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Design of Hydrogen Bond Catalysts Based on a Modular Oxazoline Template: Application to an Enantioselective Hetero Diels–Alder Reaction

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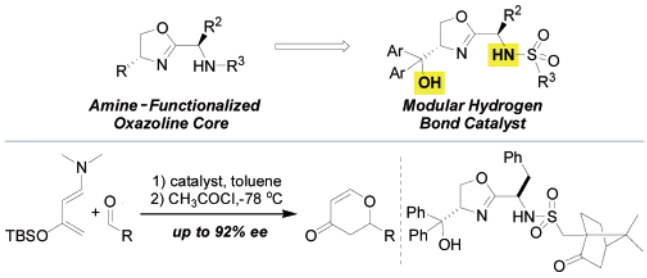
ABSTRACT



A catalyst system that displays two hydrogen bond donating arms from a rigid oxazoline backbone and its utility in a hydrogen bond promoted enantioselective hetero Diels–Alder reaction are described.

Enzymes exploit hydrogen bonds as organizational as well as catalytic motifs. Small molecules that mimic enzymes and employ hydrogen bonds for activating electrophiles have been successfully applied as catalysts in enantioselective reactions.[1−4] A critical component of such catalysts is structural rigidity in the display of hydrogen bond donors. In proteins, the tertiary structure ensures a degree of rigidity in the active site, whereas structural elements, such as β-turns, are utilized to engender this rigidity in small molecules.[5] We envisioned that an amine-functionalized oxazoline core could serve as a rigid backbone for the display of two hydrogen bond donating arms (Figure 1). In this design, the hydrogen bond donors can be independently tuned, and a pK_a range of approximately 30 units can be readily accessed through variation of the nitrogen substituent. Additionally, the ubiquity of oxazolines in asymmetric catalysis can be traced to their easy accessibility from α-amino acids.[6] Therefore, the modular nature[7] of the

(1) For a brief review on activation of carbonyls with hydrogen bonds, see: Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062−2064. (b) For a review on Brønsted acid catalysis, see: Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289−296.

(2) For examples of hydrogen bond promoted asymmetric catalysis using tertiary alcohols, see: (a) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336−1337. (b) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080−1081. (c) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846−5850. (d) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146.

(3) For examples of hydrogen bond promoted asymmetric catalysis using thiourea catalysts, see: (a) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466−468. (b) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102−4103. (c) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672−12673. (d) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901−4902.

(4) For examples of Brønsted acid catalyzed enantioselective reactions, see: (a) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418−3419. (b) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094−12095.

(5) For an example of this approach, see: Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601−610.

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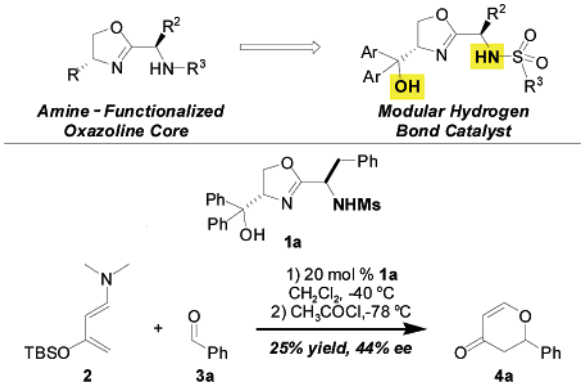


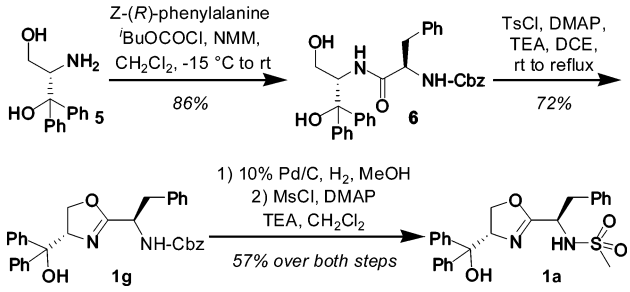
Figure 1. Catalyst design and initial catalyst discovery.

proposed ligand scaffold prompted us to evaluate their potential use as catalysts for hydrogen bond promoted reactions. Herein, we report the successful identification and optimization of a new class of hydrogen bond catalysts for an enantioselective hetero Diels−Alder reaction.

Inspired by the recent success of Rawal and co-workers in the development of hydrogen bond promoted catalytic enantioselective hetero Diels−Alder reactions,[8] we elected to assess our new catalyst design for this important reaction class. Therefore, we evaluated catalyst **1a** for the hetero Diels−Alder (HDA) reaction between benzaldehyde and diene **2** (Figure 1).[9] Decomposition of the Diels−Alder adduct with acetyl chloride yielded the corresponding pyranone with a moderate enantiomeric excess of 44% and in poor yield (25%). This proved to be an ideal starting point for demonstrating the utility of our catalyst design.

Facile access to catalyst analogues can be accomplished using the process outlined in Scheme 1. Aminodiol **5** is

Scheme 1



synthesized readily by the addition of phenylmagnesium bromide to serine methyl ester.[10] β-Hydroxyamide **6** is prepared in high yield by coupling **5** to Cbz-protected phenylalanine using isobutyl chloroformate.[11] Oxazoline **1g** is formed by selective activation of the primary alcohol as a leaving group with *p*-toluenesulfonyl chloride and triethylamine at room temperature followed by cyclization of the primary tosylate upon reflux.[12] Cleavage of the Cbz group under standard reductive conditions[13] followed by derivatization of the resulting primary amine with methanesulfonyl chloride yields catalyst **1a**. Catalysts of this type have been prepared in multiple gram quantities.

Using this sequence, an initial series of catalysts was synthesized in which the nature of the relative configuration and the nitrogen substituent could be assessed (Figure 2).

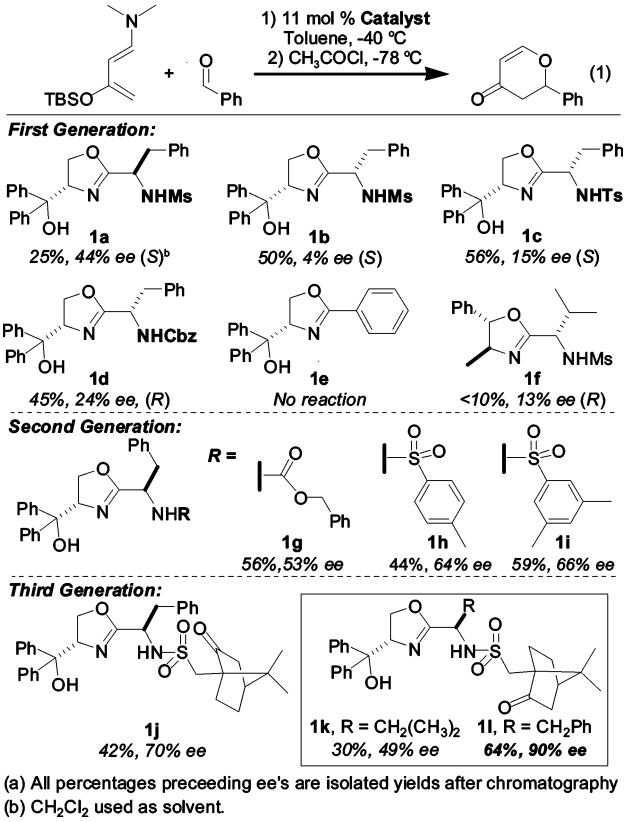


Figure 2. Catalyst optimization.

Evaluation of the initial set of catalysts for the HDA reaction (eq 1) produced the following observations: (1) the relative

(6) For reviews on oxazolines in catalysis, see: (a) McManus, H.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151−4202. (b) Braunstein, P.; Naud, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 680−699. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335. (d) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45.

(7) (a) Lee, J.-Y.; Miller, J. J.; Hamilton, S. S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 1837−1839. (b) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2002**, *4*, 3399−3401.

(8) (a) See refs 2a, 2c, and 2d. (b) For the uncatalyzed reaction at room temperature, see: Huang, Y.; Rawal, V. H. *Org. Lett.* **2000**, *2*, 3321−3323. (c) For an example of activation of ketone via hydrogen bonds, see: Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662−9663.

(9) For preparation of diene **2**, see: (a) Kozmin, S. A.; He, S.; Rawal, V. H. *Org. Synth.* **2002**, *78*, 152−159. (b) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039−3052.

(10) Sibi, M. P.; Chen, J.-X.; Cook, G. R. *Tetrahedron Lett.* **1999**, *40*, 3301−3304.

(11) Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358−12367.

(12) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. A.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541−4544.

(13) Downing, S. V.; Aguilar, E.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 826−831.

stereochemistry of the chiral elements was vital as diastereomeric catalysts showed significantly different enantioselectivity (catalysts **1a** and **1b**); (2) the size and nature of the capping functionality on the nitrogen had a modest impact on the enantiomeric excess (catalysts **1b**, **1c**, and **1d**); and (3) most importantly, both hydrogen bond donating arms were required for effective turnover (catalysts **1e** and **1f**). This last observation validates our catalyst design element of incorporating two hydrogen bond donating arms.

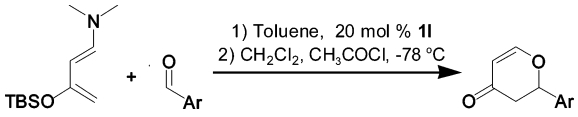
On the basis of the initial results, a second generation of catalysts was synthesized, where the relative configuration and the substitution pattern observed in **1a** were retained. To simultaneously study both the steric and electronic effect of the nitrogen substituent, various aryl sulfonamides were evaluated. Disappointingly, all aryl sulfonamides (only two pictured) evaluated gave almost identical results with ~65% ee.

Considering that an enhancement of enantiomeric excess from the methane sulfonamide (**1a**, 44% ee) to an aryl sulfonamide (**1i**, 66% ee) was observed, we reasoned that a substituent on the nitrogen with greater size may enhance the outcome. Therefore, the camphor sulfonamides were selected for evaluation. The catalyst derived from (*R*)-camphor sulfonic acid (**1j**, 70% ee) did not show any enantioselective enhancement. However, the catalyst derived from (*S*)-camphor sulfonic acid proved to be superior, giving a 90% ee (**1l**). Interestingly, a simple change from a benzyl group (**1l**, 90% ee) to an isopropyl group (**1k**, 49% ee) in the core structure showed a marked reduction in the observed enantioselectivity.

Upon determining the optimized conditions, the initial scope of the reaction was explored (Table 1). In general, aryl aldehydes proved to be effective substrates for this chemistry. Electron-poor aryl aldehydes proceed in good yield with a high degree of enantioselectivity (entries d and e). In contrast, electron-rich aryl groups require an increase in temperature to achieve reasonable isolated yields (entries c and g). The sterically demanding substrate, 1-naphthaldehyde (entry f), reacts efficiently to yield the corresponding pyranone in 72% yield and 90% ee.

In conclusion, we have developed a new class of modular oxazoline catalysts that activate aldehydes through hydrogen bonds. The activated aldehydes undergo a highly enantioselective hetero Diels−Alder reaction with diene **2**. Both hydrogen bonds in the catalyst are necessary for effective catalysis. The modular nature of the oxazoline allows for a rapid synthesis of analogues, which in turn facilitates optimization of the enantiomeric excess. Using this approach, we are investigating the possible expansion of the substrate scope to less activated substrates and elucidating the structural features that lead to successful asymmetric catalysis. Applications of this catalyst design to other catalytic enantioselective reactions are also currently being explored.

Table 1. Substrate Scope



entry	aldehyde	time (days)	temperature (°C)	yield (%)	ee (%)[a,b]
a	C_6H_5	2	−55	62	90
b	PhCH=CH	3	−65	72	88
c	4-$MeOC_6H_4$	2	−30	80	91
d	4-ClC_6H_4	2	−55	68	92
e	4-$NO_2C_6H_4$	3	−65	62	88
f	1-naphthyl	2	−55	72	90
b	2-furyl	2	−40	42	71

[a] Enantiomeric excess determined by HPLC equipped with a chiral stationary phase. See Supporting Information for details. [b] Average of multiple experiments.

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Supporting Information Available: Catalyst synthesis and characterization, catalytic procedures, and enantiomeric excess determination are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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