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# Asymmetric organocatalytic direct Mannich reaction of acetylacetone and isatin derived ketimines: Low catalyst loading in chiral cinchona-squaramides

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ABSTRACT

A highly enantioselective synthesis of 3-amino-2-oxindoles by direct Mannich reaction between acetylacetone and *N*-carbamoyl isatin ketimine has been described herein. Corresponding chiral adducts were obtained in high yields (up to 98%) and with excellent enantioselectivities (up to >99% ee) by very low (1 mol%) catalyst loading of 2-adamantyl substituted bifunctional cinchona-squaramide.



## Introduction

Structure-based approach in medicinal chemistry and chemical biology focuses on classification of bioactive compounds and their structural relationships to determine the smallest chemical probes that may serve as drug candidates.[1] Within a vast majority of drug precursors, chiral α-tertiary amines are privileged structures for being in the skeleton of many natural products and biologically active compounds.[2] Specifically, 3-aminooxindole moiety has been encountered as the core entity of many architecturally complex natural products and pharmaceuticals such as AG-041R gastrin/CCK-B receptor agonist,[3a] CRTH2 antagonist as anti-bacterial agent and an anti-tuberculosis agent,[3b] vasopressin $V_{1b}$ receptor antagonist SSR-149,415 which is used in treatment of anxiety and depression,[3c] an anti-malarial agent NITD609,[3d] HIV-1 protease inhibitor[3e] and an anti-mycobacterial against *M. tuberculosis* H37Rv[3f] (Fig. 1). Hence various stereoselective approaches for the construction of 3-amino-2-oxindole derivatives bearing a tetra-substituted stereocenter have been developed.[4] To the best of our knowledge, these synthetic strategies include asymmetric addition to isatin imines,[5] intramolecular α-arylation of amides,[6] alkylation of 3-aminooxindole,[7] amination of 3-substituted oxindoles,[8] and multicomponent reaction.[9] Specifically, direct Mannich reaction in which an enolizable carbonyl compound reacts with isatin ketimine is one of direct methods to obtain 2-oxindole derived tertiary amines.[5d,10,11] Initially, Yan et al.[5d] reported a study in which quinine-thiourea organocatalyst afforded

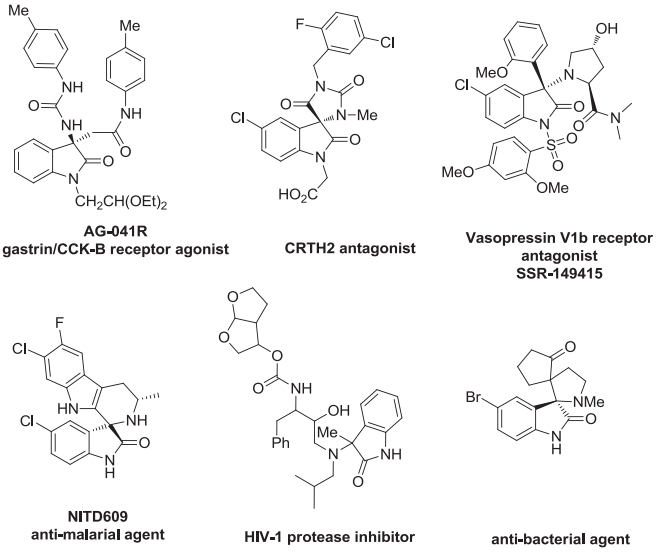


**Fig. 1.** Representative examples of biologically active compounds containing 3-amino-2-oxindole skeleton.

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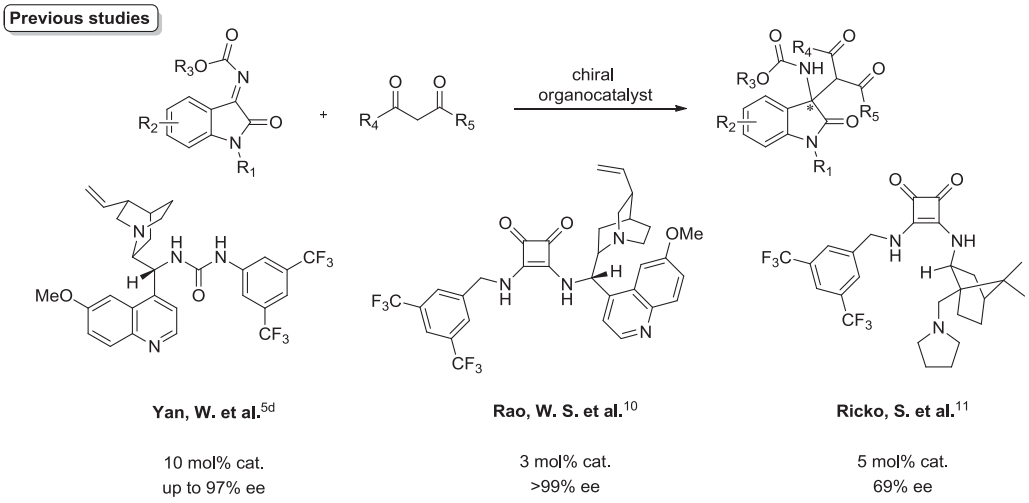
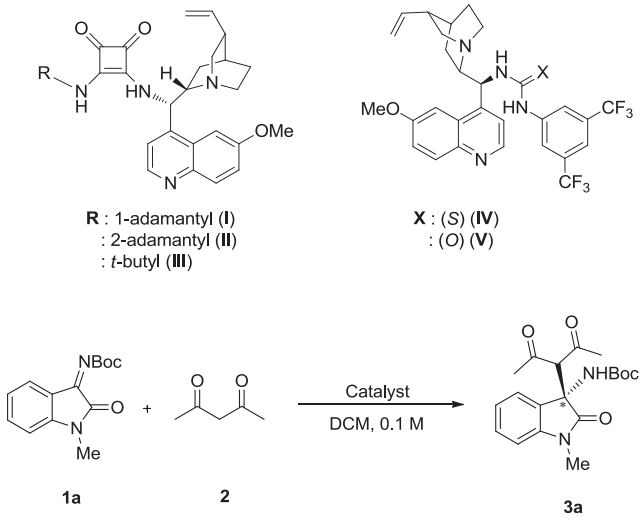



**Scheme 1.** Previous studies.

products in good yields and enantioselectivities up to 98% ee (Scheme 1). In 2016, examination of squaramide organocatalysis,[12] pioneered by Rawal and co-workers,[13] by Rao et al. resulted in satisfying enantiopurity and chemical yield as well.[10] Also, a camphor derived 1,3-diamine organocatalyst was tested in a representative reaction of acetylacetone and *N*-methyl

**Table 1**
Optimization studies.[a]




| Entry | Catalyst | Catalyst loading | Solvent | Conc. (M) | Time (h) | Yield %[b] | ee %[c] |
|---|---|---|---|---|---|---|---|
| 1 | I | 5 | DCM | 0.1 | 24 | 98 | 96 |
| 2 | II | 5 | DCM | 0.1 | 2 | 99 | 99 |
| 3 | III | 5 | DCM | 0.1 | 24 | 87 | 97 |
| 4 | IV | 5 | DCM | 0.1 | 24 | 94 | 89 |
| 5 | V | 5 | DCM | 0.1 | 24 | 92 | 93 |
| 6 | II | 2 | DCM | 0.1 | 3 | 99 | 99 |
| 7 | II | 1 | DCM | 0.1 | 8 | 99 | 99 |
| 8 | II | 0.5 | DCM | 0.1 | 22 | 88 | 93 |
| 9 | II | 0.5 | DCM | 0.2 | 22 | 99 | 98 |
| 10 | II | 0.5 | DCM | 0.3 | 22 | 99 | 98 |
| 11 | II | 1 | Toluene | 0.1 | 7 | 97 | 99 |
| 12 | II | 1 | $Et_2O$* | 0.1 | 3 | 92 | 99 |
| 13 | II | 1 | EtOAc | 0.1 | 7 | 93 | 98 |
| 14 | II | 1 | $CH_3CN$ | 0.1 | 24 | 92 | 98 |
| 15 | II | 1 | THF | 0.1 | 24 | 90 | 94 |

[a] Reaction conditions: ketimine (0.05 mmol, 0.1 M in solvent) and acetylacetone (0.05 mmol).
[b] Isolated yields are reported.
[c] Determined by HPLC equipped with chiral column.
* Desired product precipitates in the solvent.