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Organocatalytic Enantioselective *aza*-Henry reaction of Ketimines Derived from Isatins: Access to Optically Active 3-Aminooxindoles

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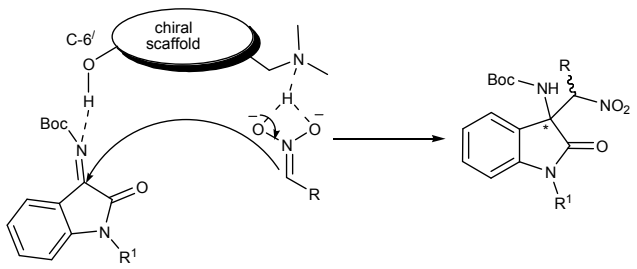
Organocatalytic asymmetric *aza*-Henry reaction of Ketimines derived from isatins with nitroalkanes has been achieved with the use of *Cinchona* alkaloid organocatalysts. This method works efficiently with several ketimines to produce the corresponding 3-substituted 3-amino-oxindoles in good yield (up to 82%) and good enantiomeric excess (up to 89% ee).

Introduction

Oxindole skeleton bearing a tetra-substituted stereogenic center at the 3-position is a privileged heterocyclic framework, that is present in the large family of bioactive natural products and series of pharmaceutically active compounds.[1] Among them, 3-substituted 3-amino-2-oxindole[2] has been recognised as a key structure because of its presence in variety of natural products and several biologically active compounds, such as potent gastrin/CCK-B receptor antagonist AG-041R[3], vasopressin VIb receptor antagonist SSR-14941533[4], anti-malarial drug candidate NITD609[5]. In this context, the development of new methodologies for the synthesis of 3-aminooxindole derivatives is of paramount importance. In the past few years, several catalytic asymmetric addition reactions of isatin-derived ketimines[6], including Mannich reaction[6a-b], Strecker reaction[6c-e], *aza*-Friedel-Crafts reaction[6f-g], Morita-Baylis-Hillman reaction[6h] *etc*. have been reported. However, the synthesis of 3-amino-2-oxindole subunit *via aza*-Henry reaction, which is a powerful and efficient method for the synthesis of nitrogen containing molecules through Carbon-Carbon bond formation[7], has not been reported. Moreover, the nitroamines adduct resulting from this addition reaction can be easily transformed into vicinal diamines[8] and α-amino acids[9], which can serve as building blocks for the synthesis of complex molecules.[10]

Since last five years, our group has been actively engaged in the development of enantioselective addition reactions of carbon nucleophiles to isatins/derivatives of isatins in the presence of bifunctional organocatalysts.[11] In this work we have extended this line of research to enantioselective addition of nitroalkanes to isatin-derived imines in the presence of bifunctional organocatalysts (**Figure 1**). Herein, we report the catalytic potential of bifunctional 6'-OH *Cinchona* alkaloids for the *aza*-Henry reaction of nitroalkane with ketimines.[12] We reasoned that enantioinduction can be achieved in this reaction through synergistic activation of *N*-Boc ketimines and nitroalkanes by a bifunctional 6'-OH *Cinchona* alkaloid catalyst (**Scheme 1**).



Scheme 1 Proposed dual activation for the asymmetric *aza*-Henry of nitroalkane with ketimine.

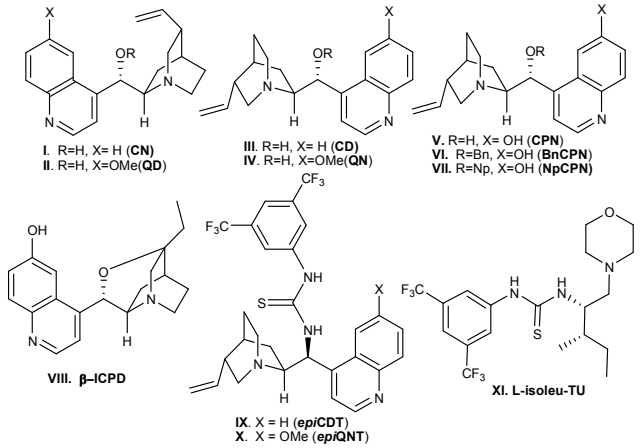


Figure 1 Screening of various organocatalysts for asymmetric addition of nitroalkane to ketimine.

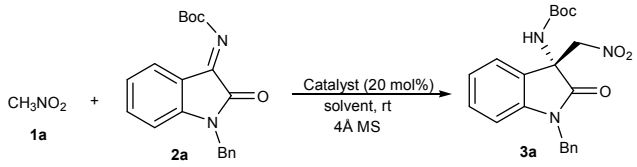
Results and discussion

We initiated our investigation by performing the reaction of *N*-boc ketimine (**2a**) with nitromethane (**1a**) in the presence of cinchonine (**I**, 20 mol%) as the catalyst in THF and 4Å molecular sieves at room temperature (**Table 1**). The reaction proceeded smoothly and provided the desired adduct **3a** in 79% yield and 68% *ee* (**Table 1, entry 1**). Screening of other natural *Cinchona* alkaloids resulted in no further enhancement in enantioinduction of **3a** (**Table 1, entry 2-4**). The same reaction with modified *Cinchona*-alkaloid CPN (**V**) yielded **3a** in 81% yield with small

enhancement of enantioselectivity (70% *ee*), thus suggesting the role of the 6'-OH group of quinoline in increasing the enantioselectivity (**Table 1, entry 5**). To determine the beneficial role of 6'-OH group in term of enantioinduction, the catalytic potential of 9-OH blocked *Cinchona* alkaloids (BnCPN and NpCPN) was evaluated on the same reaction (**Table 1, entry 6-7**). Interestingly, the BnCPN yielded the *aza*-Henry adduct **3a** with highest level of enantioselectivity (**Table 1, entry 6**). The quinidine derived catalyst β-ICPD yielded product **3a** in 67% yield with 7% *ee* (**Table 1, entry 8**). The model reaction carried out with *Cinchona*-derived thioureas (**VIII-IX**) resulted in moderate yield and low enantioselectivity (**Table 1, entry 9-10**). No improvement was observed on using amino acid derived catalyst **XI** (**Table 1, entry 11**). Lowering of the temperature to -30 °C resulted in a prolonged reaction time with lowering in the enantioselectivity of the adduct **3a** (**Table 1, entry 12**).

Further, different solvents were screened by using 20 mol% of **VI** as a catalyst (**Table 1, entry 4 and 13-18**). After screening, tetrahydrofuran was identified as the best solvent in term of enantioinduction (**Table 1, entry 6**).

Table 1 Optimization Study.[a]

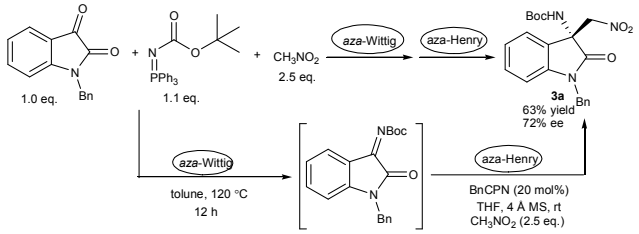


Entry	Catalyst	Solvent	Time (h)	Yield[b] [%]	ee[c] [%]
1	**I**	THF	24	79	68
2	**II**	THF	24	75	54
3	**III**	THF	24	78	-62
4	**IV**	THF	24	72	-34
5	**V**	THF	24	81	70
6	**VI**	THF	24	80	84
7	**VII**	THF	30	72	82
8	**VIII**	THF	36	62	-7
9	**IX**	THF	36	65	40
10	**X**	THF	36	69	40
11	**XI**	THF	36	65	38
12[d]	**VI**	THF	36	65	56
13	**VI**	$CHCl_3$	24	78	81
14	**VI**	DCM	24	79	80
15	**VI**	MTBE	24	80	76
16	**VI**	1,4-dioxane	24	76	74
17	**VI**	Ethyl acetate	24	74	79
18	**VI**	Toluene	24	81	83

[a]Reaction conditions : 0.1 mmol of Ketimine **2a**, 0.25 mmol of nitromethane, 4Å molecular sieves (50 mg) and catalyst in dry solvent. [b]Yield refers to isolated yield after column chromatography. [c]Enantiomeric excess (*ee*) determined by chiral HPLC. [d]Reaction was performed at -30 °C.

Once armed with best optimized conditions, the substrate scope of the **BnCPN**-catalyzed *aza*-Henry reaction was investigated by screening nitroalkane with different derivatives of *N*-Boc ketimine. 5-Halo-*N*-benzylketimines (**2b-2d**) reacted efficiently with **1a** to provide the corresponding 3-amino-2-oxindoles **3b-3d** in 74-79% yield and 67-76% *ee* (**Table 2, entry 2-4**). Different derivatives of *N*-allyl ketimine gave the corresponding adducts **3e-3h** in 73-78% yield with 70-86% *ee* (**Table 2, entry 5-8**). The *N*-protected isatins **2i-2j** reacts smoothly with nitromethane to provide adducts **3i-3j** in 70-71% yield and 75-79% *ee* (**Table 2, entry 9-10**). Ketimines **2k** derived from 5-chloroisatin yielded product **3k** in 68% yield and 65% *ee* (**Table 2, entry 11**). Nitroethane (**1b**) also react efficiently with ketimine **2i** to provide **3l** in 72% yield, 72:28 dr and 80% *ee* of major diastereomer (**Table 2, entry 12**). The nitropropane (**1c**) on reaction with ketimines (**2i** and **2h**) gave desired *aza*-Henry adducts **3m** and **3n** in good yield but with low diastereomeric ratio and moderate enantiomeric excess (**Table 2, entry 13-14**).

To improve the synthetic utility, we studied the multicomponent version of this reaction by combination of the *aza*-Wittig and *aza*-Henry reaction in a one-pot sequential protocol. The product **3a** was isolated in 63% yield and enantioselectivity of 72% *ee* (**Scheme 2**).



Scheme 2 Tendem *aza*-Wittig/aza-Henry reaction.

The (*R*) absolute configuration of adducts **3** was unambiguously assigned on the basis of single-crystal X-ray diffraction analysis of compound **3e** (**figure 2**).[13]

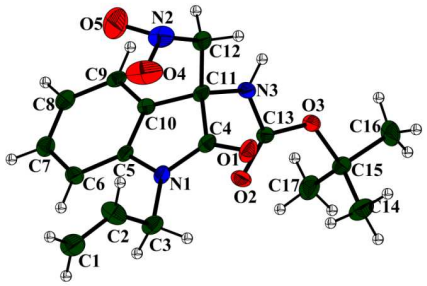
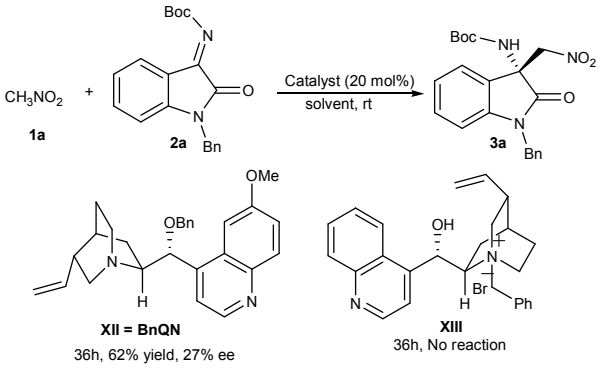


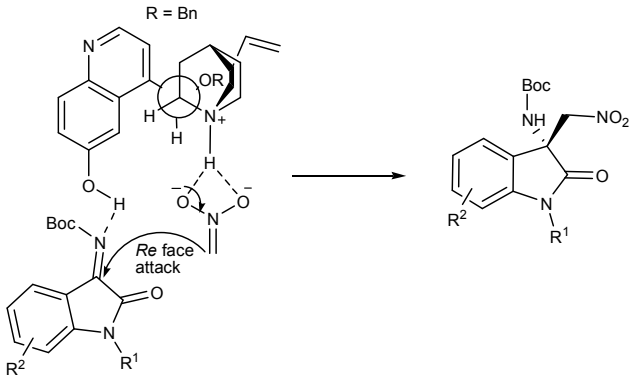
Figure 2 ORTEP diagram of the molecule (**3e**) at 30% probability.

In order to reveal the mechanism of *aza*-Henry reaction catalyzed by C6'-OH *Cinchona* alkaloid, we designed some experiments. The model reaction catalyzed by BnQN (**XII**) having no free hydroxyl group provided **3a** in moderate yield (62%) and low enantioselectivity (27% *ee*), which suggest the role of OH moiety in enhancing the reactivity and selectivity of the reaction (**Scheme 3**). The natural *Cinchona* alkaloids (CN, CD, QD and QN) having a free OH group at C9 gave product in lower enantioselectivity compared with BnCPN/NpCPN having OH group at C6' in *Cinchona* alkaloids (**Table 1, entry 1-4 and 6-7**). Thus suggesting the beneficial role of C6'-OH group in term of enantioinduction. The catalyst **XIII** having no free amine moiety failed to catalyze the model reaction, suggesting the role of free amine moiety in deprotonation of nitroalkane. These results show that the tertiary amine .present in the catalyst is a prerequisite for this reaction to occur along with the C6'-OH group, which provides favourable orientation for high enantioinduction (**Scheme 3**).



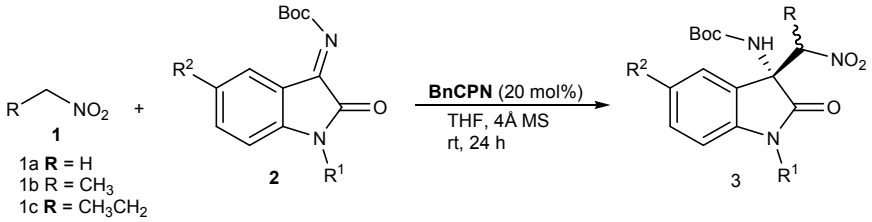
Scheme 3 Elucidation of bifunctional mode of activation.

On the basis of these experimental observations and the absolute configuration, a transition state involving a ternary complex between the catalyst and the substrates can be proposed. The quinuclidine tertiary amine can deprotonate the α-proton of nitomethane and activating it for nucleophilic attack on the *Re* face of the ketimines, which is activated through hydrogen bonding with the C6' OH group of the catalyst, thus providing the *R* enantiomer of the product (**Scheme 4**).



Scheme 4 Proposed transition-state model.

Table 2 Substrate Scope.[a]



Entry	1	2 (R_1, R_2)	3	Yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	**2a** (R_1=-$CH_2C_6H_5$, R_2=H)	**3a**	80	-	84
2	**1a**	**2b** (R_1= -$CH_2C_6H_5$, R_2=Cl)	**3b**	74	-	67
3	**1a**	**2c** (R_1= -$CH2C_6H_5$, R_2=Br)	**3c**	79	-	73
4	**1a**	**2d** (R_1=-$CH_2C_6H_5$, R_2=I)	**3d**	77	-	72
5	**1a**	**2e** (R_1= -CH_2CHCH_2, R_2=H)	**3e**	73	-	70
6	**1a**	**2f** (R_1= -CH_2CHCH_2, R_2=Cl)	**3f**	76	-	76
7	**1a**	**2g** (R_1= -CH_2CHCH_2, R_2=Br)	**3g**	77	-	73
8	**1a**	**2h** (R_1= -CH_2CHCH_2, R_2=I)	**3h**	78	-	89
9	**1a**	**2i** (R_1= -$CH_2C(CH_3)CH_2$, R_2=Cl)	**3i**	71	-	75
10	**1a**	**2j** (R_1= -$CH_2CHCHCH_3$, R_2=Cl)	**3j**	70	-	79
11	**1a**	**2k** (R_1=H, R_2=Cl)	**3k**	68	-	74
12	**1b**	**2i** (R_1= -$CH_2C(CH_3)CH_2$, R_2=Cl)	**3l**	72	72:28	80(82)[e]
13	**1c**	**2i** (R_1= -$CH_2C(CH_3)CH_2$, R_2=Cl)	**3m**	76	55:45	56(67)[e]
14	**1c**	**2h** (R_1= -CH_2CHCH_2, R_2=I)	**3n**	78	54:46	64(67)[e]

[a]Reaction conditions: 0.1 mmol of ketimines **2**, 0.25 mmol nitroalkane **1**, 4Å molecular sieves (50 mg) and catalysts **VI** (20 mol%) in dry THF. [b]Yield refers to isolated yield after column chromatography. [c]Diastereomeric ratio determined by HPLC after column purification of adducts (**3l-3m**). [d]Enantiomeric excess (ee) determined by chiral HPLC. [e]Values in the panthers for ee of minor diastereomer.

Conclusions

We have developed the first organocatalytic asymmetric *aza*-Henry reaction of ketimines derived from isatins and nitroalkanes employing C6'-OH *Cinchona* alkaloid catalyst. A variety of chiral 3-substituted 3-amino-2-oxindoles have been successfully synthesized in good yield and good enantioselectivity.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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