Asymmetric Catalysis

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Direct Catalytic Asymmetric Aldol Reaction of an α-Azido Amide**

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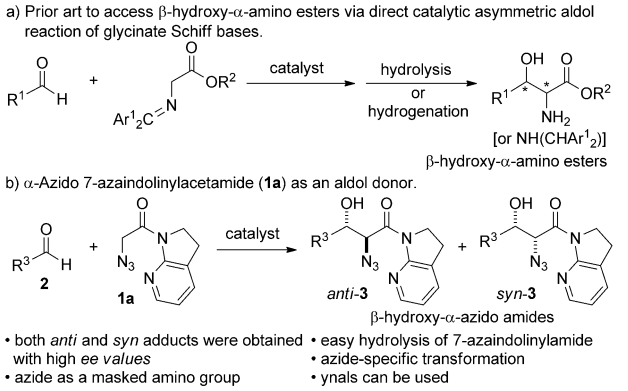
Abstract: *A direct aldol reaction of an α-azido 7-azaindolinylamide, promoted by a Cu-based cooperative catalyst, is documented. Aromatic aldehydes bearing an ortho substituent exhibited diastereodivergency depending on the nature of the chiral ligands used. Smooth reactions with ynals highlighted the broad substrate scope. A vicinal azido alcohol unit in the product allowed direct access to the corresponding aziridine and facile hydrolysis of the 7-azaindolinylamide moiety furnished enantioenriched β-hydroxy-α-azido carboxylic acid derivatives.*

Enantioenriched β-hydroxy-α-amino acid derivatives are functionalized α-amino acids and constitute a family of synthetically valuable chiral synthons.[1] Their structural motif is frequently found in a plethora of natural products and biologically active molecules, for example, glycopeptide antibiotics,[2] thus attracting considerable attention from synthetic chemists in the search of efficient stereoselective approaches to such derivatives.[1,3] A direct catalytic asymmetric aldol reaction of readily available glycinate Schiff bases and aldehydes enables expeditious access to β-hydroxy-α-amino esters with catalyst-controlled stereoselectivity. Given the particular utility of this methodology, which enables the construction of a carbon–carbon bond and two stereogenic centers in a single step, significant advances have been made over the last two decades (Scheme 1 a). A series of early attempts was reported based on phase-transfer catalysis.[4] Although the reactions using cinchoninium-based catalysts by Miller et al.[5] and Castle et al.[6] suffered from unsatisfactory stereoselectivity, a binaphthyl-type quaternary ammonium salt, newly designed by Maruoka et al., led to significant improvements in stereoselectivity.[7] Highly enantioenriched *anti*-configured β-hydroxy-α-amino esters were obtained. Metal-based catalysts were also found to be effective,[8] and Trost et al. reported that Zn/ProPhenol catalysts afforded the corresponding products with the complementary *syn* configuration.[9] However, in the aforementioned catalytic systems, only aliphatic aldehydes are competent aldol acceptors and the reaction using aromatic aldehydes produced eroded stereoselectivity.[7,9] Aldol-based approaches[10] using other glycinate derivatives, for example, α-isocyano esters[11,12] and α-isothiocyanato esters[13] or 5-alkoxyoxazoles[14] as latent enolates, have been developed, whereas these reactions afforded oxazolines or oxazoline-2-thiones as surrogates for β-hydroxy-α-amino carboxylic acid derivatives.[15]



Scheme 1. Direct aldol approach to enantioenriched β-hydroxy-α-amino carboxylic acid derivatives.

Herein, we document a direct catalytic asymmetric aldol reaction of α-azido 7-azaindolinylacetamide (**1a**), as an aldol donor, promoted by a catalyst prepared from mesitylcopper/chiral bisphosphine ligands (Scheme 1 b). Aromatic aldehydes (**2**) were viable aldol acceptors, thus affording both *anti* and *syn* adducts (**3**) with high enantioselectivity. The β-hydroxy-α-azido amide architecture of **3** is analogous to β-hydroxy-α-amino acid derivatives, in which the azide functionality can be viewed as a latent amino group. Furthermore, the product undergoes azide-specific transformations, as exemplified by the formation of an enantioenriched aziridine. In our continuing research on direct enolization chemistry, we recently found the particular utility of α-substituted 7-azaindolinylacetamide for facilitating enolization in aldol and Mannich reactions, as well as divergent transformation of the corresponding products.[16] Given the great synthetic potential of the azide functionality,[17] we focused on the development of a direct aldol reaction of **1a** to broaden the synthetic value of this latent enolate,[18] thus affording enantioenriched β-hydroxy-α-azido carboxylic acid derivatives. Although α-azido ketones, representative aldol donors bearing an α-azido functionality, display unique reactivity in a number of transformations,[19] the utility of them and other α-azido carbonyl compounds in stereoselective aldol reactions has been little explored.[20] The only example of

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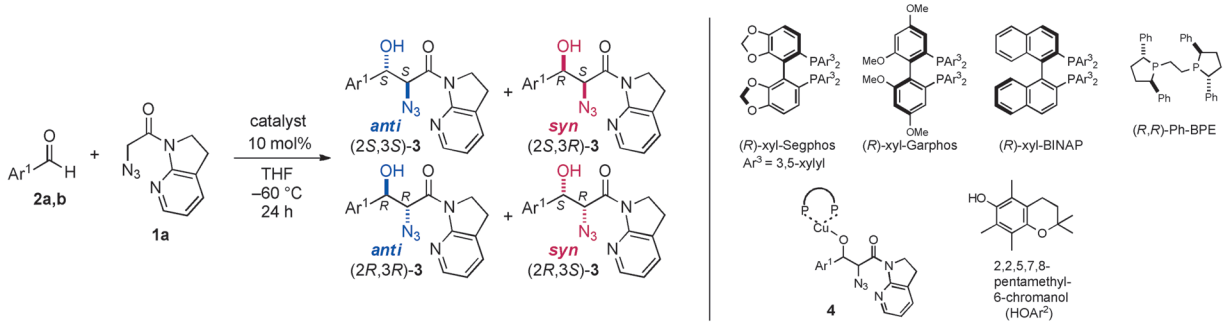
a catalytic and enantioselective version was reported by Concellón et al. and they used relatively acidic α-azido acetone as an aldol donor to afford *anti* adducts with high stereoselectivity.[21]

We reasoned that **1a** would be a suitable aldol donor in the carboxylic acid oxidation state, and could be activated to catalytically generate the corresponding enolate in the context of soft Lewis acid/hard Brønsted base cooperative catalysis.[22] Initial trials were carried out with the aldol reaction of *o*-(trifluoromethyl)benzaldehyde (**2a**) and **1a** using a cooperative catalytic system comprising $[Cu(CH_3CN)_4]PF_6$/(*R*,*R*)-Ph-BPE/LiOAr^2 ($HOAr^2$ = 2,2,5,7,8-pentamethyl-6-chromanol), the standard catalyst for direct enolization of soft Lewis basic latent enolates.[23] This catalytic system has rapidly emerged as a viable catalytic system to afford the *anti*-adduct **3a** with promising stereoselectivity (Table 1, entry 1). No conversion was observed with an impaired catalyst lacking the soft Lewis acidic Cu^I, thus suggesting the activation of the amide **1a** through coordination of the pyridino nitrogen atom to Cu^I (entry 2). The simplified catalytic system of mesitylcopper/(*R*,*R*)-Ph-BPE gave a superior reaction outcome, in which the intermediate copper(I) aldolate **4** functioned as the cooperative catalyst (entry 3). Surprisingly, a subsequent study using benzaldehyde (**2b**) predominantly produced *syn* adducts with high enantioselectivity (entries 4 and 5). This finding prompted us to screen chiral ligands and we found that biaryl-type ligands afforded *syn* products with both **2a** and **2b** (entries 6–9), and (*R*)-xyl-BINAP exhibited the best performance (entry 8).[24] Perusal of the stereochemistry indicated the following: 1) for **2a**, *anti*- and *syn*-aldol products were obtained from (*R*,*R*)-Ph-BPE and (*R*)-xyl-BINAP, respectively; 2) for **2b**, a *syn*-aldol product was obtained with either of the ligands, and (*R*)-xyl-BINAP produced lower stereoselectivity (entry 5 versus 8); 3) irrespective of the aldehyde used, the stereochemistry at the α-position of the amide was determined by the ligand [(*R*,*R*)-Ph-BPE: 2*S*, (*R*)-xyl-BINAP: 2*R*]. Preliminary ^{15}N NMR studies gave no indication of Cu–N_3 coordination, and a *Z*-enolate is probably involved in the present aldol reaction.[25] Collectively, the reaction of **2a** with (*R*)-xyl-BINAP and **2b** with both ligands would preferentially proceed through a six-membered transition state to afford *syn*-**3a** and *syn*-**3b**, whereas the reaction of **2a** with (*R*,*R*)-Ph-BPE would prefer an open transition state to afford *anti*-**3a**, and is likely a result of the enhanced steric bias.

On the basis of this stereochemical analysis, a series of *ortho*-substituted aromatic aldehydes were examined using these two ligands (Table 2).[26] As expected, the reaction using (*R*,*R*)-Ph-BPE preferred the formation of *anti* adducts (*anti*-**3a** and *anti*-**3c**–**g**), while *syn* adducts were generally produced with (*R*)-xyl-BINAP (*syn*-**3a**, *syn*-**3c**–**f**, and *syn*-**3g**). Various *ortho* substituents were valid for controlling diastereoselectivity, except for *o*-fluorobenzaldehyde (**2g**) in the *anti*-selective reaction (*anti*-**3g**), probably because of insufficient sterics to disturb the cyclic transition state. The *syn*-selective mesitylcopper/(*R*)-xyl-BINAP catalyst showed higher catalytic activity, and the addition of 2,2,5,7,8-pentamethyl-6-chromanol as a proton source enhanced catalytic efficiency in mesitylcopper/(*R*,*R*)-Ph-BPE catalyst (*anti*-**3e**,**f**). The catalytic system was sufficiently robust to run 1 gram scale reactions with high stereoselectivity (*anti*-**3a**). In contrast, aromatic aldehydes without *ortho* substituents generally afforded *syn* adducts irrespective of the chiral ligands, and (*R*,*R*)-Ph-BPE exhibited the highest stereoselectivity (Table 3). The observed *syn* selectivity with 2-naphthaldehyde (**2h**) indicated that the steric effect at the *ortho*-position

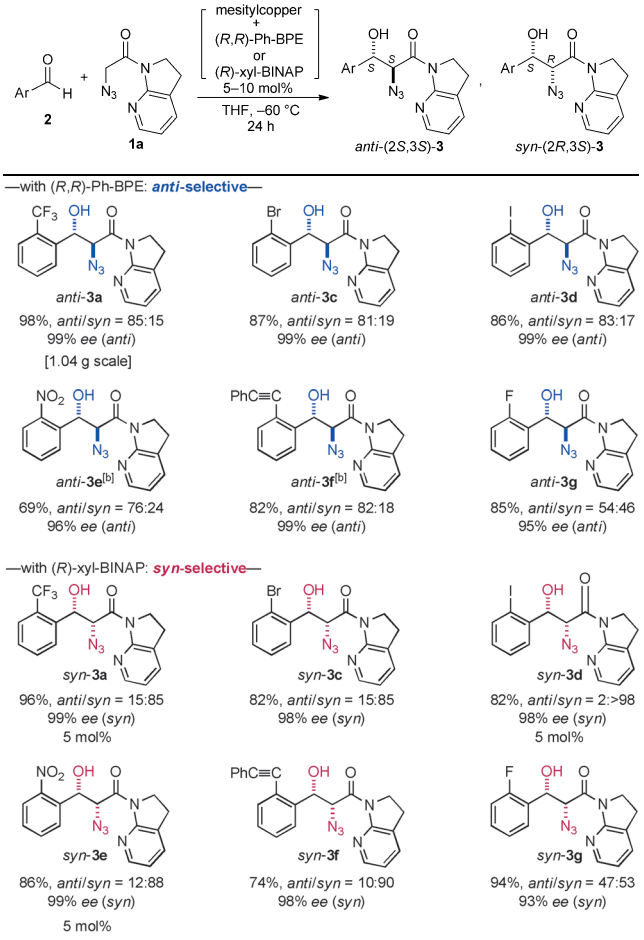
Table 1: Initial trials of the direct catalytic asymmetric aldol reaction using α-azido 7-azaindolinylacetamide (**1a**).



Entry	**2** (Ar^1)	Ligand	Catalyst	Yield [%][a]		*anti*/*syn*[b]	*ee* [%][c]	Major isomer
1	**2a** (*o*-$CF_3C_6H_4$)	(*R*,*R*)-Ph-BPE	$CuPF_6$/$LiOAr^2$[d,e]	78	**3a**	63:37	49	(2*S*,3*S*)
2	**2a** (*o*-$CF_3C_6H_4$)	(*R*,*R*)-Ph-BPE	$LiOAr^2$[e]	0	**3a**	–	–	–
3	**2a** (*o*-$CF_3C_6H_4$)	(*R*,*R*)-Ph-BPE	mesitylcopper	98	**3a**	85:15	98	(2*S*,3*S*)
4	**2b** (Ph)	(*R*,*R*)-Ph-BPE	mesitylcopper	52	**3b**	26:74	94	(2*S*,3*R*)
5[f]	**2b** (Ph)	(*R*,*R*)-Ph-BPE	mesitylcopper	86	**3b**	22:78	99	(2*S*,3*R*)
6	**2a** (*o*-$CF_3C_6H_4$)	(*R*)-xyl-Segphos	mesitylcopper	93	**3a**	7:93	97	(2*R*,3*S*)
7	**2a** (*o*-$CF_3C_6H_4$)	(*R*)-xyl-Garphos	mesitylcopper	46	**3a**	7:93	97	(2*R*,3*S*)
8	**2a** (*o*-$CF_3C_6H_4$)	(*R*)-xyl-BINAP	mesitylcopper	98	**3a**	15:85	98	(2*R*,3*S*)
9[f]	**2b** (Ph)	(*R*)-xyl-BINAP	mesitylcopper	91	**3b**	47:53	69	(2*R*,3*S*)

[a] Determined by ^1H NMR analysis using $(CHCl_2)_2$ as an internal standard. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] The *ee* value of the major diastereomer. [d] Tetrakis(acetonitrile) complex was used. [e] $HOAr^2$ = 2,2,5,7,8-pentamethyl-6-chromanol. [f] 10 mol% of $HOAr^2$ was added. THF = tetrahydrofuran.

Table 2: Diastereodivergent direct catalytic asymmetric aldol reaction of **1a** and *ortho*-substituted aromatic aldehydes (**2**).[a]



[a] Unless otherwise noted, 10 mol% of catalyst was used. Yield of isolated product reported. [b] 10 mol% of 2,2,5,7,8-pentamethyl-6-chromanol was used as a proton source.

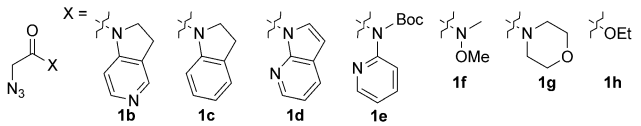
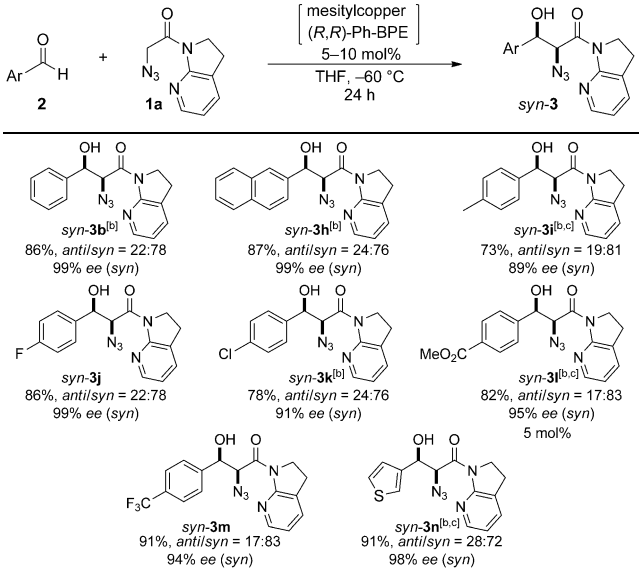


Figure 1. Structures of the ineffective α-azido aldol donors **1b–h**.

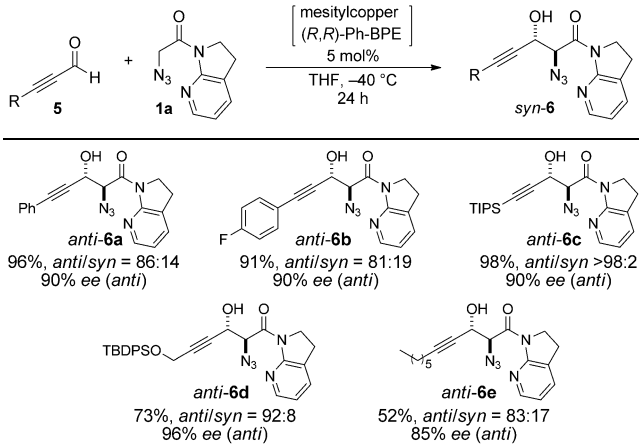
was the sole determinant to favor the *anti*-product (*syn*-**3h**). A range of *para*-substituted aldehydes (**2i–m**) preferentially afforded *syn* adducts with high enantioselectivity (*syn*-**3i–m**). A heteroaromatic aldehyde was also compatible (*syn*-**3n**). The substrate **1a** was a privileged α-azido aldol donor and no reaction proceeded with other structurally related aldol donors (**1b–h**; Figure 1). The failed reaction using the isomeric 5-azaindolinylamide **1b** and indolinylamide **1c** was indicative of the importance of the nitrogen functionality at the correct position to facilitate enolization. 7-Azaindolylamide (**1d**) was susceptible to hydrolysis. The amide **1e** of 2-aminopyridine was unreactive, even with activation by a Boc group. The Weinreb amide **1f** and as well as **1g** and **1h** also proved unreactive under the present catalytic system.

Table 3: *syn*-Selective direct catalytic asymmetric aldol reaction of **1a** and *ortho*-nonsubstituted aromatic aldehydes **2**.[a]



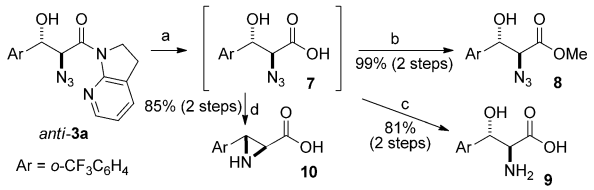
[a] Unless otherwise noted, 10 mol% of catalyst was used. Yield of isolated product reported. [b] Equimolar amount (relative to Cu) of 2,2,5,7,8-pentamethylchromanol was used as a proton source. [c] Reaction run at −40 °C.

Table 4: *anti*-Selective direct catalytic asymmetric aldol reaction of **1a** and ynals (**5**).[a]



[a] Yields of isolated products reported.

Although aliphatic aldehydes and α,β-unsaturated aldehydes showed very low reactivity and eroded stereoselectivity,[27] the ynals **5** were suitable substrates in the mesitylcopper/(*R*,*R*)-Ph-BPE catalyst system (Table 4). Because of the rich chemistry of alkynes, the corresponding aldol adducts **6**, bearing a propargylic alcohol unit, hold high synthetic value.[28] The observed *anti* diastereoselectivity was opposite to that observed with *ortho*-nonsubstituted aromatic aldehydes.[29] Ynals having aromatic (*anti*-**6a**,**b**) and silyl protecting groups (*anti*-**6c**,**d**), and an alkyl group were applicable (*anti*-**6e**).



Scheme 2. Transformation of the aldol product. Reagents and conditions: a) 6 M HCl aq., 80 °C, 4 h. b) CH_2N_2, ether, RT, < 5 min, 99% (2 steps). c) H_2, Pd/C, AcOEt, RT, 5 h, 81% (2 steps). d) PPh_3, THF, 40 °C, 5 h, 85% (2 steps).

The 7-azaindolinylamide moiety of the aldol product was readily hydrolyzed by 6 M HCl with the azide functionality intact, and 7-azaindoline was recovered in 97% yield (Scheme 2). The carboxylic acid **7** was relatively unstable and isolated after esterification with diazomethane to afford the analytically pure **8**, without purification, in 99% yield (2 steps). Hydrogenation of **7** also proceeded smoothly to afford the β-hydroxy-α-amino acid **9**. Treatment of **7** with PPh_3 induced the formation of enantioenriched aziridine **10**,[30] thus highlighting the particular utility of the azide-containing chiral building block.

In summary, a direct catalytic asymmetric aldol reaction of α-azido 7-azaindolinylamide was developed. The *ortho*-substituted aromatic aldehydes exhibited intriguing diastereodivergency depending on the chiral ligands. Smooth reaction of ynals broadened the substrate scope. Facile hydrolysis of the 7-azaindolinylamide proved that the present catalysis allows expeditious access to β-hydroxy-α-amino acid derivatives. The azide functionality was preserved as a masked amine or subsequent azide-specific transformation, and aziridination was demonstrated.

Keywords: aldol reaction · amides · asymmetric catalysis · azides · copper

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[25] For further discussions, see the Supporting Information.
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[27] Even after extensive studies on aliphatic aldehydes, only less satisfactory results were obtained. See the Supporting Information.
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