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Urea- and Thiourea-Substituted Cinchona Alkaloid Derivatives as Highly Efficient Bifunctional Organocatalysts for the Asymmetric Addition of Malonate to Nitroalkenes: Inversion of Configuration at C9 Dramatically Improves Catalyst Performance.**

*Séamus H. McCooey and Stephen J. Connon**

Inspired by the efficiency, elegance, and selectivity of enzymatic catalysis, the design of organic molecules capable of the efficient and enantioselective promotion of carbon–carbon bond-forming processes is a formidable challenge which is currently receiving considerable attention.[1] In this context, one of the fundamental enzymatic catalyst competencies that is most difficult to engineer in synthetic systems is bifunctionality; that is, the ability of a catalyst to employ Lewis/Brønsted acidic and Lewis/Brønsted basic functionality synergistically to bring about the activation of both the nucleophilic and electrophilic components of a reaction simultaneously.[2]

Over 20 years ago, Wynberg and Hiemstra[3] reported that cinchona alkaloids were efficient (albeit only moderately selective) bifunctional organocatalysts for the 1,4-addition of thiophenol derivatives to cyclohexenones, and proposed catalyst participation in the deprotonation of the thiol (through the basic quinuclidine alkaloid nitrogen atom) and in the stabilization of the enolate resulting from the 1,4-addition step (through hydrogen bonding with the hydroxy moiety of the catalyst).[4–6]

As Wynberg predicted,[3] the derivitization of cinchona alkaloids[7] with the goal of augmenting hydrogen-bond-donating ability has resulted in an expansion of catalyst scope: Hatakeyama and co-workers reported that the rigid phenolic quinidine derivative **1** promotes highly enantioselective (aza)-Baylis–Hillman reactions,[8] and Deng and co-workers demonstrated that the readily available 6′-demethylated quinine and quinidine alkaloids are considerably more active and selective catalysts for the addition of 1,3-dicarbonyl compounds to β-nitrostyrenes than their natural 6′-methylated analogues.[9,10]

[*] S. H. McCooey, Dr. S. J. Connon
Centre for Synthesis and Chemical Biology
Department of Chemistry
Trinity College, University of Dublin
Dublin 2 (Ireland)
Fax: (+353) 1-671-2826
E-mail: connons@tcd.ie

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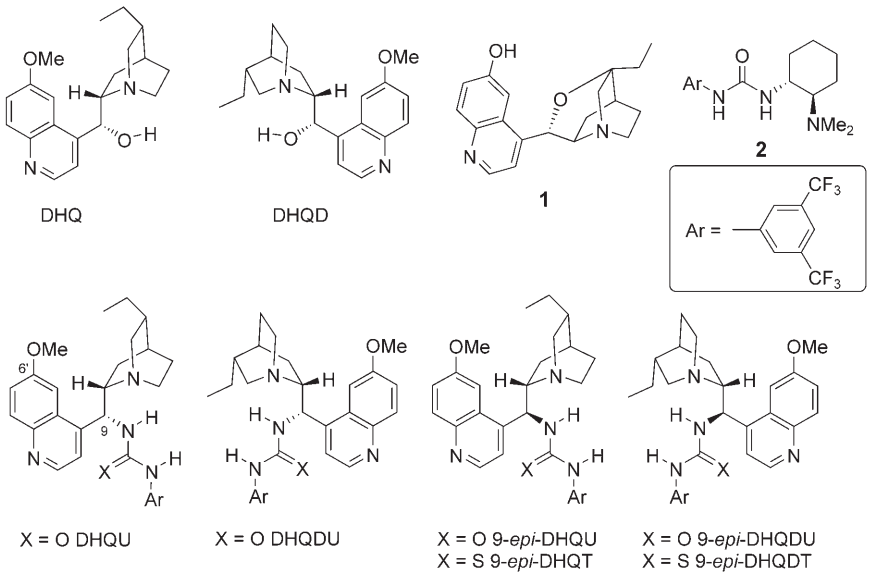
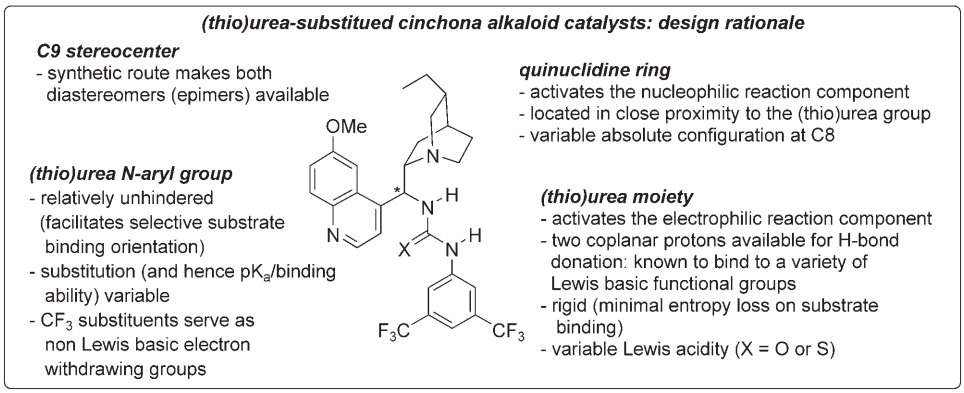
The ability of chiral urea[11] and thiourea derivatives to serve as powerful hydrogen-bond-donating organocatalysts was recently recognized by Jacobsen and co-workers, who developed a suite of thiourea catalysts that promote a diverse range of reactions with excellent enantioselectivity.[12] The compatibility of (thio)ureas with Lewis basic functionality was also demonstrated recently: Takemoto and co-workers have introduced the bifunctional catalyst **2**, which promotes Michael-type[13a,b] and aza-Henry[13c] reactions with high enantioselectivity.[14] Furthermore, we have found that bisaryl(thio)urea derivatives are significantly more efficient "mole-per-mole" promoters of the DABCO-catalyzed Baylis–Hillman reaction than either methanol or water.[15]

We were therefore intrigued by the possibility of modifying the "privileged"[16] cinchona alkaloid structural backbone by substituting the hydroxy group at C9 with an aryl(thio)urea moiety with the aim of augmenting the rigidity, tunability, and hydrogen-bond-donating proclivity of these materials. An additional advantage associated with this strategy is the opportunity to examine the (little studied) effect of inversion of configuration at C9 on catalyst performance. We therefore prepared 9-(3,5-bistrifluoromethylphenyl)urea derivatives of dihydroquinine (DHQ) and dihydroquinidine (DHQD) (DHQU and DHQDU, respectively) together with their C9-inverted analogues (Scheme 1).[17]

The asymmetric Michael addition of relatively acidic carbon pronucleophiles (such as malonates) to nitroolefins is an important C–C bond forming reaction that provides access to synthetically useful enantioenriched nitroalkanes.[18,19] Current bifunctional organocatalytic systems such as **2**[13] and 6′-demethylated quinidine[9] are capable of promoting the reaction with high enantioselectivity at typical catalyst loadings of 10 mol%, and efficient metal-based systems (chiral Mg–bisoxazoline[20a,b] and Ru–amido[20c] complexes at 2–5 mol% loadings) have been reported which require more stringent control of the reaction conditions. This reaction therefore seemed to be an ideal test for the potential activity and selectivity of the novel urea-substituted cinchona alkaloid structures.

The results of initial investigations into the addition of dimethyl malonate to (*E*)-β-nitrostyrene (**3**) catalyzed by cinchona alkaloid derivatives are presented in Table 1. Initial screening studies identified toluene as the optimal solvent for the reaction. The urea-substituted analogues (DHQU and DHQDU) with the stereochemistry of the "natural" cinchona alkaloid were more-selective albeit significantly less-active catalysts than their respective dihydroalkaloid precursors DHQ and DHQD (Table 1, entries 1, 3 and 4, 5) at room temperature. Gratifyingly, the C9 diastereoisomers of these materials (9-epi-DHQU and 9-epi-DHQDU, Figure 1)[21] exhibited decidedly superior activity and enantioselectivity (Table 1, entries 6–8); and gave complete conversion of **3** into nitroalkane **4** with high enantioselectivity at room temperature in the presence of only 2 mol% of catalyst. Further improvement was observed upon the synthesis and evaluation of their thiourea analogues (9-epi-DHQT and 9-epi-DHQDT, Figure 1). Below ambient temperature, **4** could be generated with quantitative conversion and excellent enantioselectivity (Table 1, entries 9–11) at low catalyst loadings. It is noteworthy that inversion of the absolute configuration at C9 in





Scheme 1. Modified cinchona alkaloid derivatives.

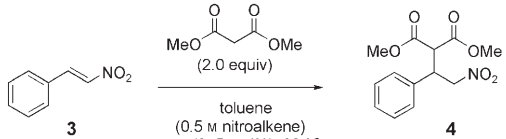
these (thio)urea-substituted systems dramatically improves catalyst activity and selectivity without altering the sense of stereoinduction observed, that is, 9-*epi*-DHQU and 9-*epi*-DHQT promote the formation of the same antipode of **4** as DHQU (and DHQ), whereas 9-*epi*-DHQDU furnishes the same product enantiomer as DHQDU (and DHQD).

This is in marked contrast to the relative performance of the hydroxy-substituted DHQ and 9-epi-DHQ: epimerization of C9 of the parent dihydroalkaloid led to a marginal increase in enantioselectivity (with inversion of the sense of stereoinduction) and a significant reduction of catalyst activity (Table 1, entries 1 and 2). It is therefore clear that although neither inversion of the C9 stereocenter nor (thio)urea substitution alone endow the parent alkaloids DHQ and DHQD with significantly improved catalytic properties (in the context of the addition reaction studied), a combination of both modifications results in a remarkable enhancement of catalyst efficacy and enantioselectivity.

We then turned our attention to the question of catalyst scope. The use of either 9-epi-DHQT or 9-epi-DHQDT allowed the conversion of both activated (**6**–**8**) and deactivated (**9**–**11**) β-nitrostyrenes (Table 2, entries 1–10) into their corresponding Michael adducts **14**–**19** in excellent yields (91–95%) and enantioselectivities (87–99% *ee*) at convenient reaction temperatures between ambient temperature and −20°C. Although we did not observe a strong correlation between the electronic properties of the substrate and the enantiopurity of the product, in general, relatively deactivated olefins gave rise to products of marginally higher enantiopurity than more-electrophilic analogues. Alkyl-substituted nitroolefins were also found to be compatible with 9-epi-DHQT; the unhindered **12** proved unproblematic and even the traditionally challenging substrate **13** (which is inert towards a binary bifunctional catalyst system, Table 2, entry 13)[22] underwent conversion into **21** with attenuated enantioselectivity (75% *ee*).

9-*epi*-DHQT and 9-*epi*-DHQDT are characterized by excellent catalytic activity at 2–5 mol% loadings and convenient reaction temperatures, and are also comparable in terms of efficacy, scope, and enantioselectivity to benchmark metal-based systems.[20] At higher concentrations catalytic asymmetric addition can be conveniently carried out at unprecedented catalyst loadings without compromising either efficiency or enantioselectivity, as exemplified by the synthesis of **16** from **8** in excellent yield and enantioselectivity promoted by 9-*epi*-DHQT (0.5 mol%) at 0°C (Scheme 2, compare with Table 2, entry 4).

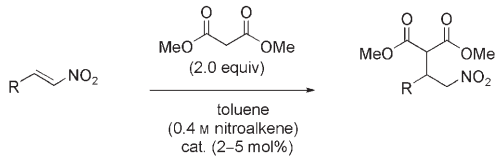
Table 1: Catalyst evaluation in the addition of dimethyl malonate to **3**.



Entry	Catalyst	mol%	*t* [h]	Conv. [%][a]	*ee* [%][b]	Product config.[c]
1	DHQ	5	24	>98	12	(*S*)
2	9-*epi*-DHQ	5	144	46	18	(*R*)
3	DHQD	5	24	>98	1	(*R*)
4	DHQU	5	24	26	25	(*S*)
5	DHQDU	5	144	25	17	(*R*)
6	9-*epi*-DHQU	5	5	>98	74	(*S*)
7	9-*epi*-DHQU	2	24	>98	88	(*S*)
8	9-*epi*-DHQDU	2	30	>98	79	(*R*)
9	9-*epi*-DHQT	2	24	>98	90	(*S*)
10	9-*epi*-DHQDT	2	30	>98	85	(*R*)
11	9-*epi*-DHQT	2	30	>98[d]	99[e]	(*S*)

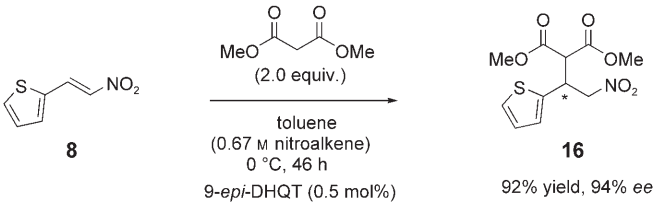
[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by chiral stationary phase (CSP)-HPLC (see Supporting Information). [c] Absolute configuration as determined by comparison with literature CSP-HPLC retention times and optical rotation data (references [9] and [13a]). [d] 93% yield of isolated product. [e] Reaction at −20°C.

Table 2: Catalyst scope for the the conversion of both activated and deactivated β-nitrostyrenes.



Entry	Substr.	R	Catalyst	mol%	*T* [°C]	*t* [h]	Prod.	Yield [%][a]	*ee* [%][b]
1	**6**	4-BrC_6H_4	9-*epi*-DHQT	2	20	17	**14**	92	87
2	**6**	4-BrC_6H_4	9-*epi*-DHQT	2	−20	40	**14**	94	93
3	**6**	4-BrC_6H_4	9-*epi*-DHQDT	2	−20	55	**14**	80	93
4	**7**	2-$NO_2C_6H_4$	9-*epi*-DHQT	2	−20	69	**15**	91	90
5	**8**	2-thienyl	9-*epi*-DHQT	2	−20	23	**16**	94	95
6	**9**	2-MeC_6H_4	9-*epi*-DHQT	5	20	25	**17**	93	93
7	**9**	2-MeC_6H_4	9-*epi*-DHQT	5	0	30	**17**	95	94
8	**10**	1-naphthyl	9-*epi*-DHQT	2	0	31	**18**	94	93
9	**11**	4-$MeOC_6H_4$	9-*epi*-DHQT	5	0	30	**19**	92	99
10	**11**	4-MeC_6H_4	9-*epi*-DHQDT	5	0	38	**19**	90	91
11	**12**	*n*-hexyl	9-*epi*-DHQT	5	−20	69	**20**	88	86
12	**13**	cyclohexyl	9-*epi*-DHQT	5	20	147	**21**	63	75
13	**13**	cyclohexyl	quinuclidine[c]	20	20	72	**21**	0	–

[a] Refers to the yield of the isolated product after column chromatography. [b] Determined by CSP-HPLC (see Supporting Information).



Scheme 2. Catalysis by 9-epi-DHQT at low catalyst loading.

The dependence of catalytic efficiency and selectivity on both the presence of (thio)urea functionality and the relative stereochemistry at C8/C9 strongly implies that these modified cinchona alkaloid systems operate through a bifunctional mechanism, that is, quinuclidine-moiety-assisted generation of the deprotonated malonate nucleophile and its addition to a single face of the (thio)urea-bound nitroolefin electrophile. A preliminary selectivity principle based on the results presented in Table 1 is outlined in Figure 1. An examination of models and MM2 calculations[23] indicate that **A** is a reasonable representation of the least strained conformation of the active and selective catalyst 9-epi-DHQU in which the bulky alkyl groups at the C9 stereogenic centre avoid steric interactions with each other and with the carbonyl group of the urea functionality.[24] In this conformation it would be expected that the nitroolefin would bind (through both oxygen atoms)[25] as shown in pretransition state (TS) assembly **B** (Figure 1) to minimize contact with the large catalyst substituents, thus allowing the proximal Brønsted basic aliphatic heterocycle to bring about enolate generation at the *Si* face of the electrophile, leading to the formation of (*S*)-**4** (Figure 1, **B** and Table 1, entry 7).

A similar MM2 examination of DHQU identifies **C** as the minimum-energy conformer, which would clearly be ill suited to efficient bifunctional catalysis and would be expected to furnish the opposite enantiomer to that observed experimentally (Figure 1, **C** and Table 1, entry 4,). We therefore propose that bifunctional catalysis involving DHQU may proceed predominantly through a minor conformer represented by **D**, in which the bifunctional catalyst components are more suitably oriented to cooperate catalytically and to generate the product enantiomer observed. The catalyst components, however, are still poorly situated relative to the catalytically active components of 9-epi-DHQU in terms of both proximity of the quinuclidine ring to the aryl urea and the ability of the catalyst to bind the nitroalkene selectively.[26]

In summary we have developed a new class of highly active and selective (thio)urea-substituted cinchona alkaloid based catalysts for the addition of dimethyl malonate to nitroalkenes. A systematic investigation into the effects of the relative stereochemistry at C8 and C9 of these materials on catalyst performance has implicated bifunctional catalysis and revealed that C9 epimeric catalysts are remarkably more efficacious in terms of rate and selectivity than analogues of

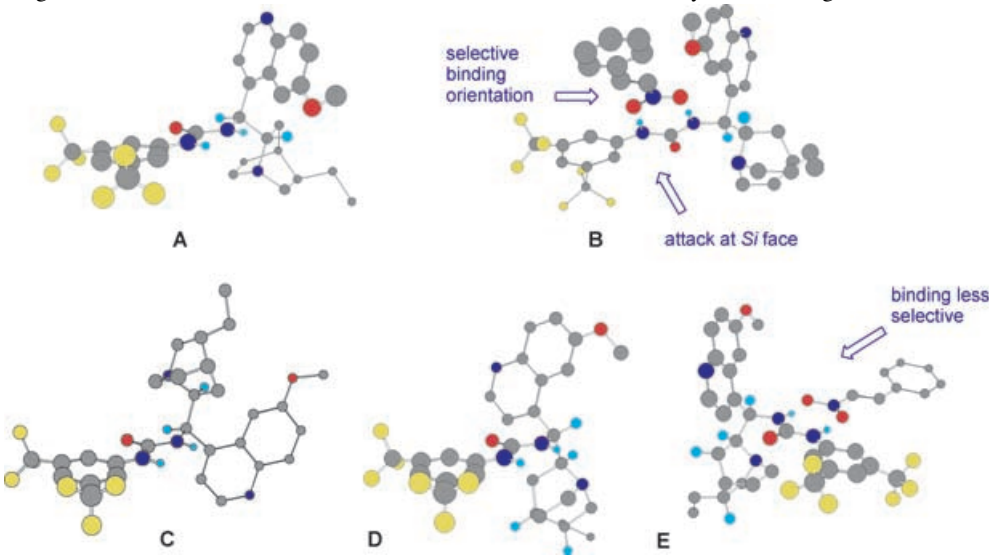


Figure 1. Selectivity model. A: Proposed catalytically active conformation of 9-epi-DHQU (MM2). B: Possible pre-TS assembly for enantioselective addition to **3** promoted by 9-epi-DHQU. C: Proposed lowest energy conformation (MM2) of DHQU. D: Proposed catalytically active conformation of DHQU. E: Possible pre-TS assembly for addition to **3** promoted by DHQU.

"natural" cinchona alkaloid stereochemistry. Highly active 9-*epi*-DHQT and 9-*epi*-DHQDT (which are readily available from DHQ and DHQD - see Supporting Information) have been identified as efficient and enantioselective catalysts with substrate-scope and selectivity profiles on a par with current benchmark literature systems and can be conveniently employed at relatively low catalyst loadings (0.5–5 mol %). Studies to determine the solution-state structure of these materials and to explore their potential as promoters of a variety of reactions susceptible to the influence of bifunctional catalysis are underway.

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[21] The prefix "*epi*" usually refers only to inversion of configuration at a single stereocenter, that is, no functional-group interconversion is implied. The term is adopted in this case for convenient identification of the relative stereochemistry of the catalyst at C8/C9.

[22] To the best of our knowledge only Deng et al. (ref. [9]) have thus far successfully selectively converted this hindered substrate by using 20 mol % 6′-demethylated quinine.

[23] MM2 force-field energy-minimization calculations were carried out with CS Chem3D Std v.4.0 software. Conformers were minimized to a minimum RMS gradient of 0.02.

[24] The catalysts were obtained as amorphous solids, and several attempts to recrystallize these materials were unsuccessful. Conformation **A** is in very good agreement with structural data associated with other (thio)urea-based catalysts in the literature which incorporate a chiral methine group adjacent to the (thio)urea functionality.[12e, 13b].

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[26] This would account for the observed product stereochemistry, and the decrease in catalyst efficiency and selectivity associated with DHQU relative to 9-*epi*-DHQU. However, it is acknowledged that alternative rationales are possible, for example, reversal of binding selectivity relative to 9-epi-DHQU, etc. It is envisaged that ongoing structural studies will provide more detailed insight into the catalytic behaviour of these C9 diastereomers.

