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An Efficient Entry to *syn*- and *anti*-Selective Isoindolinones via an Organocatalytic Direct Mannich/Lactamization Sequence

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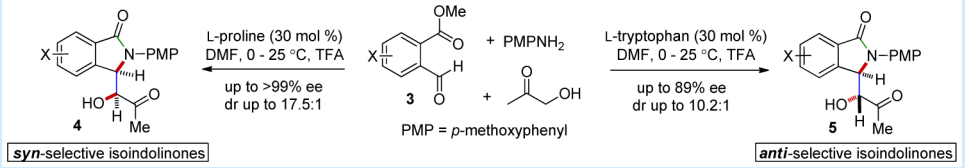
Supporting Information



ABSTRACT: An organocatalytic direct Mannich−lactamization sequence for the syntheses of pharmacologically important enantioenriched isoindolinones is reported. The method utilizes simple α-amino acids to deliver *syn*- and *anti*- selective isoindolinones with remarkably high enantioselectivity (up to >99% ee) in good to excellent yields and diastereomeric ratios. The overall sequence involves one C−C and two C−N bond forming events in one pot starting from inexpensive starting material.

Synthetically versatile enantioenriched isoindolinones (see **1a**−**f**; Figure 1) are prevalently found in many naturally occurring alkaloids and pharmaceuticals[1] with impressive biological activities.[2] Therefore, synthesis of such structural motifs in enantioenriched form has gained considerable interest in contemporary research. Prominent asymmetric approaches to this class of heterocyclics include resolution of racemates,[3] intramolecular Heck cyclization,[4] Diels−Alder approach,[5] ring-closure of chiral hydrazones,[6] reactions of chiral acyliminium ion,[7a,b] allylation to chiral imines,[7c] and a chiral appendage mediated carbanion method.[8] Most of these syntheses involve a chiral auxiliary mediated diastereoselective approach and face a limited substrate scope. Only a few enantioselective syntheses of isoindolinones are known in literature using metal catalysts.[9a−c] Toward this, we recently reported the concise enantioselective synthesis of isoindolinones (>99% ee) via a Cu[I]-*i*Pr-pybox-diPh catalyzed alkynylation−lactamization cascade.[10a]

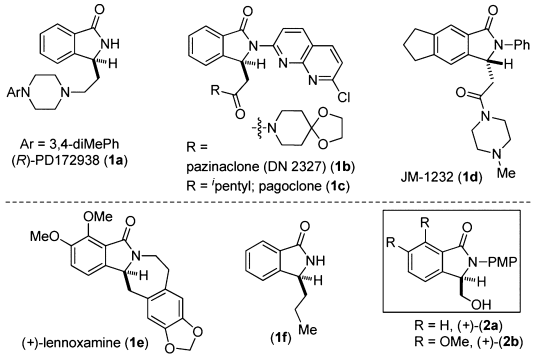


Figure 1. Selected enantioenriched isoindolinones.

Although there is a report on the thio-urea catalyzed enantioselective synthesis of isoindolinones, the enantioselectivities achieved are only up to 86%.[10b] Hence, there is a requirement of a deeper synthetic insight for the development of efficient organocatalytic enantioselective approaches. Our continued interest in this area prompted us to devise a suitable direct organocatalytic[11] enantioselective strategy. To this end, pioneering reports by List[12a] and Barbas[12b] on organocatalytic direct Mannich reactions drew our attention. The asymmetric Mannich reactions[13] are particularly appealing from a synthetic perspective owing to the prevalence of nitrogen in drugs and natural products. Herein, we report an expeditious route to both *syn*- and *anti*-selective isoindolinones following a direct organocatalytic enantioselective one-pot three-component Mannich−lactamization sequence (Scheme 1).

Organocatalytic Mannich reactions have widely been reported on preformed imines,[14] and only a handful of catalytic asymmetric direct Mannich reactions are reported to date.[12] In general, direct aldol and Mannich reactions typically compete if imines and enol equivalents are not preformed, and their rates depend on the equilibrium ratio between the aldehyde and the imine and on their respective rate constants. In this regard, especially, Mannich reactions which involve hydroxyacetone as the donor furnishing *syn*- and *anti*-1,2-amino alcohols in high chemo-, regio-, diastereo-, and enantioselectivities play an important role in organic synthesis. Thus, we selected hydroxyacetone as donor for the installation of *syn*- and *anti*-

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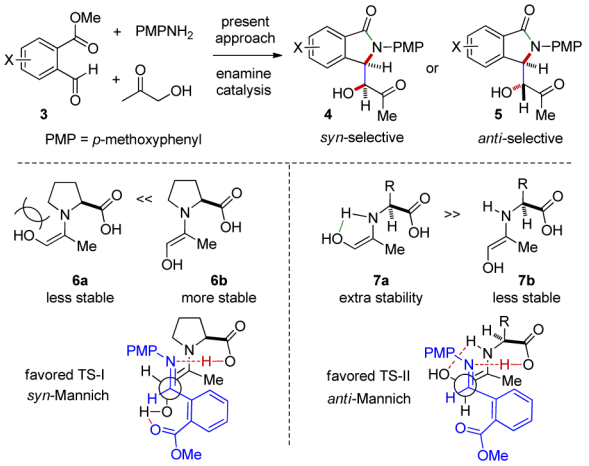
Scheme 1. Proposed Organocatalytic Route and Transition State Model[12b]



selective isoindolinones in the presence of a suitable organocatalyst through a Mannich−lactamization sequence (Scheme 1). We envisioned that one can achieve *syn*-selective isoindolinones from a 2° amine catalyzed (such as L-proline or its derivatives) Mannich−lactamization sequence via a more stable enamine intermediate **6b** over **6a** in analogy to List et al.[12a] (Scheme 1). The ester functionality at the *o*-position of aldimine may further stabilize the transition state (TS-I) via additional H-bonding with hydroxyacetone.[15] Whereas, the *anti*-selective isoindolinones could be accessed from a more stable enamine **7a** over **7b** when the reaction is catalyzed by a 1° amine as the catalyst in analogy to Barbas et al.[12b] (Scheme 1).

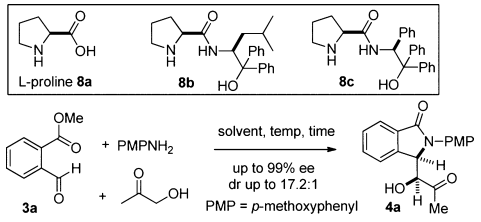
Initially, we conducted the direct organocatalytic one-pot three-component Mannich−lactamization sequence as per our hypothesis using 2° amino acid organocatalysts viz. L-proline **8a**[12] and its derivatives such as L-prolinamides **8b−c**[10] developed by us (Table 1, see Supporting Information for detailed optimization). *p*-Methoxyphenyl amine ($PMPNH_2$) was exclusively used as an amine partner, as it can readily be removed under oxidative conditions.[16,10a] Optimization studies revealed that 30 mol % of L-proline (**8a**) in DMF at 0−25 °C was superior to catalysts **8b−c**, to afford the required isoindolinone **4a** in 98% ee with 5.3:1 dr (entry 4, Table 1) albeit in lower yields. Similarly, D-proline (*ent*-**8a**) also afforded product *ent*-**4a** in 97% ee with 5.1:1 dr (entry 7). However, 10−20 mol % of **8a** afforded **4a** in the range of 83−87% ee in 45−47% yields (entries 5−6). The lower yields of the expected product is presumably due to inefficient lactamization.

Gratifyingly, we observed a sharp enhancement in yield of **4a** to 92% (99% ee), when an equivalent of TFA was added after completion of the Mannich step (monitored by TLC), thereby ensuring the complete lactamization (entry 8, Table 1).

Next, we studied a variety of aromatic amines in the Mannich−lactamization sequence under optimized conditions (entry 8, Table 1). We found that aromatic amines having a different electronic environment furnished expected isoindolinones **4b−g** in 91−97% ee with high yields (Figure 2). However, aliphatic amines such as allyl, benzyl, and 2-phenethylamine afforded products either with poor enantioselectivities or as racemic mixture, thereby indicating the requirement of a less basic and less reactive amine as a coupling partner to afford products with higher enantioselectivities. In fact, aliphatic amines itself are known to be good catalysts for the organocatalytic Mannich reaction via an enamine intermediate,[12b] which accounts for the racemization of **4h−j** (Figure 2). As *p*-methoxyaniline afforded PMP protected isoindolinone **4a** in 99% ee that can be cleaved under oxidative conditions, we decided to carry out the substrate scope of our strategy using $PMPNH_2$ as the amine source.

Differently substituted *o*-formyl methylbenzoates **3** with a variety of steric and electronic environments were tested in the presence of the PMP amine and hydroxyacetone (Figure 3). To our delight, our methodology afforded the *syn*-selective isoindolinones in excellent enantioselectivities (up to >99% ee), thereby increasing the flexibility of the reaction for a wider range of synthetically useful substrates. However, *o*-formyl methylbenzoates having *o*-substitution to the aldehyde group afforded isoindolinones with a diminished level of enantioselectivity (see **4p** and **4r**), probably indicating that sterics play a

Table 1. Optimization of *syn*-Selective Mannich Lactamization[a]



entry	catalyst	solvent	temp	time	%yield[b]	dr[c]	ee (%)[d]
1	30 mol % **8a**	DMF	25 °C	72 h	57%	5.4:1	93%
2	30 mol % **8b**	DMF	25 °C	5 d	48%	1.7:1	30%
3	30 mol % **8c**	DMF	25 °C	5 d	41%	1.6:1	22%
4	30 mol % **8a**	DMF	0 - 25 °C	72 h	48%	5.3:1	98%
5	20 mol % **8a**	DMF	0 - 25 °C	96 h	45%	5.7:1	87%
6	10 mol % **8a**	DMF	0 - 25 °C	96 h	47%	5.9:1	83%
7	30 mol % *ent*-**8a**	DMF	0 - 25 °C	72 h	58%	5.1:1	–97%
8[e]	30 mol % **8a**	DMF	0 - 25 °C	48 h	92%	17.2:1	99%

[a]Reactions were performed in 0.3 mmol of **3a** and $PMPNH_2$ in the presence of 3 equiv of hydroxyacetone. [b]Yields are reported after purification. [c]dr were determined from ^1H NMR of crude reaction mixture. [d]ee's were determined by HPLC analysis. [e]20 equiv of hydroxyacetone and 1.0 equiv of TFA was used.

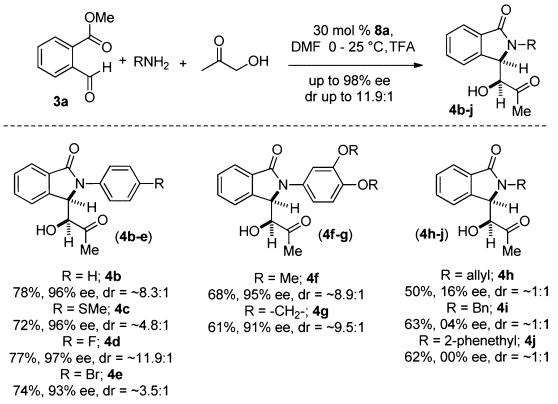


Figure 2. Effect of amines in the Mannich−lactamization sequence.

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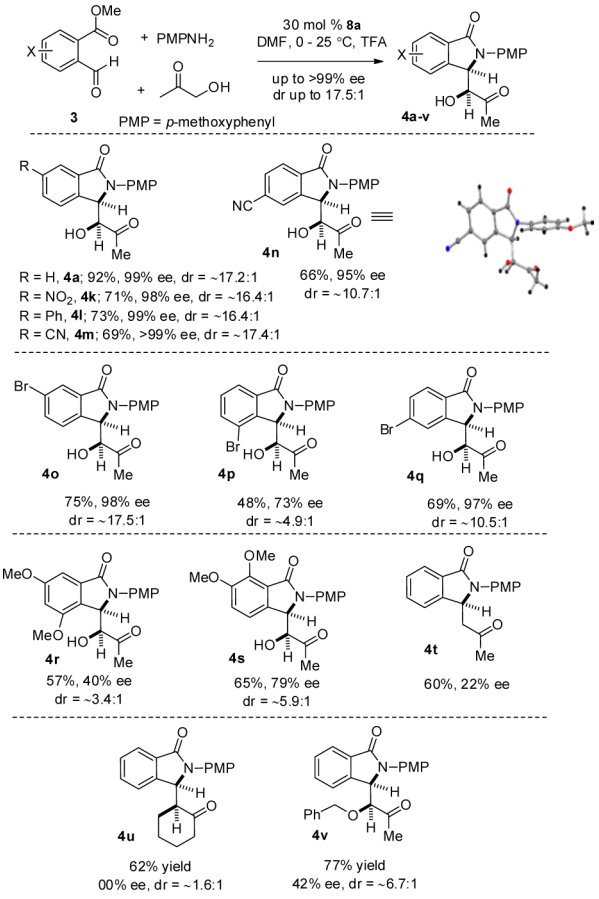


Figure 3. Substrate scope of *syn*-selective Mannich−lactamization.

crucial role in organizing the transition states of the Mannich−lactamization sequence. This might be due to the disruption of the L-proline-aldimine H-bond (see TS-I in Scheme 1). It was observed that acetone as the donor afforded isoindolinone **4t** with 22% ee, whereas cyclohexanone afforded product **4u** as a racemic mixture, thus clearly indicating the impact of hydroxyacetone on the enantioselectivity due to its H-bonding ability (see Figure 3). The poor enantioselectivity (42% ee) of **4v** yielded by benzyl protected hydroxyacetone as the donor is also consistent with this observation. The single crystal X-ray analysis of compound **4n** (CCDC 1040386) further supported the *syn*-selectivity of the product (Figure 3). Interestingly, a gram scale synthesis of compound **4a** was equivalently good to afford the product (48 h) in 89% isolated yield and 99% ee with dr 12:1 (see Supporting Information for details).

We then switched to carry out the *anti*-selective organocatalytic one-pot three-component Mannich−lactamization sequence using a primary amine as the catalyst (see Scheme 1). In this direction, we started the optimization using *o*-formyl methylbenzoate **3a**, $PMPNH_2$, and hydroxyacetone in DMF at 0−25 °C in the presence of 30 mol % of various primary *α*-amino acids. After exhaustive optimization (see Supporting Information for details), it was found that among all 1° amino acid catalysts used, L-tryptophan **9a** afforded *anti*-selective **5a** in up to 78% ee with 4.0:1 dr. Therefore, we selected L-tryptophan for further optimization and eventually found the *anti*-selective isoindolinone product in a maximum of 89% ee with 5.5:1 dr using DMF as the solvent at 0−25 °C in the presence of 1 equiv of TFA (Figure 4). A range of *anti*-selective isoindolinones **5a−i** were obtained in up to 89% ee with

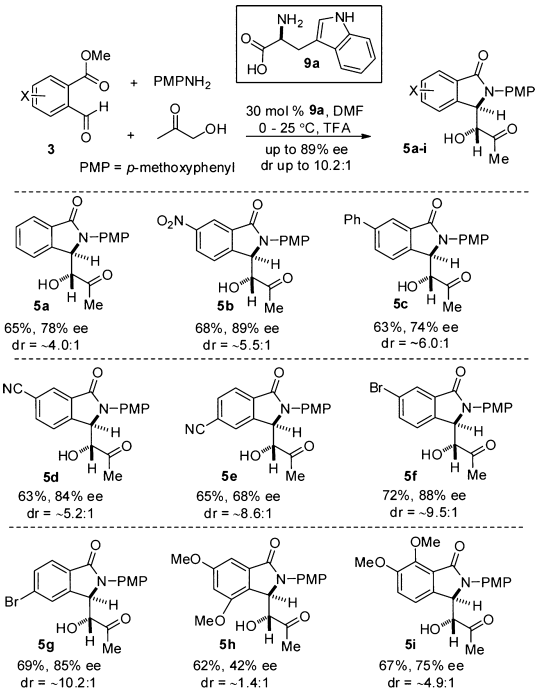
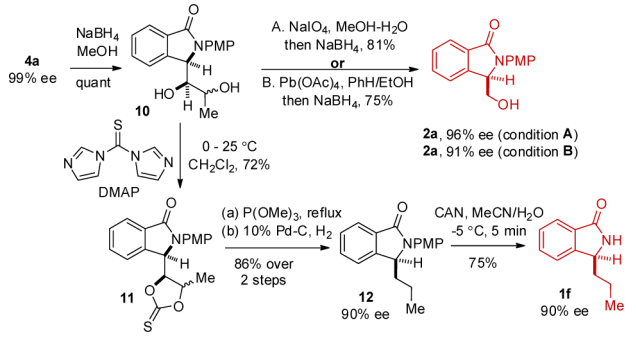


Figure 4. Substrate scope of *anti*-selective Mannich−lactamization.

10.2:1 dr. Similar to the L-proline catalyzed reaction (Figure 3), in this case as well, acetone afforded product **4t** in only 7% ee with a 62% yield.

To illustrate the synthetic utility of our organocatalytic protocol, the enantioenriched product **4a** was reduced using $NaBH_4$ to furnish **10**, which was then followed by periodate cleavage and further reduction to afford **2a** in 96% ee (Scheme 2). Alternatively, oxidative cleavage can be performed using

Scheme 2. Synthesis of 2a and 3-*n*-Propyl Isoindolinone 1f



$Pb(OAc)_4$ to afford **2a** in 91% ee (Scheme 2). In fact, enantiopure **2a** could serve as an advanced intermediate in the synthesis of **1a−f** (Figure 1). In another sequence, a diastereomeric mixture of diol **10** was treated with thiocarbonyl diimidazole in the presence of catalytic DMAP to afford **11** (Scheme 2). The latter on Corey−Winter olefination[17] followed by hydrogenation led to *n*-propylisoindolinone **12** in 90% ee. Finally, oxidative removal of the PMP group[18] of **12** in the presence of ceric (IV) ammonium nitrate (CAN) furnished pharmacologically important enantioenriched 3-*n*-propylisoindolinone **1f**[1,7c] in 75% yield (Scheme 2).

Overall, this is the first report on an organocatalytic (via enamine catalysis) enantioselective one-pot three component Mannich−lactamization sequence for the synthesis of optically

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pure isoindolinones. Important features of our strategy include the following: (1) the reactions do not require preformed imine equivalents; (2) the method is operationally simple and inexpensive; (3) it provides opportunity to access both enantiomers of *syn*-selective isoindolinones (up to 99% ee; dr = 17.5:1) using proline as the catalyst, whereas, *anti*-selective isoindolinones (up to 89% ee; dr = 10.2:1) can be accessed using L-tryptophan as the catalyst; (4) excellent enantioselectivity (99% ee) is observed even in the gram scale synthesis of **4a**. Future studies will aim to shed light on the development of other important one-pot sequences/cascades to build complex frameworks.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures and analytical data for all new compounds and CIF file of compound **4n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

‡V.B. and R.A.U. contributed equally.

Notes

The authors declare no competing financial interest.

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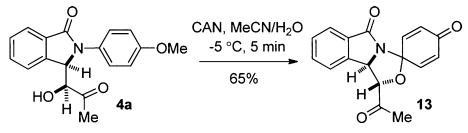
(18) Under similar conditions, **4a** provided *N*,*O*-ketal **13** in 65% yield.



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