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A New Class of Urea-Substituted Cinchona Alkaloids Promote Highly Enantioselective Nitroaldol reactions of Trifluoromethylketones

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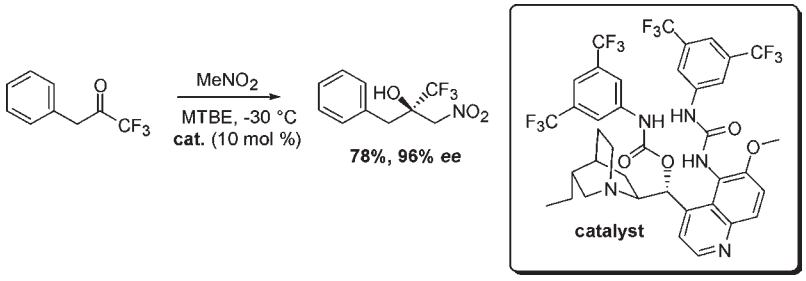
ABSTRACT



The first class of bifunctional cinchona-alkaloid catalysts incorporating a urea moiety at C-5′ has been developed. These materials catalyze the efficient and highly enantioselective 1,2-addition of nitromethane to trifluoromethylketones to form synthetically pliable products incorporating a quaternary stereocenter. Excellent product yields and levels of enantiomeric excess are possible, and the optimum catalyst structure is capable of promoting the Henry reaction involving alkyl trifluoromethylketones with unprecedented enantioselectivity.

Over the past 5 years, cinchona alkaloid derivatives incorporating a C-9-(thio)urea component (i.e., **1**−**2** Figure 1) have emerged as powerful catalysts for a range of asymmetric transformations susceptible to the influence of general acid−base catalysis, including Michael-type reactions, nonconcerted cycloadditions, and the additions of pronucleophiles to imines.[1−3] While the success of these systems is undoubtedly related to the proximity of the mutually compatible bifunctional components in a well-defined chiral environment, from a design perspective, one is limited in what can be achieved in terms of tuneability: i.e., while the (thio)urea component can be modified/replaced (as elegantly demonstrated by Rawal,[4] for example), the relative positioning of the nucleophile- and electrophile-activating components (a key feature of any bifunctional catalyst) remains relatively fixed in all such systems. Therefore, if the stereoelectronic demands of a particular general acid/base catalyzed reaction happen not to overlay neatly with the distance between the C-9-substituted catalyst's bifunctional components, it is unlikely that any amount of modification of the (thio)urea substituent will result in efficient catalysis.

With this in mind, we became interested in developing systems which retain the essential elements of the successful bifunctional system **1**−**2**, yet in which the distance between the bifunctional components has been varied.

(1) Selected reviews: (a) Hiemstra, H.; Marcelli, T. *Synthesis* **2010**, 1229. (b) Connon, S. J. *Synlett* **2009**, 354. (c) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (d) Connon, S. J. *Chem. Commun.* **2008**, 2499. (e) Doyle, A. G.; Jacobsen, E. N *Chem. Rev.* **2007**, *107*, 5713. (f) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (g) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5419. (h) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496.

(2) (a) Lee, B. -J.; Jang, L.; Liu, M.; Chen, Y. -C.; Ding, L. -S.; Wu, Y. *Synlett* **2005**, 603. (b) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (c) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (d) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun* **2005**, 4481.

(3) For an account concerning seminal work on non-cinchona alkaloid-based bifunctional (thio)urea catalysts, see: Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785.

(4) Malerich, J. P; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416.

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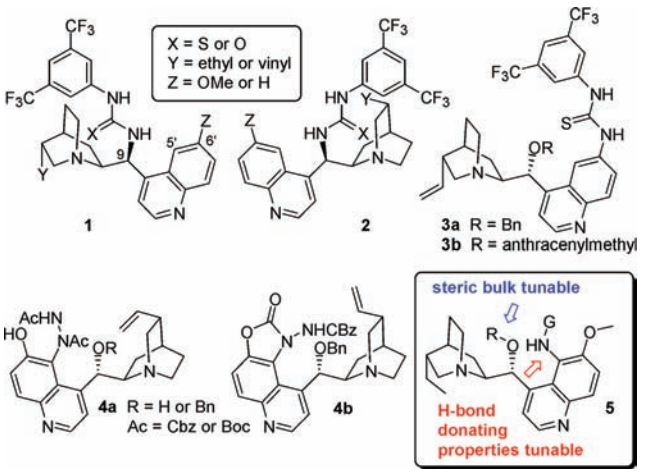


Figure 1. Representative C-9-, C-6′-, and C-5′-modified cinchona alkaloid catalysts and the proposed novel library **5**.

Inspired by the catalytically useful cupreine/cupreidine family[1a,h] of natural product derivatives, Hiemstra et al. previously developed the C-6′ thiourea-substituted cinchona alkaloid catalyst **3a** and demonstrated it capable of highly efficient asymmetric nitroaldol reactions involving aromatic aldehydes,[5] while a similar catalyst with a larger C-9 substituent for catalysis of the addition of thiols to enones was later developed by Deng.[6,7]

The installation of catalytically useful functionality at C-5′ is considerably less well explored. Jørgensen[8] and Deng[9] have independently developed hydrazide-substituted catalysts of general type **4a** and **4b**, respectively, which exploit the reaction between cupreines and diazodicarboxylate esters at C-5′. While Jørgensen demonstrated interesting catalytic activity in Michael additions to acrolein and in the amination of 2-naphthols, Deng found that **4a** failed to promote the α-amination of a β-keto ester, while use of **4b** resulted in poor yield and low levels of product enantiomeric excess. No further development of these types of catalyst have since been reported.

We therefore embarked upon the development and evaluation of a small catalyst library of general structure **5**. These systems incorporate variable substituents at C-9[10,11] and C-5′ so that the steric requirement and electronic/hydrogen bond donating properties of the catalyst can be systematically modulated. We wished to evaluate the performance of these catalysts in the enantioselective Henry reaction involving trifluoromethylketone substrates.

This reaction was selected for a number of reasons: (a) it is synthetically useful, generating trifluoromethylated chiral products (of general interest due to their unique properties[12] and pharmaceutical/agrochemical relevance[13]) incorporating a quaternary stereocenter;[14] (b) it represented a significant challenge—at the outset of this study the only direct catalytic methodology for the enantioselective catalysis of this reaction utilized 25 mol % of a chiral La complex at −40 °C;[15,16] (c) as mentioned previously, bifunctional (thio)ureas have found widespread application in the catalysis of additions to imines and Michael acceptors; however, relatively few reactions involving additions to carbonyl compounds promoted by this class of catalyst have been reported;[1,3,17] and (d) since Hiemstra[5] reported that **3a** promoted Henry reactions with aldehyde substrates, we were intrigued as to how a catalyst characterized by bifunctional components in closer proximity would fare in an analogous, yet more challenging 1,2-addition reaction.

As this work was in progress, Bandini et al.[18] reported the first organocatalytic variant of this process using a C-9 acylated cupreine derivative. Under optimized conditions, excellent product yields and enantioselectivities were possible.

Our study began with the synthesis of a small library of cinchona alkaloids substituted at C-5′ with functionality capable of hydrogen-bond donation (i.e., **5a**−**j**, Table 1). These were evaluated as promoters of the addition of nitromethane to α,α,α-trifluoroacetophenone (**6**) in THF at ambient temperature.

(5) (a) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929. (b) Hammar, P.; Marcelli, T.; Hiemstra, H.; Himo, F. *Adv. Synth. Catal.* **2007**, *349*, 2537.

(6) Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 418.

(7) Two examples of cinchona alkaloid-based catalysts substituted at C-6′ with phenyl and amide groups, respectively, have been reported; see:(a) Waldmann, H.; Khedkar, V.; Dückert, H.; Schürmann, M.; Oppel, I. M.; Kumar, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6869. (b) Abermil, N.; Masson, G.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12596.

(8) (a) Brandes, S.; Bella, M.; Kjoersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1147. (b) Brandes, S.; Niess, B.; Bella, M.; Prieto, A.; Overgaard, J.; Jørgensen, K. A. *Chem.—Eur. J.* **2006**, *12*, 6039.

(9) Liu, X.; Sun, B.; Deng, L. *Synlett* **2009**, 1685.

(10) For an early example illustrating the importance of the C-9 substituent in controlling catalyst conformation in cinchona alkaloid systems, see: Cortez, G. S.; Oh, S. H.; Romo, D. *Synthesis* **2001**, 1731.

(11) Deng has found that the C-9 substituent can play a key role in determining catalyst efficacy in cupreine-type systems; for examples, see: (a) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105. (b) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948. (c) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (d) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 947. (e) Wu, F.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4301. (f) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732.

(12) Reviews: (a) Schlosser, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1496. (b) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.

(13) For an example, see: Pierce, M. E.; Parsons, R. L., Jr.; Radesca, L. A.; Lo, Y. S.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgan, S. J.; Davis, W. P.; Confalone, P. M.; Chen, C. -Y.; Tillyer, R. D.; Frey, L.; Tan, L.; Xu, F.; Zhao, D.; Thompson, A. S.; Corley, E. G. *J. Org. Chem.* **1998**, *63*, 8536.

(14) Selected recent reviews: (a) Tur, F; Mansilla, J.; Lillo, V. J.; Saá, J. M. *Synthesis* **2010**, 1909. (b) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.(c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (d) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (e) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473.

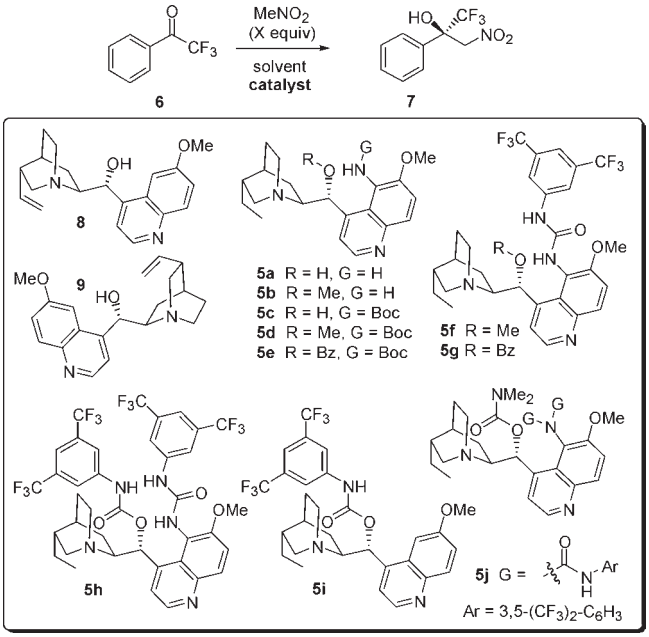
(15) Tur, F.; Saá, J. M. *Org. Lett.* **2007**, *9*, 5079.

(16) Deng has demonstrated cupreine derivatives to be highly effective catalysts for the addition of nitromethane to α-ketoesters: Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732.

(17) Our group have had a particular interest in the use of (thio)ureas to promote 1,2-addition reactions: (a) Maher, D. J.; Connon, S. J. *Tetrahedron Lett.* **2004**, *45*, 1301. (b) Procuranti, B.; Connon, S. J. *Chem. Commun.* **2007**, 1421. (c) Peschiulli, A.; Gun'ko, Y.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 2454. (d) Peschiulli, A.; Quigley, C.; Tallon, S.; Gun'ko, Y. K.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 6409. (e) Kavanagh, S. A.; Piccinini, A.; Fleming, E. M.; Connon, S. J. *Org. Biomol. Chem.* **2008**, *6*, 1339.

(18) Bandini, M.; Sinisi, R.; Umani-Ronchi, A. *Chem. Commun* **2008**, 4360.

Table 1. Evaluation of C-5′-Substituted Catalysts in the Henry Reaction Involving Trifluoroacetophenone (**6**)



entry	cat. (mol %)	X	solv	temp (°C)	time (h)	yield[a] (%)	ee[b] (%)
1	**8** (2)	10	THF	18	4	70	6
2	**9** (2)	10	THF	18	4	96	5
3	**1** (2)	10	THF	18	4	>98	−54
4[c]	**2** (2)	10	THF	18	21	91	52
5	**5a** (2)	10	THF	18	18	88	7
6	**5b** (2)	10	THF	18	18	75	13
7	**5c** (2)	10	THF	18	22	22	10
8	**5d** (2)	10	THF	18	22	91	20
9	**5e** (2)	10	THF	18	64	22	7
10[c]	**5f** (2)	10	THF	18	21	66	39
11	**5g** (2)	10	THF	18	21	2	
12[d]	**5h** (2)	10	THF	18	21	>98	62
13	**5i** (2)	10	THF	18	21	18	−8
14	**5j** (2)	10	THF	18	21	50	48
15	**5h** (2)	10	PhMe	18	21	90	12
16	**5h** (2)	10	MTBE	18	21	99	56
17	**5h** (2)	10	CH_2Cl_2	18	21	80	10
18	**5h** (2)	5	THF	18	21	98	66
19	**5h** (2)	3	THF	18	21	50	69
20	**5h** (2)	10	THF	−25	21	77	87
21	**5h** (20)	7	MTBE	−25	72	81	88
22	**5h** (20)	5	MTBE	−25	72	62	90
23	**5h** (10)	7	MTBE	−25	72	72	90

[a] Determined by ^{1}H NMR spectroscopy using an internal standard. [b] Determined by CSP-HPLC; see the Supporting Information. [c] 76% yield after 4 h reaction time. [d] After 4 h reaction time: 30% yield, 40% ee. [e] After 4 h reaction time: 83% yield, 62% ee.

The parent alkaloids, quinine (**8**) and quinidine (**9**), proved efficient catalysts of the reaction at just 2 mol % loading; however the β-nitro alcohol product **7** was formed with very low levels of enantiomeric excess (entries 1 and 2). The benchmark C-9 thiourea-modified catalysts **1** and **2** (X = S, Y = Et, Z = OMe) also promoted the smooth formation of **7**, with significantly higher levels of enantiomeric excess (ca. 50% ee, entries 3 and 4). 5-Aminodihydroquinine (**5a**) catalyzed rapid 1,2-addition relatively unselectively, as did its C-9 methylated analogue **5b** (entries 5 and 6 respectively). Conversion of the C-5′ amino group to a Boc moiety (to augment its hydrogen-bond donating characteristics) led to significant improvement in catalyst performance (entries 7 and 8); however, product ee remained modest. Benzoylation of **5c** at C-9 (i.e., catalyst **5e**, entry 9) resulted in a dramatic loss of catalyst activity.

We were pleased to find that the conversion of catalyst **5b** to the corresponding urea derivative **5f**[19] resulted in a catalyst capable of promoting the reaction with significantly higher enantioselectivity (39% ee, entry 10), while again installation of a benzoyl unit at C-9 proved unhelpful (i.e., catalyst **5g**, entry 11). Given the deleterious effect of acylation at C-9 on catalyst performance, we were surprised to observe that the C-9 carbamoyl derivative **5h** possessed excellent catalytic activity and could promote the reaction with superior product enantiomeric excess (quantitative conversion, 62% ee at 2 mol % catalyst loading) to that obtained using any of the other catalysts in this study (entry 12).[20]

To shed some light on the influence of the carbamoyl group on catalyst efficacy we prepared **5i**, which is devoid of the C-5′ urea. This catalyst was both relatively inactive and unselective (entry 13). It also promoted the formation of the opposite dominant enantiomer to that observed in reactions mediated by **5h**. We would therefore suggest that the superiority of **5h** to **5f** and the inferiority of **5i** to **5h** signals that the C-9 carbamoyl moiety is not directly involved in catalysis by hydrogen-bond donation. It is obvious, however, that its presence in conjunction with the C-5′ urea is advantageous, most likely because it plays an as yet unidentified role in controlling catalyst conformation.

Interestingly, the attempted replacement of the C-9 carbamoyl moiety with another carbamate substituent incapable of hydrogen bond donation led to the formation of the *N*-acylurea **5j** as the major product.[21] This catalyst promoted the reactions with respectable enantioselectivity, albeit at a considerably slower rate than **5h** (entry 14).

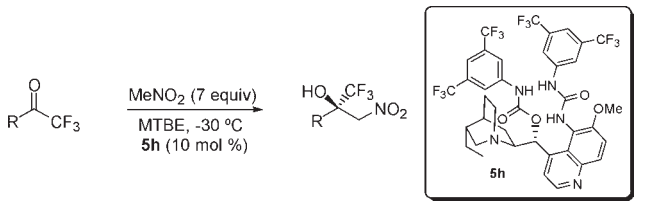
With the identification of the best catalyst complete, we next proceeded to optimize the reaction conditions: enantioselectivity diminished when the reactions were conducted in toluene and dichloromethane, while the use of MTBE as the reaction medium facilitated faster 1,2-addition with similar levels of product ee to those observed in THF (entries 15−17). Lower loadings of the nucleophile led to improved enantioselectivity at the expense of reaction rate (entries 18 and 19), while reduced reaction temperature

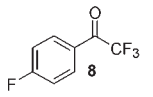
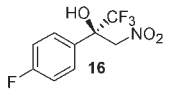
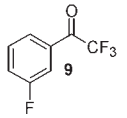
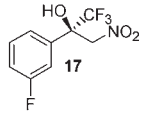
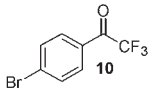
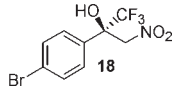
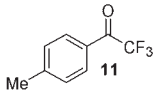
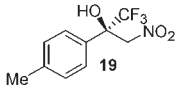
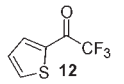
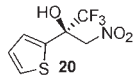
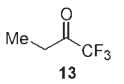
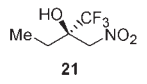
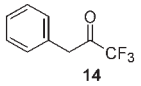
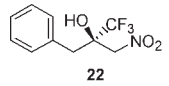
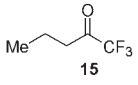
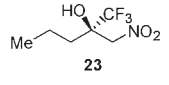
(19) The corresponding C-5′ thiourea derivatives proved hydrolytically unstable. We suspect this is related to general-base catalysis of thiourea hydrolysis by the proximal quinuclidine ring.

(20) Interestingly, nitroethane proved a poor nucleophile in these reactions. Selected data (rt, THF solvent, nitroethane in 10-fold excess). Cat. **5f** (2 mol %): 89 h, 35% conv, dr 1:7, 33% ee (major), 5% ee (minor). Cat. **1** (2 mol %): 4 h, 17% conv, dr 1.4:1, 22% ee (major), 5% ee (minor). Cat. **5h** (10 mol %): 63 h, 59% conv, dr 2:1, 12% ee (major), 3% ee (minor).

(21) Catalyst **5j** was formed from the reaction of 5′-amino-(*N*,*N*-dimethylcarbamoyldihydroquinine with 1 equiv of 3,5-bis-trifluoromethylphenyl isocyanate in dichloromethane solvent.

Table 2. Evaluation of Substrate Scope



entry	ketone	product	yield (%)[a]	*ee* (%)[b]
1	 **8**	 **16**	78	90
2	 **9**	 **17**	76	85
3	 **10**	 **18**	77	85
4[c]	 **11**	 **19**	69	83
5[c]	 **12**	 **20**	85	82
6	 **13**	 **21**	73	95
7	 **14**	 **22**	78	96
8	 **15**	 **23**	70	96

[a] Isolated yield. [b] Determined by CSP-HPLC. [c] Reaction at −25 °C.

resulted in the formation of (*R*)-**7** with higher ee (entries 20−22). Combining these findings allowed the generation of the product in good yield and 90% enantiomeric excess (entry 23).[22]

(22) No conversion was observed when acetophenone derivatives devoid of the $-CF_3$ substituent were utilized in these reactions.

The next task was to evaluate the substrate scope: we were pleased to find that *p*-fluoro-α,α,α-trifluoroacetophenone (**8**) could be converted to **16** in good yield and excellent enantiomeric excess (Table 2, entry 1). The corresponding *m*eta-isomer **9** afforded **17** in slightly lower ee (entry 2), as did the *p*-bromo and *p*-methyl analogues **10** and **11** (i.e., products **18** and **19**, respectively, entries 3 and 4). The thienyl-substituted alcohol **20** was formed in 82% ee, which, while lower than that obtained using nonheterocyclic acetophone derivatives, represents a significant improvement over the previous literature benchmark for substrate **12** (entry 5).

Gratifyingly, alkyl trifluoromethylketones (i.e., **13**−**15**)—a substrate class which has more proven problematic in previous studies[15,18]—proved particularly susceptible to the influence of catalyst **5h**. Good yields and excellent levels of product ee (≥95%) were recorded in all cases (i.e., **21**−**23**, entries 6−8). To the best of our knowledge this represents the most enantioselective general process for the catalytic asymmetric Henry reaction involving this substrate class to date.

In summary, we have developed a new class of cinchona alkaloid-based organocatalyst characterized by the presence of a C-5′ urea moiety, which an examination of models suggests is in very close proximity to the quinuclidine ring nitrogen atom. In a challenging nitroaldol reaction process, the most selective of these materials (catalyst **5h**) outperformed the traditional C-9-thiourea substituted catalysts **1** and **2** from both catalyst activity and product enantioselectivity standpoints. Under optimized conditions **5h** could promote the formation of the products of significant potential synthetic utility possessing quaternary stereocenters in good yields and excellent enantiomeric excess. Alkyl-substituted trifluoromethylketone substrates were converted to the corresponding nitroaldol products with the highest levels of enantiomeric excess recorded in the literature thus far. The exploration of the applicability of this class of catalyst in other reactions is underway in our laboratory.

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Supporting Information Available. General experimental procedures, synthesis of catalyst **5h**, ^1H and ^{13}C NMR spectra, characterization data, and HPLC assays. This material is available free of charge via the Internet at http://pubs.acs.org.