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Quinine-Based Trifunctional Organocatalyst for Tandem Aza-Henry Reaction-Cyclization: Asymmetric Synthesis of Spiroxindole-Pyrrolidine/Piperidines

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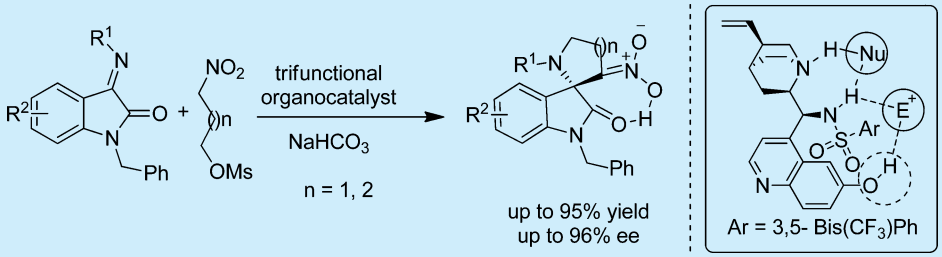
Supporting Information

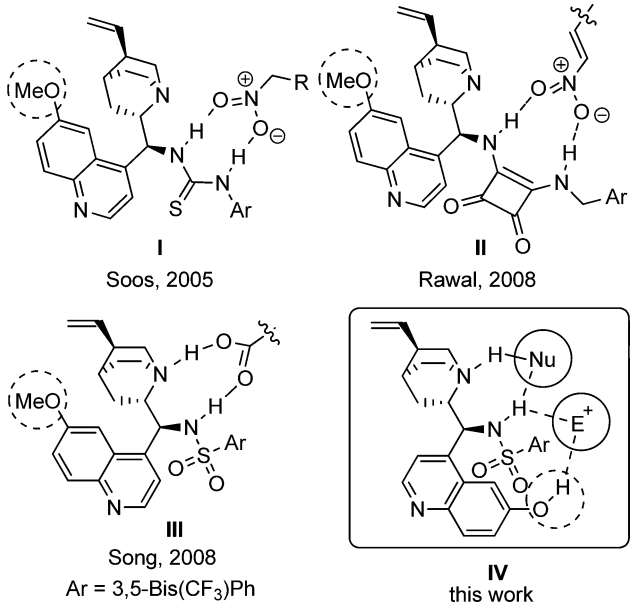


ABSTRACT: A quinine-derived trifunctional sulphonamide catalyst has been developed for the effective asymmetric organocatalytic tandem aza-Henry reaction-cyclization of isatin-derived ketimines and nitroalkane-mesylates for the synthesis of spiro-pyrrolidine/piperidine-oxindoles. Demethylation of traditional bifunctional catalyst to incorporate an additional hydrogen bonding C6′−OH group plays the key role toward remarkable enantioselectivity.

In the past decade, organocatalysis has emerged as one of the cornerstones for asymmetric synthesis.[1] Environmentally benign and structurally unique organic frameworks have been designed for stereodefined activation of nucleophiles and electrophiles to render unparalleled stereoselectivity. Cinchona alkaloid-derived catalysts are one of the important subclasses of the organocatalyst library.[2] The mode of activation and catalytic activity have been studied using computational methods.[3] Particularly, in the thiourea **I** catalyzed addition of nitromethane[4] and squaramide **II** catalyzed reaction of nitroolefins,[5] catalysts exhibit double-point hydrogen binding with two N-Hs (Scheme 1). Later, the Song and List group reported a newly designed quinine-based sulphonamide catalyst **III** for desymmetrization of meso anhydrides[6a] and decarboxylative aldol reaction.[6b] Very recently, a comprehensive computational and NMR study on the mechanism of sulphonamide catalysis has been disclosed[3b] where the quinuclidine moiety, after subsequent protonation, acts as an alternative hydrogen bond donor to facilitate effective enantioactivation (Scheme 1).

We hypothesized that further modification of the sulphonamide catalysts **III** can be done by demethylation of C6′-O-methyl group on the quinoline ring to incorporate an additional hydrogen bonding group dedicated for the activation of an electrophile (Scheme 1). Such tailored trifunctionality of the catalyst **IV** would be one step further to the traditional bifunctional organocatalysts, encompassing both the activation of electrophile and nucleophile, resulting in a more rigid transition state of the reaction. We envisioned that this class of trifunctional catalysts would be particularly effective for the

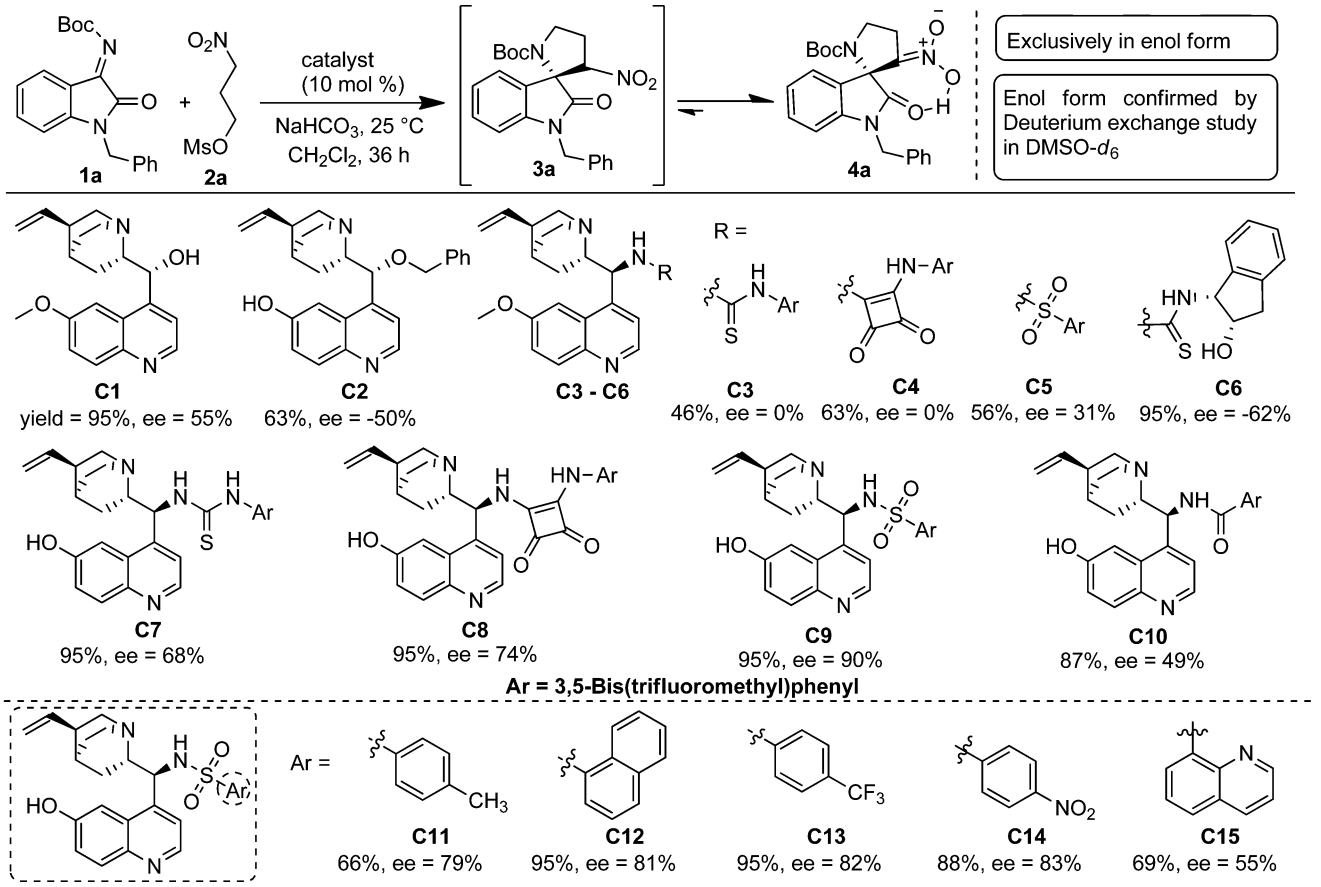
Scheme 1. Literature-Reported Bifunctional Catalysts and Our Hypothesis of Trifunctional Catalysis



Received: July 14, 2017

DOI: 10.1021/acs.orglett.7b02150
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Catalyst Screening of Tandem Aza-Henry Reaction-Cyclization[a]



[a]General reaction conditions: **1**a (0.1 mmol), **2**a (0.5 mmol) in 0.5 mL CH_2Cl_2, catalyst (0.01 mmol), $NaHCO_3$ (0.5 mmol) at 25 °C. Isolated yield after flash column chromatography; ee determined by HPLC analysis on a chiral stationary phase.

reactions where bifunctional catalysts are inadequate and thereby providing an alternate aid to the toolbox of organocatalysts.

To prove our hypothesis, we selected isatin-derived ketimine **1a** as a model substrate[7] for the enantioselective aza-Henry reaction with nitro alkane **2a** (Scheme 2).[8] The nitro alkane **2a** was equipped with a distant leaving group purposely designed for tandem cyclization[9] to afford spiroxindole 3,2′-heterocycle **3a** under mild conditions. 3,2′-Pyrrolidines[10] are of recent interest for their potential therapeutic activities.[11]

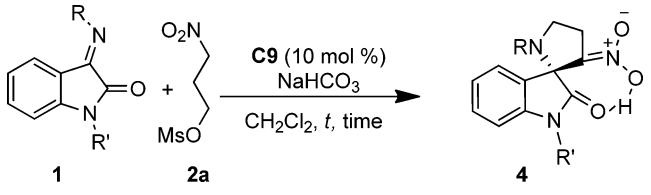
Cinchona alkaloids were first loaded in a model reaction of *N*-Boc ketimine **1a** with 3-nitropropylmethanesulfonate **2a** in dichloromethane in the presence of $NaHCO_3$ at 25 °C (Scheme 2). Quinine (**C1**) furnished excellent yield and an encouraging 55% ee. It is to be noted that the nitro group so formed exists exclusively in enol form as confirmed by the NMR experiment (see the Supporting Information). Change of H-bond donor group from secondary −OH to a C6′−OH in **C2** led to reversal of selectivity (−50% ee) with reduced yield. Bifunctional thiourea catalyst **C3** and squaramide catalyst **C4** were unable to render any enantioinduction (0% ee). Interestingly, corresponding sulphonamide catalyst **C5** gave 31% ee with 56% yield. The presence of an additional −OH group in **C6** straightaway increased the enantioselectivity to −62%. This result encouraged us to verify our initial hypothesis of the effect of added hydroxyl moiety in the catalyst. Trifunctional catalyst **C7** possessing the C6′−OH group[12] straightaway increased the ee from 0% (**C3**) to 68%. When demethylated catalyst **C8** was employed, selectivity was elevated to 74% from 0% (**C4**). Reaction with trifunctional sulphonamide catalyst **C9** increased the enantioinduction to 90% from 31% (**C5**). Selectivity sharply reduced when aromatic amide catalyst **C10** was employed (87% yield, 49% ee). Because the stereoelectronic environment of the aromatic moiety largely affects the extent and ease of the H-bonding, we then evaluated these effects in the enantioinduction (Scheme 2). Electron-rich as well as electron-withdrawing substituents at the aromatic ring were extensively studied (**C11**−**C15**) but failed to induce any better selectivity.

Effect of solvent was then studied ranging from nonpolar to polar aprotic solvents, but dichloromethane was best in terms of isolated yield and enantioselectivity (see the Supporting Information). Gratifyingly, lowering the reaction temperature to 0 °C afforded the desired product in an increased enantioselectivity (95% yield and 93% ee) (Table 1, entry 2). Finally, the use of MS 4 Å to trap H_2O (MsOH so formed in the reaction was quenched by $NaHCO_3$ to form CO_2 and H_2O) resulted in remarkable stereoselection of the product (95% yield and 96% ee) (entry 3). Further lowering of temperature or reduced catalyst loading resulted in a reduced yield with no improvement in the enantioselectivity (entries 4 and 5). Pivotal effect of isatin N-protection as well as imine functionalization was observed in the reaction (entries 6 and 7).

Upon identifying our optimal catalyst **C9**, we expanded the scope of the aza-Henry reaction-cyclization with a variety of aromatic substituted *N*-benzyl isatin-derived *N*-Boc ketimines

DOI: 10.1021/acs.orglett.7b02150
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of Reaction Conditions[a]

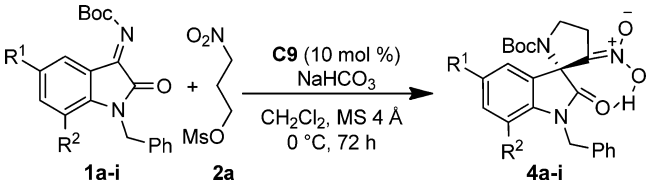


entry	R	R′	t (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	Boc	Bn	25	36	95	90
2	Boc	Bn	0	72	95	93
3[d]	**Boc**	**Bn**	**0**	**72**	**95**	**96**
4[d]	Boc	Bn	−10	96	95	96
5[d]	Boc	Bn	−20	96	62	96
6[d]	Boc	Me	0	72	92	89
7[d]	Cbz	Bn	0	72	95	90

[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.5 mmol) in 0.5 mL CH_2Cl_2, catalyst (0.01 mmol), $NaHCO_3$ (0.5 mmol) at specific temperature. [b]Isolated yields after flash column chromatography. [c]ee determined by HPLC analysis on a chiral stationary phase. [d]In the presence of MS 4 Å.

(**1a−i**) (Table 2). Gratifyingly, regardless of the differences in the stereoelectronic nature, all the ketimines were smoothly

Table 2. Substrate Scope of the Tandem Aza-Henry Reaction-Cyclization[a]



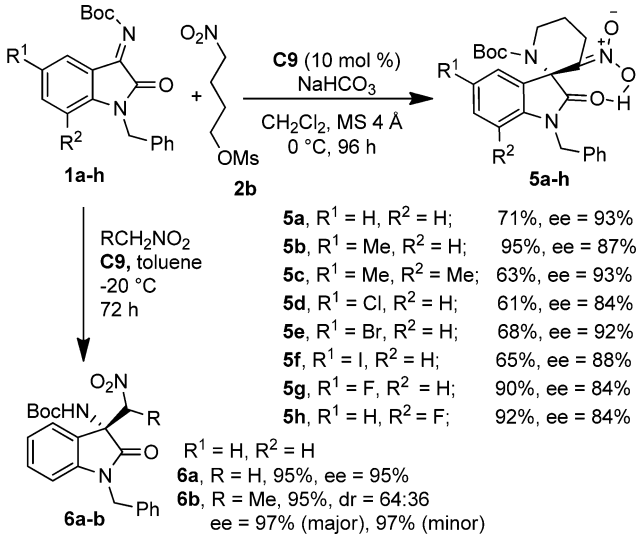
entry	imine	R^1	R^2	product	yield (%)[b]	ee (%)[c]
1	1a	H	H	4a	95	96
2	1b	Me	H	4b	87	96
3	1c	Me	Me	4c	94	96
4	1d	Br	H	4d	91	95
5	1e	I	H	4e	95	92
6	1f	Cl	H	4f	95	94
7	1g	F	H	4g	95	94
8	1h	H	F	4h	95	93
9	1i	OMe	H	4i	94	96
10[d]	1a	H	H	4a	93	95

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.5 mmol) in 0.5 mL CH_2Cl_2, **C9** (0.01 mmol), $NaHCO_3$ (0.5 mmol), MS 4 Å, 72 h at 0 °C. [b]Isolated yields after flash column chromatography. [c]ee determined by HPLC analysis on a chiral stationary phase. [d]Reaction was performed with **1a** (2.0 mmol), **2a** (10.0 mmol) in 10 mL CH_2Cl_2, **C9** (0.2 mmol), $NaHCO_3$ (10 mmol), MS 4 Å, 72 h at 0 °C.

reacted to afford spiroxindole 3,2′-pyrrolidines (**4a−i**) with excellent yields and enantioselectivities (Table 2, entries 1−9). We are pleased to report that the reaction in 2.0 mmol scale also proceeded without any significant reduction in yield and enantioselectivity (93% yield, 95% ee; entry10).

To further demonstrate the effectiveness of the trifunctional catalysis, nitrobutanol-mesylate **2b** was reacted with ketimines (**1a−h**) to afford spiroxindole 3,2′-piperidines (**5a−h**) in moderate to high isolated yields with high enantioselectivity (Scheme 3). The catalyst was also effective for the direct addition reaction of nitroalkanes (**6a−b**). The stereochemistry

Scheme 3. Synthesis of Spiroxindole 3,2′-Piperidines and Nitroalkane Addition[a]

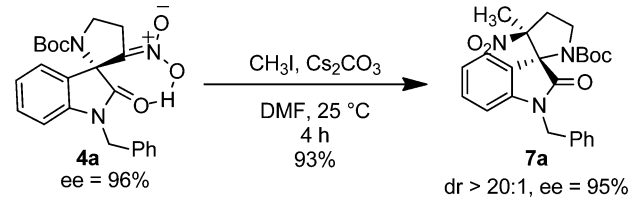


[a]General reaction conditions: **1a** (0.1 mmol), **2b** (0.5 mmol) in 0.5 mL CH_2Cl_2, **C9** (0.01 mmol), $NaHCO_3$ (0.5 mmol) at 0 °C, 96 h. Reaction of nitroalkanes: **1a** (0.1 mmol), nitroalkane (0.25 mL), 0.25 mL toluene, **C9** (0.01 mmol) at −20 °C. Isolated yields after flash column chromatography; ee determined by HPLC analysis on a chiral stationary phase. For **1c**, **1d**, **1e**, and **1f**, time: 120 h.

of the nitromethane addition product **6a** was assigned as *R* isomer by comparing the HPLC data with the reported literature,[8i] and from this analogy, the stereochemistry of spiroxindoles **4a−i** and **5a−h** were tentatively assigned.

As an appended application, spiroxindole 3,2′-pyrrolidine **4a** was further methylated to form compound **7a** in excellent yield (93%) and stereoselectivity (dr: >20:1; 95% ee) (Scheme 4). The configuration of the newly formed stereocenter was assigned as 3′*S* by NOESY analysis.

Scheme 4. Methylation of 4a



To obtain a clear insight into the reaction mechanism and the mode of catalytic activation, we performed ESI-MS analysis of the crude reaction mixture (Scheme 5). To our great delight, we were able to detect the catalyst-imine adduct **B**. However, no mass of catalyst-nitroalkane complex was detected. This indicated the ligation of imine to the catalyst prior to the chelation of nitroalkane **2a**. In light of these observations, we proposed a plausible transition state of the reaction where the addition of nitroalkane can be facilitated only from the Re face of the imine, which led to excellent stereoinduction.

In summary, we disclose the reactivity of a new class of trifunctional catalysts in the enantioselective aza-Henry reaction-cyclization of isatin-derived ketimines. The unprecedented increase in yield and enantioselectivity was achieved with the installation of C6′−OH group in the catalyst. Further

DOI: 10.1021/acs.orglett.7b02150
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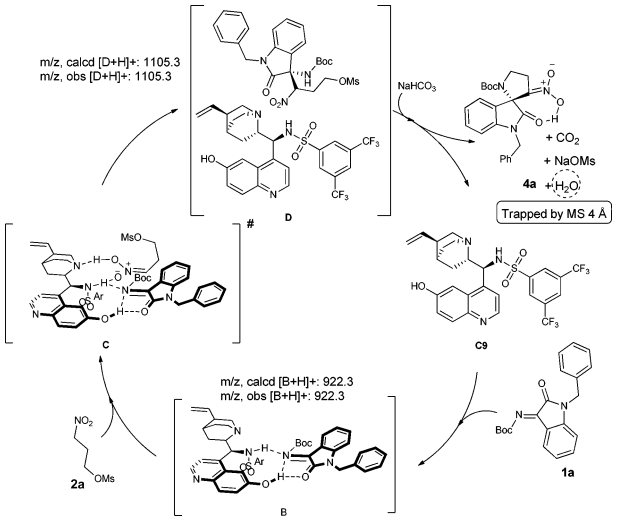
Scheme 5. Proposed Catalytic Cycle and Crude Reaction ESI-MS Analysis



development and application of these trifunctional catalysts for new efficient asymmetric transformations are currently in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02150.

All the experimental and spectroscopic data of compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by SERB, New Delhi (SR/S1/OC-97/2012 and EMR/2016/001161). B.J. thanks UGC, New Delhi for research fellowship. We thank Director, CBMR for research facilities.

■ DEDICATION

Dedicated to Professor Chunni Lal Khetrapal (CBMR, Lucknow) on his 80th birthday.

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DOI: 10.1021/acs.orglett.7b02150
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