Homogeneous Catalysis

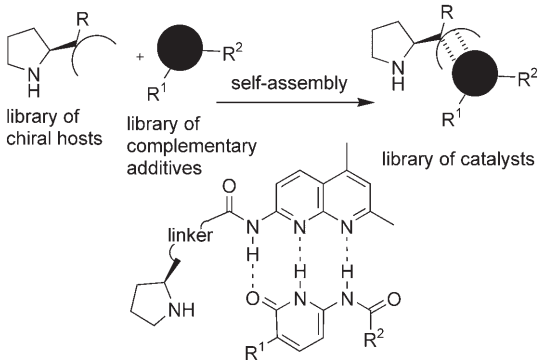
DOI: 10.1002/anie.200602912

Self-Assembly of Organocatalysts: Fine-Tuning Organocatalytic Reactions**

Matthew L. Clarke and José A. Fuentes*

The important advances made in enantioselective catalytic C–H and C–C bond-forming reactions generally rely on the careful and time-consuming optimization of the structure of the chiral catalyst to obtain the maximum enantioselectivity and catalytic activity. Very subtle changes to the catalyst structure can often make large (and unpredictable) differences to the performance of the catalyst, especially in terms of the enantioselectivity. Given the great advances made in high-throughput screening and analysis techniques, the slow step in the screening of asymmetric catalysts is now the synthesis of the catalyst. There is therefore great interest in new methodology that allows the synthesis of libraries of structurally diverse catalysts.[1]

The most common approach has been to design modular ligands and catalysts. These are built up by using high-yielding reactions with two or more simple generic components. For example, libraries of peptide ligands and organocatalysts can be assembled relatively easily from combinations of the many commercially available amino acids.[2] In recent years, several new methodologies that facilitate the synthesis of catalyst libraries have been introduced. A particularly intriguing approach, exemplified by the pioneering work of Breit and co-workers as well as others, has utilized two distinct monodentate ligands that interact with each other through noncovalent interactions. This supramolecular approach allows the synthesis of bidentate ligands.[3] Noncovalent bonds form very rapidly and quantitatively, which offers the tantalizing possibility of using the potential simplicity of the supramolecular approach to build libraries of enantioselective catalysts. Our contrasting approach to catalyst libraries is to use complementary hydrogen bonding between chiral precatalysts and a library of achiral additives such that each additive would alter the steric environment presented by the catalyst (Scheme 1). If this were successful, enantioselectivity could be fine-tuned to a substrate or specific reaction without needing to prepare new chiral catalysts. Each chiral catalyst prepared is therefore adjustable to the requirements of the reactions under study. Herein, we present the first successful application of this approach. In the examples reported herein, the presence of an achiral hydrogen-bonding additive does not just fine-tune the enantioselectivity of a catalyst, but transforms an unselective catalyst into a highly effective promoter of the Michael addition reaction of ketones to nitroalkenes.



Scheme 1. The proposed approach to catalyst libraries (in schematic form) and the structure of the self-assembled catalyst libraries.

In the area of organocatalysis there is a considerable range of reactions that are catalyzed with high enantioselectivity by proline. However, proline is not effective for a considerable range of reactions or substrates, which has inspired research on the synthesis of new chiral organocatalysts. As a testing ground for the new approach we elected to study the enantioselective Michael addition of ketones to nitroalkenes. This reaction is now a well-known and potentially useful organocatalytic reaction, but is not effectively catalyzed by (*S*)-proline.[4] More encouraging results have been obtained by other research groups using custom-made organocatalysts, but improvements in enantioselectivity, diastereoselectivity, turnover frequency, and reduced ketone/alkene ratios (generally ketones are used in 20-fold excess) are needed before it can be considered a genuinely practical procedure.

For our proof of concept experiments we elected to use complementary recognition motifs that were well established to strongly associate in apolar solvents. Kelly et al. successfully used the recognition between amidonaphthyridines and pyridinones to template an S_N2 reaction.[5] Given that amidonaphthyridines are easily prepared and a wide range of pyridinones should be readily accessible, these supramolecular building blocks were used throughout this current study. A novel proline-derived organocatalyst (designated ProNap) was prepared by amide coupling between aminonaphthyridine and (*S*)-proline. Peptide-type catalysts in

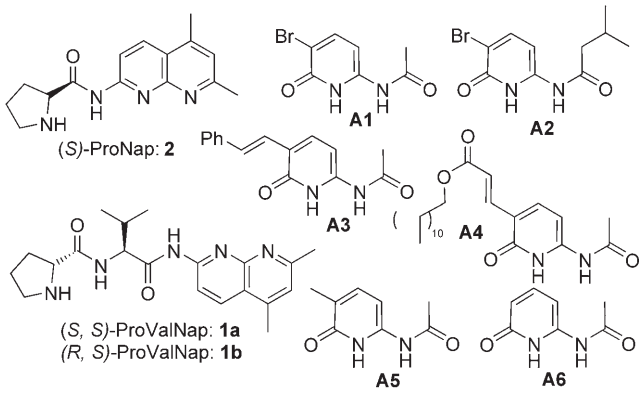
[*] Dr. M. L. Clarke, Dr. J. A. Fuentes
School of Chemistry
University of St Andrews
EaSTCHEM
St Andrews, Fife, KY 16 9ST (UK)
Fax: (+44) 133-446-3808
E-mail: mc28@st-andrews.ac.uk

[**] We thank the EPSRC for funding this project and for the use of the National mass spectrometry service.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

which a further amino acid linker (in this case (*S*)-valine; ProValNap) is present can also be prepared.

The basic catalyst system is modular in nature, and offers an opportunity for structural diversity. However, our main interest lies in using these catalysts in combination with a library of achiral pyridinone additives to multiply the number of new catalysts available by way of complementary hydrogen-bonding interactions. Pyridinones are readily available, and the use of Heck coupling on the bromide precursor of **A1** allows for a range of these additives to be synthesized readily.[6] For our proof of concept studies, a relatively small library was generated, and the discussion here focuses on catalysts generated from ProNap and ProValNap and additives **A1**–**A6** (Scheme 2).

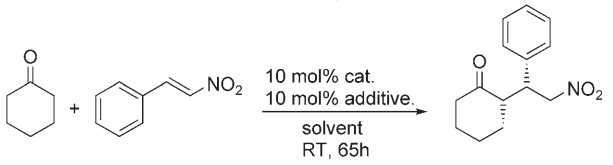


Scheme 2. Structure of the new organocatalyst hosts and some of the pyridinone additives.

Before the catalytic studies were initiated, the complementary binding of several of the additive/host combinations was examined by ^{1}H NMR titration experiments. These revealed that the equilibrium between host–additive duplexes and free components was typically 50:1, and confirms the proposed structure in Scheme 1. The binding was considered to be sufficiently strong to prove the potential of the approach. The majority of the Michael addition experiments were carried out on the model reaction between cyclohexanone and β-nitrostyrene. Illustrative examples can be found in Table 1.

The first experiments were rather discouraging: both the ProNap and ProValNap catalysts gave almost racemic products, albeit with good diastereoselectivity and with at least the same level of reactivity as catalysts reported in the literature. One of the first key experiments was the discovery that the configuration of the product changes when ProValNap is treated with an additive (−27 to +6% *ee*): clear evidence that the additive was having some effect on the reaction. High *ee* values were never realized with either diastereomer of the ProValNap catalyst in this reaction, hence the greater part of the discussion focuses on the results obtained with the ProNap catalysts. A remarkable improvement in enantioselectivity (7 to 47% *ee*) was observed when the reactions were carried out in the presence of **A1**. Surprisingly, there was also a clear reproducible increase in

Table 1: Optimization studies for the asymmetric nitro-Michael reaction.



Entry	Cat.	Additive	solvent	Yield [%][a]	d.r.[a]	*ee* [%][b]
1[c]	Pro	none	MeOH	35	n.d.	28
2[f]	Pro	none	MeOH	20	n.d	45
3[e]	Pro	none	$CHCl_3$	1	n.d.	27
4[c]	**1a**	none	$CHCl_3$	84	10:1	5[d]
5[c]	**1a**	**A4**	$CHCl_3$	86	n.d.	1
6	**1b**	none	$CHCl_3$	51	18:1	27
7	**1b**	**A1**	$CHCl_3$	58	23:1	6[d]
8[e]	**2**	none	$CHCl_3$	87	15:1	15
9	**2**	none	$CHCl_3$	70	41:1	7
10	**2**	**A1**	$CHCl_3$	82	31:1	47
11	**2**	**A2**	$CHCl_3$	74	33:1	34
12	**2**	**A3**	$CHCl_3$	91	42:1	32
13	**2**	**A4**	$CHCl_3$	69	77:1	16
14	**2**	**A5**	$CHCl_3$	59	41:1	35
15	**2**	**A6**	$CHCl_3$	98	59:1	72
16[f,i]	**2**	**A6**	$CHCl_3$	91	72:1	74
17[g]	**2**	**A6**	$CHCl_3$	88	46:1	63
18[h]	**2**	**A6**	$CHCl_3$	63	58:1	79
19	**2**	AcOH	$CHCl_3$	72	28:1	23
20	**2**	**A6**	CH_2Cl_2	97	37:1	67
21	**2**	**A6**	toluene	58	43:1	58
22	**2**	**A6**	$PhCF_3$	81	36:1	62
23	**2**	**A6**	EtOH	12	15:1	22
24	**2**	**A6**	DMSO	traces	n.d.	n.d.

[a] Determined by ^{1}H NMR spectroscopy. Reactions were carried out using 10 mol% catalyst, 4.8 equiv of ketone at 15°C for 65 h unless indicated. [b] Determined by HPLC using a chiralpak AD column. [c] 19.2 equiv of ketone. [d] Opposite enantiomer. [e] 19.2 equiv of ketone, 91 h. [f] 1.5 equiv of ketone. [g] 5 mol% of catalyst. [h] $T = 3$–5°C. [i] 81% yield of isolated product. Pro = (*S*)-proline.

the catalytic turnover when this (and other) additives were employed. All the new catalyst combinations (including ProNap alone) are much more reactive than proline catalysts. Diastereoselectivity was also generally higher when additives were employed. A second key concept that was established in this catalyst screen was that different additives have different effects on the enantioselectivities of the reactions. For this class of reaction, it is the simplest, and least sterically demanding, additive **A6** that gives the highest enantioselectivity: the *ee* value can be increased from 7 to 79% by the addition of 10 mol% of **A6**. A major limitation of the catalysts reported thus far for this reaction is the use of a large excess of ketone (10–20 equiv). It was possible to reduce the ketone/nitroalkene ratio from the commonly used 20:1 to just 1.5:1 when the supramolecular catalysts were employed, with no serious detrimental effects on the yield, diastereomeric ratio, or enantioselectivity (Table 1, entry 16).

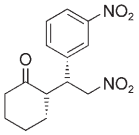
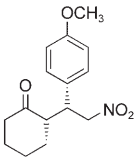
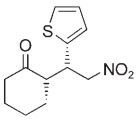
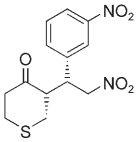
Our working hypothesis involves the self-assembly of a single catalyst from ProNap and **A1**–**A6** that can inhibit the reversible Michael addition between the catalyst and the nitroalkene and provide a more well-defined chiral environment for the enamine intermediate than ProNap alone. It is also conceivable that the additive could dissociate from the

ProNap and play a role in the activation of the nitroalkene. However, we have investigated a range of other additives that would be expected to interact less effectively with ProNap, but are potentially capable of hydrogen bonding to substrates. These included acetic acid, phthalimide, acetanilide, and *N*,*N*′-diphenylthiourea. None of these had any effect, which is consistent with the proposed origin of the remarkable additive effect. Furthermore, a proline-derived amide that lacks the hydrogen-bonding network gives identical results whether the reactions are carried out with additive **A6** or not. These results, all of which point towards the retention of a self-assembled single catalyst, are discussed in the Supporting Information.

A solvent screen revealed that $CHCl_3$, CH_2Cl_2, and benzotrifluoride were preferred, and very polar solvents, which are known to inhibit hydrogen-bonding interactions, were a very poor choice for these reactions. We have examined other ketone and nitroalkene substrates, and observed the same pronounced additive effect (Table 2). The thiophene-substituted nitroalkene gave only moderate enantioselectivity, but in this case, the addition of the achiral additive gives the opposite enantiomer to the simple ProNap-catalyzed reaction. Reactions with the thioether ketone are extremely sluggish without additives present. However, on addition of the additive **A6**, which seems to be the preferred additive for the Michael additions examined thus far, a high yield of product with excellent diastereo- and enantioselectivity could be achieved. The results obtained so far show that the presence of the additive alters the diastereo- and enantioselectivity as well as the reaction rate in a dramatic and reproducible manner.

In summary, these results show that the addition of achiral additives to a chiral organocatalyst host can transform an unselective catalyst into a highly effective one. All the results obtained so far suggest that the origin of this effect involves self-assembly of a new organocatalyst. Further mechanistic studies are underway, including the isolation of catalytic intermediates. It remains to be seen whether this will prove to be a general technique in homogeneous catalysis, but our current studies are focusing on a range of proline-catalyzed reactions and the development of ligands for transition metals that can utilize the same concept of the noncovalent modification of an intact catalyst. It is hoped that in the future, it will be possible to optimize enantioselectivity for reactions that currently can not be achieved by using this approach.

Table 2: (*S*)-ProNap-catalyzed asymmetric Michael additions to nitroalkenes.

Entry	Product	Additive	Yield [%][a]	d.r.[a]	*ee* [%][b]
1[c]		none	63	10:1	16
2[d]		**A6**	94[g]	19:1	75
3[e]		none	36	12:1	13
4[e]		**A6**	81[h]	26:1	61
5[e]		none	55	14:1	−10
6[e]		**A6**	87[i]	50:1	+47[f]
7[c]		none	7	n.d.	n.d.[k]
8[e]		**A6**	70[j]	35:1	94

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by HPLC using a Chiralpak AD column. [c] 42 h. [d] 22 h. [e] 65 h. [f] Opposite enantiomer formed with additive present. [g] 71% yield of isolated product. [h] 70% yield of isolated product. [i] 70% yield of isolated product. [j] 60% yield of isolated product. [k] Without additive, the reaction was very slow: A 29% yield was observed after 10 days in the reaction without additive. This product consisted of a 13:1 ratio of diastereomers with 21% *ee*.

Experimental Section

General procedure for the conjugate addition of a ketone to a nitroolefin: Catalyst (10 mol%) and additive (10 mol%) were stirred in $CHCl_3$ (2 mL) in an inert atmosphere for 30 minutes. The relevant ketone (1.2 mmol) and nitroolefin (0.25 mmol) were then added. The resulting mixture was stirred for the time given in Tables 1 and 2. The reaction was then quenched with 1M HCl (1 mL), diluted with CH_2Cl_2 (1 mL) and H_2O (1 mL), and the aqueous phase extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography. The *ee* value of the product was determined by HPLC analysis on a chiral stationary phase, with the absolute configuration determined by comparison with the known ^{1}H NMR data and optical rotation data.

Other experimental procedures, results showing how noncomplementary additive/catalyst combinations are ineffective, selected spectroscopic data, and NMR spectra can be found in the Supporting Information.

Received: July 20, 2006
Revised: October 17, 2006
Published online: December 15, 2006

Keywords: asymmetric organocatalysis · homogeneous catalysis · Michael addition · self-assembly · supramolecular chemistry

[1] a) C. Gennari, U. Piarulli, *Chem. Rev.* **2003**, *103*, 3071; b) M. T. Reetz, *Angew. Chem.* **2001**, *113*, 292; *Angew. Chem. Int. Ed.* **2001**, *40*, 284; c) M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem.* **2003**, *115*, 814; *Angew. Chem. Int. Ed.* **2003**, *42*, 790; d) K. L. Ding, A. Ishii, K. Mikami, *Angew. Chem.* **1999**, *111*, 519; *Angew. Chem. Int. Ed.* **1999**, *38*, 497; e) C. Bolm, C. Tanyeli, A. Grenz, C. L. Dinter, *Adv. Synth. Catal.* **2002**, *344*, 649.

[2] a) S. R. Gilbertson, X. F. Wang, *Tetrahedron Lett.* **1996**, *37*, 6475; b) S. R. Gilbertson, S. E. Collibee, A. Agarkov, *J. Am. Chem. Soc.* **2000**, *122*, 6522; c) J. R. Porter, W. G. Wirschun, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 2657;

d) J. E. Imbriglio, M. M. Vasbinder, S. J. Miller, *Org. Lett.* **2003**, *5*, 3741.

[3] Latest publications on supramolecular (transition-metal) catalysis: a) B. Breit, W. Seiche, *Angew. Chem.* **2005**, *117*, 1666; *Angew. Chem. Int. Ed.* **2005**, *44*, 1640. b) X.-B. Jiang, L. Lefort, P. Elspeth-Goudriaan, A. H. M. DeVries, P. W. N. M. Van Leeuwen, J. G. De Vries, J. N. H. Reek, *Angew. Chem.* **2006**, *118*, 1629; *Angew. Chem. Int. Ed.* **2006**, *45*, 1223; c) J. M. Takacs, D. Sahadeva Reddy, S. A. Moteki, D. Wu, H. Palencia, *J. Am. Chem. Soc.* **2004**, *126*, 4494; d) M. Weis, C. Waloch, W. Seiche, B. Breit, *J. Am. Chem. Soc.* **2006**, *128*, 4188; e) F. Chevalier, B. Breit, *Angew. Chem.* **2006**, *118*, 1629; *Angew. Chem. Int. Ed.* **2006**, *45*, 1599; perspectives on this emerging area: f) M. J. Wilkinson, P. W. N. M. Van Leeuwen, J. N. H. Reek, *Org. Biol. Chem.* **2005**, *3*, 2371; g) B. Breit, *Angew. Chem.* **2005**, *117*, 6976; *Angew. Chem. Int. Ed.* **2005**, *44*, 6816.

[4] a) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423; b) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, *Angew. Chem.* **2006**, *118*, 3165; *Angew. Chem. Int. Ed.* **2006**, *45*, 3093; c) Y. Xu, W. Zou, H. Sunden, I. Ibrahem, A. Córdova, *Adv. Synth. Catal.* **2006**, *348*, 418; d) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas, *J. Am. Chem. Soc.* **2006**, *128*, 4966; e) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369; f) O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2003**, *5*, 2559; g) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611; h) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84; i) T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558.

[5] T. R. Kelly, G. J. Bridger, C. Zhao, *J. Am. Chem. Soc.* **1990**, *112*, 8024.

[6] M. Sollogoub, K. R. Fox, V. E. C. Powers, T. Brown, *Tetrahedron Lett.* **2002**, *43*, 2131.

