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Organocatalysis

# Organocatalytic Enantioselective Mukaiyama–Mannich Reaction of Isatin-Derived Ketimines for the Synthesis of Oxindolyl-$\beta^{3,3}$-Amino Acid Esters

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*Dedicated to Professor Vinod K. Singh (IIT Kanpur) on the occasion of his 60th birthday*

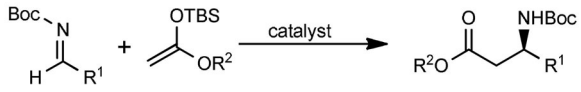
**Abstract:** Mukaiyama–Mannich reactions of ester enolate equivalents with aldimines have been elegantly used for the asymmetric synthesis of β-amino acids; nevertheless, the corresponding asymmetric reaction employing ketimines are unexplored. Herein, the first organocatalytic enantioselective Mukaiyama–Mannich reaction employing isatin-derived ketimines with unsubstituted silyl ketene acetals is disclosed towards the scalable synthesis of 2-oxoindolinyl-$\beta^{3,3}$-amino acid esters at room temperature with excellent enantioselectivities (*ee* >99.5%). Ultra-low catalyst loadings (as low as 250 ppm) could be used for the quantitative product formation with high enantiopurity. The synthetic utility of this protocol has been showcased in the short formal synthesis of pharmaceutically demanded (+)-AG-041R, a potent gastrin/CCK-B receptor antagonist.

## Introduction

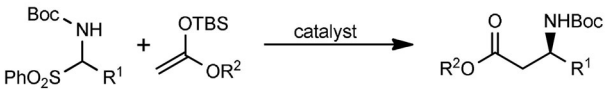
β-Amino acid derivatives have emerged as an essential building block en route to the synthesis of complex natural products,[1] pharmaceutical targets,[2] β-lactam antibiotics,[3] and peptidomimetics[4] with unique structural properties. Consequently, tremendous efforts have been devoted toward the catalytic asymmetric synthesis of β-amino acid motif.[5–6] Among the available strategies, the Mukaiyama–Mannich reaction of structurally distinct imines with silyl ketene acetals is especially attractive as it involves the straightforward construction of carbon–carbon bonds by employing two units of similar complexity in a catalytic asymmetric manner.[7] Recent efforts have focused on the advancement of the enantioselective Mukaiyama–Mannich reaction with unsubstituted silyl ketene acetals, which provides α-unsubstituted-β-amino acid derivatives (Scheme 1 a–b).[7a,g,i] Nevertheless, the corresponding catalytic asymmetric Mukaiyama–Mannich reaction with ketimines to afford a tetrasubstituted stereogenic center has remained elusive and a daunting unmet challenge (Scheme 1 c). Derived products of such a reaction, indolyl $\beta^{3,3}$-amino acid derivatives, belong to the core unit of several therapeutic agents (Figure 1).

***Previous work***

a) Addition of silyl ketene acetals to *N*-Boc-aldimines[7a,g]

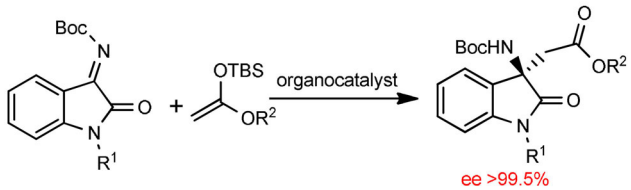



b) Addition of silyl ketene acetals to *N*-Boc-amino sulfones[7i]




***This work***

c) First catalytic enantioselective Mukaiyama-Mannich reaction employing isatin derived ketimines with unsubstituted silyl ketene acetals




# Ultra low catalyst loading (as low as 250 ppm)
# Gram-scale reaction and sustainable conditions

**Scheme 1.** Catalytic enantioselective Mannich-type reaction of unsubstituted silyl ketene acetals with imines.

The indole-based $\beta^{3,3}$-amino ester, bearing a C3-tetrasubstituted stereogenic center is a privileged structural motif in the development of new drug candidates, notably (+)-AG-041R, a clinically potent gastrin/cholecystokinin-B receptor antagonist

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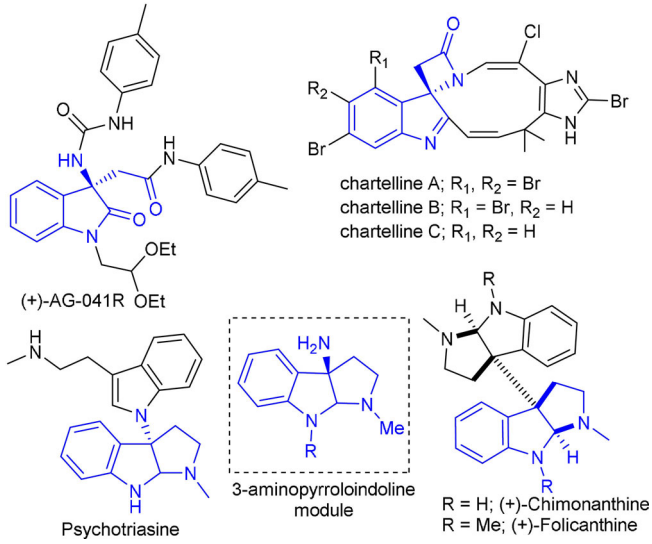



**Figure 1.** Representative natural products and clinical candidates containing 2-oxoindolinyl-$\beta^{3,3}$-amino acid ester and 3-aminopyrroloindoline module.

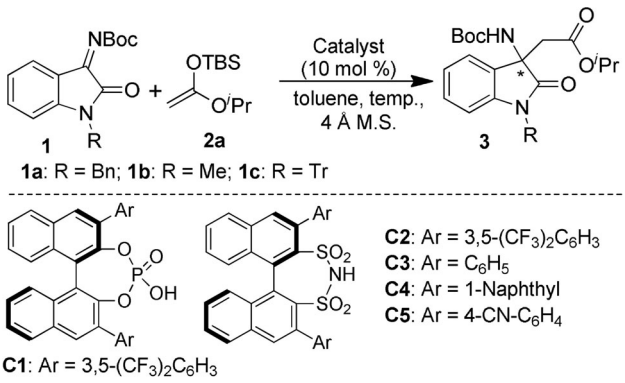
(Figure 1).[8] Indeed, the framework is a very promising precursor for the facile construction of 3-aminopyrroloindoline towards the total synthesis of complex pyrroloindoline alkaloids (Figure 1).[9] In accord with its medicinal relevancy, few fascinating indirect approaches have been well documented towards the catalytic asymmetric synthesis of 2-oxoindolinyl-$\beta^{3,3}$-amino esters.[8b,9b–c,10] Surprisingly, only two direct, elegant catalytic enantioselective approaches have been reported by Shibata et al. and Ohshima et al., involving decarboxylative Mannich-type addition of malonic acid half-thioesters (MAHT) to isatin-derived ketimines, achieving enantioselectivities of up to 86% *ee*.[11] Thus, finding an unprecedented reaction pathway to render the 2-oxoindolinyl-$\beta^{3,3}$-amino esters with excellent enantioselectivities under sustainable reaction conditions would be significantly rewarding.

We speculated that the direct addition of ester enolate equivalents to the isatin-derived ketimines (Mukaiyama–Mannich variant) could be a robust route to deliver the medicinally demanded 2-oxoindolinyl-$\beta^{3,3}$-amino esters (Scheme 1c). However, the sluggish reactivity of the ketimine system with concomitant creation of an enantiofacial tetrasubstituted stereocenter poses a formidable challenge. We further anticipated that the nature of the ketimines should also influence the outcome of the reaction. Indeed, we sought to develop scalable approach in an organocatalytic fashion. Strikingly, chiral Brønsted acids, typically chiral phosphoric acids (CPAs), have recently blossomed as efficient catalysts for asymmetric Mannich-type reactions, replacing transition-metal catalysts.[12] Herein, we report the first disulfonimide-catalyzed enantioselective Mukaiyama–Mannich reaction of isatin-derived ketimines with unsubstituted silyl ketene acetals, achieving the scalable synthesis of 2-oxoindolinyl-$\beta^{3,3}$-amino acid esters (*ee* >99.5%) at room temperature.

## Results and Discussion

To probe the immediate feasibility of our hypothesis, a model reaction of *N*-benzyl protected isatin-derived *N*-Boc ketimine **1a** (Table 1, entry 1) and the silyl ketene acetal **2a** was conducted in the presence of 10 mol% *rac*-BINOL-derived phosphoric acid (BNP acid) in toluene at room temperature. Gratifyingly, the strategy worked efficiently, affording the desired racemic 2-oxoindolinyl-$\beta^{3,3}$-amino ester **3a** (Table 1, entry 1) in good yield (86%). Immediately, we employed a chiral surrogate **C1** to furnish enantioselectivity (Table 1, entry 2). Disappointingly, the desired $\beta^{3,3}$-amino ester was obtained in moderate yield with negligible asymmetric induction (68% yield, 13% *ee*). Meanwhile, before commencing the routine investigation with the toolbox of auxiliary chiral phosphoric acids (CPAs), we attempted to recruit chiral disulfonimides (DSIs) in the model reaction as the chiral disulfonimide conjugated silylium-based "*asymmetric counter anion-directed catalysis*" (ACDC) has recently been proven to be an efficient chiral pre-catalyst in Mukaiyama-type reactions.[13] Pioneering progress in this particular field has been done by the List group utilizing chiral disulfonimides as stereoinducing counter anions to enable asymmetric

**Table 1.** Optimization of the reaction conditions.[a]




| No. | 1 | Catalyst | Time | 3 | Yield [%] | *ee* [%][b] |
|---|---|---|---|---|---|---|
| 1 | **1a** | *rac*-BNP | 48 h | **3a** | 86 | – |
| 2 | **1a** | **C1** | 48 h | **3a** | 68 | 13 |
| 3 | **1a** | **C2** | 3 h | **3a** | 95 | 56 |
| 4[c] | **1a** | **C2** | 10 h | **3a** | 63 | 17 |
| 5 | **1a** | **C3** | 5.5 h | **3a** | 86 | 58 |
| 6 | **1a** | **C4** | 32 h | **3a** | 74 | 04 |
| 7 | **1a** | **C5** | 18 h | **3a** | 72 | 07 |
| 8 | **1b** | **C1** | 34 h | **3b** | 79 | 55 |
| 9 | **1b** | **C2** | 4 h | **3b** | 71 | 28 |
| 10 | **1c** | **C1** | 96 h | **3c** | 32 | 02 |
| 11 | **1c** | **C2** | <5 min | **3c** | 95 | >99.5 |
| 12 | **1c** | **C3** | 30 h | **3c** | 70 | 82 |
| 13[d,e] | **1c** | **C2** | 20 min | **3c** | 95 | 99 |
| 14[d,f] | **1c** | **C2** | 1 h | **3c** | 94 | 99 |

[a] Reactions were carried out with 0.1 mmol of imine and 0.3 mmol of silyl ketene acetal in 1.0 mL of toluene at 25 °C. [b] Determined by HPLC with a chiral stationary phase. [c] The reaction was carried at 0 °C. [d] Reactions were carried out with 0.25 mmol of imine **1c** and 0.75 mmol of silyl ketene acetal **2a** in 2.5 mL of toluene (entry 13) and 1.25 mL of toluene (entry 14) at 25 °C. [e] Using 0.5 mol% of catalyst **C2**. [f] Using 0.25 mol% of catalyst **C2**.

transformations. To implement our assumption, the disulfonimide **C2** has been employed in the model reaction (Table 1, entry 3). To our delight, the desired product **3a** was obtained in almost quantitative yield with a significant increase in enantioselectivity (95% yield, 56% *ee*). Encouraged by this proof-of-principle result, a systematic exploration of different reaction conditions was conducted. The subsequent solvent screening revealed toluene to be the optimal choice (see the Supporting Information). The rate of the uncatalyzed racemic reaction was also found to be moderate (≈25% yield in 48 h), indicating the influence of the background reaction in diminishing the enantioselectivity through the catalytic pathway. To prevent this situation, we turned our attention to decreasing the reaction temperature to 0 °C; although the chemical yield dropped to 63% with poor enantioselectivity (17% *ee*, Table 1, entry 4). Screening of other disulfonimides (Table 1, entries 5–7) showed that the use of **C3** was encouraging as the selectivity was elevated to 58%. At this juncture, two principle parameters could be taken into account to improve the enantioselectivity: a) steric and electronic remodulation of the catalyst and b) restructuring the ketimine substrate by installing other protecting groups.

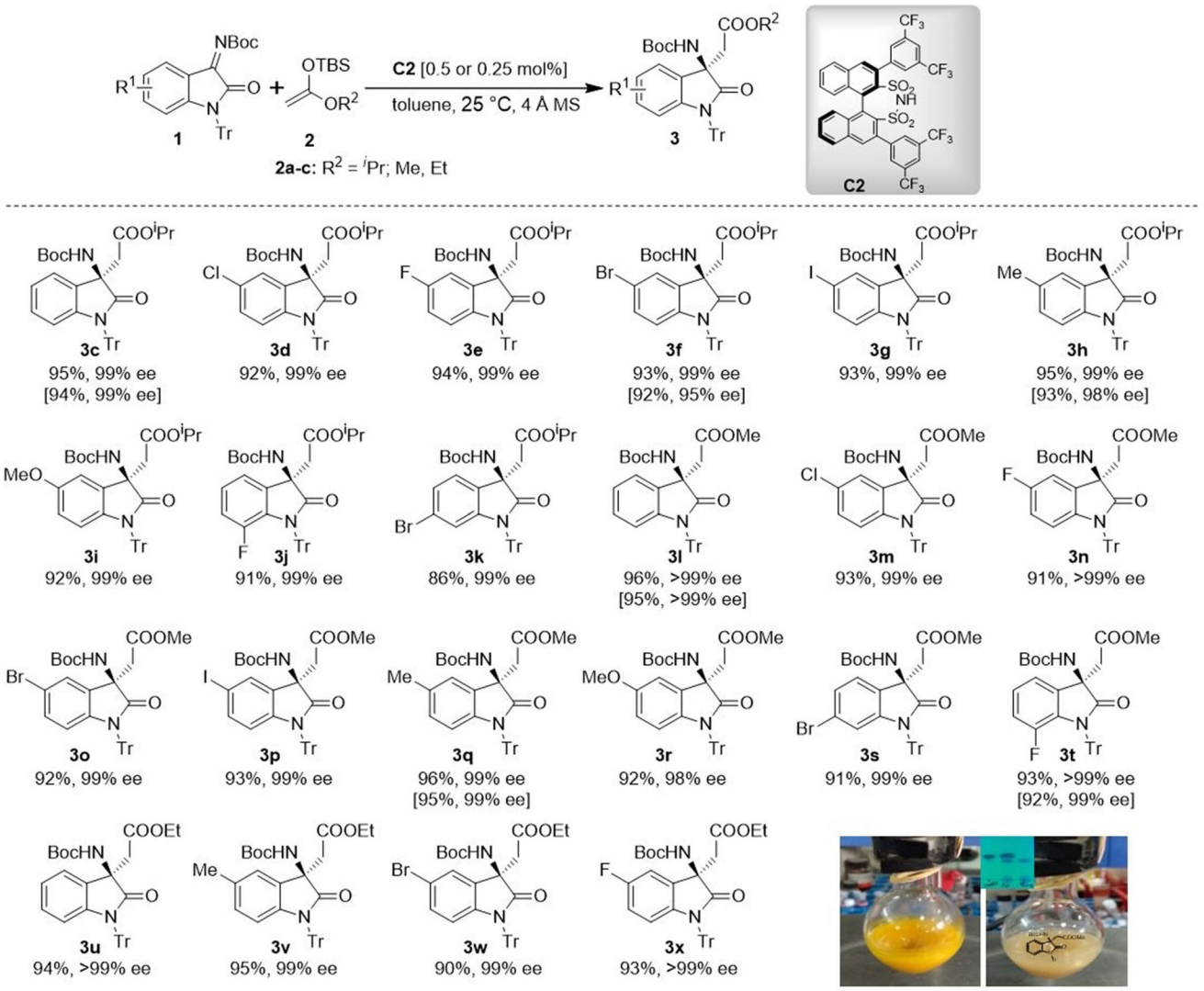
We envisioned that reconstructing the ketimine system could be the superior choice as the catalyst (**C2**) is readily available in addition to its potency in ACDC catalysis. Pleasingly, our speculation was in harmony with the following experimental results. When ketimine **1c**, containing a triphenylmethyl (trityl = Tr) group, was employed as the substrate, the desired product **3c** was obtained in excellent yield with outstanding enantioselectivity (95% yield, >99.5% *ee*) within 5 min at room temperature (Table 1, entry 11). Catalyst **C2** was deemed to be the optimal choice owing to its enhanced reactivity compared with catalysts **C1** and **C3** (Table 1, entries 10 and 12). The disulfonimide catalyst **C2** was also found to be superior to catalyst **C1** when applying the ketimine **1a** (Table 1, entries 2 and 3), but the catalyst **C1** was suited better for the ketamine **1b** in terms of enantioselectivity although the reaction was faster with catalyst **C2** (Table 1, entries 8 and 9). The concomitant steric effect of the *N*-trityl functionality was a clear advantage for achieving high enantioselectivity. The results also led us to consider the possibility of additional noncovalent interactions between the catalyst (**C2**) and the trityl group of the imine substrate during the reaction.

Although organocatalysis has already been recognized as the third pillar in modern asymmetric catalysis toward the total synthesis of natural and pharmaceutical products, one criticism is that organocatalytic processes commonly require a large catalyst loading in comparison with the metal-catalyzed pathways to furnish the reactions useful. It is noteworthy that very few enantioselective organocatalytic C–C bond-forming reactions have been reported as using ultra-low catalyst loadings (<0.5 mol%) or even with ppm and sub-ppm levels of loading.[14] Fortunately, we were able to determine that only 0.25 mol% catalyst loading was sufficient to afford the desired 2-oxoindolinyl-$\beta^{3,3}$-amino ester **3c** in excellent yield while maintaining the high enantioselectivity (Table 1, entries 13–14, for details please see the Supporting Information).

Under the optimized conditions, the scope of the enantioselective Mukaiyama–Mannich reaction of the *N*-trityl-protected isatin-derived *N*-Boc ketimines catalyzed by disulfonimide **C2** was next investigated (Scheme 2). Ketimines possessing both electron-rich and electron-withdrawing substituents at the 5, 6, and 7 positions of the indolinone ring were examined in this newly developed protocol. The effect of various alkoxy substituents on the silyl ketene acetals was also considered. Remarkably, all the reactions proceeded smoothly and the desired 2-oxoindolinyl-$\beta^{3,3}$-amino esters **3c**–**3x** were obtained in excellent yields with outstanding enantiopurities. In general, all the reactions were very clean, energy-efficient, and could easily be followed by visual color check of the reaction mixture. Notably, with a *tert*-butyl substituent on the silyl ketene acetal, the reaction was not successful at all because of the steric hindrance. It is also worth noting that the tetrasubstituted silyl ketene acetal derived from methyl *iso*-butyrate does not respond to the reaction with the ketamine **1c** under the optimized conditions or even at higher temperature (up to 80 °C).

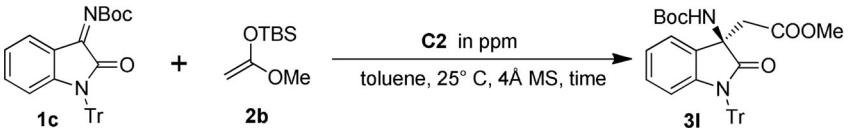
To further demonstrate the practicability and robustness of the developed protocol, a gram-scale synthesis was conducted with 2.0 g (4.124 mmol) of isatin-derived ketimine **1c** and commercially available silyl ketene acetal **2b** in the presence of 1000 ppm (0.10 mol%) of disulfonimide catalyst **C2** (Table 2, entry 1). We are pleased to report that the reaction proceeded smoothly and led to the final product **3l** in excellent yield with outstanding enantioselectivity (96% yield, >99% *ee*). It is noteworthy that further reduction of the catalyst loading to 250 ppm (0.025 mol%) could still successfully catalyze the Mukaiyama–Mannich reaction of ketimine **1c** (500 mg batch, 1.031 mmol) in full conversion with good enantioselection albeit with longer reaction time (5 days; Table 2, entries 2–3). To the best of our knowledge, this is the lowest catalyst loading achieved to date for the Mukaiyama–Mannich reaction with excellent enantioselectivity. This chiral disulfonimide catalyzed Mukaiyama acetate Mannich reaction followed the analogous ACDC reaction mechanism reported in the literature.[13b]

To demonstrate the utility of the newly developed enantioselective Mukaiyama–Mannich protocol, we pursued the formal synthesis of (+)-AG-041R, a potential cholecystokinin-B/gastrin receptor antagonist (Scheme 3). Starting from the enantiopure building block **3l**, the single-step deprotection of both the Boc and trityl groups by the employment of TFA in dichloromethane afforded the *N*-unprotected 2-oxoindolinyl-$\beta^{3,3}$-amino ester **7**. The compound **7** could be converted into (+)-AG-041R by following the reported literature procedure, thereby accomplishing the formal synthesis of (+)-AG-041R.[10] The obtained 2-oxoindolinyl-$\beta^{3,3}$-amino ester **7** could also serve as a precursor for the synthesis of spiro-β-lactam **11**, a skeleton of the natural product chartellines. The absolute configuration of the compound **3l** was determined as the (*R*)-configuration by correlating the sign of the specific rotation of **7** with the literature data (for details see the Supporting Information).[10] The absolute configuration of the other compounds was tentatively assigned by analogy.




**Scheme 2.** Substrate scope and visual check of the reaction. The data in parenthesis refers to the reaction with 0.25 mol% catalyst loading. Images of the crude reaction mixtures with thin-layer chromatography (TLC eluent: ethyl acetate/hexane = 1:4) on a 2 g scale with 1000 ppm catalyst loading (left image: at the beginning of the reaction, right image: upon full conversion after 4.5 h).

**Table 2.** The practicability of the developed protocol.

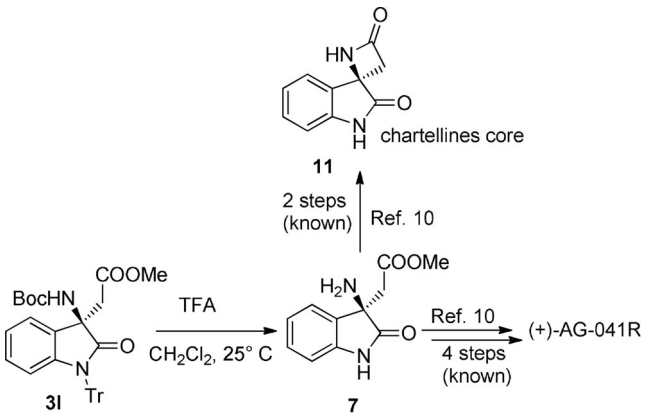



| Entry | **C2** loading [ppm] | Weight of **1c** (mmol)/mmol of **2b**/concentration | Time | Yield [%] | *ee* [%][a] |
|---|---|---|---|---|---|
| 1 | 1000 | 2.0 g (4.124 mmol)/10.31 mmol/1 M | 4.5 h | 96 | >99 |
| 2 | 500 | 1.0 g (2.062 mmol)/4.124 mmol/2 M | 16 h | 92 | 99 |
| 3[b] | 250 | 0.5 g (1.031 mmol)/2.062 mmol/4 M | 5 days | 88 | 90 (>99.5)[c] |

[a] Determined by HPLC with a chiral stationary phase. [b] The reaction was conducted at 40 °C. [c] After a single recrystallization.

## Conclusion

We have explored the first highly enantioselective facile Mukaiyama–Mannich reaction employing isatin-derived ketimines with unsubstituted silyl ketene acetals by using a commercially available chiral disulfonimide organocatalyst. Notably, the products directly achieved through such a reaction are medicinally useful indolyl-$\beta^{3,3}$-amino acid derivatives. Ultra-low catalyst loading (as low as 250 ppm), gram-scale synthesis, short reaction times, and the creation of a tetrasubstituted stereo-




**Scheme 3.** Synthetic utility towards the formal synthesis of (+)-AG-041R.

center are the unique features of the present protocol. The synthetic utility of the newly developed methodology has been demonstrated through the short formal synthesis of pharmaceutically demanding (+)-AG-041R.

## Experimental Section

### General procedure for the catalytic asymmetric Mukaiyama–Mannich reaction of isatin-derived ketimines with silyl ketene acetals (3 c–3 x)

A septum-capped oven-dried vial (cooled in argon flow) containing a Teflon-coated magnetic stirring bar was charged with the corresponding ketimine (0.2 mmol, 1.0 equiv) and molecular sieves (50 mg, 4 Å MS). Disulfonimide catalyst **C2** (0.5/0.25 mol%; from freshly prepared catalyst stock solution in dry toluene) was loaded into the reaction vial via a syringe and dry toluene was further added to adjust the reaction concentration to 0.2 M (with respect to ketimine). The corresponding silyl ketene acetal (0.6 mmol, 2.0 equiv) was then added to the reaction mixture via a microliter syringe and the resulting solution was left to stir at room temperature for 15–105 min under argon atmosphere. The progress of the reaction course was monitored by TLC. Upon completion of the reaction, the reaction mixture was directly applied to silica gel, and purified by flash column chromatography using hexanes/EtOAc as eluent. The desired products were obtained as viscous liquids or colorless solids.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** asymmetric synthesis · disulfonimide catalysts · ketimines · low catalyst loading · Mukaiyama–Mannich reaction

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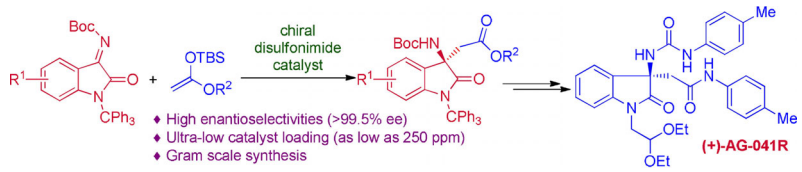


**Low loading**: Ultra-low chiral disulfonimide catalyst loading (as low as 250 ppm) is used in the asymmetric Mukaiyama–Mannich reaction of isatin-derived ketimines with unsubstituted silyl ketene acetals. The reaction has been developed under sustainable reaction condition for the synthesis of medicinally useful indolyl-$\beta^{3,3}$-amino acid esters with outstanding enantioselectivity (*ee* $>$ 99.5 %).

**Organocatalysis**

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**Organocatalytic Enantioselective Mukaiyama–Mannich Reaction of Isatin-Derived Ketimines for the Synthesis of Oxindolyl-$\beta^{3,3}$-Amino Acid Esters**