Organic LETTERS

Letter

pubs.acs.org/OrgLett

Direct Catalytic Asymmetric Aldol Reaction of α-Alkylamides

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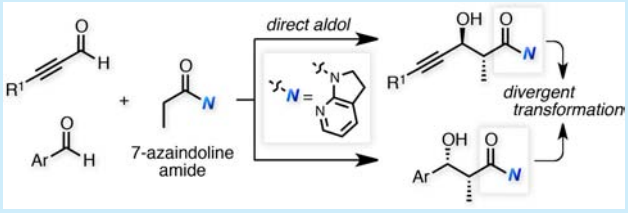
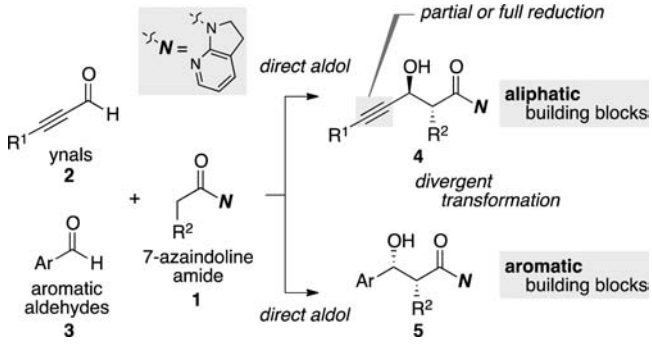
Supporting Information

ABSTRACT: A catalytic asymmetric aldol reaction directly employing amides as latent enolates has remained elusive because of the resistance of amides to enolization. A direct aldol reaction of α-alkylamides without any electron-withdrawing group harnessed by specific activation of 7-azaindoline amides under soft Lewis acid/Brønsted base cooperative catalysis is reported. Diastereo- and enantioselective coupling with ynals and aromatic aldehydes as well as divergent functional group interconversion of the amide provided expeditious access to a variety of aliphatic and aromatic chiral building blocks.



The aldol reaction has an indispensable role in a robust methodology for providing synthetically versatile β-hydroxy carbonyl units via carbon−carbon bond formation.[1] Because this reaction involves the coupling of two carbonyl fragments with intrinsically similar functional group characteristics, chemoselectivity is often more elusive than stereoselectivity in the efficient delivery of the desired aldol products. Although the use of preformed enolates eliminates the chemoselectivity issue with sacrifice of the activating reagents,[2,3] recent demands for sustainable chemistry and atom- and step-economical reactions have steered the chemistry community to direct and catalytic aldol reactions, in which chemoselective cross- and direct coupling of electrophilic carbonyl substrates (aldol acceptors) and latent enolates (aldol donors) is catalytically manifested without the use of activating reagents.[4,5] Because catalytic and chemoselective enolate formation is a primary determinant of the overall efficiency of direct aldol reactions, readily enolizable aldehydes and ketones are preferably used as aldol donors with the careful selection of aldol acceptors. The successful use of amides as aldol donors in a direct aldol manifold, which is much more resistant to enolization, is seldom reported with the aid of an electron-withdrawing group at the α-position to enhance enolization.[6,7] Kobayashi and co-workers reported an elegant example of the *anti*-selective direct catalytic aldol reaction of α-alkylamides bearing an *N*-Boc group, while one enantioselective entry was provided with moderate selectivity.[8] Herein we report a highly enantioselective protocol for a direct catalytic asymmetric aldol reaction of α-alkyl-7-azaindoline amides **1** with differential diastereoselectivity depending on the nature of the aldehyde used (Scheme 1). In view of the potential synthetic utility of the products, ynals **2** and aromatic aldehydes **3** were selected as aldol acceptors to give aldol adducts **4** and **5**, respectively, for which reduction of the triple bond and diverse transformations of amides provided a range of chiral building blocks.

Scheme 1. Direct Aldol Strategy for the Synthesis of Diverse Chiral Building Blocks



In our continuing program on catalytic enolization methodology, we identified 7-azaindoline amides **1** as highly suitable for both facilitated enolization and diverse functional group interconversion.[9] While **1** is stable and intrinsically prefers the *E* conformation, it readily isomerizes to the *Z* conformation in the presence of a soft Lewis acid to form activated chelate **6** (Figure 1a), which is readily enolized by a Brønsted base. This enolization is manifested in a catalytic manner by a soft Lewis acid/Brønsted base cooperative catalytic system,[10] and the thus-formed enolate engages in subsequent addition to electrophiles. We recently found that enolization was facilitated without an electron-withdrawing group at the α-position, allowing for the use of α-alkyl-7-azaindoline amide **1** in a direct catalytic asymmetric Mannich-type reaction with *N*-Boc imines.[9f] This prompted us to expand the direct enolization chemistry of propionamide **1a** to the aldol reaction manifold, affording synthetically versatile enantioenriched propionate units. We began our study using ynals **2** as aldol acceptors

Received: December 30, 2016
Published: January 26, 2017

DOI: 10.1021/acs.orglett.6b03890
Org. Lett. 2017, 19, 710−713

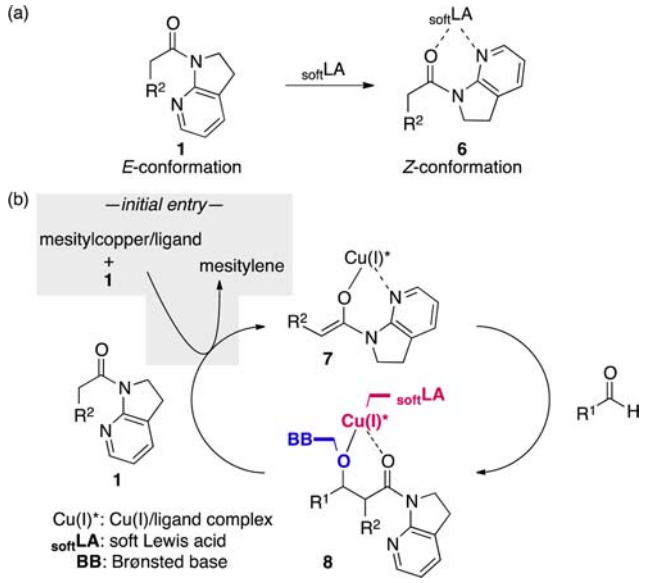
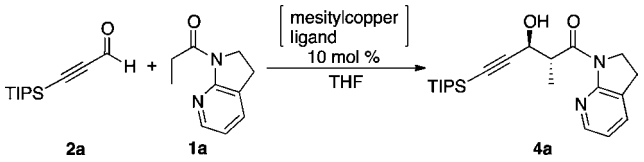


Figure 1. (a) Conformational flip of 7-azaindoline amide **1**. (b) Plausible initial entry and the following catalytic cycle using mesitylcopper/ligand as a catalyst.

due to the rich chemistry of the propargylic alcohol motif of the products for diverse transformations.[11] For easy setup of the reaction, a mesitylcopper/chiral ligand was used as the catalyst,[12] which initially reacts with amide **1** to produce the corresponding Cu(I) enolate **7** (Figure 1b). Subsequent addition to aldehydes delivers Cu(I) aldolate **8**, which acts in the following catalytic cycle as a soft Lewis acid/Brønsted base catalyst. In the reaction of archetypal TIPS-protected ynal **2a**, chiral ligands were screened as summarized in Table 1. The use of 10 mol % mesitylcopper and (*S*,*S*)-Ph-BPE (**L1**), a privileged bisphosphine ligand used in a range of reactions utilizing 7-azaindoline amides with high stereoselectivity,[9a,e] promoted the direct aldol reaction at −30 °C to give *anti*-aldol adduct **4a** in moderate yield with encouraging stereoselectivity (entry 1). In an effort to achieve higher *anti* selectivity, biaryl-type bisphosphine ligands were investigated (entries 2−7). These ligands generally gave higher *anti* selectivity, albeit with lower conversion and enantioselectivity, and bulkier aromatic groups on the phosphorus impeded the reaction (entry 7). (*R*)-Trimethoxy-Biphep (**L6**) exhibited promising stereoselectivity with somewhat eroded conversion that was likely due to the increasing steric factor (entry 6). With **L6**, the use of 2,2,5,7,8-pentamethylchromanol (**9**) as a proton source improved the catalytic efficiency, where a Cu(I) aryloxide was likely involved as a catalyst,[13] facilitating the liberation of aldol adducts by the protonation of Cu(I) aldolate **8** and the subsequent deprotonation of **1** (entry 8). The stoichiometry of **2a** was attenuated to 1.2 equiv, and a longer reaction time under more concentrated conditions at −20 °C afforded aldol product **4a** in high yield with only a marginal loss of enantioselectivity (entry 9).

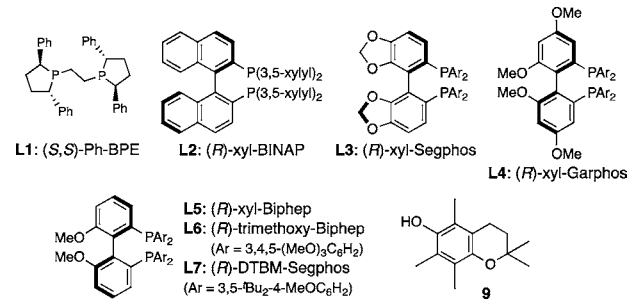
The catalyst comprising mesitylcopper/**L6**/**9** was applicable to a range of ynals **2** (Table 2).[14] In addition to silyl-protected ynal **2a** (entry 1), ynals **2b**−**n** bearing aromatic groups were competent substrates affording high stereoselectivity (entries 2−14). Generally, uniform stereoselectivity was observed irrespective of the electronic nature and position of substituents on the aromatic ring, presumably due to the distal position of the aromatic groups from the reactive carbonyl group. These

Table 1. Screening of Chiral Ligands[a]



entry	ligand[f]	additive (10 mol %)	temp (°C)	time (h)	yield (%)[b]	*anti*/*syn*[c]	ee[d]
1	**L1**		−30	40	60	88/12	89
2	**L2**		−30	40	82	>96/4	66
3	**L3**		−30	40	44	>96/4	54
4	**L4**		−30	40	59	>96/4	68
5	**L5**		−30	40	62	>96/4	64
6	**L6**		−30	40	31	>96/4	92
7	**L7**		−30	40	trace	–	–
8	**L6**	**9**	−30	40	56	>96/4	92
9[e]	**L6**	**9**	−20	72	90	>96/4	90

[a] **1a** (0.1 mmol), **2a** (0.2 mmol), 0.33 M on **1a**. [b] Determined by ^{1}H NMR analysis with 3,4,5-trichloropyridine as an internal standard. [c] Determined by ^{1}H NMR analysis of the crude mixtures. [d] Determined by HPLC analysis. [e] 0.5 M on **1a**; 0.12 mmol of **2a** was used. [f] Ligand structures:

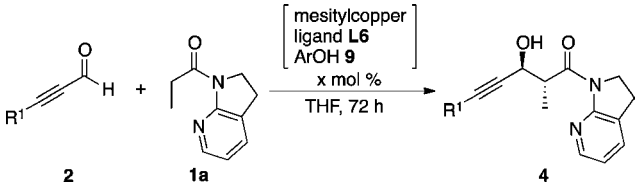


ynals were marginally less reactive than **2a**, leading us to use a slightly higher amount of the catalyst (entries 3−7 and 9−13) or higher temperatures (entries 2, 8, and 14). A Lewis basic thienyl group had no detrimental effects on the catalytic efficiency or stereoselectivity (entry 14). The diastereoselectivity of ynal **2o** having an alkyl substituent was reduced (entry 15).

The successful implementation of ynals **2** prompted us to explore enals, α-sp^3 aldehydes, and aromatic aldehydes **3** as aldol acceptors, revealing that the former two types of aldehydes were intractable in the catalytic system described above.[15] **L1** was optimal for aromatic aldehydes **3**, and the reaction in DMF at −40 °C preferentially afforded the *syn*-aldol adducts **5** with an identical absolute configuration at the α-position (Table 3, entry 1).[16] Since the Cu(I) of enolate **7** is coordinatively saturated, the addition to the aldehyde likely proceeded through an open transition state, where sterics around the carbonyl group or weak secondary interactions of the triple bond with Cu(I) might lead to a significant difference in the prochiral face selection of aldehydes. While an electron-donating substituent retarded the reaction (entry 2), halogen and nitro substituents were well-tolerated (entries 3−6). Aldehydes with a Lewis basic sulfide or a thienyl group had little detrimental effect on the conversion and stereoselectivity (entries 6 and 8). For both ynals **2** and aromatic aldehydes **3**, 7-azaindoline amide **1a** was uniquely reactive in soft Lewis acid/Brønsted base cooperative catalysis, whereas the structurally related amides **1b**−**f** failed to react (Figure 2).

DOI: 10.1021/acs.orglett.6b03890
Org. Lett. 2017, 19, 710−713

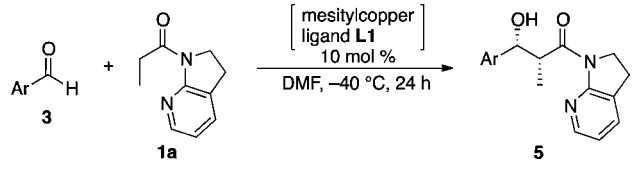
Table 2. *Anti*-Selective Direct Catalytic Asymmetric Aldol Reaction of 7-Azaindoline Propionamide 1a with Ynals 2[a]



entry	R^1 (2)	x	temp (°C)	prod.	yield (%)[b]	anti/syn[c]	ee[d]
1	TIPS (**2a**)	10	−20	**4a**	90	98/2	90
2[e]	Ph (**2b**)	10	−10	**4b**	72	87/13	93
3	4-MeC_6H_4 (**2c**)	12	−20	**4c**	82	89/11	93
4	4-$MeOC_6H_4$ (**2d**)	12	−20	**4d**	83	88/12	94
5	2-$MeOC_6H_4$ (**2e**)	12	−20	**4e**	86	92/8	91
6	2-FC_6H_4 (**2f**)	12	−20	**4f**	80	91/9	92
7	4-FC_6H_4 (**2g**)	12	−20	**4g**	80	87/13	94
8	2-ClC_6H_4 (**2h**)	10	−10	**4h**	83	91/9	90
9	3-ClC_6H_4 (**2i**)	12	−20	**4i**	72	84/16	97
10	4-ClC_6H_4 (**2j**)	12	−20	**4j**	76	85/15	93
11	4-BrC_6H_4 (**2k**)	12	−20	**4k**	72	86/14	90
12	2-$CF_3C_6H_4$ (**2l**)	12	−20	**4l**	81	91/9	90
13	4-$CF_3C_6H_4$ (**2m**)	12	−20	**4m**	75	86/14	94
14	2-thienyl (**2n**)	10	−10	**4n**	86	93/7	92
15	^{c}Hex (**2o**)	12	−20	**4o**	80	62/38	90

[a]**1a** (0.1 mmol), **2** (0.12 mmol), 0.5 M on **1a**. [b]Isolated yields. [c]Determined by ^{1}H NMR analysis of the crude mixtures or HPLC analysis. [d]Determined by HPLC analysis. [e]**1a** (5 mmol), **2b** (10 mmol), 0.5 M on **1a**.

Table 3. *Syn*-Selective Direct Catalytic Asymmetric Aldol Reaction of 7-Azaindoline Propionamide 1a with Aromatic Aldehydes 3[a]



entry	Ar (3)	prod.	yield (%)[b]	syn/anti[c]	ee[c]
1[d]	Ph (**3a**)	**5a**	84	85/15	93
2	3-$MeOC_6H_4$ (**3b**)	**5b**	66	88/12	92
3	4-ClC_6H_4 (**3c**)	**5c**	87	82/18	92
4	4-BrC_6H_4 (**3d**)	**5d**	95	88/12	86
5	4-$NO_2C_6H_4$ (**3e**)	**5e**	87	90/10	81
6	4-$MeSC_6H_4$ (**3f**)	**5f**	72	86/14	87
7	2-furyl (**3g**)	**5g**	87	78/22	92
8	2-thienyl (**3h**)	**5h**	91	82/18	87

[a]**1a** (0.1 mmol), **3** (0.12 mmol), 0.5 M on **1a**. [b]Isolated yields. [c]Determined by HPLC analysis. [d]**1a** (5 mmol), **3a** (10 mmol), 0.5 M on **1a**.

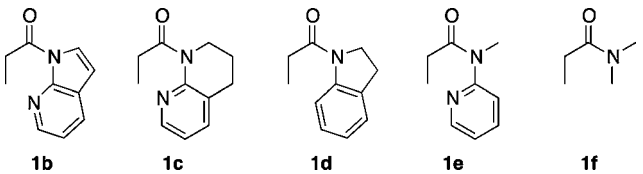
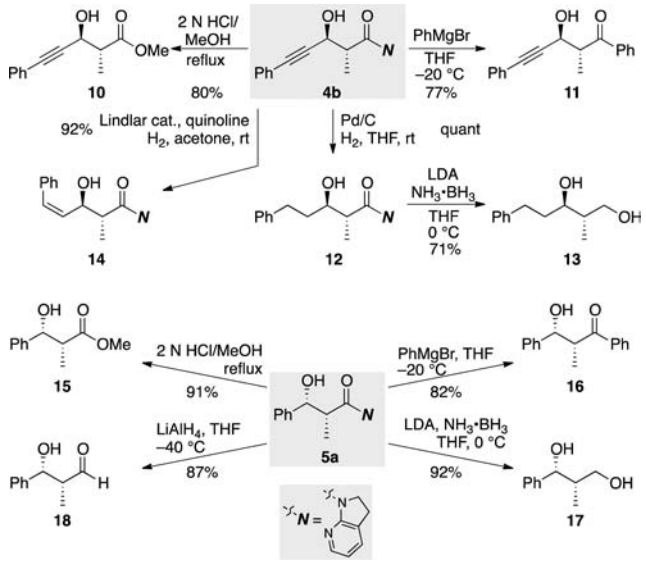


Figure 2. Unreactive structurally related amides.

The divergent transformation of the amide moiety of the aldol products confers synthetic utility on the present direct aldol protocol (Scheme 2). Methanolysis of *anti*-**4b** derived from ynal **2b** with 2 N HCl/MeOH at 70 °C proceeded smoothly to give ester **10** without epimerization, while treatment with PhMgBr delivered ketone **11** exclusively. Although associated side reactions prevented amide reduction of **4b**, reduction to alcohol **13** was successful with lithium amidotrihydroborate after hydrogenation to **12**. Partial hydrogenation of **4b** by Lindlar's catalyst with the combined use of quinoline gave (*Z*)-styryl derivative **14**. Identical conditions resulted in the facile transformation of *syn*-**5a** to **15**−**17** in high yield. In the case of *syn*-**5a**, the corresponding *β*-hydroxy aldehyde **18**, could be obtained by treatment with $LiAlH_4$ at reduced temperature.

Scheme 2. Transformations of the Aldol Products



In conclusion, we have developed a direct catalytic asymmetric aldol reaction of 7-azaindoline propionamide. The interplay of a soft Lewis acid/Brønsted base cooperative catalyst and 7-azaindoline amide was crucial for promoting the otherwise intractable direct aldol reaction. The diastereoselectivity differed depending on the nature of the aldehyde. Divergent transformations of the aldol adducts increase the synthetic utility of the products as chiral building blocks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03890.

Detailed experimental procedures and spectroscopic data of new compounds (PDF)

Crystallographic data for **4a** (CIF)

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DOI: 10.1021/acs.orglett.6b03890
Org. Lett. 2017, 19, 710−713

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by JST ACT-C and JSPS KAKENHI (25713002, JP16H01043). Dr. Tomoyuki Kimura at the Institute of Microbial Chemistry is gratefully acknowledged for technical assistance with X-ray crystallographic analysis of **4a**.

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(13) The conjugate base of **9** is more basic than that of common phenol derivatives because of the electron-donating groups on the aromatic ring. The Cu(I) phenoxide of **9** would be formed in the catalytic cycle and sufficiently basic to promote enolization.

(14) Unfortunately, 7-azaindoline amides bearing longer alkyl chains at the α-position failed in the reaction, which is the subject of future study.

(15) The reaction with octanal proceeded in a highly enantioselective manner, albeit with low conversion and diastereoselectivity. Conditions: 10 mol% $[Cu(CH_3CN)_4]$/**L6**/Li salt of **9**, DMF, −40 °C, 18 h; 14% yield, dr 63:37, 98% ee (major diastereomer).

(16) The use of **9** gave no beneficial effect for the reactions of aromatic aldehydes **3**.

DOI: 10.1021/acs.orglett.6b03890
Org. Lett. 2017, 19, 710−713