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Highly tunable arylated cinchona alkaloids as bifunctional catalysts†‡

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We report the design and evaluation of a library of chiral bifunctional organocatalysts in which the distance between the catalytically active units can be systematically varied.

The inexpensive cinchona alkaloids quinine (**1**) and quinidine (**2**) have been intensely studied as structural templates upon which bifunctional hydrogen-bond donating organocatalysts can be constructed.[1] For instance, C-9 substituted (thio)urea-, sulfonamide-, and more recently squaramide derivatives (*e.g.* **3**,[2,3] **4**[4] and **5**[5] respectively) together with C-6′ demethylated cupreine-derived materials (*e.g.* **6–8**[1,6]) have been developed (*inter alia*) with the goal of controlling the encounter of two reacting components in a chiral environment *via* interaction between the substrates and the hydrogen bond donating (blue)/Brønsted basic (red) catalyst functionality.[1]

While undoubtedly broad in scope, there is an inherent inflexibility associated with these materials which frustrates the ambition of designing catalysts genuinely tuned to meet the demands of any given process. For example, the relative positioning of the nucleophile- and electrophile-activating components is key to successful bifunctional catalyst design (Fig. 1). An examination of **3–8** reveals that the practitioner is offered two options: hydrogen bond donating functionality at either C-9 or C-6′.[7] Therefore if the stereoelectronic demands of a particular general acid/base catalysed process do not correlate well with the spatial relationship between the catalyst's C-9/C-6′ substituted bifunctional components, *it is unlikely that any modification of the catalytically relevant functionality will improve efficacy*.

More desirable and potentially useful would be the identification of a stable structural template, the chemical space around which could be easily modified in such a way that the relative positioning (and relative orientation) of the catalytically critical groups could be systematically modified.

With this in mind, we noted a recent report from Skarżewski *et al.* detailing the synthesis of 9-phenyl-9-deoxyquinine (**9**, Fig. 2) and its quinidine counterpart,[8] together with a number of derivatives. We were intrigued as to the catalytic potential of such templates, as they seem to represent a potential (partial) solution to the questions posed above: they are stable, easily synthesised[8] materials, the conformation of **9** (*i.e.* **9a**, Fig. 2) in both the solid state and solution is known[8] and would seem to be conducive to bifunctional catalysis if a phenolic hydrogen bond donor were installed (due to its relative proximity to the quinuclidine base). However, no catalytic applications of this class of materials have been reported thus far. We reasoned that we would be able to design a small library of catalysts based on this motif (*i.e.* **10**, Fig. 2) which would be tunable to an unprecedented extent: for example: (a) the C-9 position would be devoid of a heteroatom, thus one would expect the basicity of the quinuclidine nitrogen atom to be augmented relative to traditional catalyst structures **1–8**; (b) the size of the aromatic moiety could be readily varied—allowing the distance between the catalytically competent components to be systematically varied without significantly altering the overall electronic characteristics.

To test this hypothesis, **9–18** were synthesised and evaluated as promoters of the dynamic kinetic resolution (DKR)[9] of azlactones by alcoholysis (Table 1) – a mechanistically complex process for the enantioselective synthesis of orthogonally protected α-amino acids. Of the available organocatalytic protocols for this reaction,[10] the squaramide derivative-catalysed methodology developed by Song *et al.*[5b] boasts the highest levels of activity/enantioselectivity across the broadest substrate range.

Exposure of **19** to allyl alcohol (**20**) in the presence of catalyst **9** (devoid of hydrogen-bond donating functionality) failed to result in the formation of the amino-acid derivative **21** (Table 1, entry 1). Interestingly, under identical unoptimised conditions the three analogues of **9** incorporating a phenolic hydroxy group in the *o*-position, all proved capable of appreciable catalysis, with **10** mediating the formation of **21** in 40% *ee* (entries 2–4). The corresponding *m*- and *p*-phenols

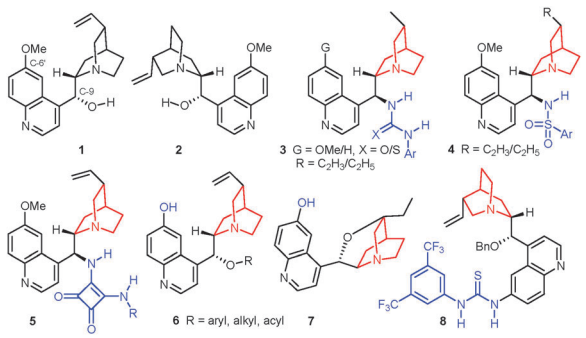

Fig. 1 Cinchona alkaloid-based catalysts: selected examples.

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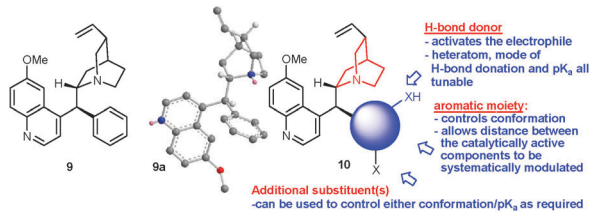
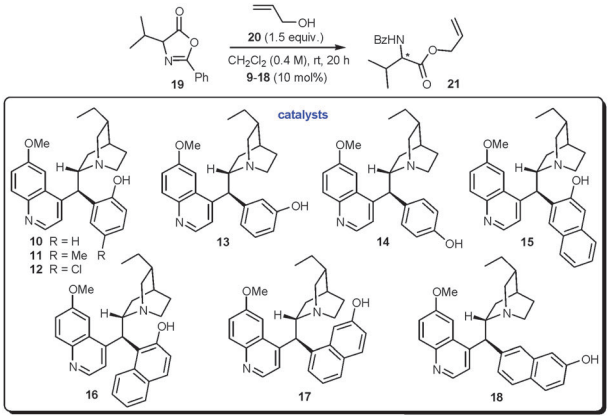


Fig. 2 9-Phenyl-9-deoxyquinine (**9**), the proposed design rationale.

Table 1 Preliminary catalyst evaluation



Entry	Catalyst	Yield (%)[a]	*ee* (%)[b,c]	Abs. config.
1	**9**	0	—	—
2	**10**	20	40	S
3	**11**	20	35	S
4	**12**	32	43	S
5	**13**	3	n.d.	—
6	**14**	3	n.d.	—
7	**15**	15	12	*R*
8	**16**	15	40	*R*
9	**17**	0	n.d.	—
10	**18**	4	n.d.	—

[a] Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [b] Determined by CSP-HPLC. [c] n.d. = not determined.

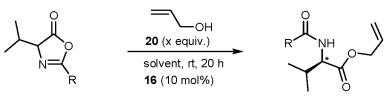
13 and **14** respectively proved largely inactive as expected (entries 5–6). The novel naphthyl-substituted **15** and **16** were included in the library to examine the possible influence of the conformation of the C-9 aryl group on catalysis. These materials exhibited very different selectivity profiles: use of **15** resulted in considerably attenuated product *ee* (entry 7), while the 1,2-substituted variant **16** catalysed the reaction with the same level of enantioselectivity as that observed using **10** – however, this process favoured the opposite product antipode (entry 8). The previously unknown **17** and **18** - which are characterised by the location of the acidic functionality at a further remove from the quinuclidine ring - were not active (entries 9 and 10). *Thus, in the case of this 1,2-addition process, the location of the phenolic hydroxy group in close proximity to the amine base results in significant catalytic activity, while catalysts characterised by greater distances between the two catalytically competent groups proved inactive.* Significantly, a considerable measure of control over product configuration is possible through variation of the C-9 aryl unit.

In order to demonstrate the potential utility of such an approach to catalyst design, azlactone DKR catalysed by **16** was investigated further (Table 2). We found that the stereochemical outcome was sensitive to the steric and electronic nature of the aryl moiety of the protecting group, with the readily synthesised 2,4,6-trichlorophenyl substituted substrate **32** proving optimal (entries 1–12). Lower nucleophile loadings resulted in improved product *ee* with an attendant reduction in reaction rate (entries 12–15). A solvent screen then identified $CDCl_3$ as the most suitable medium from an enantioselectivity perspective (entries 16–19). Dilution to 0.1 M concentration also improved enantioselectivity, which allowed the *room temperature* DKR of **32** catalysed by **16** to afford **(R)-43** in 93% yield and 90% *ee*.

DKR reactions catalysed by **16** resulting in the formation of other amino acids were also investigated (Scheme 1). Azlactone substrates incorporating unhindered α-alkyl substituents (*e.g.* **44** and **45**) traditionally furnish products with lower enantiomeric excess than more hindered analogues. Using catalyst **16** both could be isolated in gratifyingly high enantiomeric excess (> 80%) and excellent yield.[11] Branched amino acid derivatives (*i.e.* **43** and **46–48**) could be prepared in excellent yield and enantiopurity. It is interesting to note that in addition to the synthesis of protected variants of (*R*)-valine, and (*R*)-cyclohexylglycine in ≥ 90% *ee* (**43** and **46**), the methodology could also be used to generate **47**—an orthogonally protected analogue of the abiotic, extraterrestrial amino acid **47a** from the Murchison meteorite.[12]

To the best of our knowledge this is the first time that a derivative of **47a** has been prepared with excellent enantiopurity *via* a *catalytic* asymmetric synthesis. We were also able to

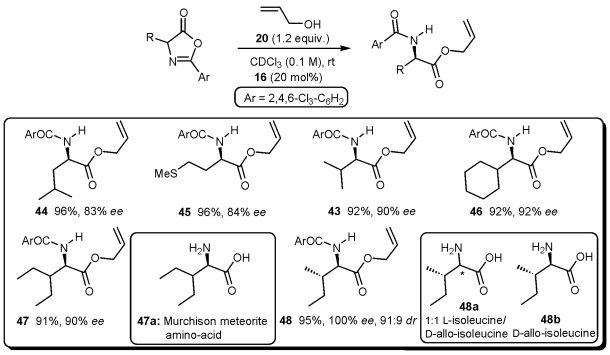
Table 2 Optimisation of azlactone DKR catalysed by **16**



19 R = C_6H_5
22 R = 1-naphthyl
23 R = 4-OCH_3-C_6H_4
24 R = 4-CF_3-C_6H_4
25 R = 3,5-$(CF_3)_2$-C_6H_3
26 R = C_6F_5
27 R = 2-furanyl
28 R = 2,4,6-$(CH_3)_3$-C_6H_2
29 R = *t*-butyl
30 R = trityl
31 R = 2,6-Cl_2-C_6H_3
32 R = 2,4,6-Cl_3-C_6H_2
21 R = C_6H_5
33 R = 1-naphthyl
34 R = 4-OCH_3-C_6H_4
35 R = 4-CF_3-C_6H_4
36 R = 3,5-$(CF_3)_2$-C_6H_3
37 R = C_6F_5
38 R = 2-furanyl
39 R = 2,4,6-$(CH_3)_3$-C_6H_2
40 R = *t*-butyl
41 R = trityl
42 R = 2,6-Cl_2-C_6H_3
43 R = 2,4,6-Cl_3-C_6H_2

Entry	Product	x	Solvent	Conc. (M)	*t* (h)	Yield (%)[a]	*ee* (%)[b]
1	**21**	1.5	CH_2Cl_2	0.4	20	15	40
2	**33**	1.5	CH_2Cl_2	0.4	20	20	53
3	**34**	1.5	CH_2Cl_2	0.4	20	11	34
4	**35**	1.5	CH_2Cl_2	0.4	20	36	60
5	**36**	1.5	CH_2Cl_2	0.4	20	86	67
6	**37**	1.5	CH_2Cl_2	0.4	20	95	71
7	**38**	1.5	CH_2Cl_2	0.4	24	59	75
8	**39**	1.5	CH_2Cl_2	0.4	20	19	74
9	**40**	1.5	CH_2Cl_2	0.4	500	95[c]	41
10	**41**	1.5	CH_2Cl_2	0.4	500	95[d]	53
11	**42**	1.5	CH_2Cl_2	0.4	21	69	76
12	**43**	2.0	CH_2Cl_2	0.4	20	100	78
13	**43**	1.5	CH_2Cl_2	0.4	16	52	81
14	**43**	1.2	CH_2Cl_2	0.4	16	45	84
15	**43**	1.0	CH_2Cl_2	0.4	16	36	86
16	**43**	1.2	MeCN	0.4	16	14	n.d.
17	**43**	1.2	MTBE	0.4	16	14	n.d.
18	**43**	1.2	PhMe	0.4	16	72	85
19	**43**	1.2	$CDCl_3$	0.4	16	57	87
20[e]	**43**	1.2	$CDCl_3$	0.1	72	92	90

[a] Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [b] Determined by CSP-HPLC. [c] The yield after 20 h was 4%. [d] The yield after 20 h was 3%. [e] Using 20 mol% catalyst.



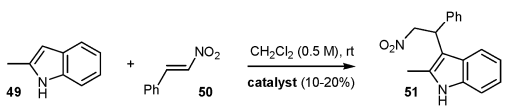
Scheme 1 DKR catalysed by **16**: investigation of substrate scope.

develop a novel class of DKR reaction whereby a commercially available 1 : 1 mixture (**48a**) of the inexpensive L-isoleucine and the highly expensive D-allo-isoleucine (**48b** – also present in the Murchison meteorite,[12] Scheme 1), after *N*-acylation and dehydrative cyclisation, could be converted to **48** (an orthogonally protected variant of the rare and expensive D-allo-isoleucine) with good diastereoselectivity.

Finally, we were also naturally interested in whether catalysts characterised by the location of the hydroxy group at a further remove from the amine base would preferentially promote a conjugate addition. In a preliminary study 2-methylindole (**49**) was reacted with nitroalkene **50** (Table 3). We were pleased to find that both the monofunctional catalyst **9** and analogues bearing *o*-hydroxy substituents at the C-9 aryl ring (*i.e.* **10** and **16**) proved barely capable of promoting the Michael addition faster than the uncatalysed reaction (entries 1–4). However the 2,7-substituted naphthol-based **18** — which is inactive in the 1,2-addition process — was capable of significantly more efficient catalysis than any other member of the library (entry 5). This superiority was further underlined at 20 mol% loading (entries 6–7). Unfortunately, the enantioselectivity of these reactions was unsatisfactory ($< 5\%$ *ee*). It is clear that the further development of catalysts such as **17–18** with the goal of improving upon their activity and selectivity profiles is the next challenge.

To conclude, we have prepared a small library of novel cinchona alkaloid-derived materials with the aim of rationally designing a library of catalysts in which the relative proximity and orientation of the catalytically relevant components can be rapidly and systematically modified. In these preliminary studies it was found that catalysts designed to favour 1,2-additions did so (*with conformational control over the sense of stereoinduction also possible*), while catalysts characterised by a greater distance between the acidic and basic functionality proved inactive. This order of catalytic efficacy was completely reversed in a 1,4-addition process. The study resulted in the catalysis of highly enantioselective DKR processes, including the catalytic enantioselective preparation of an orthogonally protected extraterrestrial amino acid for the first time.

Table 3 Catalyst evaluation in a 1,4-addition process



Entry	Catalyst	Loading (mol%)	*t* (d)	Yield (%)
1	—	—	3	7
2	**9**	10	3	8
3	**10**	10	3	10
4	**16**	10	3	12
5	**18**	10	3	30
6	**10**	20	7	35
7	**18**	20	7	61

Financial support from Science Foundation Ireland and The Irish Research Council for Science Engineering and Technology is gratefully acknowledged.

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