CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200801212

Diversity-Oriented Synthesis towards Conceptually New Highly Modular Aminal–Pyrrolidine Organocatalysts

Adrien Quintard, Chloée Bournaud, and Alexandre Alexakis*[a]

Since the last decade, asymmetric organocatalysis has emerged as a powerful method for the construction of new stereogenic centers.[1] Among those, 1,4-conjugate addition by an activated carbonyl compound is a privileged method in organic synthesis.[2] It allows the formation of a new C–C bond that can be a valuable synthon for fine chemistry.[3] Impressive development has been made in this area in the last five years. Research has mainly focused on the enamine addition to nitroolefins that leads to highly versatile compounds as demonstrated by our group in the synthesis of (−)-botryodiplodin.[4] This research lead to the design of a multitude of new catalysts for the addition of either aldehydes or ketones.[5] Concerning nitroalkenes, a wide range of donors can be used in these reactions but most of the catalysts still suffer limitations. Many of them remain highly substrate specific, are used in high catalyst loading and several equivalent of carbonyl donors are usually required. Furthermore, none of those catalysts possess a tunable moiety potentially leading to different catalytic properties.

Recently, powerful catalytic systems have been described by controlling several interesting aspects. Introduction of a hydrogen bonding to control the selectivity,[6] discovery of new substrates,[7] or increased steric hindrance on the pyrrolidine substituent lead to increased results both in terms of selectivity and in reaction efficiency. The last factor seemed interesting to us since some of those catalysts developed on increased bulkiness were effective on both ketones and aldehydes for different enamine based reactions.[8]

This prompted us to design our own catalyst by increasing the bulkiness on the pyrrolidine moiety with an aminal group. Aminals are interesting nitrogen equivalents of acetals.[9] Due to their structure (determined by X-ray analysis),[10] they are able to bring a strong steric hindrance to adjacent carbons. Indeed, each substituents on the nitrogen atoms are located *trans* to the substituent of the adjacent carbons (Figure 1). This configuration is fixed by the stereochemistry of the starting diamine and makes the nitrogen atom a stereogenic center. Since chiral diamines are highly efficient on these reactions, we thought that incorporating an aminal moiety would increase the bulkiness close to the catalytic site while keeping a strong catalytic activity (Figure 1).

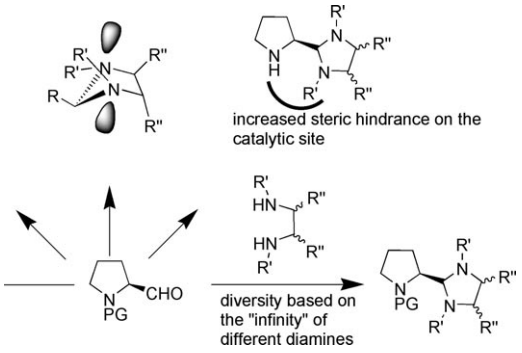


Figure 1. Aminal structure and proposed catalysts by diversity-oriented synthesis.

Furthermore, those catalysts would be highly modular since varying the substituents on the different parts of the aminal could potentially totally change their properties. Indeed, applying the principles of diversity-oriented synthesis[11] to protected prolinal, and considering the wide variety of different diamines would lead to a conceptually new family of modular catalysts (Figure 1).

Herein we describe the synthesis of new aminal–pyrrolidine derivatives and their applications in various Michael addition reactions.

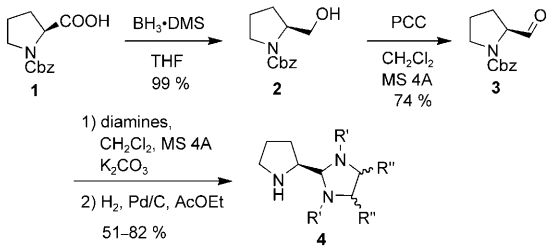
Catalysts **4a–f** were prepared starting from protected L-prolinal **3**, easily obtained in two steps from commercially available Cbz-L-proline. Aminal formation with various dia-

[a] A. Quintard, Dr. C. Bournaud, Prof. Dr. A. Alexakis
Department of organic Chemistry, University of Geneva
Quai Ernest Ansermet 30, 1211 Geneva (Switzerland)
Fax: (+41) 22-379-32-15
E-mail: alexandre.alexakis@chiorg.unige.ch

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801212.

mines followed by classical deprotection under hydrogen led to compound **4a–f** in moderate to good yields (Scheme 1).

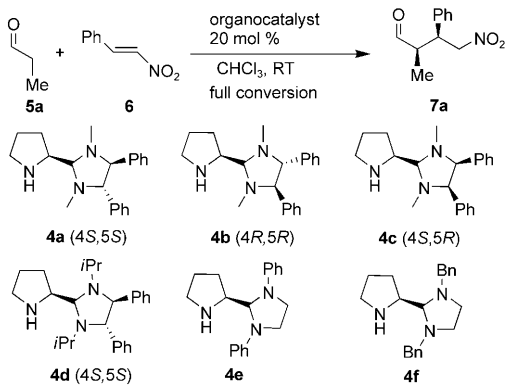
In order to completely study the influence of the configuration of the aminal on the catalytic outcome, three diastereoisomers **4a–c** were prepared; while catalysts **4d–f** were synthesized in order to study the influence of the different substituents. All catalysts were stable after prolonged conservation period. It must be noticed that catalyst **4c** was obtained as a single all *cis* diastereoisomer.



Scheme 1. Synthesis of aminal–pyrrolidine catalysts.

In a first part, the newly synthesized catalysts were tested in the reaction of propionaldehyde with nitrostyrene in conditions optimized in our group (Table 1).[5d]

Table 1. Catalyst screening for the addition of propionaldehyde **5a** to nitrostyrene **6**.[a]



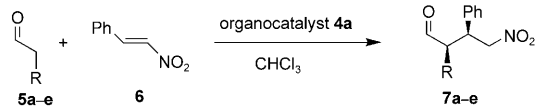
Entry	Cat.	*t* [h]	dr (*syn*/*anti*)[b]	*ee* (*syn*) [%][c]
1	**4a**	15	75:25	79 (+)
2	**4b**	19	66:34	49 (+)
3	**4c**	18	78:22	57 (+)
4	**4d**	21	71:29	76 (+)
5	**4e**	7	75:25	66 (+)
6	**4f**	4	77:23	66 (+)

[a] Reactions were performed using 10 equivalents of aldehyde. [b] dr determined by ^{1}H NMR of the crude product [c] *ee* values determined by super fluid chromatography.

All the catalysts lead to full conversion after a short reaction time. As expected, the influence of the stereochemistry of the aminal was crucial in terms of selectivity (entries 1, 2 and 3). Impressively, the enantioselectivity varied from *ee* 49% in the case of diastereoisomeric catalyst **4b** (entry 2) to the best enantioselectivity (*ee* 79%) using catalyst **4a** (entry 1). In all three cases, the configuration of the adduct is the same. This means that, whatever the configuration of the diamine, the most important stereoselector is the 2 position of the pyrrolidine ring.[12] Surprisingly, increasing the bulkiness on the nitrogen with an isopropyl group (catalyst **4d**) did not lead to any increase in the enantioselectivity (entry 4). These results suggest that the phenyl group of the aminal interacts during the transition state in catalyst **4a** and **4d**. The results are also in agreement with the importance of the aminal configuration. Finally using a phenyl or benzyl group on the nitrogen of the aminal in catalyst **4e** and **4f** did not bring further increase in the enantioselectivity (entries 5 and 6).

The best catalyst **4a** was then evaluated by addition of various aldehydes to nitrostyrene **6** (Table 2). Moderate enantioselectivities (*ee* 79%) and diastereoselectivities (dr up to 75:25) were obtained at room temperature with aldehydes **5a**, **5b** and **5c** but with high reactivity since the reactions were completed in 4 to 15 h (entries 1, 3 and 5). This prompted us to decrease the catalyst loading to 10 mol% and the temperature to −25°C. Using these conditions, the catalyst gave the Michael adducts in two to three days in good diastereoselectivities (dr up to 95/5), and good enantioselectivities (*ee* up to 87%, entries 2, 4 and 6). A further decrease in the temperature to −40°C with aldehyde **5c** lead to a slight increase in selectivity while decreasing the reaction rate (entry 7). Using more hindered aldehyde **5d** lead to a strong decrease in reactivity (Yield = 86% after 3 d) and enantioselectivity (*ee* 67%, entry 8) while using catalyst **4b** gave better results in this case (entry 9). Furthermore, more hindered aldehyde **5e** did not react at all. These results indicate that the aminal moiety must interact strongly with the aldehyde in the transition state.

Table 2. Conjugate addition of aldehydes **5a–e** to nitrostyrene **6** catalyzed by **4a**.

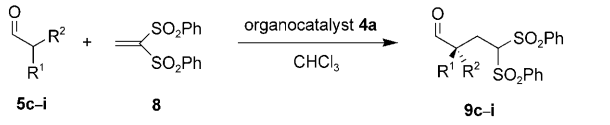


Entry	R	*T* [°C]	mol% **4a**	*t* [h]	Yield [%][a]	dr[b] (*syn*/*anti*)	*ee* (*syn*) [%][c]
1	Me (**5a**)	RT	20	15	84	75:25	79
2	Me (**5a**)	−25	10	72	81	90:10	87
3	Et (**5b**)	RT	20	5.5	100[e]	72:28	74
4	Et (**5b**)	−25	10	72	76	80:20	87
5	*n*Pr (**5c**)	RT	20	4	100[e]	73:27	78
6	*n*Pr (**5c**)	−25	10	40	94	95:5	84
7	*n*Pr (**5c**)	−40	15	96	89	95:5	88
8	*i*Pr (**5d**)	RT	20	72	86	67:33	67
9[d]	*i*Pr (**5d**)	RT	20	18	99	>99%	67
10	Me,Me (**5e**)	RT	20	72	–[f]	–	–

[a] Yield of isolated product after column chromatography. [b] dr determined by ^{1}H NMR of the crude product. [c] *ee* values determined by super fluid chromatography. [d] Catalyst **4b** was used. [e] Full conversion observed by ^{1}H NMR. [f] Only traces of the product.

With these good results at hand, we decided to test our catalysts in the addition of aldehydes to vinyl sulfone,[13] reaction recently developed in our group.[14] This reaction is really interesting due to the versatility of the sulfonyl group in organic chemistry.[15] Furthermore, moderate enantiocontrol had been achieved for the formation of compound **9d** (Table 3). 71% yield and 75% *ee* were obtained using 25 mol% of bipyrrolidine catalyst iPBP and only 55% *ee* using bimorpholine derivatives.[5e]

Table 3. Conjugate addition of aldehydes **5c–i** to vinylsulfone **8** catalyzed by **4a**.



5c–i **8** **9c–i**

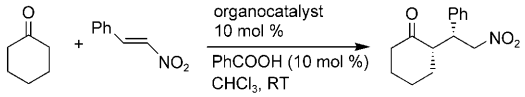
Entry	R^1, R^2	Aldehyde equivalent, mol% **4a**	Reactions conditions	Yield [%][a]	*ee* [%][b]
1	*n*Pr, H (**5c**)	10 equiv, 10 mol%	−60°C, 2 h	87	74
2	*i*Pr, H (**5d**)	10 equiv, 10 mol%	−60°C, 2 h	90	85
3	*i*Pr, H (**5d**)	2 equiv, 5 mol%	−60°C, 3 h	86	85
4	*t*Bu, H (**5f**)	2 equiv, 10 mol%	−60°C, 4 h	96	75
5	allyl, H (**5g**)	2 equiv, 10 mol%	−60°C, 2 h	84	77
6	cHex, H (**5h**)	10 equiv, 10 mol%	−60°C, 3 h	82	91
7	Ph, Me (**5i**)	10 equiv, 10 mol%	RT, 4 h	84	16

[a] Yield of isolated product after column chromatography on florisil. [b] *ee* values determined by super fluid chromatography.

Reactions performed using linear aldehydes gave excellent results. Impressive reactivity (yield around 90%) and good enantioselectivities were obtained with only 10 mol% of catalyst **4a**. More substituted aldehydes **5d** and **5h** gave the best enantioselectivities (*ee* up to 91%, entries 1 and 6) while less hindered ones gave slightly lower enantioselectivities (entries 1, 4 and 5). The more bulky 3,3-dimethylbutyraldehyde **5f** gave only 75% *ee* probably due to a too strong interaction between the *tert*-butyl group and the catalyst. Impressively, only two equivalents of aldehydes could be used with aldehydes **5d**, **5f** and **5h** (entries 3, 4 and 5) and 5 mol% was used with aldehyde **5d** without loosing reactivity (entry 3). Unfortunately, poor enantiocontrol was observed in the formation of the quaternary center with **5i** (entry 7). These results represent an impressive increase in both reactivity and enantioselectivity compared with iPBP. This good stereoselectivity can be explained by the same transition state as proposed with iPBP. A strong interaction of the sulfonyl group with the aminal associated with a good control of the geometry of the enamine in the transition state lead to this higher stereocontrol.

In order to study the reactivity of our catalysts with ketones, their efficiency was tested in the reaction of cyclohexanone **10** with nitrostyrene **6**, a classical model commonly used (Table 4). Surprisingly, catalyst **4b**, the less efficient catalyst using aldehydes lead to a total conversion after 4 d (entry 2). Furthermore this catalyst, the diastereoisomer of the best catalyst for aldehyde, also gave the best results in terms of enantioselectivity (*ee* 80%, entry 2). Catalyst **4a** and **4c** gave much lower reactivity and a dramatic loss in enantioselectivity (entries 1 and 3). Finally, the more hindered catalysts **4d–f**, highly reactive for aldehyde did not catalyze the reaction (entries 4, 5 and 6).

Table 4. Catalyst screening for the addition of cyclohexanone **10** to nitrostyrene **6** catalyzed by **4a**.[a]



10 **6** **11**

Entry	Cat.	*t* [d]	Conv (yield)[b] [%]	dr (*syn*/*anti*)[c]	*ee* (*syn*) [%][d]
1	**4a**	4	60	95:5	61
2	**4b**	4	100 (73)	90:10	80
3	**4c**	4	85	95:5	50
4	**4d**	4	0	–	–
5	**4e**	4	13	>95:5	25
6	**4f**	5	0	–	–
7[e]	**4b**	3	100 (81)	92:8	87

[a] Reactions were performed using 6 equivalents of ketone. [b] Conversions were determined by ^{1}H NMR of the crude product, isolated yields are shown in brackets. [c] dr determined by ^{1}H NMR of the crude product. [d] *ee* determined by super fluid chromatography. [e] Reaction performed in cyclohexane.

These results demonstrate how a slight modification in the catalyst structure can totally change its properties. This difference of reactivity relies on the different proposed transition state between ketones and aldehydes, where the geometry of the enamine plays a crucial role.[16] Finally a short solvent and co-catalyst screening showed that the enantioselectivity could be increased to 87% *ee* by using cyclohexane instead of chloroform (entry 7).

In conclusion, a conceptually new family of chiral aminal–pyrrolidine derivatives has been synthesized. From their evaluation in diverse Michael additions, this family of catalysts is highly modular since the catalytic properties toward different substrates can easily be tuned by varying the substituents on the aminals. Finally, excellent results (*ee* up to 91%) have been obtained in the addition of aldehydes to vinyl sulfones. This is to date the best published results on such additions and represents a promising result.

Investigations are currently under progress in our laboratory in order to improve those catalysts and toward a better understanding of the influence of the various aminal groups on the reactivity other different organocatalyzed reactions.

Keywords: asymmetric catalysis · diversity-oriented synthesis · enamines · Michael addition · organocatalysis

[1] For reviews on organocatalysis see: a) P. I. Dalko, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; b) G. Guillena, D. J. Ramon, *Tetrahedron: Asymmetry* **2006**, *17*, 1465; c) M. J. Gaunt, C. C. Johansson, A. Mc Nally, N. T. Vo, *Drug Discovery Today* **2007**, *12*, 8; d) R. M. De Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575; e) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**; f) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267; g) special issue on different aspects of organocatalysis see: *Chem. Rev.* **2007**, *107*, 5413.

[2] a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; c) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123; d) D. Almasi. D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299; e) J. L. Vicario, D. Badia, L. Carrillo, *Synthesis* **2007**, 2065; f) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471.

[3] P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press, Oxford, **1992**.

[4] O. Andrey, A. Vidonne, A. Alexakis, *Tetrahedron Lett.* **2003**, *44*, 7901.

[5] For selected articles on enamine-catalyzed asymmetric conjugate addition of aldehydes and ketones to nitroolefins, see a) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423; b) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737; c) J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 4441; d) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611; e) D. Enders, A. Seki, *Synlett* **2002**, 26; f) O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2003**, *5*, 2559; g) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147; h) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527; i) J. M. Betancort, K. Sakthivel, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Synthesis* **2004**, 1509; j) T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558; k) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xiu, J.-P. Cheng, *Angew. Chem.* **2006**, *118*, 3165; *Angew. Chem. Int. Ed.* **2006**, *45*, 3093; l) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366; m) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966; n) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170; o) S. Mossé, M. Laars, K. Kriis, T. Kanger, A. Alexakis, *Org. Lett.* **2006**, *8*, 2559; p) C.-L. Cao, M.-C. Ye, X.-L. Sun, Y. Tang, *Org. Lett.* **2006**, *8*, 2901; q) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861; r) S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599; s) V. K. Singh, V. K. Singh, *Org. Lett.* **2007**, *9*, 1117; t) K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li, J-A. Ma, *Org. Lett.* **2007**, *9*, 923; u) E. Alza, X. C. Cameiro, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2007**, *9*, 3717; v) D.-Q. Xu, L.-P. Wang, S.-P. Luo, Y-Fi. Wang, S. Zhang, Z.-Y. Xu, *Eur. J. Org. Chem.* **2008**, 1049; w) P. Li, L. Wang, M. Wang, Y. Zhang, *Eur. J. Org. Chem.* **2008**, 1157.

[6] a) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369; b) C. Palomo, S. Vera, A. Mielgo, E. Gómez-Bengoa, *Angew. Chem.* **2006**, *118*, 6130; *Angew. Chem. Int. Ed.* **2006**, *45*, 5984; c) J. Wang, H. Li, B. Lou, L. Zu, H. Guo, W. Wang, *Chem. Eur. J.* **2006**, *12*, 4321; d) M. Wiesner, J. D. Revell, H. Wennemers, *Angew. Chem.* **2008**, *120*, 1897; *Angew. Chem. Int. Ed.* **2008**, *47*, 1871.

[7] a) S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555; *Angew. Chem. Int. Ed.* **2008**, *47*, 545; b) Y. Chi, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 5608; c) M. Wiesner, J. D. Revell, S. Tonazzi, H. Wennemers, *J. Am. Chem. Soc.* **2008**, *130*, 5610.

[8] a) J. Franzen, M. Marigo, D. Fienlenbach, T. C. Wabnitz, A. Kjaersgaard, K. A. Jorgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; c) T. Mandal, C.-G. Zhao, *Tetrahedron Lett.* **2007**, *48*, 5803; d) P. Diner, A. Kjaersgaard, M. A. Lie, K. A. Jorgensen, *Chem. Eur. J.* **2008**, *14*, 122.

[9] a) For reviews on aminals see: A. Alexakis, P. Mangeney, *Chiral aminals in asymmetric synthesis in Advanced Asymmetric Synthesis* (Ed.: G. R. Stephenson) Springer, London, **1996**; b) A. Alexakis, P. Mangeney, N. Lensen, J- P. Tranchier, R. Gosmini, S. Rausou, *Pure Appl. Chem.* **1996**, *68*, 531.

[10] a) S. Kanemasa, T. Hayashi, J. Tanaka, H. Yamamoto, T. Sakurai, *J. Org. Chem.* **1991**, *56*, 4473; b) A. Alexakis, N. Lensen, J.-P. Tranchier, P. Mangeney, J. Feneau-Dupont, J. P. Declercq, *Synthesis* **1995**, 1038.

[11] M. D. Burke, S. L. Schreiber, *Angew. Chem.* **2004**, *116*, 48; *Angew. Chem. Int. Ed.* **2004**, *43*, 46.

[12] The absolute configuration of the products of addition to nitroolefins and vinyl-sulfones was determined by comparison with the results obtained using iPBP.

[13] For results obtained with the other catalysts (**4b** to **4e**) see Supporting Information.

[14] S. Mossé, A. Alexakis, *Org. Lett.* **2005**, *7*, 4361.

[15] N. S. Simpkins, *Sulfones in Organic Synthesis*, Pergamon Press, Oxford, **1993**.

[16] D. Seebach, J. Golinski, *Helv. Chim. Acta* **1981**, *64*, 1413.

Received: June 19, 2008
Published online: July 30, 2008

