Asymmetric Synthesis

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# Direct Asymmetric Vinylogous Aldol Reaction of Allyl Ketones with Isatins: Divergent Synthesis of 3-Hydroxy-2-Oxindole Derivatives**

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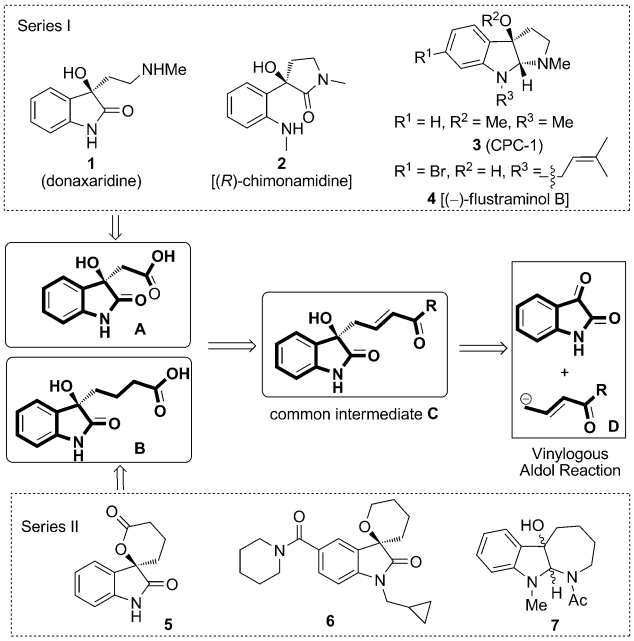
3-Hydroxy-2-oxindole derivatives, which contain a quaternary stereogenic center at the 3-position, are a family of structurally diverse natural or nonnatural products with interesting biological activities.[1] The asymmetric synthesis of 3-hydroxy-2-oxindole derivatives, such as donaxaridine (**1**),[1b–c] (*R*)-chimonamidine (**2**),[1d] CPC-1 (**3**),[1e] and (−)-flustraminol B (**4**)[1f] (Scheme 1, series I), has recently been intensely pursued, as these compounds exhibit a broad spectrum of biological activities and are promising potential drugs. Previously established methods[2] for the preparation of these derivatives mainly focused on the asymmetric hydroxylation of 3-substituted 2-oxindoles[3] and the nucleophilic addition to isatins,[4] employing compound **A** as a viable synthon (Scheme 1). The synthesis of related 3-hydroxy-2-oxindole derivatives (**5**–**7**) of series II has attracted considerable interest for a long time because of their fascinating architectures and potential biological activities. For example, spirolactone **5** has shown potential cytotoxic activity.[1g–i] Spiroether **6** was reported to be a CB2 agonist and is thus a potential drug candidate for reducing neuropathic and bone pains, and for treating a host of diseases, including osteoarthritis, atherosclerosis, osteoporosis, and cancers.[1g] Hexahydrozaepino[2,3-*b*]indole **7**, which bears a unique 5,7-bicyclic framework, can be used as a tranquilizer for mammals and birds.[1h–i] However, to the best of our knowledge, no asymmetric protocol that affords this class of compounds has been presented to date.

Compared with the traditional "single target" approach, the design of a common intermediate is the key in the total synthesis of different products through a divergent synthesis strategy, which has enabled the formation of a variety of target molecules without compromising efficiency.[5] As part of our ongoing research efforts toward the development and utilization of synthetic tools for the formation of quaternary stereogenic centers,[3b,6] we were interested in designing a novel organocatalytic asymmetric reaction to achieve the divergent synthesis of 3-hydroxy-2-oxindole derivatives, including those in series I and II.




***Scheme 1.*** Representative examples of biologically active 3-hydroxy-2-oxindole derivatives and the design of a vinylogous aldol reaction from retrosynthetic analysis.

Retrosynthetic analyses suggested that the synthetic route to intermediates **A** and **B** was reasonable. We deduced that compound **C** could be assembled as the common intermediate for the divergent synthesis of 3-hydroxy-2-oxindole derivatives of series I and II. We therefore focused on the asymmetric vinylogous aldol reaction of the carbonyl-activated allyl nucleophile **D** with isatin (Scheme 1).

The Mukaiyama-type aldol reaction of silyl dienol ethers is the favored protocol to furnish vinylogous aldol adducts, but can suffer from low atom economy and efficiency.[7] In this context, a direct asymmetric approach for these reactions would be highly valuable. In recent years, cyclic 2-furanone derivatives have been used as versatile nucleophiles in direct vinylogous aldol reactions, as shown by the research groups of Zhang,[8a] Terada,[8b] Feng,[8c] and Lu.[8d] However, because of the low electron density at the γ position of the generated dienolate,[9] the direct vinylogous aldol reaction of a simple

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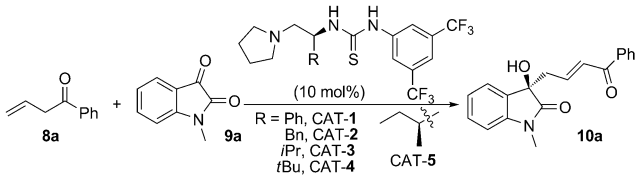
acyclic nucleophile is not favored, and the use of a bulky modifier at the α position is necessary to discriminate the reactive enolate site.[10] In 2010, Shibasaki and co-workers disclosed the first direct asymmetric vinylogous aldol reaction of acyclic allyl cyanide to ketones, catalyzed by a soft Lewis acid/hard Brønsted base, with excellent enantioselectivities for the quaternary center and (*Z*) selectivity for the alkene moiety.[11] We envisioned that allyl ketones, which are similar to allyl cyanide, but are more readily prepared and modified, could be used as the precursors of **D** to achieve the desired direct vinylogous aldol reaction. It is worth noting that, over the past few years, allyl ketones have been widely employed as valuable intermediates in organic synthesis,[12] but that there is no reported example on their applications in catalytic asymmetric reactions. Herein, we report a highly enantio- and *E*-selective direct vinylogous aldol reaction of allyl ketones with isatins, and the divergent synthesis of various related 3-hydroxy-2-oxindole derivatives with important biological activities.

At the onset of our studies to probe the feasibility of the proposed strategy, allyl phenyl ketone **8a** was reacted with *N*-methyl isatin **9a** in the presence of $Et_3N$ in toluene at 25 °C. The reaction worked smoothly, and the proposed vinylogous aldol product **10a**, which bears an *E*-configured olefin, was obtained as the sole adduct (Table 1, entry 1). Encouraged by our preliminary results, we examined the enantioselective variant in the presence of various bifunctional tertiary amine/thiourea catalysts (CAT-**1**–CAT-**5**), which can be conveniently prepared from l-amino acids and are effective in a variety of asymmetric reactions, as reported by us and other groups.[6c,8d,13] Our screening of reaction conditions revealed

***Table 1:*** Screening studies.[a]




| Entry | Catalyst | Solvent | *T* [°C] | *t* [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | $Et_3N$ | toluene | 25 | 12 | 88[d] | n.a. |
| 2 | CAT-**1** | toluene | 25 | 3 | 89 | 57 |
| 3 | CAT-**2** | toluene | 25 | 3 | 91 | 85 |
| 4 | CAT-**3** | toluene | 25 | 3 | 86 | 88 |
| 5 | CAT-**4** | toluene | 25 | 3 | 82 | 79 |
| 6 | CAT-**5** | toluene | 25 | 5 | 83 | 85 |
| 7 | CAT-**5** | hexane | 25 | 1 | 99 | 85 |
| 8 | CAT-**5** | $Et_2O$ | 25 | 0.1 | 99 | 88 |
| 9 | CAT-**5** | THF | 25 | 0.2 | 99 | 87 |
| 10 | CAT-**5** | $Et_2O$ | 0 | 0.5 | 99 | 90 |
| 11 | CAT-**5** | $Et_2O$ | −20 | 2 | 99 | 93 |
| 12 | CAT-**5** | $Et_2O$ | −40 | 12 | 84 | 93 |
| 13[e] | CAT-**5** | $Et_2O$ | −20 | 4 | 93 | 92 |
| 14[f] | CAT-**5** | $Et_2O$ | −20 | 12 | 96 | 92 |

[a] Reactions were performed with **8a** (0.075 mmol), **9a** (0.05 mmol), and catalyst (0.005 mmol) in 0.5 mL solvent. [b] Yield of isolated product (*E*/*Z* > 99:1, determined by $^1$H NMR analysis of the crude reaction mixture). [c] Determined by HPLC. [d] *E*/*Z* = 49:1. [e] 5 mol% catalyst was used. [f] 1 mol% catalyst was used. n.a. = not applicable.

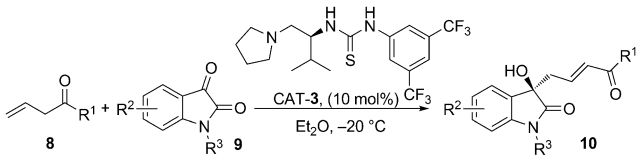
that all reactions proceeded well within 3–5 h in toluene at 25 °C in the presence of 10 mol% of catalyst, and afforded the chiral vinylogous aldol *E*-adduct **10a** in high yields with moderate to good enantioselectivities (Table 1, entries 2–6). The best selectivity was achieved with catalyst CAT-**3**, which was derived from L-valine (Table 1, entry 4, 88% *ee*). To further optimize the reaction conditions, the reaction was performed in different solvents with CAT-**3** as the catalyst (Table 1, entries 7–9),[14] and the use of $Et_2O$ resulted in the highest enantioselectivity with enhanced reaction rates (Table 1, entry 8). A variation of the reaction temperature showed that the enantioselectivity improved only slightly at a lower temperature (Table 1, entries 10–12), and that the best results were achieved at −20 °C (entry 11). Moreover, the catalyst loading could be reduced to 1.0 mol%, and after 12 h, **10a** was isolated with an excellent yield and without compromising the enantiomeric excess (Table 1, entry 14).

With the optimal conditions established, we investigated the scope of the reaction (Table 2). First, we attempted the direct vinylogous aldol reaction of a variety of allyl ketones with *N*-methyl isatins in the presence of 10 mol% of CAT-**3** in $Et_2O$ at −20 °C (Table 2, entries 1–14). The corresponding products **10a**–**n** were obtained in 57–98% yields with 88–96% *ee* and *E*/*Z* ratios of 19:1 to more than 99:1. Notably, the vinylogous aldol product **10g**, derived from allyl *tert*-butyl ketone, was obtained with 89% *ee* (entry 8). Subsequently, we examined the vinylogous aldol reaction of allyl ketones with *N*-benzyl isatins, and the desired products **10o–q** were obtained with excellent yields, enantio- and diastereoselectivities (entries 15–17). We also found that simple filtration was enough to isolate these *E*-configured adducts with an ee value of 98% to more than 99%.[15] Furthermore, various other allyl ketones **8** and commercially available isatins **9** were reacted under the established conditions to give the vinylogous aldol adducts (**10r–z**) with yields of 81–92%, enantioselectivities of 90–96%, and *E*/*Z* ratios of 13:1 to more than 99:1 (entries 18–26). These results demonstrated that the best reaction outcome was achieved with unprotected isatins.[2,16] Most importantly, we carried out the reactions toward **10d** and **10x** on a gram scale, and found that the reactivity and enantioselectivity remained excellent, and the corresponding adducts were obtained after a simple filtration. Since all adducts precipitate from their reaction mixture, this methodology is suitable for large-scale production.

Density-functional theory (DFT) was employed to elucidate the observed enantioselectivity and preference for γ over α alkylation.[17] We suspected that the pendent pyrrole moiety of bifunctional catalyst CAT-**3** first deprotonates allyl ketone **8a** at the γ position, and that the protonated catalyst then brings the resulting enolate and the isatin electrophile together to form the hydrogen-bonded complex for the crucial C–C bond formation. We found that binding of a) the electrophile to the two N–H bonds of the thiourea moiety and b) the enolate to the pyrrolium arm gives the transition state (TS) with the lowest Gibbs free energy (*Si*-*R*-TS), which leads to the γ-alkylated *R* product, consistent with our experimental observation (see the Supporting Information for all structures). Upon a close analysis of the Mayer bond order,[18] this preference of the thiourea to be H-bonded

***Table 2:*** Direct asymmetric vinylogous aldol reaction of allyl ketones **8** to various isatins **9**.[a]




| Entry | $R^1/R^2/R^3$ (**10**) | *t* [h] | Yield [%][b] | *ee* [%][c] | *E*/*Z*[d] |
|---|---|---|---|---|---|
| 1 | Ph/H/Me (**10a**) | 4 | 86 | 92 | 34:1 |
| 2 | 4-ClPh/H/Me (**10b**) | 5 | 93 | 96 | >99:1 |
| 3 | 4-BrPh/H/Me (**10c**) | 48 | 87 | 91 | 38:1 |
| 4[l] | 4-MeOPh/H/Me (**10d**) | 24 | 85 | 96[e,f] | >99:1[e,f] |
| 5 | 3-MeOPh/H/Me (**10e**) | 24 | 82 | 94 | >99:1 |
| 6 | 2-naphthyl/H/Me (**10f**) | 6 | 98 | 95 | 28:1 |
| 7 | 2-thienyl/H/Me (**10g**) | 48 | 80 | 93 | >99:1 |
| 8 | *t*Bu/H/Me (**10h**) | 96 | 57 | 89 | >99:1 |
| 9 | Ph/4-Br/Me (**10i**) | 48 | 89 | 96 | 19:1 |
| 10 | Ph/5-Me/Me (**10j**) | 5 | 89 | 91 | 29:1 |
| 11 | Ph/5-Br/Me (**10k**) | 2 | 92 | 90 | 24:1 |
| 12 | Ph/6-Br/Me (**10l**) | 5 | 90 | 92 | 32:1 |
| 13 | Ph/7-Cl/Me (**10m**) | 5 | 86 | 88 | 49:1 |
| 14 | 2-naphthyl/5-Me/Me (**10n**) | 2 | 93 | 95 | 42:1 |
| 15 | Ph/H/Bn (**10o**) | 3 | 93 | 98[e,g] | >99:1[e,g] |
| 16 | 4-MeOPh/H/Bn (**10p**) | 24 | 95 | 99[e,h] | >99:1[e,h] |
| 17 | Ph/5-Me/Bn (**10q**) | 8 | 92 | >99[e,i] | >99:1[e,i] |
| 18[j] | Ph/H/H (**10r**) | 24 | 82 | 96 | 42:1 |
| 19 | Ph/4-Br/H (**10s**) | 24 | 85 | 95 | 13:1 |
| 20[j] | Ph/5-Me/H (**10t**) | 30 | 90 | 93 | >99:1 |
| 21 | Ph/5-Cl/H (**10u**) | 30 | 92 | 92 | >99:1 |
| 22 | Ph/6-Br/H (**10v**) | 24 | 91 | 92 | 48:1 |
| 23 | 4-MeOPh/H/H (**10w**) | 24 | 85 | 90 | 13:1 |
| 24[m] | 4-MeOPh/5-Me/H (**10x**) | 24 | 87 | 96[e,k] | >99:1[e,k] |
| 25 | 3-MeOPh/6-Br/H (**10y**) | 30 | 81 | 94 | >99:1 |
| 26 | 3-MeOPh/7-Cl/H (**10z**) | 30 | 83 | 92 | >99:1 |

[a] Reactions were performed with **8** (0.15 mmol), **9** (0.1 mmol), and CAT-**3** (0.01 mmol) in 1.0 mL $Et_2O$. [b] Yields of isolated products based on **9**. [c] The *ee* values were determined by HPLC on a chiral stationary phase. [d] The *E*/*Z* ratios were determined by $^1H$ NMR analysis. [e] The *ee* value and *E*/*Z* ratio were obtained after single recrystallization. [f] Initial data: *ee* = 90%, *E*/*Z* = 33:1. [g] Initial data: *ee* = 93%, *E*/*Z* = 28:1. [h] Initial data: *ee* = 90%, *E*/*Z* = 19:1. [i] Initial data: *ee* = 95%, *E*/*Z* > 99:1. [j] Ethyl acetate was used as solvent. [k] Initial data: *ee* = 92%, *E*/*Z* > 99:1. [l] 6 mmol scale, 1.75 g of **10d** was obtained with 87% yield in 90% *ee* by simple filtration using $Et_2O$ as eluent. [m] 6 mmol scale, 1.647 g of **10x** was obtained in 81% yield with 92% *ee* by simple filtration using $Et_2O$ as eluent.

with the electrophile is likely a result of N–H···O and two additional nonclassical C–H···O hydrogen-bonding interactions between the acidic N–H and C–H bonds and the carbonyl groups of isatin (Figure 1). The bond order of the C–C bond that is formed is 0.434.

To establish a rationale for the preferred formation of the γ-C–C bond in the *Si*-*R* orientation, we compared the local electronic properties of the optimized TS structure. Interestingly, a significant secondary interaction was observed between C3 of the nucleophile and the carbonyl O of isatin in *Si*-*R*-TS (with a Mayer bond order of 0.047, Figure 2). The high stereochemical discrimination can be further elaborated by constructing a simple orbital-correlation diagram to illustrate the symmetries of molecular-orbital interactions

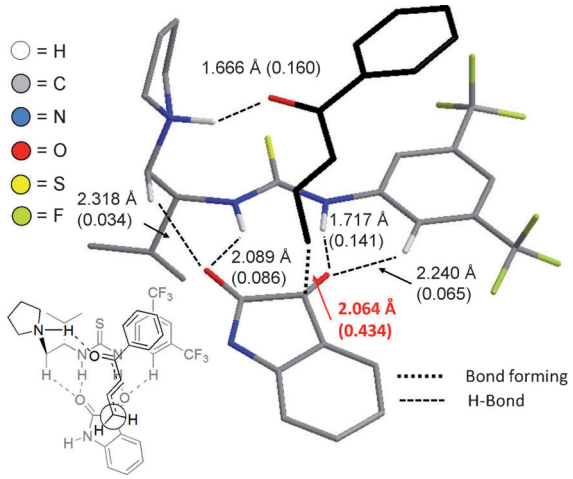



***Figure 1.*** Transition-state structure featuring the possible binding orientation of isatin to catalyst CAT-**3** and γ alkylation by the allylic nucleophile to lead to observed *R*-γ-product. Non-H-bonded hydrogen atoms were omitted for clarity. Mayer bond orders of H-bonds (>0.03) are given in parentheses.

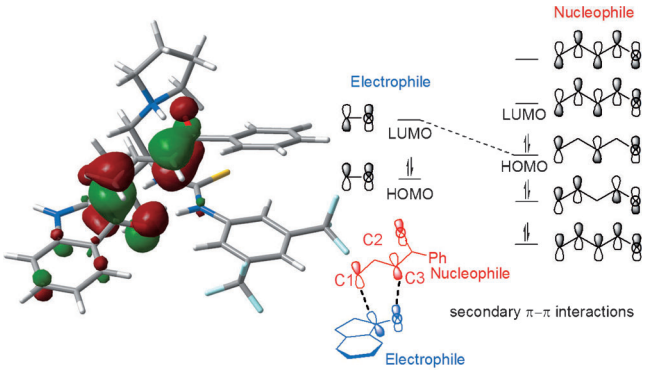
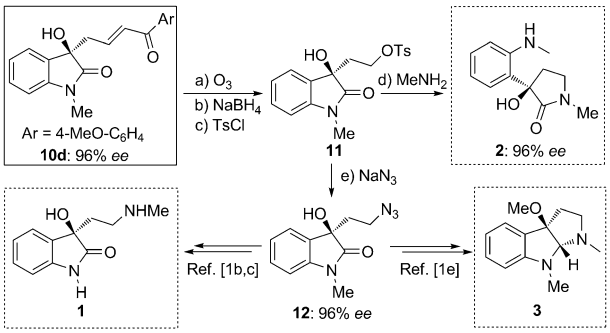



***Figure 2.*** Orbital correlation diagram between allyl ketone and isatin.

between the allyl phenyl ketone and isatin. Matching orbital phases were identified between C1 with carbonyl C, and C3 with carbonyl O (3.173 Å). In hindsight, the extra π–π* interaction in *Si*-*R*-TS from the suitable alignment of the orbitals offers greater thermodynamic stability to the transition state. We rationalize that the preference for γ over α alkylation is as a result of steric influences. From the perspective of the TS for the formation of the C–C bond through α alkylation, steric interaction between the allyl phenyl ketone nucleophile and isatin electrophile is clearly involved. Overall, the TS structures that lead to α-alkylated products are 5.5–8.5 kcal mol$^{-1}$ more endergonic than the *Si*-*R*-TS (see the Supporting Information).

With the protocol for the asymmetric vinylogous aldol reaction established, we proceeded to prepare the proposed 3-hydroxy-2-oxindole derivatives. The syntheses of compounds **1**–**3** from series I were first demonstrated (Scheme 2). The activated alkene of **10d** was ozonolyzed with $O_3$, reduced with $NaBH_4$, and then treated with tosyl chloride to afford the corresponding product **11**. Tosylate **11** was then converted to the desired (*R*)-chimonamidine **2** with

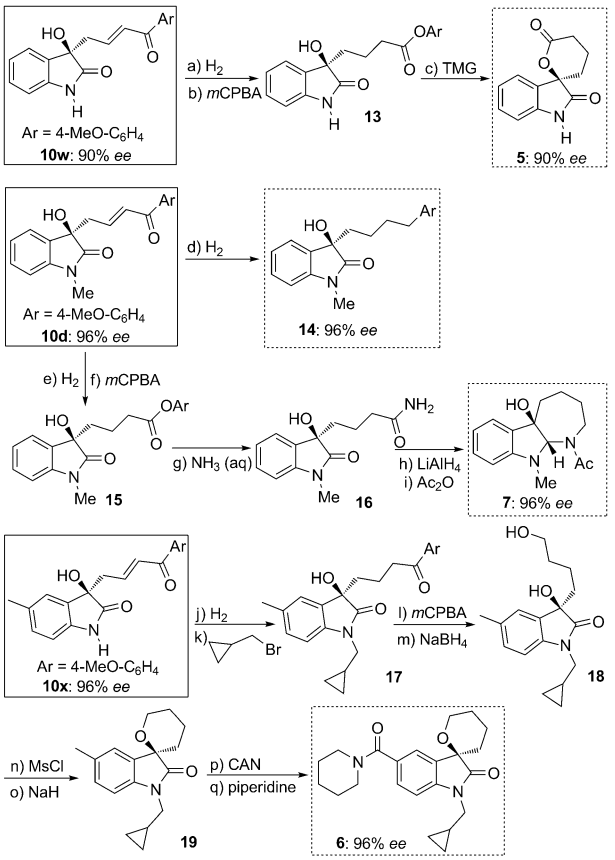



***Scheme 2.*** Synthesis of (*R*)-chimonamidine and the key intermediates of donaxaridine and CPC-1. Reagents and conditions: a) $O_3$, $CH_2Cl_2$, −78 °C, 30 min; b) $NaBH_4$ (4.0 equiv), $CH_3OH$, 25 °C, 3 h, 76% yield (over two steps); c) TsCl (1.5 equiv), pyridine, 25 °C, 12 h, 68% yield; d) $MeNH_2$ (33% in $C_2H_5OH$), 75 °C, 10 h, 76% yield, 96% *ee*; e) $NaN_3$ (3.0 equiv), DMF, 60 °C, 12 h, 86% yield, 96% *ee*. DMF = *N*,*N*-dimethylformamide, TsCl = *p*-toluenesulfonyl chloride.

96% *ee* through the treatment with methylamine. Upon treatment with $NaN_3$, compound **11** afforded azide **12**, which is an important intermediate in the preparation of donaxaridine **1**[1b–c] and CPC-1 **3**[1e].

We next prepared 3-hydroxy-2-oxindole derivatives of series II from our vinylogous aldol adducts (Scheme 3). Ester **13** was obtained from the reduction of **10w** with $H_2$ on Pd/C for 30 min, followed by a Baeyer–Villiger rearrangement (BVR) with *m*CPBA. Spirolactone **5** was conveniently obtained with 90% *ee* from **13** through its treatment with 1,1,3,3-tetramethylguanidine (TMG). Reduction of adduct **10d** with $H_2$ on Pd/C for 2 h afforded **14**, which bears an interesting 4-aryl-substituted butyl group at C3 and belongs to a novel class of 3-hydroxy-2-oxindole derivatives with some potential bioactivities. Alternatively, compound **10d** could be converted to amide **16** through a sequence of reduction, BVR, and reaction with a solution of ammonia in methanol. To our delight, treatment of **16** with $LiAlH_4$ and then acetic anhydride afforded the expected hyxahydrozaepino[2,3-b]indole **7** without compromising the *ee* value. In an effort to obtain spiroether **6**, the important intermediate **17** was prepared through reduction and protection of **10x**. After a BVR and another reduction, alcohol **18** was obtained, which gave spiroether **19** after reaction with MsCl and NaH. Following a highly efficient oxidation with ceric ammonium nitrate (CAN), an aldol reaction, and an oxidation with piperidine and $H_2O_2$, spiroether **6**, the CB2 agonist, was successfully obtained with 96% *ee* and 42% overall yield from **10x**.

In conclusion, we have developed the first highly enantioselective direct vinylogous aldol reaction between allyl ketones and isatins catalyzed by a readily prepared L-valine-derived bifunctional tertiary amine/thiourea catalyst. A series of *E*-configured vinylogous aldol adducts were obtained with 88% to more than 99% *ee*. This is the first application of allyl ketones in a catalytic asymmetric reaction. Most importantly, the reported synthetic method provides easy access to various biologically important 3-hydroxy-2-oxindole derivatives through divergent synthesis of with excellent results. Computational studies strongly supported that the observed stereochemistry is a result of favorable secondary π–π* and H-bonding interactions. Further investigations, which involve the use of allyl ketones in other asymmetric reactions and the application of this catalytic approach to the divergent synthesis of other natural products, are ongoing and will be reported in due course.




***Scheme 3.*** Synthesis of bioactive 3-hydroxy-2-oxindole derivatives of series II. Reagents and conditions: a) Pd/C, $H_2$, $CH_3OH$, RT, 30 min, 97% yield; b) *m*CPBA (2.5 equiv), $Na_2HPO_4$, $CH_2Cl_2$, RT, 6 h, 83% yield; c) TMG (1.1 equiv), THF, RT, 7 h, 93% yield, 90% *ee*; d) Pd/C, $H_2$, $CH_3OH$, RT, 2 h, 95% yield, 96% *ee*; e) Pd/C, $H_2$, $CH_3OH$, RT, 30 min, 95% yield; f) *m*CPBA (2.5 equiv), $Na_2HPO_4$, $CH_2Cl_2$, RT, 6 h, 80% yield; g) $NH_3$ (aq), $CH_3OH$, RT, 1 h, 90% yield; h) $LiAlH_4$, THF, 0 °C→RT; i) $Ac_2O$, 50% yield of two steps, 96% *ee*; j) Pd/C, $H_2$, $CH_3OH$, 25 °C, 30 min, 92% yield; k) $Cs_2CO_3$, (bromomethyl)cyclopropane, DMF, 0 °C→RT, 98% yield; l) *m*CPBA (2.5 equiv), $Na_2HPO_4$, $CH_2Cl_2$, RT, 6 h, 87% yield; m) $NaBH_4$ (20 equiv), $CH_3OH$, RT, 5 h, 89% yield; n) MsCl, $Et_3N$, $CH_2Cl_2$, −10 °C, 1 h, 91% yield; o) NaH (1.5 equiv), DMF, 0 °C→RT, 1 h, 92% yield; p) CAN (4.0 equiv), $CH_3OH/CH_3CN$ (v/v = 2:1), RT, 5 min, 95% yield; q) $H_2O_2$, piperidine, 76% yield, 96% *ee*. *m*CPBA = meta-chloroperbenzoic acid.

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**Keywords:** 3-hydroxy-2-oxindoles · aldol reaction · allyl ketones · asymmetric synthesis · divergent synthesis

  

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