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Development of ProPhenol Ligands for the Diastereo- and Enantioselective Synthesis of β-Hydroxy-α-amino Esters

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Supporting Information

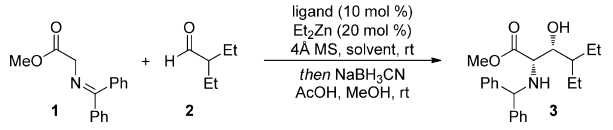
ABSTRACT: A zinc−ProPhenol-catalyzed direct asymmetric aldol reaction between glycine Schiff bases and aldehydes is reported. The design and synthesis of new ProPhenol ligands bearing 2,5-*trans*-disubstituted pyrrolidines was essential for the success of this process. The transformation operates at room temperature and affords *syn* β-hydroxy-α-amino esters in high yields with good to excellent levels of diastereo- and enantioselectivity.

Optically active β-hydroxy-α-amino acids represent an important class of α-amino acids that can be found in numerous complex natural and/or biologically active molecules such as vancomycin and teicoplanin antibiotics.[1] They are also synthetically useful as precursors to valuable chiral building blocks, as demonstrated by their conversion to β-lactams or aziridine carboxylic acid derivatives.[2] As a result, various catalytic asymmetric methods have been reported for the construction of enantioenriched β-hydroxy-α-amino acid derivatives.[3]

The direct catalytic asymmetric aldol reaction between glycinate Schiff bases and aldehydes represents a particularly elegant and straightforward method to access β-hydroxy-α-amino esters in which the 1,2-aminoalcohol functionality is assembled simultaneously with the formation of a new C−C bond.[4,5] Miller and Gasparski reported the first catalytic asymmetric synthesis of β-hydroxy-α-amino esters by the direct aldol reaction between *N*-(diphenylmethylene)glycine *tert*-butyl ester and various aldehydes using the O'Donnell cinchoninium chloride phase-transfer catalyst, but low diastereoselectivities and negligible enantiomeric excesses were obtained.[6] Further evaluation of other monomeric and dimeric cinchoninium catalysts by Castle *et al.* revealed variable enantioselectivities despite modest diastereoselectivities.[7] Maruoka *et al.* achieved a significant breakthrough when they demonstrated that their *N*-spiro, binaphthyl-based ammonium catalysts could provide a variety of *anti* β-hydroxy-α-amino esters in high yields with high diastereo- and enantioselectivities,[8] but obtention of *syn* diastereomers proved problematic.[9] Additionally, Shibasaki described the use of the heterobimetallic $Li_3[La(S\text{-BINOL})_3]$ but moderate stereoselectivities were obtained.[10,11] It is worth noting that, in each one of these processes, only the *tert*-butyl glycinate derivative is a competent partner. Additionally, the aforementioned reactions had to be conducted under cryogenic conditions. Thus, access to the *syn* aldol adducts with control of both diastereo- and enantioselectivity constitutes an important unsolved problem.

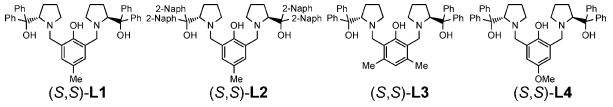
Our research group has a longstanding interest in the development of dinuclear zinc−ProPhenol catalysts for the asymmetric direct aldol reaction.[12−14] Therefore, we initiated our studies by evaluating our standard ProPhenol catalyst **L1** in the direct aldol reaction between *N*-(diphenylmethylene)glycine methyl ester **1** and 2-ethyl-butyraldehyde **2** in dioxane at rt. After one-pot reductive workup to provide a convenient benzhydryl protected amino group, the reaction afforded the desired diastereomeric β-hydroxy-α-amino esters in a 2.7:1 ratio, favoring *syn* adduct **3** which was isolated in 45% yield and with an encouraging enantiomeric excess of 77% (Table 1, entry 1).[15]

Table 1. Selected Solvent and Ligand Optimization[a]



entry	ligand	solvent	conversion[b]	dr[b]	% yield[c]	% ee[d]
1	(*S*,*S*)-**L1**	dioxane	60%	2.7:1	45	77
2	(*S*,*S*)-**L1**	DME	67%	4.0:1	53	77
3	(*S*,*S*)-**L1**	THF	66%	4.0:1	52	81
4	(*S*,*S*)-**L1**	Et_2O	60%	4.3:1	47	81
5	(*S*,*S*)-**L1**	toluene	72%	7.3:1	63	81
6	(*S*,*S*)-**L2**	toluene	70%	4.9:1	56	75
7	(*S*,*S*)-**L3**	toluene	70%	3.8:1	55	49
8	(*S*,*S*)-**L4**	toluene	70%	7.1:1	60	60

[a]All reactions were performed at rt for 24 h using 1 equiv of **1** and 2 equiv of **2** in the designated solvent at c = 0.5 M, followed by a reductive treatment with $NaBH_3CN$ (2.5 equiv) and AcOH (2 equiv) in MeOH at rt for 16 h. [b]Determined by analysis of the ^1H NMR spectrum of the crude material. [c]Yield of isolated pure *syn* diastereomer. [d]Determined by HPLC with a chiral stationary phase.



Examination of solvent effects in the reaction revealed that toluene was most suitable in terms of conversion as well as diastereo- and enantioselectivity (Table 1, entries 1−5). Other Prophenol ligands **L2**−**L4** possessing different steric (Table 1, entries 6 and 7) or electronic (Table 1, entry 8) properties were also screened; however these ligands did not perform better than the standard ProPhenol **L1**. Addition of Lewis basic additives,

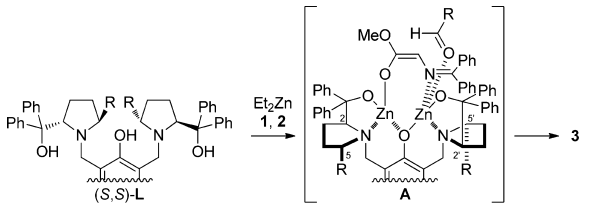
Received: January 6, 2014
Published: February 6, 2014

dx.doi.org/10.1021/ja4129394 | *J. Am. Chem. Soc.* 2014, 136, 3016−3019

which proved effective in enhancing stereoselectivities in other zinc−ProPhenol-catalyzed processes, had little or no effect here.[16]

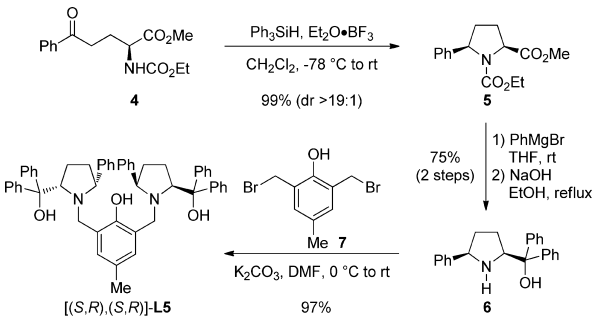
Based on our previous model for the zinc−ProPhenol-catalyzed direct aldol reaction of α-hydroxyketones, we propose that the stereochemical outcome of the transformation can be rationalized by intermediate **A** in which the (*Z*)-enolate, arising from **1**, serves as a bidentate ligand of the dinuclear zinc complex. Coordination of the aldehyde to the more Lewis acidic zinc atom directs its approach, allowing the enolate to attack the *Si* face and deliver (2*S*,3*R*)-β-hydroxy-α-amino ester **3** as the major product. Following this model, we speculated that catalysts bearing additional substitution on the C5/C5′ carbon of the pyrrolidine rings would provide a more sterically constrained catalytic pocket that in turn may yield the desired aldol adduct with enhanced stereoselectivities (Scheme 1).

Scheme 1. Stereochemical Rationalization



We were first interested in assessing a ProPhenol ligand bearing *cis* 2,5-disubstituted pyrrolidines since this feature introduces more steric interactions between the C5 substituent and the reactants. The synthesis of [(*S*,*R*),(*S*,*R*)]-**L5** as shown in Scheme 2 set the stereochemistry by the reduction of the iminium derived from δ-ketocarbamate **4**.[17]

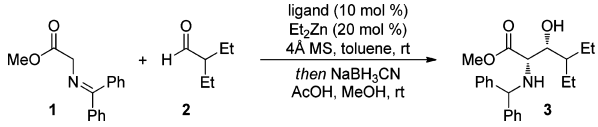
Scheme 2. Synthesis of ProPhenol Ligand Containing *cis* 2,5-Disubstituted Pyrrolidine Moieties



We also sought to evaluate the catalytic activity of zinc−ProPhenol complexes integrating *trans*-2,5-pyrrolidines wherein the C5 substituent exerts its constraining effect by interaction with the central phenoxy ring. The synthesis of these ligands **L6**−**L9** started with highly diastereoselective (dr >12:1) copper-mediated arylations of the iminium derived from known hemiaminal ether **8**.[18] *trans*-Pyrrolidines **9**−**12** were isolated in yields ranging from 20% to 99%. These products were treated with an excess of phenylmagnesium bromide (THF, rt), followed by cleavage of the Boc groups under basic conditions (NaOH, EtOH, reflux) to generate the unprotected aminoalcohols **13**−**16** (41−87%, 2 steps). Coupling these intermediates with dibromide **7** (K_2CO_3, DMF, 0 °C to rt) provided the desired ProPhenol [(*S*,*S*),(*S*,*S*)]-**L6**−**L9** in 80−99% yield (Table 2).

With the new set of ligands in hand, we re-examined the direct asymmetric aldol reaction between methyl glycinate **1** and aldehyde **2**. The use of [(*S*,*R*),(*S*,*R*)]-**L5**, bearing the *cis* pyrrolidines led to a dramatic decrease in reactivity, and the desired adduct **3** was isolated in 20% yield with negligible enantiopurity (Table 3, entry 2). In contrast, when ligands **L6**−**L9** incorporating *trans* 5-arylpyrrolidine 2-diarylcarbinol moieties were screened, marked increases in conversion with diastereo- and enantioselectivity were observed, compared to the standard ProPhenol ligand **L1**. Overall, **L6** performed best and afforded *syn* β-hydroxy-α-amino ester **3** in 84% yield and an

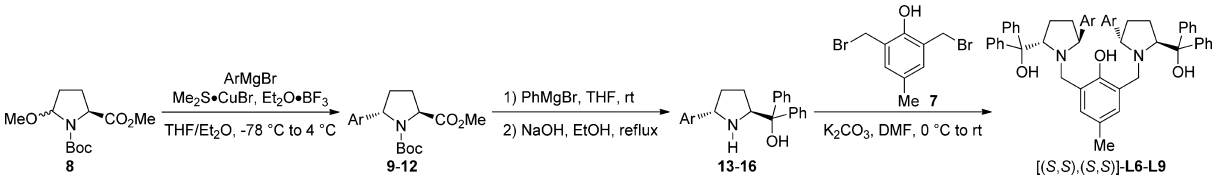
Table 3. Evaluation of the New Ligands L5−L9[a]



entry	ligand	conversion[b]	dr[b]	% yield[c]	% ee[d]
1	(*S*,*S*)-**L1**	72%	7.3:1	63	81
2	[(*S*,*R*),(*S*,*R*)]-**L5**	25%	–	20	3
3	[(*S*,*S*),(*S*,*S*)]-**L6**	95%	10:1	84	89
4	[(*S*,*S*),(*S*,*S*)]-**L7**	85%	10:1	79	87
5	[(*S*,*S*),(*S*,*S*)]-**L8**	90%	7.3:1	78	85
6	[(*S*,*S*),(*S*,*S*)]-**L9**	85%	9.0:1	70	89
7[e]	[(*S*,*S*),(*S*,*S*)]-**L10**	80%	5.7:1	67	81

[a]All reactions were performed at rt for 24 h using 1 equiv of **1** and 2 equiv of **2** in toluene at *c* = 0.5 M, followed by a reductive treatment with $NaBH_3CN$ (2.5 equiv) and AcOH (2 equiv) in MeOH at rt for 16 h. [b]Determined by analysis of the ^1H NMR spectrum of the crude material. [c]Yield of isolated pure *syn* diastereomer. [d]Determined by HPLC with a chiral stationary phase. [e]For 48 h at 0 °C.

Table 2. Synthesis of ProPhenol Ligands Bearing *trans* 2,5-Disubstituted Pyrrolidines



Ar	dr[a]	% yield[b]	% yield (2 steps)[b]	% yield[b]
phenyl	>19:1	99 (**9**)	87 (**13**)	99 (**L6**)
1-naphthyl	12:1	90 (**10**)	87 (**14**)	95 (**L7**)
2-naphthyl	>19:1	61 (**11**)	41 (**15**)	84 (**L8**)
4-biphenyl	>19:1	20 (**12**)	77 (**16**)	80 (**L9**)

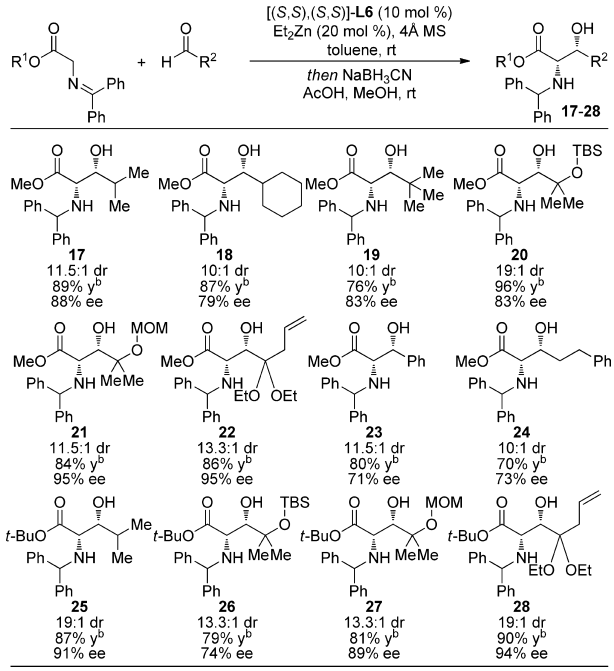
[a]Determined by analysis of the ^1H NMR spectrum of the crude material. [b]Isolated yield.

dx.doi.org/10.1021/ja4129394 | J. Am. Chem. Soc. 2014, 136, 3016−3019

excellent 89% ee (Table 3, entries 3–6). Interestingly, decreasing the reaction temperature had a detrimental effect on the conversion and stereoselectivity (Table 3, entry 7).[19] Thus, in contrast to the previous catalytic systems which require cryogenic conditions, this system is ideal at ambient temperature.

With an optimized set of conditions in hand (Table 3, entry 3), the scope of the reaction was examined next (Table 4), initially

Table 4. Enantioselective Zinc–ProPhenol-Catalyzed Aldol Reaction of Glycine Schiff Bases with Ligand L6[a]

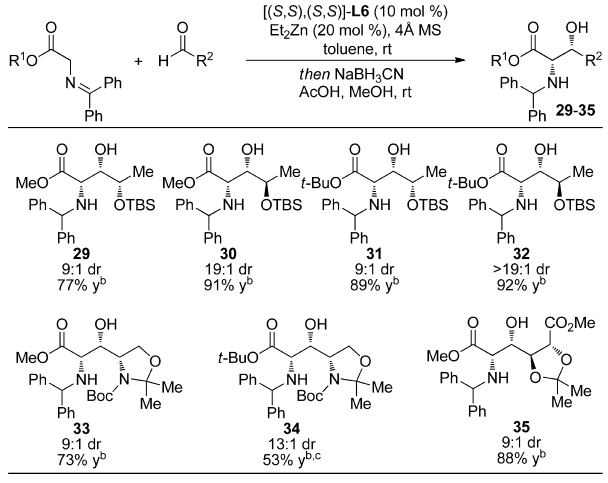


[a]All reactions were performed at rt for 24 h using 1 equiv of glycinate Schiff base and 2 equiv of aldehyde in toluene at c = 0.5 M, followed by a reductive treatment with $NaBH_3CN$ (2.5 equiv) and AcOH (2 equiv) in MeOH at rt for 16 h. dr was determined by analysis of the ^1H NMR spectrum of the crude material. [b]Yields are of the isolated pure *syn* diastereomer. Enantiomeric excesses were determined by HPLC with a chiral stationary phase.

focusing on the methyl glycinate derivative since it has not previously been shown to provide adequate stereocontrol. In all cases examined, complete consumption of the starting material was observed and the reactions proceeded with high to excellent levels of diastereoselectivity (dr >10:1). Aldol reaction of methyl glycinate **1** with α-tertiary aldehydes, such as isobutyraldehyde or cyclohexanecarboxaldehyde, afforded the corresponding *syn* aminoalcohols **17** and **18** in excellent yields and good to very good enantiomeric excesses. Even sterically hindered pivaldehyde provided adduct **19** in 76% yield and 83% ee. Interestingly, when aldehydes bearing a protected α-tertiary alcohol were used, we observed that the nature of the protecting group had a significant effect in the enantioselectivity of the reaction; while a TBS protected α-hydroxy aldehyde generated the desired adduct **20** in 96% yield and 83% ee, the presence of a MOM group provided the corresponding α-amino-β,γ-dihydroxy ester **21** (84%) in an excellent 95% ee. This significant effect was also observed when employing an aldehyde possessing a diethyl ketal at the α-carbon, and the corresponding aminoalcohol **22** was obtained in excellent yield (86%) and ee (95%) presumably due to an additional coordination point to the zinc atom. On the other hand, aromatic or linear alkyl aldehydes, such as benzaldehyde or hydrocinnamaldehyde, gave less satisfactory results and the β-hydroxy-α-amino esters **23** and **24** were obtained with moderate enantioselectivity (71% and 73% ee, respectively). The potential of the *N*-(diphenylmethylene)-glycine *tert*-butyl ester was also evaluated as a donor partner. Its reaction with isobutyraldehyde worked well, and the product **25** was isolated in 87% yield and 91% ee. The fact that the stereocontrol for both the methyl and *tert*-butyl ester is virtually the same exemplifies the high catalyst control of the reaction. Aldehydes bearing a coordinating oxygenated group at the α-position again performed well, and adducts **27** and **28** were isolated in 81% and 90% yield (ee = 89% and 94%, respectively).

We were also interested in utilizing α-chiral aldehydes with the new zinc–ProPhenol system to determine their performance in a diastereoselective aldol reaction. To this end, *N*-(diphenylmethylene)glycine methyl ester **1** was coupled with enantiopure TBS-protected (*S*)- and (*R*)-lactaldehyde using [(*S*,*S*),(*S*,*S*)]-**L6** as the ligand. When the (*S*) aldehyde was utilized, the desired reaction proceeded with a high diastereoselectivity (dr = 9:1, ratio of desired *syn*,*syn* adduct **29** vs other diastereoisomers) and the single diastereomeric product **29** was isolated in 77% yield. Reaction with the (*R*) aldehyde afforded the *syn*,*anti* product **30** also with an excellent diastereoselectivity (19:1, 91% yield) and possessing the same absolute stereochemistry at C2 and C3. Comparable results were obtained when analogous glycinate *tert*-butyl ester was used as the donor partner to afford the *syn*,*syn* α-amino-β,γ-dihydroxy ester **31** (dr = 9:1, 89% yield) and the *syn*,*anti* α-amino-β,γ-dihydroxy ester **32** (dr > 19:1, 92% yield), respectively. Hence, for this class of aldehydes bearing an α-stereocenter, a very minimal match/mismatch effect was observed, the matched case being between the [(*S*,*S*),(*S*,*S*)] ligand **L6** and the (*R*) aldehyde while the mismatched case involves [(*S*,*S*),(*S*,*S*)]-**L6** and the (*S*) aldehyde. Garner aldehyde was also a competent partner in our zinc–ProPhenol-catalyzed transformation. Its aldol reaction with glycinate methyl and *tert*-butyl ester derivatives proceeded with excellent levels of

Table 5. Zinc–ProPhenol-Catalyzed Aldol Reaction of Glycine Schiff Bases with α-Chiral Aldehydes[a]



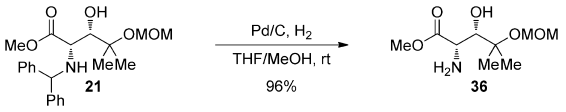
[a]All reactions were performed at rt for 24 h using 1 equiv of glycinate Schiff base and 2 equiv of aldehyde in toluene at c = 0.5 M, followed by a reductive treatment with $NaBH_3CN$ (2.5 equiv) and AcOH (2 equiv) in MeOH at rt for 16 h. dr was determined by analysis of the ^1HNMR spectrum of the crude material. [b]Yields are of the isolated pure *syn* diastereomer. [c]Conversion stopped at 60% (analysis of the ^1H NMR spectrum of the crude material).

dx.doi.org/10.1021/ja4129394 | J. Am. Chem. Soc. 2014, 136, 3016–3019

diastereoselectivity and afforded the corresponding α,γ-diamino-β,δ-dihydroxy esters **33** and **34** in 73% and 53% yield, respectively. Finally, the aldol reaction between methyl glycinate **1** and the monoaldehyde derived from dimethyl 2,3-*O*-isopropylidene-L-tartrate proceeded in high diastereoselectivity (dr = 9:1) and provided the highly functionalized diester **35** in 88% yield (Table 5).

Additionally, cleavage of the benzhydryl protecting group can be easily achieved under mild conditions. For instance, hydrogenolysis of **21** (Pd/C, H_2, THF/MeOH, rt) afforded the free aminoalcohol **36** in 96% yield (Scheme 3).

Scheme 3. Hydrogenolysis of the Benzhydryl Group



In summary, we have developed a direct zinc−ProPhenol-catalyzed asymmetric aldol reaction between glycinate Schiff base derivatives and aldehydes. Functionalized *syn* β-hydroxy-α-amino esters were obtained with very good to excellent diastereo- and enantioselectivity enabling isolation of the adducts in high yields as pure diastereomers. Further, the stereochemical outcome, in additions to substrates containing α-stereocenters, was demonstrated to be catalyst controlled. Thus, single diastereomers could be obtained in excellent yields after chromatography in these cases. The high level of stereocontrol was achieved by the development of novel ProPhenol ligands incorporating *trans* 2,5-disubstituted pyrrolidines. This success of the *trans* ligands suggests that conformational constraints due to the interaction of the C5/C5′ substituent with the phenol ring rigidifying the asymmetry of the chiral space without impeding reactivity is best accomplished with such *trans* isomers. On the other hand, in the case of the ProPhenol bearing *cis* 2,5-disubstituted pyrrolidines, the steric crowding due to the *cis*-1,3-relationship between the substituents at C2 and C5 disrupts the chiral space as well as makes the "active site" too sterically encumbered to provide access to the substrate. A complete evaluation of the potential of this class of ligands in other direct aldol reactions, as well as the development of other ProPhenol ligands, is currently underway in our laboratory.[20]

■ ASSOCIATED CONTENT

Supporting Information

Detail experimental details, compound characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Foundation (CHE-1145236) and the National Institute of Health (GM033049) for their generous support of our programs.

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(15) Configurational assignments of the aldol adducts were determined by chemical correlation of **17** and analogy (see SI).

(16) The addition of PPh_3S or PPh_3O (20 mol %), 1,3-propanediol, *cis* 1,2-cyclopentanediol, or methyl 2,2-dimethyl-3-hydroxy-propionate (10 mol %) had no significant effect on the reaction.

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(18) **8** is accessible in four steps from (*S*)-pyroglutamic acid, see: Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1998**, *39*, 4789−4792.

(19) Decreasing the catalyst loading to 5 mol % of [(*S*,*S*)-(*S*,*S*]-**L6** resulted in a sluggish reaction which was incomplete after 24 h.

(20) For a 2,5-disubstituted ProPhenol type ligand, see: Kim, Y. B.; Kim, M. K.; Kang, S. H.; Kim, Y. H. *Synlett* **2005**, 1995−1998.