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Asymmetric Nitroaldol Reaction Catalyzed by a C_2-Symmetric Bisoxazolidine Ligand

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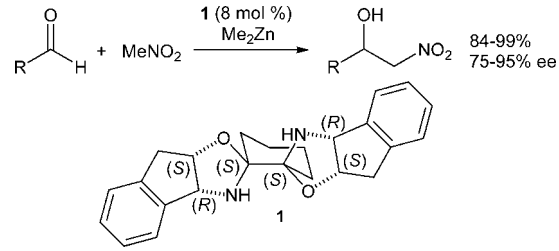
ABSTRACT



A C_2-symmetric bisoxazolidine was found to effectively catalyze the asymmetric Henry reaction of aliphatic and aromatic aldehydes. β-Hydroxy nitroalkanes were produced in up to 99% yield and 95% ee. The bisoxazolidine-catalyzed nitroaldol formation requires relatively short reaction times, proceeds under mild conditions and is applicable to a wide range of substrates including sterically hindered aldehydes.

The ever-increasing industrial and academic demand for enantiopure chemicals continues to nurture the development of powerful synthetic methods that utilize highly efficient chiral catalysts and auxiliaries.[1] The nitroaldol (Henry) reaction provides an atom-economical entry to β-hydroxy nitroalkanes which are invaluable precursors for a wide range of synthetic targets including (*R*)-denopamine and (*R*)-arbutamine.[2] The nitro group can be conveniently converted into several other functionalities by reduction, Nef reaction, nucleophilic displacement, or other means, thus generating α-hydroxy ketones, aldehydes, carboxylic acids, azides, sulfides, and other important bifunctional compounds. In particular, reduction of β-hydroxy nitroalkanes gives convenient access to β-amino alcohols which have found widespread use as chiral ligands in asymmetric catalysis and as important building blocks of natural products or pharmaceuticals.[3]

It is therefore surprising that few efficient asymmetric variants of the Henry reaction have been developed to date. While some of these methods require the use of activated silyl nitronates and tetrabutylammonium triphenylsilyldifluorosilicate (TBAT),[4] others provide excellent results with aromatic aldehydes; however, yields and ee values typically decrease when aliphatic or sterically hindered aldehydes are used.[5] Despite significant advances in this field, critical

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(4) (a) Risgaard, K. V.; Gothelf, K. A.; Jorgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 153–156. (b) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054–2055.

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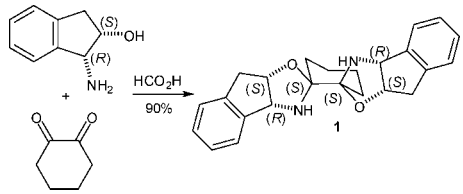
shortcomings of many catalytic nitroaldol reactions reported to date include long reaction times that often exceed 48 h, the use of expensive catalysts, and the need for additives such as molecular sieves.

We recently reported the synthesis of the first diketone-derived C_2-symmetric bisoxazolidine from readily available, inexpensive starting materials and demonstrated the usefulness of this new class of chiral ligands in asymmetric catalysis. Bisoxazolidine **1** exhibits a catalytically useful (*S*,*S*)-*N*,*O*-diketal unit and is easily prepared in 90% yield and 99% de by formic acid-promoted condensation of (1*R*,2*S*)-*cis*-1-amino-2-indanol and 1,2-cyclohexanedione (Scheme 1).

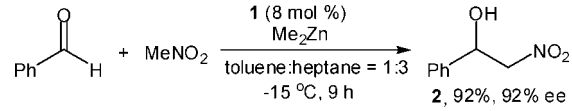
Scheme 1. Formation of Bisoxazolidine Catalyst **1**



Ligand **1** possesses a rigid C_2-symmetric structure and average separation between the nitrogen and oxygen atoms of 2.35 Å which facilitates bidentate coordination to metal ions and organometallic compounds. We found that this aminoindanol-derived *N*,*O*-diketal catalyzes the enantioselective alkynylation of a range of aromatic and aliphatic aldehydes, generating chiral propargylic alcohols in high yield and ee.[6] Excellent results and positive nonlinear effects due to enantioselective dual phase distribution behavior of scalemic **1** were obtained when this catalyst was applied in the alkylation of aldehydes with dimethyl- and diethylzinc reagents.[7]

Encouraged by the success with bisoxazolidine-catalyzed asymmetric additions of alkyl- and alkynylzinc reagents to aldehydes, we decided to explore the use of **1** in the asymmetric Henry reaction. Screening of typical reaction parameters including solvent, temperature, and catalyst loading revealed that β-hydroxy nitroalkanes can be obtained in excellent yields and ee's. Employing 8 mol % of **1**, nitromethane, and dimethylzinc to generate a zinc nitronate species in situ, and benzaldehyde in apolar solvents at −15 °C, we obtained 2-nitro-1-phenylethanol, **2**, in 92% yield and 92% ee within 9 h (Scheme 2).

Scheme 2. Bisoxazolidine-Catalyzed Nitroaldol Reaction



The optimized procedure was then applied to a variety of benzaldehyde derivatives and the corresponding β-nitro alcohols **3**−**11** were generally isolated in high yield and enantiomeric excess (Table 1). Aromatic aldehydes bearing electron-withdrawing groups proved more reactive and furnished nitroaldol products **5** to **8** in up to 96% yield and 95% ee within 10 h (entries 4−7). Less reactive aldehydes such as 4-methoxybenzaldehyde required longer reaction times but gave excellent results (entries 2, 3 and 8). Importantly, the bisoxazolidine-catalyzed Henry reaction is also suitable to sterically hindered and heteroaromatic aldehydes. 2-Nitro-1-(2,6-dimethylphenyl)ethanol, **10**, and 2-nitro-1-(3-thienyl)ethanol, **11**, were formed in 84% to 96% yield and 88% to 91% ee, respectively (entries 9 and 10). Several aliphatic aldehydes were then employed in the same procedure. We were pleased to find that the corresponding Henry reaction products **12** to **18** were formed in 84−96% yields with ee values ranging from 75% to 86% (Table 2). It is noteworthy that both linear and branched aliphatic aldehydes gave excellent results within 12 h. For example, heptanal was converted to 1-nitro-2-heptanol, **14**, in 90% yield and 84% ee, and sterically hindered pivalaldehyde gave 3,3-dimethyl-1-nitro-2-butanol, **16**, in 92% yield and 86% ee (entries 3 and 5). The Henry reaction is also applicable to α,β-unsaturated substrates, and cinnamaldehyde was converted to nitroaldol product **15** in almost quantitative yields and 82% ee (entry 4).

Shibasaki was first to demonstrate the potential of nitro aldol reactions for the formation of multifunctional products bearing several stereocenters. For example, a sequence of two nitrolaldol reactions and subsequent diastereomerization in the presence of an (*R*)-binaphthoxide-derived lanthanoid catalyst gave bicyclic **20** from aldehyde **19** in 41% yield and 65% ee (Scheme 3).[10] To date, several groups have

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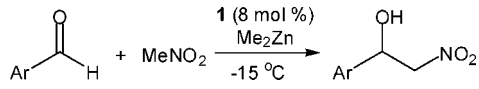
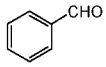
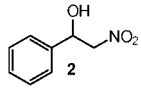
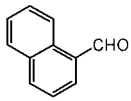
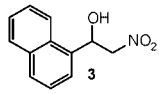
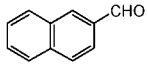
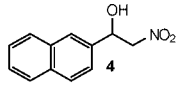
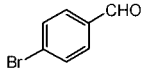
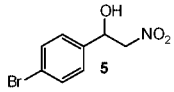
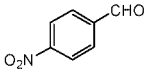
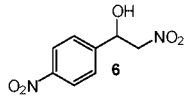
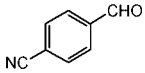
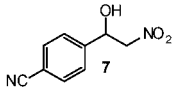
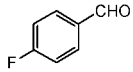
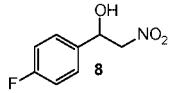
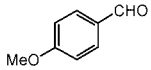
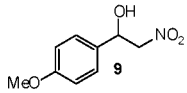
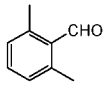
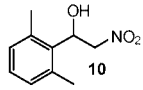
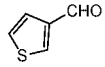
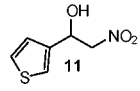
(11) (a) For *syn*-selective reactions, see : Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388–7389. (b) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, 2894–2897. (c) For anti selective reactions, see : Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054–2055. (d) Sohtome, Y.; Takemura, N.; Iguchi, T.; Hashimoto, Y.; Nagasawa, K. *Synlett* **2006**, 144–146.

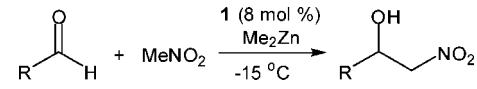
Table 1. Enantioselective Nitroaldol Reaction of Aromatic Aldehydes[a]

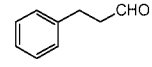
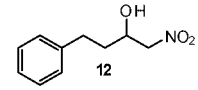
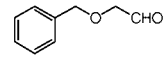
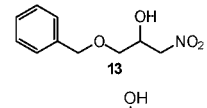
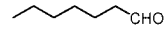
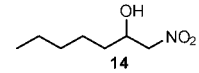
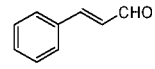
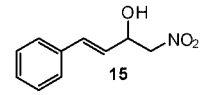
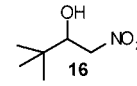
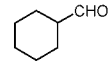
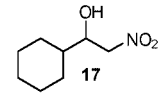
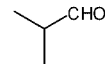
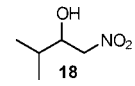


entry	aldehyde	product	yield (%)[b]	ee (%)[c,d]	time (h)
1		 **2**	92	92 (*R*)	9
2		 **3**	92	90 (*R*)	14
3		 **4**	95	92 (*R*)	12
4		 **5**	96	94	8
5		 **6**	88	95 (*R*)	8
6		 **7**	85	92 (*R*)	10
7		 **8**	89	94 (*R*)	10
8		 **9**	97	95 (*R*)	24
9		 **10**	84	88	24
10		 **11**	96	91	12

[a] All reactions were performed on a 1 mmol scale using 8 mol % of **1** as catalyst, 10 equiv of nitromethane, and 3 equiv of dimethyl zinc. [b] Isolated yields. [c] Determined by HPLC on Chiralcel OD and Chiralpak AD or by GC on octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin. [d] The absolute configuration of the major enantiomer was determined by chiral HPLC analysis using Chiralcel OD and OJ as described in the literature.[5d,8]

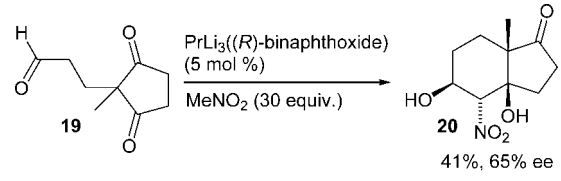
Table 2. Bisoxazolidine-Catalyzed Henry Reaction of Aliphatic Aldehydes[a]



entry	aldehyde	product	yield (%)[b]	ee (%)[c,d]	time (h)
1		 **12**	99	85 (*R*)	12
2		 **13**	93	75 (*R*)	12
3		 **14**	90	84	12
4		 **15**	98	82 (*R*)	12
5		 **16**	92	86	12
6		 **17**	94	83	12
7		 **18**	90	81	12

[a] All reactions were performed on a 1 mmol scale using 8 mol % of **1** as catalyst, 10 equiv of nitromethane, and 3 equiv of dimethyl zinc. [b] Isolated yields. [c] Determined by HPLC on Chiralcel OD and Chiralpak AD or by GC on octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin. [d] The absolute configuration of the major enantiomer was determined by chiral HPLC analysis using Chiralcel OD and Chiralpak AD as described in the literature.[5h,9]

Scheme 3. Shibasaki's Synthesis of Bicyclic Nitroaldol Product **20**

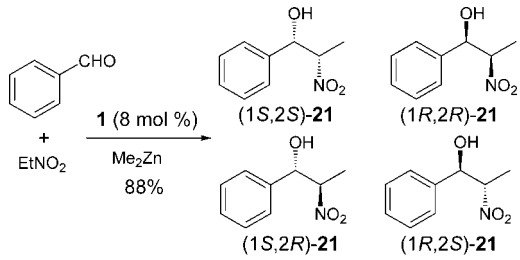


reported enantio- and diastereoselective procedures using chiral aldehydes or nitromethane homologues such as nitroethane.[11] In most cases, however, expensive catalysts or silyl nitronates are required to achieve high yields and stereoselectivity. We therefore decided to test the potential of **1** to overcome some of these drawbacks.

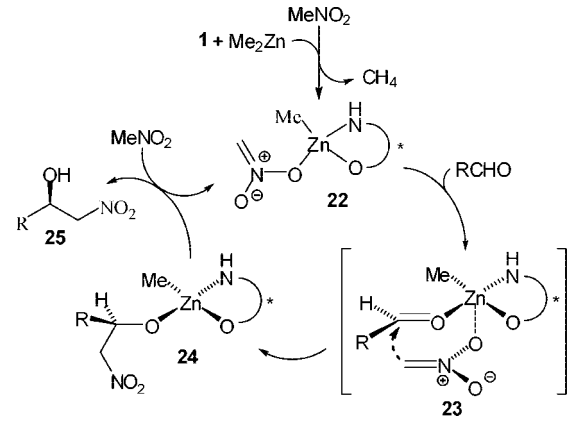
We observed that bisoxazolidine **1** catalyzes the Henry reaction between benzaldehyde and nitroethane with remarkable stereocontrol and apparently favors formation of the syn diastereomer. 2-Nitro-1-phenylpropanol, **21**, was obtained in 88% yield and the ratio of the syn to the anti isomer was determined as 87:13. Both diastereoisomers were produced in excellent enantiomeric excess (Scheme 4).

The reaction probably involves zinc-mediated dual activation of the nitronate and the aldehyde substrate (Scheme 5). Deprotonation of nitromethane by dimethylzinc in the presence of bisoxazolidine **1** is expected to generate zinc complex **22**. Coordination of the aldehyde then sets the stage for enantioselective carbon−carbon bond formation via transition state **23**. Replacement of the formed alkoxide from

Scheme 4. Formation of 2-Nitro-1-phenylpropanol



Scheme 5. Dual Activation in the Zn-Catalyzed Henry Reaction Using **1** as Ligand



complex **24** by another prenucleophilic reagent finally produces the nitroaldol product **25** and regenerates the loaded catalyst **22**.

Our results show that bisoxazolidine **1** is an effective catalyst of the asymmetric nitroaldol reaction and produces β-hydroxy nitroalkanes in high yield and enantiomeric excess. We believe that this procedure has several merits including simplicity of operation, relatively short reaction times, and high stereocontrol with a wide range of substrates. In particular, the excellent results obtained with sterically hindered aliphatic and aromatic aldehydes extend the scope of this reaction. The rigid, C_2-symmetric structure and the simplicity of the preparation of enantiopure **1** make this an attractive new chiral ligand that may find multiple use in asymmetric catalysis. Further studies of catalytic applications of bisoxazolidines are currently underway in our laboratory.

Supporting Information Available: Synthetic procedure and full characterization of nitroaldol products. This material is available free of charge via the Internet at http://pubs.acs.org.

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