmetric Michael reaction.



Entry	Solvent	Cat. mol%	Ketone equiv.	Yield (%)[a]	dr (*syn*/*anti*)[b]	er (*syn*)[c]
1	Neat	10	10	92	90:10	90:10
2	H_2O	10	10	60	85:15	84:16
3	MeOH	10	10	28	90:10	87:13
4	DMF	10	10	70	90:10	88:12
5	CH_2Cl_2	10	10	74	90:10	88:12
6	Toluene	10	10	75	90:10	85:15
7	$BMImPF_6$	10	10	60	90:10	90:10
8	BMImBr	10	10	37	89:11	88:11
9	Neat	15	10	88	88:12	87:13
10	Neat	5	10	75	91:9	89:11
11	Neat	2.5	10	60	91:9	90:10
12	Neat	10	8	92	88:12	86:14
13	**Neat**	**10**	**6**	**92**	**90:10**	**90:10**
14	Neat	10	4	85	88:12	87:13
15	Neat	10	2	76	89:11	90:10
16	Neat	10	1	72	90:10	90:10

[a] Determined after purification by flash chromatography. [b] Determined by ^{1}H NMR from the crude reaction product. [c] Determined by HPLC with chiral stationary phase.

In view of the beneficial effect induced by *p*-NBA as an acidic additive, it was deemed of interest to explore the potential effect of other Brønsted acids in the reaction. Benzoic acid and salicylic acid gave similar results to those obtained with *p*-NBA (Table 3, compare entries 1, 2 and 3). By contrast, formic acid and acetic acid afforded the Michael product with lower yields (Table 3, entries 4 and 5). On the other hand, and contrary to previous observations,[8] chiral Brønsted acid additives (*R*)- and (*S*)-mandelic acid did not improve the reaction's stereoselectivity (Table 3, entries 6 and 7). Interestingly enough, strong acids such as oxalic and trifluoroacetic acid inhibited product formation (Table 3, entries 8 and 9). Based on these observations, subsequent studies were carried out with *p*-NBA as an additive.

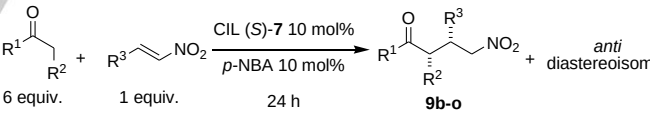
Table 3. Evaluation of acid additives in the outcome of the asymmetric Michael reaction.

Entry	Additive	Yield (%)[a]	dr (*syn*/*anti*)[b]	er (*syn*)[c]
1	***p*-NBA**	**92**	**90:10**	**90:10**
2	Benzoic acid	88	88:12	85:15
3	Salicylic acid	91	90:10	90:10
4	Formic acid	76	88:12	86:14
5	Acetic acid	43	90:10	77:23
6	(*S*)-Mandelic acid	8	90:10	87:13
7	(*R*)-Mandelic acid	89	90:10	86:14
8	Oxalic acid	n/r	-	-
9	TFA	n/r	-	-

[a] Determined after purification by flash chromatography. [b] Determined by ^{1}H NMR from the crude product. [c] Determined by HPLC with chiral stationary phase.

The reaction was also carried out at 3 °C in order to examine the effect of low temperature on stereoinduction by the organocatalyst. However, stereoselectivities remained unchanged. Thus, ambient temperature was deemed as most convenient.

Table 4. Scope of the asymmetric Michael reaction.



Entry	R^1	R^2	R^3	Yield (%)[a]	dr (*syn*/*anti*)[b]	er (*syn*)[c]
1	$-(CH_2)_4-$		2-Cl-C_6H_4	97	93:7	94:6
2	$-(CH_2)_4-$		2-MeO-C_6H_4	99	94:6	92:8
3	$-(CH_2)_4-$		2-Br-C_6H_4	99	93:7	89:11
4	$-(CH_2)_4-$		4-F-C_6H_4	94	85:15	95:5
5	$-(CH_2)_4-$		4-MeO-C_6H_4	92	91:9	84:16
6	$-(CH_2)_4-$		4-Cl-C_6H_4	96	91:9	90:10
7	$-(CH_2)_4-$		4-BnO-C_6H_4	85	88:12	65:35
8	$-(CH_2)_4-$		4-Me-C_6H_4	95	89:11	91:9
9	$-(CH_2)_3-$		C_6H_5	n/r	-	-
10	$-(CH_2)_5-$		C_6H_5	n/r	-	-
11[d]	$-(CH_2)_2C[O(CH_2)_2O]CH_2-$		C_6H_5	85	88:12[e]	90:10
12	Me	H	C_6H_5	99	-	55:45
13	Et	Me	C_6H_5	n/r	-	-
14	Ph	H	C_6H_5	n/r	-	-

[a] Determined after purification by flash chromatography. [b] Determined by ^{1}H NMR from the crude product. [c] Determined by HPLC with chiral stationary phase. [d] Reaction performed with 2 equiv. of the ketone and 0.1 mL of CH_2Cl_2 to dissolve the solid reagents. [e] Determined by HPLC chiral stationary phase.

In order to establish the scope of the reaction, cyclohexanone was added to several substituted β-nitrostyrenes (Table 4). The Michael products were obtained with excellent yields ranging from 85% to 99%, while diastereomeric ratios varied from 85:15 to 93:7, and enantioselectivities from 65:35 to 95:5.

With the exception of acetone, other ketones failed to react in the Michael addition reaction. Nevertheless, although acetone gave the Michael product with 99% yield, this was practically racemic (Table 4, entry 12). Cyclopentanone, cycloheptanone, and acetophenone either gave no reaction or proceeded in very low yields (Table 4, entries 9, 10, 13 and 14).

With these observations, catalyst (*S*)-**7** was next employed in the asymmetric Michael reaction of 1,4-cyclohexanedione monoethylene acetal and β-nitrostyrene, obtaining excellent results both in terms of yield and stereoselectivity (Table 4, entry 11).

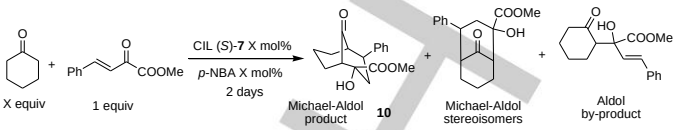
Catalyst (*S*)-**7** was also employed in the asymmetric Michael reaction of 1,4-cyclohexanedione monoethylene acetal and β–nitrostyrene, obtaining satisfactory results both in terms of yield and stereoselectivity (Table 4, entry 11).

To the best of our knowledge, presently there is only one cascade reaction that uses chiral ionic liquids. This cascade reaction was reported by Zlotin and coworkers and consists in an aza-Michael addition followed by intramolecular acetalization reaction during the stereoselective preparation of 5-hydroxy-3-arylisoxazolidines.[9]

Motivated by the high stereoselectivity attained with our chiral ionic liquid in the asymmetric Michael addition reaction with cyclohexanone substrates (see above), we decided to expand its application in a cascade reaction, in particular in the Michael-Aldol cascade reaction organocatalyzed by *N*-(pyrrolidin-2-ylmethyl)trifluoromethanesulfonamide previously reported by Tang *et al.*[10] This cascade reaction gives rise to bicyclic compounds containing up to four stereocenters via a formal [3+3] intramolecular annulation.

To this end, we carried out an evaluation of the catalyst and *p*-NBA additive loads, as well as the amount of cyclohexanone, finding that the desired cascade reaction proceeds efficiently with 10 mol% of CIL (*S*)-**7**, 10 mol% *p*-NBA and 6 equivalents of cyclohexanone (Table 5, entry 1). A yield of 50% of the main bicyclic product, whose relative and absolute configurations proved to be similar to those assigned by Tang and coworkers to their product. In particular, ^{1}H and ^{13}C NMR spectra are identical and the optical rotation is of the same sign. Furthermore, comparison of HPLC chromatograms corroborated the assignment, and indicated a 91:9 enantiomeric ratio. The major bicyclic product was accompanied by four minor stereoisomers (combined yield = 14%) and by the aldol product that is generated in the first step of the cascade reaction (yield = 16%). In contrast with the report of Tang *et al.*, we did not observe any Diels-Alder by-product. It is worthy of mention that only 6 equivalents of cyclohexanone were required in the present work instead of the 48 equivalents employed by Tang *et al*. Furthermore, our reaction employs 10 mol% of organocatalyst and additive, to be compared with the 20 mol% used with Tang's organocatalyst.

Table 5. Optimization of reaction conditions for the Michael-intramolecular aldol cascade reaction.



Essay	mol% CIL (*S*)-**7** and *p*-NBA	equiv. ketone	Yield of **10** (%)[a]	er[b]
1	**10**	**6**	**50**	**91:9**
2	20	6	52	89:11
3	20	10	50	88:12

[a] Determined after purification by flash chromatography. [b] Determined by HPLC with chiral stationary phase.

Interestingly, the major bicyclic product is structurally similar to the tropane alkaloids, that are important compounds used as drugs (Fig. 1, atropine and scopolamine) or narcotics (Fig.1, cocaine and ecgonine).

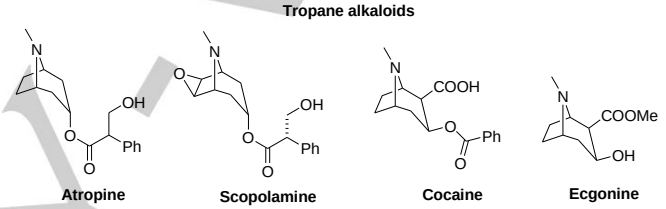
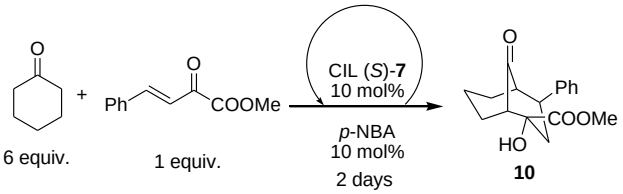


Figure 1. Representative tropane alkaloids structurally related to the major cascade product reported herein.

Anticipating that chiral ionic liquid (*S*)-**7** could be recovered and reused, this catalyst was precipitated once the reaction was complete by addition of diethyl ether, and separated by decantation. Upon exposure to a new load of substrate and *p*-NBA additive it was observed the enantioselectivity of the reaction is maintained (Table 6) although the reaction yield decreases significantly.

Table 6. Evaluation of chiral ionic liquid recyclability in the asymmetric Michael-intramolecular aldol cascade reaction.

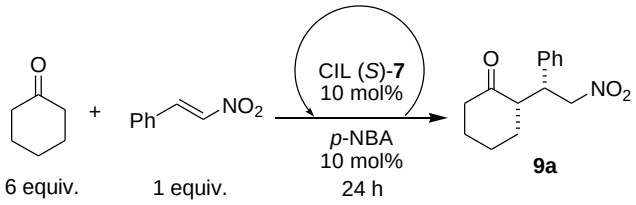


Cycle	Yield (%)[a]	er[b]
1	50	91:9
2	21	91:9
3	10	90:10

[a] Determined after purification by flash chromatography. [b] Determined by HPLC with chiral stationary phase.

The catalyst recyclability was also examined in the model Michael addition reaction, recording similar observations, that is the stereoselectivity in the product is maintained although the reaction yield decreases in subsequent cycles (Table 7).

Table 7. Evaluation of chiral ionic liquid recyclability in the model asymmetric Michael reaction.



Cycle	Yield (%)[a]	dr (*syn*/*anti*)[b]	er (*syn*)[c]
1	93	91:9	90:10
2	63	90:10	88:12
3	40	88:12	86:14

[a] Determined after purification by flash chromatography. [b] Determined by ^{1}H NMR from the crude product. [c] Determined by HPLC with chiral stationary phase.

Seeking an explanation for the fast deactivation of catalyst (*S*)-**7** in recycling experiments, MS-TOF spectra of both the recovered catalyst (precipitated upon diethyl ether addition to the crude reaction product) and the ethereal phase were acquired and analysed (see Supporting Information). It was found that part of the catalyst dissolves in the ether phase, and thus lost in each cycle. This observation might be in line with the observations recorded in Table 2, entries 10 and 11: as the catalyst load is diminished, the yield of product decreases, although the observed stereoselectivity of the process remains high.

Conclusions

Novel chiral imidazolium ionic liquids (*S*)-**4**, (*S*)-**7** and (*S*)-**8** were synthesized and tested in the asymmetric Michael addition reaction between cyclohexanone and several substituted β-nitrostyrenes, affording moderate to excellent reaction yields and good to excellent stereoselectivities (see entries 1 to 8 in Table 4). Most importantly, for the first time a chiral ionic liquid was used as organocatalyst in an asymmetric Michael-intramolecular aldol cascade reaction achieving good stereoselectivities although with moderate reaction yields. Reuse of the chiral ionic liquid catalyst was evaluated observing no loss in stereoselectivity. Studies in other asymmetric cascade reactions are being conducted in order to expand the applicability of chiral ionic liquids as sustainable, enantioselective organocatalysts.[11]

Experimental Section

(*S*)-Benzyl 2-((2-bromoacetamido)methyl)pyrrolidine-1-carboxylate, (*S*)-2. In a 100 mL round bottomed flask provided with magnetic stirrer and addition funnel, was placed (*S*)-prolinamine (4.637 g, 19.79 mmol) and triethylamine (3.00 mL, 21.7 mmol) and dissolved in CH_2Cl_2 (20 mL). Then bromoacetyl bromide (1.90 mL, 21.7 mmol) dissolved in 20 mL of CH_2Cl_2 was added to the addition funnel. The flask was submerged in an ice bath and the reagents in the funnel were added dropwise. After that, the stirring was continued for 24 h at room temperature. Finally, the solvent was removed under vacuum and the product was purified by flash chromatography using hexane/EtOAc 1:1 as mobile phase. (*S*)-**2** was obtained as a viscous yellow liquid, 5.30 g (14.97 mmol, 76% yield). ^{1}H NMR (399.78 MHz, DMSO-d_6, 120 °C): δ 7.37-7.25 (m, 5H, Ar), 5.08 (bs, 2H, N-CH_2-Ph), 3.98 (bs, 2H, Br-CH_2-CO), 3.97 (bs, 1H, NH), 3.81 (m, 1H, N-C*H*-CH_2), 3.43-3.20 (m, 4H, N-C*H*$_2$-CH and N-C*H*$_2$-CH_2), 1.91-1.72 ppm (m, 4H, CH_2-CH_2). ^{13}C NMR (100.52 MHz, DMSO-d_6, 120 °C): δ 172.6, 155.0, 137.8, 128.8, 128.1, 127.9, 66.5, 62.2, 57.5, 47.0, 41.8, 28.9, 23.4 ppm. IR film (cm^{-1}): 3298, 2952, 2880, 1659, 1536, 1409, 1358. HR MS-TOF: calcd. for $C_{15}H_{20}O_3N_2Br^+$: 355.0652, found: 355.0655. $[\alpha]_D^{25}$ = −46.69, c = 1.037, MeOH.

(*S*)-3-(2-((1-(Benzyloxycarbonyl)pyrrolidin-2-yl)methylamino)-2-oxoethyl)-1-methyl-1*H*-imidazol-3-ium bromide, (*S*)-3. In a 50 mL round bottomed flask provided with magnetic stirrer, bromoamide (*S*)-**2** (5.538 g, 15.59 mmol) was dissolved in 30 mL of EtOAc. 1-Methylimidazole (1.50 mL, 18.7 mmol) was then added and the reaction mixture was let to react with vigorous stirring for 18 h at ambient temperature. The crude product (yellow viscous precipitate) was decanted and washed with additional EtOAc (3x2 mL) to remove the excess of 1-methylimidazole. The product was dissolved in MeOH (4 mL) and then precipitated with Et_2O (40 mL). The heterogeneous mixture was left standing for 90 minutes to assure complete precipitation. The upper layer was removed and the pure product was dried under vacuum until constant weight. (*S*)-**3** was isolated as a highly hygroscopic creamy solid, mp = 63-66 °C, 6.688 g (15.29 mmol, 98% yield). ^{1}H NMR (399.78 MHz, DMSO-d_6, 120 °C): δ 8.98 (bs, 1H, N-CH-N), 8.15 (bs, 1H, NHCO), 7.58 (m, 1H, N-CH-C*H*-N$^+$), 7.56 (bs, 1H, $^+$N-C*H*-CH-N), 7.36-7.26 (m, 5H, Ar), 5.07 (bs, 2H, CH_2-Ph), 4.93 (bs, 2H, N-CH_2-CO), 3.96-3.91 (m, 1H, N-C*H*-CH_2), 3.88 (bs, 3H, N-CH_3), 3.43-3.29 (m, 4H, N-C*H*$_2$-CH and N-C*H*$_2$-CH_2), 1.94-1.71 ppm (m, 4H, CH_2-CH_2). ^{13}C NMR (100.52 MHz, DMSO-d6, 120 °C): δ 165.6, 155.2, 138.2, 137.7, 128.9, 128.2, 127.9, 124.1, 123.7, 66.6, 57.3, 51.5, 47.0, 42.4, 36.4, 28.8, 23.4 ppm. IR film (cm^{-1}): 3206, 3062, 2878, 1681, 1563, 1412, 1358. HR MS-TOF: calcd. for $C_{19}H_{25}N_4O_3$: 357.1921, found: 357.1924. Mp = 63 – 66 °C. $[\alpha]_D^{25}$ = −14.48, c = 1.05, MeOH.

General metathesis method: preparation of compounds (*S*)-5 and (*S*)-6 from (*S*)-3. In a 50 mL round bottomed flask provided with magnetic stirrer, imidazolium salt (*S*)-**3** (1.0 g, 2.287 mmol) was placed and dissolved in 23 mL of water. The appropriate salt (KPF_6 or Tf_2NLi) (1.1 equiv.) was added to the resulting solution and the reaction mixture turned cloudy. The reaction mixture was vigorously stirred for 4 hours. The upper layer was decanted and the precipitated product was washed with water (2x10 mL). Finally, the product was dried in vacuum until constant weight. No further purification process was required.

(*S*)-3-(2-((1-(Benzyloxycarbonyl)pyrrolidin-2-yl)methylamino)-2-oxoethyl)-1-methyl-1*H*-imidazol-3-ium hexafluorophosphate(V), (*S*)-5 The General procedure was followed to afford (*S*)-**5** as a white solid, mp = 51-55 °C, 0.968 g (1.92 mmol, 84% yield). ^{1}H NMR (399.78 MHz, DMSO-d_6, 120 °C): δ 8.97 (bs, 1H, N-CH-N), 8.10 (bs, 1H, NHCO), 7.60 (t, 1H, *J* = 3.4 Hz, *J* = 1.8 Hz, $^+$N-C*H*-CH-N), 7.57 (t, 1H, *J* = 3.4 Hz, *J* = 1.8 Hz, N-CH-C*H*-N$^+$), 7.37-7.25 (m, 5H, Ar), 5.10 (d, 2H, *J* = 1.58 Hz, CH_2Ph), 4.90 (bs, 2H, N-CH_2-CO), 3.98-3.91 (m, 1H, N-C*H*-CH_2), 3.90 (bs, 3H, N-CH_3), 3.47-3.30 (m, 3H, N-C*H*$_2$-CH and N-C*H*H-CH_2), 3.30-3.19 (m, 1H, N-CH*H*-CH_2), 1.95-1.71 ppm (m, 4H, CH_2-CH_2). ^{13}C NMR (100.52 MHz, DMSO-d_6, 120 °C): δ 165.5, 155.1, 138.3, 137.8, 128.9, 128.2, 127.9, 124.2, 123.7, 66.6, 57.4, 51.5, 47.0, 42.4, 36.4, 28.8, 23.4 ppm. ^{31}P NMR (161.83 MHz, DMSO-d_6, 120 °C): δ −142.7, ppm ($J_{P\text{-}F}$ = 710.8 Hz). IR film (cm^{-1}): 1674, 1544, 1415, 1360, 1343, 1178, 1107. Elemental analysis: calcd. C: 45.42%, H: 5.02%, N: 11.15%, found. C: 45.39%, H: 4.76%, N: 10.91%. HR MS-TOF: calcd. for $C_{19}H_{25}N_4O_3^+$:

357.1921, found: 357.1919. Calcd. for PF_6^-: 144.9647, found: 144.9647. $[\alpha]_D^{25}$ = –13.56, c = 1.01, MeOH.

(*S*)-3-(2-((1-(Benzyloxycarbonyl)pyrrolidin-2-yl)methylamino)-2-oxoethyl)-1-methyl-1*H*-imidazol-3-ium bis(trifluoromethylsulfonyl)-amide, (*S*)-6. The General procedure was followed to afford (*S*)-**6** as an amber viscous liquid, 1.297 g (2.03 mmol, 89% yield). ^{1}H NMR (399.78 MHz, DMSO-d_6, 120 °C): δ 8.99 (bs, 1H, N-CH-N), 8.11 (bs, 1H, NHCO), 7.61 (t, 1H, *J* = 3.39 Hz, *J* = 1.81 Hz, $^+$N-C*H*-CH-N), 7.59 (t, 1H, *J* = 3.4 Hz, *J* = 1.8 Hz, N-CH-C*H*-N$^+$), 7.36-7.25 (m, 5H, Ar), 5.10 (d, 2H, *J* = 1.6 Hz, CH_2Ph), 4.91 (bs, 2H, N-CH_2-CO), 3.95-3.91 (m, 1H, N-C*H*-CH_2), 3.90 (bs, 3H, N-CH_3), 3.48-3.31 (m, 3H, N-C*H*$_2$-CH and N-*CH*H-CH_2), 3.31-3.20 (m, 1H, N-CH*H*-CH_2), 1.95-1.70 ppm (m, 4H, CH_2-CH_2). ^{13}C NMR (100.52 MHz, DMSO-d_6, 120 °C): δ 165.4, 155.0, 138.4, 137.8, 128.8, 128.2, 127.9, 124.2, 123.7, 66.6, 57.4, 51.5, 47.0, 41.3, 36.4, 28.9, 23.4 ppm. IR film (cm^{-1}): 1681, 1592, 1416, 1346, 1177, 1133. HR MS-TOF: calcd. for $C_{19}H_{25}N_4O_3^+$: 357.1921, found: 357.1927. Calcd. for $C_2F_6NO_4S_2^-$: 279.9178, found: 279.9182. $[\alpha]_D^{25}$ = –12.7, c = 0.393, MeOH.

General method for the hydrogenolysis reaction: preparation of compounds (*S*)-4, (*S*)-7 and (*S*)-8). In a 25 mL round bottomed flask provided with magnetic stirrer, substrate (*S*)-**3**, (*S*)-**5** or (*S*)-**6** (1 mmol) was dissolved in 10 mL of MeOH before the addition of 10 wt% of Pd/C. The reaction flask was sealed with a septum, purged with H_2 and allowed to react for 24 hours at ambient temperature with vigorous stirring and under H_2 atmosphere. The heterogeneous mixture was filtered through Celite to remove the Pd/C catalyst, and the solvent was removed under vacuum until a constant weight of the product was reached.

(*S*)-1-Methyl-3-(2-oxo-2-(pyrrolidin-2-ylmethylamino)ethyl)-1*H*-imidazol-3-ium bromide, (*S*)-4. The General procedure for hydrogenolysis was followed to afford (*S*)-**4** as a highly hygroscopic yellow syrup, 0.299 g (0.99 mmol, 99% yield). ^{1}H NMR (500.16 MHz, DMSO-d_6): δ 9.09 (bs, 1H, N-CH-N), 8.57 (bs, 1H, NHCO), 7.67 (bs, 2H, N-CH-CH-N), 4.97 (bs, 2H, N-CH_2-CO), 3.85 (s, 3H, N-CH_3), 3.45 (bs, 1H, NH), 3.11 (m, 1H, N-C*H*-CH_2), 3.11-3.05 (m, 2H, CH-C*H*$_2$-CO), 2.85-2.70 (m, 2H, N-C*H*$_2$-CH_2), 1.81-1.54 (m, 3H, C*H*HC*H*$_2$), 1.36-1.23 ppm (m, 1H, CH*H*CH_2). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 165.5, 138.2, 124.2, 123.5, 57.9, 51.1, 46.1, 43.9, 36.3, 29.2, 25.2 ppm. IR film (cm^{-1}): 3404, 3222, 3149, 3062, 2949, 2870, 1681, 1563, 1410, 1172. HR MS-TOF: calcd. for $C_{11}H_{19}N_4O^+$: 233.1553, found: 233.1550. $[\alpha]_D^{25}$ = –6.34, c = 1.467, MeOH.

(*S*)-1-Methyl-3-(2-oxo-2-(pyrrolidin-2-ylmethylamino)ethyl)-1*H*-imidazol-3-ium hexafluorophosphate(V), (*S*)-7. The General procedure for hydrogenolysis was followed to afford (*S*)-**7** as a slightly yellow serous solid, mp = 58-61 °C, 0.342 g (0.93 mmol, 93% yield). ^{1}H NMR (399.78 MHz, DMSO-d_6): δ 9.05 (bs, 1H, N-CH-N), 8.55 (bs, 1H, NHCO), 7.65 (bs, 2H, N-CH-CH-N), 4.96 (bs, 2H, N-CH_2-CO), 3.87 (s, 3H, N-CH_3), 3.45 (bs, 1H, NH), 3.18-3.00 (m, 3H, N-C*H*-CH_2 and CH-C*H*$_2$-CO), 2.90-2.70 (m, 2H, N-C*H*$_2$-CH_2), 1.86-1.56 (m, 3H, C*H*HC*H*$_2$), 1.40-1.24 ppm (m, 1H, CH*H*CH_2). ^{13}C NMR (100.52 MHz, DMSO-d_6): δ 165.48, 138.24, 124.29, 123.52, 57.91, 51.06, 46.19, 44.09, 36.31, 29.30, 25.34 ppm. ^{31}P NMR (161.83 MHz, DMSO-d_6): δ –143.00 ppm ($J_{P\text{-}F}$ = 710.8 Hz). IR film (cm^{-1}): 3419, 3169, 2965, 2875, 1678, 1567, 1429, 1364, 1260, 1178. HR MS-TOF: calcd. for $C_{11}H_{19}ON_4^+$: 223.1553, found: 223.1554. Calcd. for PF_6^-: 144.9647, found: 144.9647. $[\alpha]_D^{25}$ = –5.00, c = 1.60, MeOH.

(*S*)-1-Methyl-3-(2-oxo-2-(pyrrolidin-2-ylmethylamino)ethyl)-1*H*-imidazol-3-ium bis(trifluoromethylsulfonyl)amide, (*S*)-8. The General procedure for hydrogenolysis was followed to afford (*S*)-**8** as an amber viscous syrup, 0.493 g (0.98 mmol, 98% yield). ^{1}H NMR (399.78 MHz, DMSO-d_6): δ 9.02 (bs, 1H, N-CH-N), 8.39 (bs, 1H, NHCO), 7.64 (bs, 2H, N-CH-CH-N$^+$), 4.92 (bs, 2H, N-CH_2-CO), 3.84 (bs, 3H, N-CH_3), 3.23 (m, 1H, N-C*H*-CH_2), 3.13 (s, 1H, CH_2-N*H*-CH), 3.10-2.98 (m, 2H, CH-C*H*$_2$-CO), 2.85-2.68 (m, 2H, N-C*H*$_2$-CH_2), 1.94-1.53 (m, 3H, C*H*HC*H*$_2$), 1.32-1.21 ppm (m, 1H, CH*H*CH_2). ^{13}C NMR (100.52 MHz, DMSO-d_6): δ 165.4, 138.2, 124.3, 123.5, 121.3, 118.7, 57.8, 51.0, 46.3, 44.4, 36.3, 29.4, 25.5 ppm. IR film (cm^{-1}): 3382, 3126, 2964, 1667, 1570, 1423, 1346, 1176, 1133, 1052. HR MS-TOF: calcd. for $C_{11}H_{19}N_4O^+$: 223.1553, found: 223.1554. Calcd. for $C_2F_6NO_4S_2^-$: 279.9178, found: 279.9176. $[\alpha]_D^{25}$ = –8.50, c = 0.4, MeOH.

General procedure for the asymmetric Michael addition reaction. In a small vial, CIL (0.05 mmol), *p*-NBA (8.3 mg, 0.05 mmol), β-nitrostyrene (0.5 mmol) and ketone (3.0 mmol) were placed. The reaction was stirred at room temperature for 24 hours or until TLC showed no presence of β-nitrostyrene. Subsequently, the reaction was washed with diethyl ether (3 x 1 mL) and the precipitated CIL was subjected to the next reaction cycle, by means of the addition of additive and substrates. The crude ethereal phase was subjected to flash chromatography using silica gel as stationary phase and Hexane/EtOAc (9:1 to 6:4) as mobile phase to afford the pure Michael products.

General procedure for the asymmetric Michael-intramolecular aldol cascade reaction. In a small vial, CIL (*S*)-**7** (18.4 mg, 0.05 mmol), *p*-NBA (8.3mg, 0.05 mmol), benzylidenpyruvate (95 mg, 0.5 mmol) and cyclohexanone (0.31 mL, 3.0 mmol) were placed. The reaction was stirred at room temperature for 48 hours. Subsequently, the reaction was washed with diethyl ether (3 x 1 mL) and the precipitated CIL was subjected to the next reaction cycle, by the addition of additive and substrates. The crude ethereal phase was subjected to column chromatography using silica gel as stationary phase and Hexane/EtOAc (9:1 to 1:1) as mobile phase to afford the pure cascade product and its by-products.

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Keywords: Chiral ionic liquids • Imidazolium ionic liquids • Michael reaction • Cascade reaction • Asymmetric reaction

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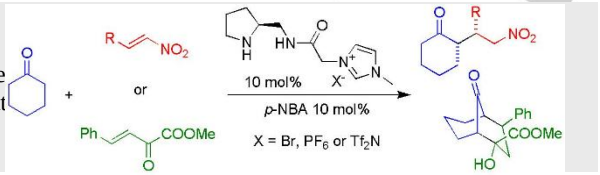

Ionic liquids

*Arturo Obregón-Zúñiga, Marco Guerrero-Robles and Eusebio Juaristi**

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Chiral Imidazolium Ionic Liquids derived from (*S*)-Prolinamine as Organocatalysts in the Asymmetric Michael Reaction and Michael-Aldol Cascade Reaction under Solvent-Free Conditions

A solvent-free enantioselective synthesis of Michael adducts employing chiral imidazolium ionic liquids is described. The same strategy can be used in Michael-intramolecular aldol cascade reactions affording enantioenriched products that are analogues of tropane alkaloids, containing four stereocenters.

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