Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Direct Catalytic Asymmetric Mannich-Type Reaction en Route to α-Hydroxy-β-amino Acid Derivatives

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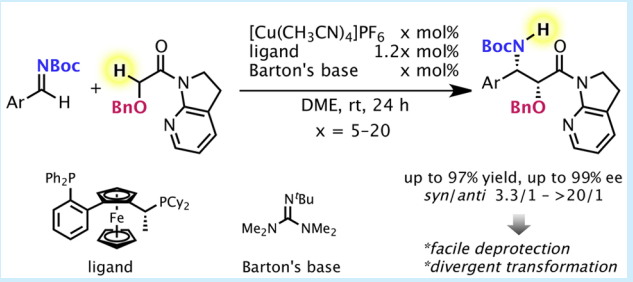
Supporting Information

ABSTRACT: A direct catalytic Mannich-type reaction of α-oxygen-functionalized amides was achieved. The use of 7-azaindoline amide was crucial to facilitate direct enolization and subsequent stereoselective addition to imines in a cooperative catalytic system comprising a soft Lewis acid and Brønsted base. The operationally simple room-temperature protocol furnished a *syn*-Mannich adduct with high stereoselectivity. Divergent functional group transformation of the amide moiety of the product allowed for expeditious access to enantioenriched *syn*-configured α-hydroxy-β-amino carboxylic acid derivatives, highlighting the synthetic utility of the present catalysis.



The α-hydroxy-β-amino acid unit is a privileged structural motif in a wide variety of biologically active natural products and therapeutics. Highly representative examples of this are paclitaxel and docetaxel, marketed as Taxol and Taxotere, respectively, which have proven potency against various types of cancer and possess this specific unit with the *syn*-configuration at the functional side chain (Figure 1a).[1] Considerable effort has been devoted to devising expeditious access to this class of compounds in both a catalytic and stereoselective manner.[2−7]

The integration of a C−C bond-forming process and stereoselective installation of the α-hydroxyl and β-amino functional groups in a single step to efficiently furnish these units can be achieved by Mannich reaction of imines and α-oxygen-functionalized latent enolates.[8] Recent advances in Mannich reactions render the whole process catalytic, where both enolate formation and stereoselective addition to imines are driven by the designed catalysts.[9] Due to the inherent difficulty of the initial catalytic enolization of carbonyl-type pronucleophiles, enolization−prone ketones and aldehydes have been incorporated in direct Mannich chemistry with remarkable stereoselectivity (Figure 1b).[9a,b,d−f] The limited synthetic utility of these Mannich products, however, led us to focus on the use of latent enolates in the carboxylic acid oxidation state to furnish versatile α-hydroxy-β-amino carboxylic acid derivatives. Although we developed a Mannich-type reaction of α-hydroxy-*N*-acetylpyrrole utilizing *N*-*o*-Ts imines as electrophiles via In(III) catalysis, there is much room for improvement toward practical organic synthesis; i.e., low catalytic turnover (≤4.9), moderate diastereoselectivity, and difficult removal of the *o*-Ts group on the nitrogen (Figure 1c).[9c] In our continuing program of enolization chemistry using 7-azaindoline amides, α-oxygen functionalized amides has remained elusive, despite the successful implementation of α-alkyl-,[10] fluoroalkyl-,[11] nitrogen-,[12] thio-,[13] and halo-functionalized amides.[14] Herein, we document the successful incorporation of α-oxygen functionalized 7-azaindoline amide into a direct Mannich manifold, delivering *syn*-configured β-amino-α-hydroxy amides (Figure 1d). Facile functional group transformation of the amide moiety

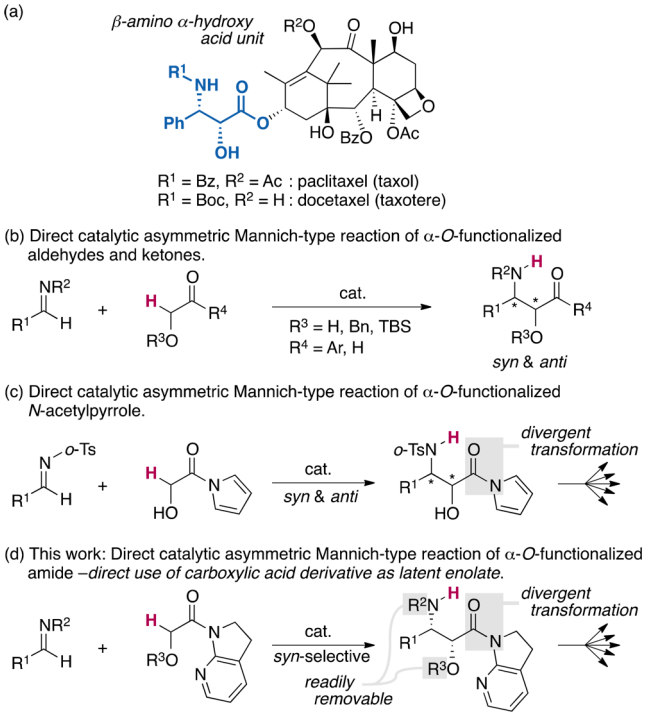


Figure 1. (a) Structures of taxol and taxotere. (b, c) Prior schemes of direct catalytic asymmetric Mannich-type reactions. (d) Present work.

Received: November 20, 2017

DOI: 10.1021/acs.orglett.7b03609
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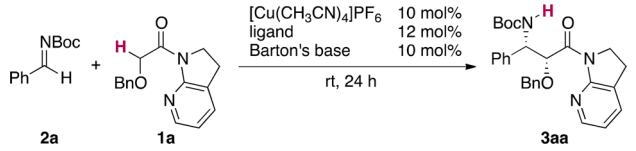
as well as readily removable protecting groups on the oxygen and nitrogen highlight the synthetic versatility of these Mannich products.

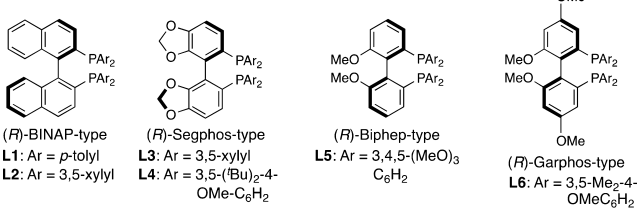
To enhance the prospective utility of the Mannich products as chiral building blocks, a benzyloxy group was selected as an α-substituent of 7-azaindoline amide pronucleophile **1a**. As for imine electrophiles, those with readily cleavable *N*-carbamoyl-protected imines[15] were suitable, and *N*-Boc imine **2a** was used as a model substrate for the initial screening. Based on the properties of 7-azaindoline amide, a cooperative catalytic system comprising Cu(I) salt and Barton's base was tested with a variety of chiral phosphine ligands (Table 1).[14,16] Generally, the desired

Table 1. Direct Catalytic Asymmetric Mannich-Type Reaction of α-OBn 7-Azaindoline Amide 1a and *N*-Boc-imine 2a[a]



2a 1a 3aa

entry	ligand	solvent	yield[b] (%)	*syn*/*anti*[c]	ee (%) (*syn*)[d]
1	**LI**	THF	91	1.8/1	50
2	**L2**	THF	95	5.4/1	31
3	**L3**	THF	88	4.3/1	−45
4	**L4**	THF	50	1.5/1	−45
5	**L5**	THF	93	1.3/1	17
6	**L6**	THF	88	3.4/1	5
7	**L7**	THF	72	1.9/1	−87
8	**L8**	THF	50	1.1/1	−53
9	**L9**	THF	93	2.5/1	73
10	**L10**	THF	90	6.0/1	94
11	**L10**	DME	91[e]	9.0/1	95

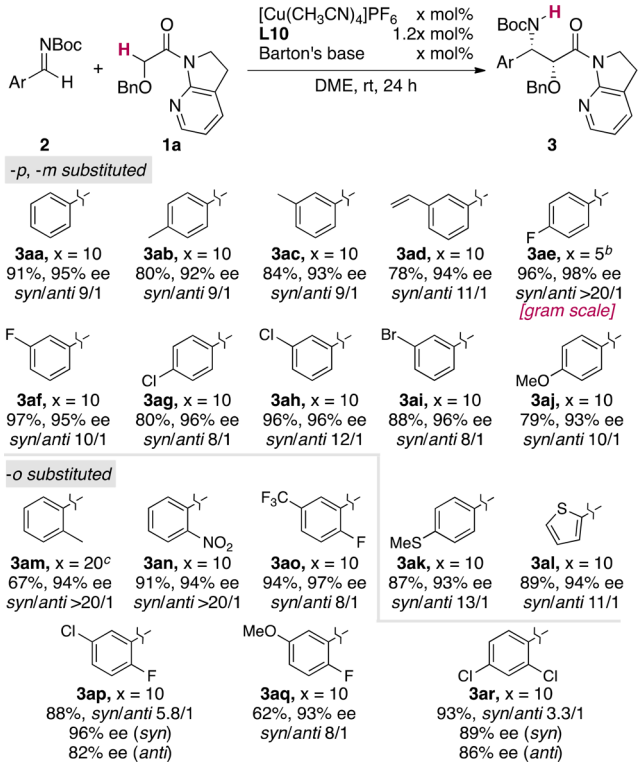


[a]**1a**: 0.1 mmol, **2**: 0.2 mmol. [b]Determined by ^{1}H NMR analysis of crude mixture using mesitylene as an internal standard. [c]Determined by ^{1}H NMR analysis. [d]Determined by HPLC analysis. Negative sign denotes the enantiomer. [e]Isolated yield.

reaction proceeded with 10 mol % catalyst in THF at room temperature to give the desired product **3aa** in a *syn*-selective manner. Although the biaryl-type ligands of four different core architectures **L1**−**6** afforded **3aa** in high yield, except for bulky ligand **L4**, the diastereo- and enantioselectivity were moderate, and conceivable trends between the selectivity and ligand structures were barely detected (entries 1−6). Structurally distinct alkyl phosphine ligand **L7** significantly improved the enantioselectivity, albeit with moderate *syn*-selectivity (entry 7). Ferrocene-embedded bisphosphine ligands were then evaluated and Walphos-type ligand **L10** outperformed the others to afford **3aa** in *syn*/*anti* = 6/1 and 94% ee (entries 8−10). Switching the solvent from THF to DME further improved the stereoselectivity with an isolated yield of 91% (entry 11).

The substrate generality for imines under optimized reaction conditions is summarized in Scheme 1. Mannich-type reactions

Scheme 1. Direct Catalytic Asymmetric Mannich-Type Reaction of α-OBn 7-Azaindoline Amide 1a[a]



[a]**1a**: 0.1 mmol, **2**: 0.2 mmol (except for **3ae**), isolated yield shown. [b]**1a**: 5.0 mmol, **2e**: 7.5 mmol, 2.36 g of **3ae** was obtained. [c]Run for 48 h.

of imines **2** bearing *m*- or *p*-substituents proceeded uneventfully to afford corresponding *syn*-adducts with high enantioselectivity, irrespective of the electronic nature of the substituents (**3aa**−**al**). *p*-F-substituted imine exhibited sufficient reactivity with 5 mol % of catalyst loading, and a gram-scale reaction proceeded with no detrimental effect on stereoselectivity (**3ae**). Inherently coordinative, soft Lewis basic thioether or thienyl groups were tolerated in the present Cu(I) catalysis (**3ak**, **3al**). The *o*-Me substituent retarded the reaction, and 20 mol % of catalyst was required for reasonable yield, while *o*-nitro-substituted imine was sufficiently reactive, resulting in excellent stereoselectivity (**3am**, **3an**). *o*-Halogen-substituted imines were partly compatible, and eroded *syn*-selectivity was observed depending on the additional substituents (**3ao**−**ar**). It is noteworthy that the present Mannich method enables expeditious access to the side chains of both Taxol and Taxotere; *N*-Bz imine **2s** as well as *N*-Boc-imine **2a** afforded the desired *syn*-adduct **3as** preferentially with high enantioselectivity (Scheme 2).[17] By taking into account the broad scope of aromatic groups of imines in Scheme 1 and facile hydrolytic capability of the amide moiety (vide infra), the direct Mannich protocol allows for the synthesis of a variety of enantioenriched derivatives for these important drugs. Amides possessing other oxygen functionalities were also compatible (Scheme 3). Amide **1b** with a phenyl ether at the α-position gave a Mannich adduct with an identical stereochemical configuration

DOI: 10.1021/acs.orglett.7b03609
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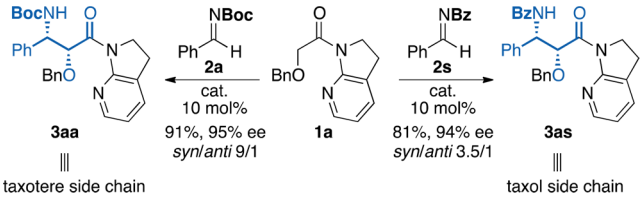
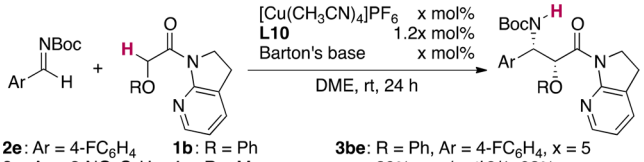
Scheme 2. Direct Catalytic Asymmetric Mannich-Type Reaction Using *N*-Boc- and *N*-Bz-imines To Furnish Both Side Chains for Taxol and Taxotere[a]



[a]Optimized conditions shown in Scheme 1 were used.

Scheme 3. Direct Catalytic Asymmetric Mannich-Type Reaction of α-OMe and α-OPh 7-Azaindoline Amides 1b,c



2e: Ar = 4-FC_6H_4 **1b**: R = Ph
2n: Ar = 2-$NO_2C_6H_4$ **1c**: R = Me

3be: R = Ph, Ar = 4-FC_6H_4, x = 5
89%, *syn/anti* 8/1, 98% ee
3bn: R = Ph, Ar = 2-$NO_2C_6H_4$, x = 10
82%, *syn/anti* 12/1, 94% ee
3cn: R = Me, Ar = 2-$NO_2C_6H_4$, x = 10
87%, *syn/anti* 6.3/1, 99% ee

and a similar level of stereoselectivity (**3be**, **3bn**).[18] Somewhat lower *syn*-selectivity was observed for methyl ether derivative **1c**, albeit with excellent enantioselectivity (**3cn**). The remarkable enolization propensity and stereoselective addition to imines were exclusive to 7-azaindoline amide **1a**−**c**; 7-azaindole derivative **1d**, indoline derivative **1e**, and *N*-Boc 2-pyridyl amide **1f** all failed the reaction under the optimized reaction conditions (Figure 2).

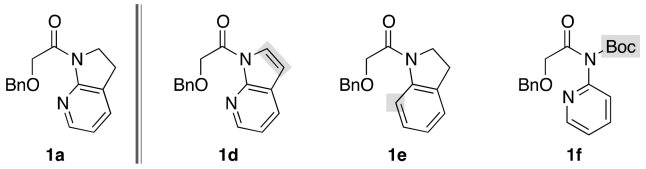
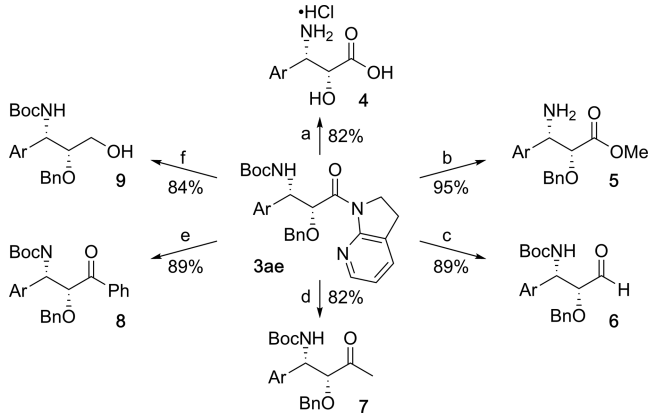


Figure 2. Structure of reactive (**1a**) and unsuccessful α-OBn amides (**1d**−**f**).

The synthetic utility of the Mannich adduct is highlighted by divergent transformation of the 7-azaindoline amide moiety (Scheme 4). Treatment of **3ae** with 12 N HCl aq effected hydrolysis and global deprotection to furnish α-hydroxy-β-amino acid **4**, while Cu(I)-mediated acidic methanolysis gave methyl ester **5** with preservation of the Bn ether.[19] Due to stabilization of the tetrahedral intermediate by 7-azaindoline upon the addition of hydride or carbanions to amides, hydride reduction and the addition of organolithium or Grignard reagents produced the corresponding aldehyde **6** and ketones **7**,**8** without overreaction. Primary alcohol **9** could be directly accessed using Myers' protocol with $BH_3{\cdot}NH_3$ and LDA.[20] Of note, epimerization did not occur in these transformations.

In summary, 7-azaindoline amides bearing α-oxygen-functionalities were incorporated into direct enolization chemistry. The direct Mannich-type reaction proceeded at room temperature, affording versatile chiral building blocks of acyclic acid derivatives possessing α-hydroxyl and β-amino groups with high *syn*- and

Scheme 4. Transformation of the Mannich Adduct[a]



[a]Reagents and conditions: (a) 12 N HCl aq, 100 °C, 2 h, 82%; (b) CuCl, 2 M HCl/MeOH, 60 °C, 8 h, 95%; (c) $LiAlH_4$, THF, −78 °C, 2 h, 89%; (d) MeLi, Et_2O, −78 °C, 1 h, 82%; (e) PhMgBr, THF, −10 °C, 1 h, 89%; (f) $BH_3{\cdot}NH_3$, LDA, THF, rt, 1 h, 84%.

enantioselectivity. Application of this class of latent enolates to the aldol reaction manifold is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03609.

Experimental procedures and spectroscopic data of new compounds; NMR spectra (PDF)

Accession Codes

CCDC 1584885−1584887 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by ACT-C (JPMJCR12YO) from JST and KAKENHI (17H03025 and JP16H01043 in Precisely Designed Catalysts with Customized Scaffolding) from JSPS. R.P. thanks JSPS for a postdoctoral fellowship. Dr. Ryuichi Sawa, Ms. Yumiko Kubota, and Dr. Kiyoko Iijima at the Institute of Microbial Chemistry are gratefully acknowledged for their assistance with the spectroscopic analysis. We thank Dr.

DOI: 10.1021/acs.orglett.7b03609
Org. Lett. XXXX, XXX, XXX−XXX

Tomoyuki Kimura at the Institute of Microbial Chemistry for assistance with the X-ray crystallography.

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(17) The reaction using *N*-Boc imines derived from α,β-unsaturated imines was not successful.

(18) The absolute configuration of **3am** was determined by X-ray crystallographic analysis after conversion into the corresponding free alcohol **S1** via hydrogenolysis. The absolute configuration of products **3be** and **3bn** derived from **1b** was determined by X-ray crystallographic analysis. See the Supporting Information for details.

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DOI: 10.1021/acs.orglett.7b03609
Org. Lett. XXXX, XXX, XXX–XXX