Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 8035–8038
Tetrahedron Letters

Benzoimidazole–pyrrolidine (BIP), a highly reactive chiral organocatalyst for aldol process

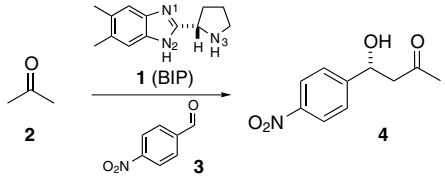
Eric Lacoste,[a] Yannick Landais,[a,*] Kurt Schenk,[b] Jean-Baptiste Verlhac[a] and Jean-Marc Vincent[a,*]

[a]*University Bordeaux-1, 351 Cours de la Libération, 33405 Talence Cedex, France*
[b]*Institute of Crystallography, University of Lausanne, BPS Dorigny, CH-1015 Lausanne, Switzerland*

Received 30 July 2004; revised 30 August 2004; accepted 31 August 2004
Available online 17 September 2004

Abstract—A new chiral benzoimidazole–pyrrolidine ligand (BIP) was shown to catalyze an aldol process in the presence of an equimolar amount of a Brönsted acid, leading to the aldol adduct in high yield and enantioselectivity. Remarkably, the aldol reaction was still effectively catalyzed when starting from equimolar amounts of aldehyde and ketone in THF.

Organocatalyzed reactions have recently enjoyed a renewed interest, and spectacular progress has been made in new catalytic methods based on the use of metal-free chiral organic molecules.[1] Amongst the most efficient inducers, proline occupies a prominent place, and was shown to act as a bifunctional acid–base catalyst in a large array of organic transformations including aldol and Michael reactions, leading to products with generally high levels of diastereo- and enantiocontrol.[2] However, there remain transformations in which the use of proline gives unsatisfactory results, suggesting the need for more efficient organocatalysts having a tunable structure. In this context, we recently started an investigation on a new class of ligand, which may be useful for both metal and metal-free catalyzed organic processes.[3] We thus report on the design and the utilization of a simple bifunctional benzoimidazole–pyrrolidine **1** (BIP) (Scheme 1), which can be considered as a nitrogenated proline analogue,[4] providing, *under acid catalysis*, aldol adducts in high yields and stereoselectivities. Such a catalyst was found to mediate at 5 mol% loading, the aldol reaction using an equimolar amount of aldehyde and ketone, thus circumventing the limitation of the proline catalyzed process where a large excess of the ketone is required.



Scheme 1. Aldol reaction catalyzed by BIP **1**.

Such catalysts are easily available by simply heating L-proline and a substituted 1,2-diaminobenzene under acidic conditions.[5] Under these conditions, **1** is obtained in 60% yield without racemization. Interestingly, the X-ray crystal structure of **1** incorporates a water molecule, which binds two BIP ligands through a four hydrogen bond network (Fig. 1). The oxygen atom of water is ligated to the two N–H's of **1** with O–HN(3) and O–HN(2) bond lengths of 2.71 and 1.87 Å, respectively. The two hydrogen atoms of the water molecule are also ligated to the electron lone pairs of the two nitrogen atoms of a second BIP molecule.

Preliminary investigations on the aldol reaction starting from acetone **2** and *p*-nitrobenzaldehyde **3** in DMSO using **1** as a catalyst (30 mol%) led to the aldol adduct **4** with moderate yield and 44% ee (Table 1, entry 1). Under similar conditions, proline was shown to provide **4** in 64% yield and 76% ee.[6] We found that addition of a Brönsted acid into the reaction medium led to a significant improvement in terms of reaction rate and yield

Keywords: Organocatalyst; Aldol; Proline; Benzoimidazole; Enamine.
* Corresponding authors. Tel.: +33 5 40 00 22 89; fax: +33 5 40 00 62 86 (Y.L.); tel.: +33 5 40 00 89 42; fax: +33 5 40 00 61 58 (J.-M.V.); e-mail addresses: y.landais@lcoo.u-bordeaux1.fr; jm.vincent@lcoo.u-bordeaux1.fr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.08.171

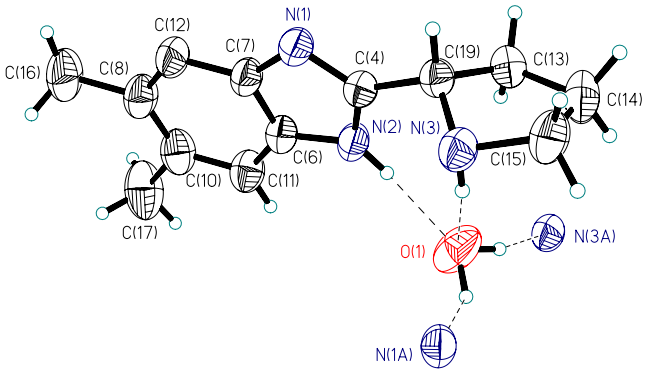


Figure 1. X-ray crystal structure of **1**-0.5H_2O.

(entries 2 and 3 vs 1).[7,8] The reaction conditions were then systematically varied using 20 mol% of catalyst. The rate of the aldol process was shown to be solvent dependent, in the order: THF > CH_2Cl_2 > DMF (entries 4–7). Better yields but lower ee's were observed in CH_2Cl_2 (entry 7). Varying the temperature led to the observation that the reaction was still efficient and generally more enantioselective at −20 °C. But the most remarkable improvement of the process was observed by varying the nature of the proton source. Using the stronger CF_3CO_2H (TFA) instead of AcOH led to both an enhancement of the yield and the enantioselectivity (entry 9 vs 8). The use of even stronger triflic acid did not bring any further change (entry 12). It was observed that only 2 mol% of the ligand/TFA system, in neat acetone, was sufficient to lead to **5** with a high yield and an optimal 82% ee (entry 11).[9]

More importantly, we found that the aldol process was still efficiently catalyzed when starting from equimolar amounts of **2** and **3**, using THF as a solvent (entry 13). The aldol **4** was thus obtained in 67% yield and 82% ee in THF at −5 °C in the presence of **1** (20 mol%) and TFA (20 mol%) (entry 13). Noteworthy, proline was found to be inactive under such conditions. Finally, when the reaction was carried out under the same conditions but with only 5 mol% of **1** aldol **4** was obtained in good yield and enantioselectivity, albeit at a slower rate (entry 14).

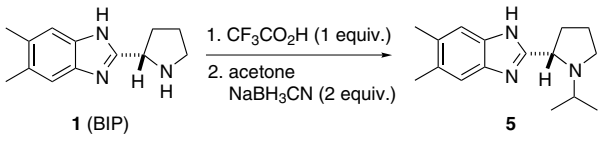
BIP–TFA appears to be much more reactive than proline for this reaction, which requires the use of a large excess of acetone (~25 equiv) with respect to the aldehyde and 20–30 mol% of catalyst loading. It is also noteworthy that aldol experiments have been repeatedly carried out on 10 mmol scale, demonstrating the practical value of this protocol. As a comparison, we showed that the combination of **1** and a Lewis acid such as $Zn(OTf)_2$ may also efficiently catalyze the aldol process, suggesting that these ligands also have the potential as bidendate ligands for metal-catalyzed asymmetric processes (entry 15).

In contrast to proline,[6] BIP **1** has two potential nucleophilic sites. When adding an acid, protonation occurs on the more basic site, that is, the pyrrolidine nitrogen center ($pK_a \sim 9$–10 at N3 vs $pK_a \sim 5$–6 at N1). Formation of the enamine may still occur on the pyrrolidine moiety as rate enhancements have been observed during acid-mediated aldol processes using pyrrolidine-based catalysts.[7] However, the occurrence of an alternative intermediate with the enamine located on the benzoimidazole ring could not be ruled out. To test this hypothesis, a reductive amination reaction was carried out on **1** in the presence of acetone using $NaBH_3CN$ as a reducing agent (Scheme 2).[10] Whether TFA was added in the reaction mixture or not, only the BIP derivative **5** with the isopropyl group on the pyrrolidine moiety was obtained. A BIP derivative with an isopropyl on the benzoimidazole ring or the bis-isopropyl compound were not detected. Clearly, under these reaction conditions, the benzoimidazole is not nucleophilic enough to generate the enamine function. Accordingly, when the aldol process was performed using **5**,[11] from which the

Table 1. BIP **1**-catalyzed asymmetric aldol process between acetone **2** and aldehyde **3**

Entry	**1** (mol%)	Acid (mol%)	T (°C)	Solvent	Time (h)	%Yield[a]	ee[b]
1	30	—	20	DMSO[c]	8	40	44
2	20	AcOH (100)	20	DMSO[c]	0.5	65	50
3	20	AcOH (30)	20	DMSO[c]	1	65	46
4	20	AcOH (20)	−20	DMSO[d]	4	65	54
5	20	AcOH (20)	−20	DMF[c]	24	61	75
6	20	AcOH (20)	−20	THF[c]	8	70	64
7	20	AcOH (20)	−20	CH_2Cl_2[c]	18	92	36
8	20	AcOH (20)	−20	Acetone	4	78	62
9	20	TFA (20)	−20	Acetone	18	86	82
10	10	TFA (10)	−20	Acetone	24	95	80
11	2	TFA (2)	−5	Acetone	24	87	82
12	20	TfOH (20)	−20	Acetone	24	84	80
13	20	TFA (20)	−5	THF[e]	24	67	82
14	5	TFA (5)	−5	THF[e]	48	69	80
15	20	$Zn(OTf)_2$ (20)	20	Acetone	17	87	74

[a] Isolated yield after purification.
[b] ee Determined by ^1H NMR spectroscopy of the corresponding Mosher's ester.
[c] Acetone (25 equiv).
[d] DMSO/acetone 1:2.5.
[e] Acetone (1.1 equiv).



Scheme 2. Reductive amination on BIP **1**.

reaction may only take place with an enamine function located on the benzoimidazole ring, no reaction occurs.

In all studied cases, aldol adduct **4** was shown to possess the same (*R*)-absolute configuration as that obtained with L-proline.[6] The stereochemistry of the process may be rationalized invoking transition state as in Figure 2, with the aldehyde binding to one of the protons on the benzoimidazolium ring.[12] Based on estimated pK_a values (enamonium $pK_a \sim 4$ vs benzoimidazole $pK_a \sim 5$–6) protonation is likely to occur on the benzoimidazole ring. Within this arrangement, the aldehyde thus approaches the *Si*-face of the enamine, to provide the (*R*)-aldol. Increased acidity of the benzoimidazole N–H proton would thus allow a better activation of the aldehyde. This would explain the higher enantioselectivity observed with TFA ($pK_a \sim -1$) where complete protonation should occur in comparison with AcOH ($pK_a \sim 4.7$) in which the protonation is only partial.

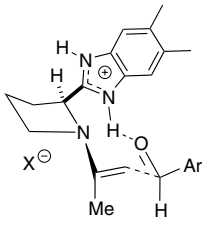
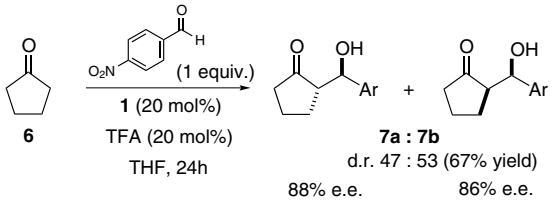


Figure 2. TS model for BIP **1**-mediated aldol reaction.

In an attempt to further extend the methodology, we submitted cyclopentanone **6** (1.1 equiv) to the aldol process with **3** in the presence of BIP **1** (20 mol%). Aldols **7a**,**b** were thus obtained in a satisfying 67% yield and more importantly with 88% and 86% ee for *anti*- and *syn*-diastereomers, respectively (Scheme 3).[13] This compares favorably with the results previously reported for the related proline catalyzed aldol reaction.[6b,7b,14]



Scheme 3. BIP **1**-mediated aldol reaction of cyclopentanone.

In summary, we described here a highly efficient asymmetric aldol process catalyzed by a new benzoimidazole–pyrrolidine ligand **1** (BIP) in the presence of an equimolar amount of Brönsted acid. The efficiency of the process is noteworthy as equimolar amounts of acetone and aldehyde may be employed, thus opening new perspectives for such aldol reactions. Moreover, the presence on the ligand of several nucleophilic and basic sites acting synergistically, as well as various functionalizable sites, suggest that **1** is a potentially attractive template. Further refinement of the ligand structure and extension of the utility of this new organocatalyst class to synthetically relevant organic processes are under active investigation and will be reported in due course.

Acknowledgements

This work was supported by the CNRS, the Région Aquitaine and the *Institut Universitaire de France*. E.L. thanks the MNERT for a Ph.D. fellowship. We gratefully acknowledge Dr. D. Bassani for helpful discussions.

References and notes

1. For recent reviews on organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3727–3748; (b) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481–2495; For recent examples, see: (c) Alexakis, A.; Bernardinelli, G.; Andrey, O. *Org. Lett.* **2003**, *5*, 2559–2561; (d) Jørgensen, K. A.; Melchiorre, P. *J. Org. Chem.* **2003**, *68*, 4151–4157; (e) Mocquet, C. M.; Warriner, S. L. *Synlett* **2004**, 356–358; (f) Jørgensen, K. A.; Aburel, P. S.; Halland, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 661–665; (g) Barbas, C. F., III; Chowdari, N. S.; Suri, J. T. *Org. Lett.* **2004**, *6*, 2507–2510; (h) Northrup, A. B.; Mangion, I. K., F.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152–2154.
2. For recent studies on aldol processes with proline as a catalyst, see: (a) List, B. *Tetrahedron* **2002**, *58*, 5573–5598; (b) Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529–532; (c) Suzuki, N.; Hayashi, Y.; Shoji, M.; Tsuboi, W. *J. Am. Chem. Soc.* **2003**, *125*, 11208–11209; (d) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247–4250; (e) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677–3680; (f) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975–978; (g) List, B.; Vignola, N.; Hoang, L.; Pidathala, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785–2788; (h) MacMillan, D. W. C.; Northrup, A. B. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799; (i) Barbas, C. F., III; Notz, W.; Còrdova, A. *J. Org. Chem.* **2002**, *67*, 301–303; (j) Anders, B.; Nagaswamy, K.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620–621; (k) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Eur. J.* **2002**, *8*, 36–44; (l) Córdova, A.; Sundén, H.; Casas, J. *Tetrahedron Lett.* **2004**, *45*, 6117–6119.
3. Vincent, J.-M.; Philouze, C.; Pianet, I.; Verlhac, J.-B. *Chem. Eur. J.* **2000**, *6*, 3595–3599.
4. For the use of a closely related proline tetrazole as an organocatalyst, see: (a) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808–1809; (b) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558–560; (c) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986; (d) Hartikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834.
5. *5,6-Dimethyl-2-pyrrolidin-2-yl-1H-benzoimidazole (BIP)* (**1**). L-Proline (6.8 g, 59 mmol) was reacted with 4,5-dimethyl-1,2-phenylenediamine (6.2 g, 46 mmol) in a 4 M

aqueous solution of HCl (50 mL) under reflux for four days. The solution was then neutralized with a 4 M aqueous solution of NaOH, then filtered, and the precipitate was washed with diethyl ether (10×) to afford **1** as a beige powder (5.9 g, 60%). Mp 94 °C (MeOH/H_2O); IR (KBr): ν, cm^{-1} 3280 (NH), 2970, 2871, 2282, 1634, 1444, 1310, 825. ^1H NMR (250 MHz, DMSO-d_6): δ 7.30 (2H, s), 4.46–4.41 (1H, m), 3.06–2.98 (2H, m), 2.34 (6H, s), 2.22–2.13 (1H, m), 2.02–1.98 (1H, m), 1.85–1.77 (2H, m). ^{13}C NMR (75.55 MHz, DMSO-d_6): δ 155.2, 136.9, 131.2, 115.1, 56.3, 46.5, 32.2, 25.5, 20.2. MS (EI) 215 (75, M^+), 216 (20), 187 (55), 186 (37), 173 (100), 172 (95), 160 (75), 147 (30), 145 (20). Anal. Calcd for $C_{13}H_{17}N_3 + 1.5H_2O$: C, 64.46; H, 8.26; N, 17.35. Found: C, 64.50; H, 7.85; N, 17.25. (a) Cohen, V. I. *J. Heterocycl. Chem.* **1979**, *16*, 13–16; (b) McKee, V.; Zvagulis, M.; Dogdigian, J. V.; Patch, M. G.; Reed, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 4765–4772.

6. (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; (c) List, B.; Houk, K. N.; Bahmanyar, S.; Martin, H. J. *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479.
7. For a recent study on the influence of a proton source on the rate of aldol process, see: (a) Barbas, C. F., III; Tanaka, F.; Mase, N. *Org. Lett.* **2003**, *5*, 4369–4372; (b) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167–8177; (c) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108–4109.
8. (a) Oka, N.; Saigo, K.; Wada, T. *J. Am. Chem. Soc.* **2003**, *125*, 8307–8317; (b) Greco, M. N.; Maryanoff, B. E. *Tetrahedron Lett.* **1992**, *33*, 5009–5012.
9. Representative experimental aldol reaction: (Table 1, entry 14): BIP **1** (10.4 mg, 45 μmol) and TFA (3.8 μL, 49 μmol) were stirred with acetone (81 μL, 1.1 mmol) and THF (1 mL) for 5 min, then *p*-nitrobenzaldehyde (150.6 mg, 1 mmol) was added. The reaction progress was monitored using TLC (hexanes–EtOAc 7/3). The crude reaction mixture was then purified by flash column chromatography on silica gel (hexanes–EtOAc 7/3) to give the aldol adduct **4**. Enantiomeric excesses were determined using ^1H NMR spectroscopy of the corresponding Mosher's ester.
10. *2-(1-Isopropyl-pyrrolidin-2-yl)-5,6-dimethyl-1H-benzoimidazole* (**5**). Compound **1** (50 mg, 0.23 mmol) and TFA (18 μL, 0.23 mmol) were stirred in acetone for 10 min, then $NaBH_3CN$ (30 mg, 0.5 mmol) was added by portion. After 24 h at rt, the resulting solution was treated with water and Na_2CO_3. The reaction mixture was extracted with ethyl acetate and the resulting organic layer dried over $MgSO_4$. The solvent was evaporated in vacuo to afford **5** as a white powder (39 mg, 65%). Mp 160–178 °C; IR (KBr): ν, cm^{-1} 2966, 1635, 1417, 1309. ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (2H, s), 4.11–4.08 (1H, m), 3.15–3.05 (1H, m), 2.85–2.75 (1H, m), 2.60–2.40 (1H, m), 2.28 (6H, s), 2.25–2.15 (1H, m).^{13}C NMR (75.55 MHz, DMSO-d_6): δ 159.2, 131.3, 115.4, 59.7, 53, 50.3, 33.8, 24.7, 22.2, 20.7,19.4. MS (FAB+) 280 ($[M+Na]^+$), 258 (100, $[M+H]^+$), 257 (26), 256 (80), 214 (65), 212 (22). HRMS for $C_{16}H_{24}N_3$ ($[M+H]^+$): 258.196543, found: 258.197023.
11. The following conditions were used: **5** (10 mol%), TFA (10 mol%) in neat acetone from −20 °C to rt over 48 h.
12. (a) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527–2530; (b) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420–2423; (c) Brown, S. P.; Brochu, M. P.; MacMillan, D. W. C.; Sinz, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809.
13. The enantiomeric excess was determined by chiral phase HPLC analysis (Chiralcel OD® column; hexane–*i*-PrOH 9:1).
14. Proline-catalyzed aldol reaction of cyclopentanone led to a 1:2 *syn*/*anti* isolated ratio with 63% and 69% ee, respectively, in the presence of 20 mol% of catalyst.[6b]