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3-Trifluoromethanesulfonamido-pyrrolidine: A General Organocatalyst for *anti*-Selective Mannich Reactions

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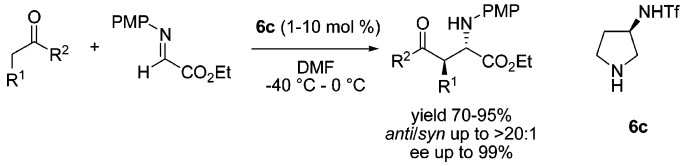
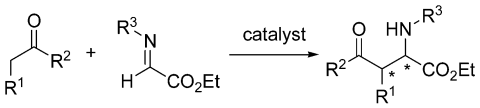
ABSTRACT



Mannich-type reactions of a glyoxylate imine with carbonyl compounds catalyzed by 3-trifluoromethanesulfonamidopyrrolidine proceed with high yields and *anti*-stereoselectivity. The catalyst is easily prepared and the transformation appears to be quite general accommodating aldehydes or ketones.

With the aim of achieving reactions of high synthetic potential, the search for asymmetric catalysts which are not only highly reactive but stereoselective and easily available from commercial sources is an ongoing quest for organic chemists. The Mannich reaction, roughly the addition an enolizable donor carbonyl compound with an imine to yield β-amino carbonyl compounds, is one of these challenging reactions (Scheme 1).[1,2] Over the past years, the use of

Scheme 1. Direct Mannich Reaction with Preformed Imine



organic molecules as catalysts has been intensively developed, thus avoiding expensive and/or toxic metals. High *syn* diastereo- and enantioselectivity were achieved using natural (*S*)-proline and its derivatives,[3,4] cinchona alkaloids,[5] Brønsted[6] and amino acids.[7] However, only a few examples of *anti*-selective, catalytic, asymmetric Mannich reactions either with a preformed imine[8] or in a three-component reaction[9] have been described.

The first *anti*-selective asymmetric Mannich reaction of unmodified aldehydes with an activated imine was reported in 2002 using 20% mol of catalyst **I** (Figure 1).[8a] The

(1) Mannich, C. *Arch. Pharm.* **1912**, *250*, 647.

(2) For reviews, see: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044−1070. For the enantioselective organocatalyzed Mannich reaction see: (a) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102−112. (b) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348−352. (c) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *1*, 29−41. (d) Ting, A.; Schaus S. E. *Eur. J. Org. Chem.* **2007**, 5797−5815. (e) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187−2209. (f) Kobayashi, S.; Ishitami, H. *Chem. Rev.* **1999**, *99*, 1069−1094.

(3) With a preformed imine: (a) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 609−611. (b) Cordova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2003**, *44*, 1923−1926. (c) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476−4478. (d) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84−96.

(4) Three-component Mannich reaction and miscellaneous: (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336−9337. (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827−833. (c) Pojarliev, P.; Biller, W. T.; Martin, H. J.; List, B. *Synlett* **2003**, 1903−1905. (d) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677−3680. (e) Cordova, A. *Chem. Eur. J.* **2004**, *10*, 1987−1997. (f) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079−4083. (i) Westermann, B.; Neuhaus, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4077−4079.

(5) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. *J. Am. Chem. Soc.* **2005**, *127*, 11256−11257.

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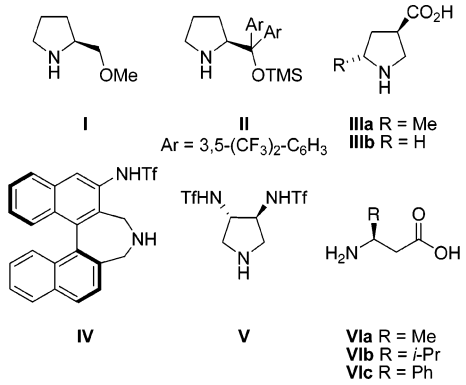


Figure 1. Previously reported *anti*-selective Mannich catalysts.

identification of **II**[8b] led to a significant improvement in terms of yields and enantioselectivity. Chiral amino sulfonamide **IV**[8c] afforded high stereoselectivities with low catalyst loading (0.5−2 mol %) as did **IIIa**.[8e] However, all of these compounds are poor nucleophiles and are efficient in the Mannich reaction mainly with linear aldehydes as donors.

To circumvent this limitation, pyrrolidine bis-sulfonamide **V**[8d] and less hindered β-proline **IIIb**[8f] were successfully developed for the reaction of ketones and hindered aldehydes. Finally, β-amino acids **VI** have recently shown interesting selectivities with cyclohexanone derivatives.[8g] However, most of these catalysts did not match the broad scope of (*S*)-proline. Moreover, efficient catalysts **IIIa**, **IV**, and **V** require tedious multistep syntheses, and thus their use is limited.[10]

As a part of our ongoing project on the synthesis and application of 3-substituted pyrrolidines,[11] we report our results concerning the development of a new and easily available catalyst for the *anti*-selective direct Mannich reaction.[12]

A comparison of the data obtained with catalysts **IIIa**,**b** and **V** suggests that only one hydrogen bond is necessary to stabilize the postulated transition state[8f] leading to the *anti*-diastereoisomer (**A**, Figure 2). According to the propensity

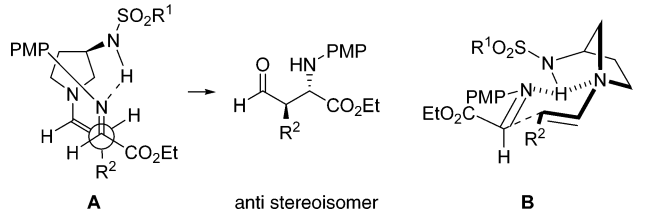
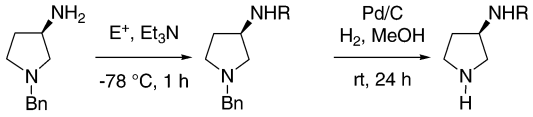


Figure 2. Postulated transition state.

of substituted 3-aminopyrrolidines to adopt an aza-norbornyl conformation,[13] a rigid transition state involving a three-centered hydrogen bond is proposed (**B**, Figure 2).[14] To check this hypothesis we synthesized a set of pyrrolidine 3-sulfonamides.

Methanesulfonyl (Ms), 4-nitrobenzenesulfonyl (Ns), trifluoromethanesulfonyl (Tf), and nonafluorobutane-sulfonyl (Nf) 3-aminopyrrolidine **6a**−**6d** were prepared in a two-step procedure from commercially available 3-aminopyrrolidine (*R*)-**4** (Scheme 2).

Scheme 2. Preparation of 3-Sulfonamidopyrrolidines



R	E^+		yield (%)		yield (%)
Ms	MsCl	**5a**	63	**6a**	100
Ns	NsCl	**5b**	74	**6b**	92
Tf	Tf_2O	**5c**	94	**6c**	100
Nf	Nf_2O	**5d**	88	**6d**	100

The pyrrolidines **6a**−**d** were first evaluated in a test reaction with butanal **2a** and imine **1** in DMF at 0 °C. As shown in Table 1, the reaction proceeded smoothly, giving

(6) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566−1568. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356−5357.

(7) (a) Ibrahem, I.; Zou, W.; Engqvist, M.; Xu, Y.; Cordova, A. *Chem. Eur. J.* **2005**, *11*, 7024−7029.

(8) (a) Cordova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 7749−7752. (b) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjaersgaard, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296−18304. (c) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408−16409. (d) Kano, T.; Hato, Y.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 8467−8469. (e) Mitsumori, S.; Zhang, H.; Ha-Yeon, P.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040−1041. (f) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 9630−9631. (g) Dziedzic, P.; Cordova, A. *Tetrahedron: Asymmetry* **2007**, *18*, 1033−1037. (h) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc* **2007**, *129*, 288−289.

(9) (a) Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790−3791. (b) Cheng, L.; Wu, X.; Lu, Y. *Org. Biomol. Chem.* **2007**, *5*, 1018−1020.

(10) β-Proline **IIIb** is not widely available, although protected derivatives can be purchased at onerous cost. See : Blanchet, J.; Pouliquen, M.; Lasne, M.-C.; Rouden, J. *Tetrahedron Lett.* **2007**, *48*, 5727−5730.

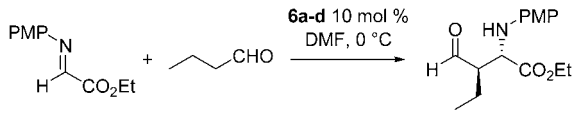
(11) (a) Jean, L.; Baglin, I.; Rouden, J.; Maddaluno, J.; Lasne, M.-C. *Tetrahedron Lett.* **2001**, *42*, 5645−5649. (b) Jean, L.; Rouden, J.; Maddaluno, J.; Lasne, M.-C. *J. Org. Chem.* **2004**, *69*, 8893−8902. (c) Cabello-Sanchez, N.; Jean, L.; Maddaluno, J.; Lasne, M.-C.; Rouden, J. *J. Org. Chem.* **2007**, *72*, 2030−2039.

(12) This work was presented at the *Journées de Chimie Organique 2007*, Palaiseau, France, on 19th September 2007 (Société Française de Chimie). During the submission of this manuscript, two related studies appeared : Kano, T.; Hato, Y.; Yamamoto, A.; Maruoka, K. *Tetrahedron* **2008**, *64*, 1197−1203. (b) Zhang, H.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, K.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2008**, *3*, 875−886.

(13) Corruble, A.; Davoust, D.; Desjardins, S.; Fressigné, C.; Giessner-Prettre, C.; Harrison-Marchand, A.; Houte, H.; Lasne, M.-C.; Maddaluno, J.; Oulyadi, H.; Valnot, J.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 15267−15279.

(14) To the best of our knowledge, such 3-centered hydrogen bonding has not been proposed nor ruled out by computational studies. This unusual interaction is a generally accepted concept. See Jeffrey, G. A.; Mitra, J. *J. Am. Chem. Soc.* **1984**, *106*, 5546−5553 and Okamoto, I.; Nabeta, M.; Hayakawa, Y.; Morita, N.; Takeya, T.; Masu, H.; Azumaya, I.; Tamura, O. *J. Am. Chem. Soc.* **2007**, *129*, 1892−1893. One reviewer is aknowledged to have drawn our attention on this point.

Table 1. Prelimary Study of Various Catalysts



1 2a 3a

entry[a]	catalyst	time (h)	yield[b] (%)	*anti*:*syn*[c]	ee *anti*[d] (%)	ee *syn*[d] (%)
1	**6a**	12	84	2:1	18	8
2	**6b**	18	72	4:1	24	11
3	**6c**[e]	**0.5**	**92**	**9:1**	**97**	nd
4	**6d**	12	54	1:1	7	0

[a] Reaction conditions: **1** (1 equiv), butanal **2a** (3 equiv), catalyst **6a**−**d** (10 mol %) in DMF (0.15 M), 0 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC. [e] 5 mol % **6c** was used.

moderate to excellent yields of aminoaldehyde (2*S*,3*R*)-**3a**.[15] A dramatic effect of the sulfonamido group was observed. As the acidity of the sulfonamido proton increased, the selectivity (absolute and relative) and the reactivity improved (trifluorosulfonamide **6c** being the best catalyst in the series [entry 3, Table 1]). Surprisingly, the nonaflyl derivative **6d** proved to be poorly efficient, giving a 1:1 mixture of racemic diasteroisomers (entry 4, Table 1).

Those results demonstrate the critical role of the acidity of sulfonamide proton in the reaction and the importance of the distance between the nucleophilic nitrogen and the proton, a sluggish result being previously obtained with an homologated derivative of **6c**.[8e]

Optimization of the reaction using 5 mol % (*R*)-**6c** to afford (2*S*,3*R*)-**3a** in various solvents at −20 °C has shown that methanol is not suitable: only hydrolysis of imine **1** was observed (entry 1, Table 2).

Table 2. Influence of Solvent on Selectivity with **6c**

entry[a]	solvent	yield[b] (%)	*anti*:*syn*[c]	ee *anti*[d] (%)	ee *syn*[d] (%)
1	MeOH	0	–	–	
2	*i*-PrOH	78	6:1	74	55
3	THF	86	8:1	79	57
4	dioxane	92	7:1	74	51
5	CH_2Cl_2	81	5:1	74	57
6	toluene	76	4:1	64	46
7	Et_2O	85	5:1	68	45
8	**MeCN**	**96**	**10:1**	**95**	nd
9	**DMF**	**96**	**9:1**	**98**	nd

[a] Reaction conditions: **1** (1 equiv), butanal **2a** (3 equiv), catalyst **6c** (5 mol %) in appropriate solvent (0.15 M) at −20 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC.

In isopropanol (entry 2, Table 2) the desired product was formed in 78% with a moderate steroselectivity. Similar results were observed in the THF, dioxane, dichloromethane, toluene, and ether (entries 3−7). In acetonitrile or DMF, catalyst **6c** gave high yields and stereoselectivities (entries 8−9, Table 2).

Table 3. Influence of Temperature and **6c** Loading on Selectivities

entry[a]	temp (°C)	**6c** (mol %)	yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
1	20	5	97	8:1	97
2	0	5	92	9:1	97
3	−20	5	96	9:1	98
4	**−40**	**5**	**86**	**12:1**	**98**
5	−40	10	87	15:1	99
6	−40	1[e]	92	10:1	95

[a] Reaction conditions: **1** (1 equiv), butanal **2a** (3 equiv), catalyst **6c** (x mol %) in DMF (0.15 M), 0.5−2 h. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC. [e] Reaction time 8 h.

The effect of temperature was next studied (Table 3). Temperatures higher than −20 °C shortened reaction times with preserved selectivities (entries 1−4, Table 3). Lowering the temperature to −40 °C improved the *anti*/*syn* ratio to 12:1 with a complete conversion in 2 h. With 10 mol % of catalyst **6c** the *anti* selectivity reached 15:1, and the ee reached 99% (entry 5, Table 3). The catalyst is still efficient using a 1 mol % amount, although a slight erosion of selectivity was observed (entry 6, Table 3). As a compromise we decided to use 5 mol % of catalyst **6c** to study the scope of the reaction with various linear and branched aldehydes and ketones.

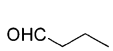
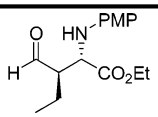
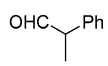
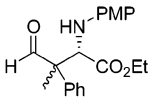
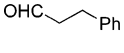
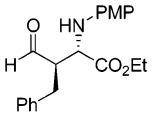
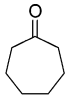
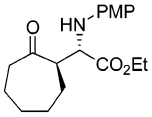
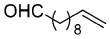
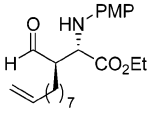
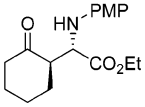
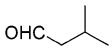
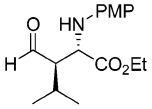
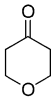
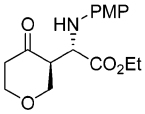
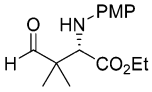
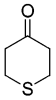
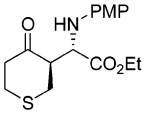
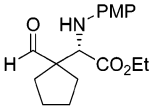
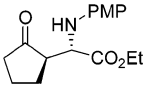
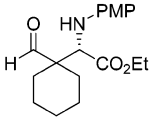
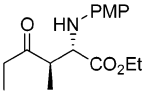
With the optimal conditions in hand, the scope of the reaction was investigated (Table 4). Linear aldehydes gave high dr and ee (entry 1−4, Table 4). Even hindered 3-methylbutanal reacted rapidly at −20 °C (entry 5). The Mannich adduct was systematically found to be configurationally stable enough to be isolated by standard chromatographic purification. With hindered branched aldehydes, no reaction occurred at low temperature but gave excellent results at 0 °C (entries 6−9, Table 4). Importantly, **6c** afforded higher selectivity than proline with milder conditions and a lower catalyst loading with the latter substrates.[16] Cycloheptanone and pentan-2-one required a 20 mol % loading of **6c** to improve both yield and dr (entries 12 and 18, Table 4). Surprisingly, cyclopentanone failed to afford the desired compound (entry 16, Table 4).

Finally, the optimized conditions were applied to a direct three-component reaction involving glyoxaldehyde, 4-methoxyaniline, and butanal. (2*S*,3*R*)-**3a** was formed in 79% yield (*anti*/*syn* 13:1, ee 97%) similar to that obtained previously (entry 1, Table 4). During the reaction, no cross-aldol side product was detected.

(15) Relative configuration was assigned by comparison of ^{1}H NMR shifts, and absolute configuration was assigned by direct comparison of the sign of optical rotation with reported data (see ref 8). HPLC peaks of *anti*- and *syn*-diastereomers were attributed by carrying out *syn*-Mannich reaction with proline. Absolute configuration of the *syn*-diastereomer was not determined.

(16) Cyclohexane carboxaldehyde and cyclopentane carboxaldehyde gave respectively 55% ee and 98% ee with 30 mol % proline in DMSO at room temperature, see: Chowdari, N. S.; Suri, J. T.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2507−2510.

Table 4. Scope of the Reaction

entry[a]	donor	temp time (°C, h)	product	yield[b] (%) (*anti*:*syn*)[c]	ee[d] (%) *anti* 2*S*,3*R*	entry[a]	donor	temp time (°C, h)	product	yield[b] (%) (*anti*:*syn*)[c]	ee[d] (%) *anti* 2*S*,3*R*
1		-40, 2		**3a**, 86 (12:1)	98	10		0, 24		**3h**, 82 (4:1)	20
2		-20, 1		**3b**, 88 (12:1)	98	11		20, 72		**3i**, 56 (13:1)	98
3	"	-40, 2	"	85 (13:1)	99	12	"	20, 48[e]	"	84 (>20:1)	98
4		-40, 2		**3c**, 77 (15:1)	>99	13		20, 2		**3j**, 95 (>20:1)	>99
5		-20, 6		**3d**, 86 (13:1)	>99	14		20, 20		**3k**, 87 (20:1)	96
6		0, 8		**3e**, 76	92 (2*S*)	15		20, 24		**3l**, 85 (10:1)	99
7		0, 3		**3f**, 92	99 (2*S*)	16		20, 72		**3m**, 0	-
8		0, 8		**3g**, 73	60 (2*S*)	17		20, 48		**3n**, 62 (4:1)	99
9	"	-10, 20	"	79	97 (2*S*)	18	"	20, 12[e]	"	70 (9:1)	>99

[a] Reaction conditions: **1** (1 equiv), aldehyde or ketone **2a** (3 equiv), catalyst **6c** (5 mol %) in DMF (0.15 M) at −40 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC. [e] 20 mol % **6c** was used.

In summary, we have identified a new *anti*-selective catalyst for the direct or three-component Mannich reaction that achieved high yields and selectivities for various substrates ranging from linear and branched aldehydes to ketones at low temperatures and under three-component conditions. The acidity of the trifluoromethylsulfonamide group was critical to achieve high stereoselectivity. The results confirmed our hypothesis and showed that C_2 symmetry of catalyst **V** is not a key structural feature for a high stereoselectivity. The broad scope of the reaction associated to the availability of catalyst **6c** will trigger applications in enantioselective synthesis of complex molecules.

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Supporting Information Available: Experimental procedure, characterization data, HPLC charts, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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