Chiral Bipyridine-N,N′-dioxides Catalysts: Design, Synthesis, and Application in Synthesis of 1H-pyrazolo[3,4-b]pyridine Analogues

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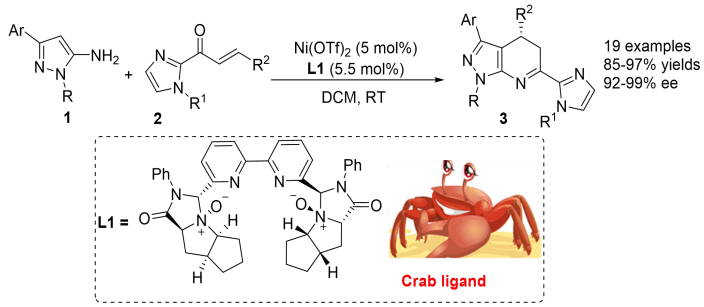
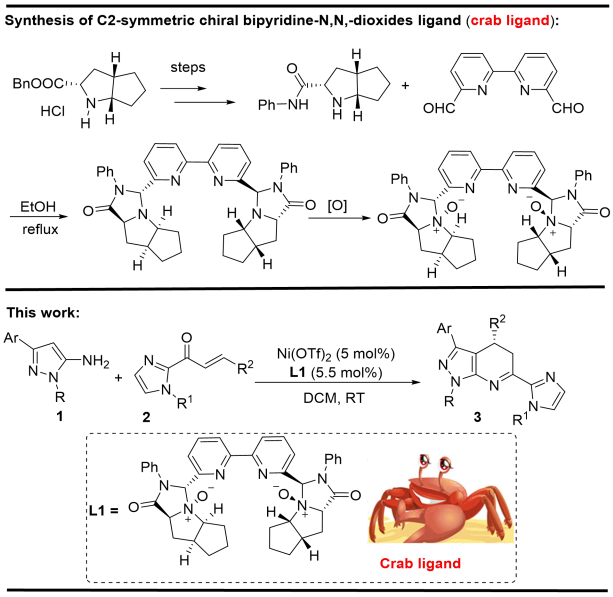
Supporting Information Placeholder



ABSTRACT: A novel type of highly efficient chiral C2-symmetric bipyridine-N,N'-dioxides catalysts to catalyze Michael addition/Cyclization of 5-amino pyrazoles with α,β-unsaturated 2-acyl imidazoles has been developed, affording the corresponding adducts in 85-97% yield with up to 99% enantioselectivity. Remarkably, this protocol exhibits extraordinary advantages in terms of reactivity and enantioselectivity, given the fact that as low as 2.2 mol % of L1 and 2.0 mol % of $Ni(OTf)_2$ can promote the title reaction on gram scale to afford desired product with excellent enantioselectivity.

Chiral amine N-oxides feature an electron-donating oxygen atom in the N^+-O^- group and have proved to be effective ligandsand organocatalysts in asymmetric catalysis since 1993.[1] For example, Nakajima, Hayashi, Takenaka and co-workers reported the use of biquinoline/pyridine N,N-dioxides as catalytic ligands for the asymmetric allylation of aldehydes and conjugate additions of thiols.[2] However, the application of chiral N-heteroaromatic N-oxide ligands in asymmetric catalytic reactions for different reaction types and substrates is still limited. It was not until Feng's group developed a new family of C2-symmetric N,N′-dioxide amides from readily available chiral amino acids insensitive to moisture and air demonstrated to be privileged by their applications in more than 70 types of asymmetric reactions not only as organocatalysts.[3] Recently, Guo, Xie and co-workers have developed a new class of chiral DMAP-derived N-oxides as e ffi cient organocatalysts.[4] In addition, Liu and co-workers invented a novel family of tertiary amine-derived C2-symmetric chiral pyridine-N,N′-dioxide ligands (Py-2NO) applied in Friedel-Crafts reaction affording the corresponding adducts in excellent yields and enantioselectivity.[5] Although the previous research has left a deep impression on us, not all existing ligands could meet every reaction, so the development of novel type of highly efficient chiral C2-symmetric N-dioxides catalysts was still needed. Inspired by previous research and combined with our experience in developing chiral-at-metal Rh(III) complexes,[6] herein we designed and synthesized a new tetradentate C2-symmetric chiral bipyridine-N,N,-dioxides ligand and successfully applied them to synthesize chiral pyrazolo[3,4-b]pyridine analogues (Scheme 1).[7]

Scheme 1 Chiral bipyridine-N,N'-dioxides catalysts: design, synthesis and application.



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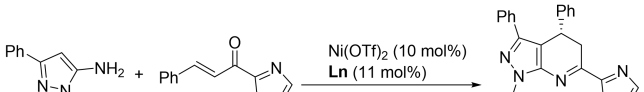
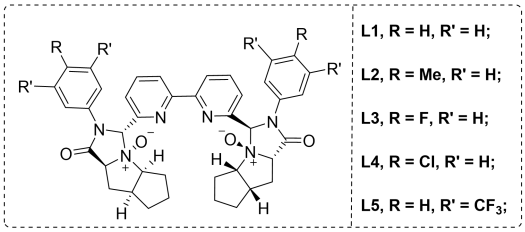
To commence our studies, the reaction between 5-amino pyrazoles **1a**[8] and α,β-unsaturated 2-acyl imidazole **2a** was conducted in the presence of 11 mol % of L1 and 10 mol % of $Ni(OTf)_2$ in DCM at room temperature, resulting in the esterified Michael addition/Cyclization[9] product 3a in 97% yield with 98% ee (Table 1, entry 1). Inspired by this promising result, a variety of $Ni(OTf)_2$ with different chiral ligands were investigated in the title reaction (entries 2-5). To our delight, L2-L4 obtained excellent enantioselectivity, giving the desired product in 95-96% yield with 95-98% ee (entries 2-4). While in the presence of L5, the reaction could afford product 3a with 72% ee (entry 5). Next, we screened the metal and found that $Ni(OTf)_2$ is still the best. Further screening of solvents revealed that DCM was still the best solvent. Further decreasing the catalyst loading to 5.5 mol % of L1 and 5 mol % of $Ni(OTf)_2$, the reaction could still maintain the reactivity and generate desired product **3a** in 97% yield with 98% ee (entry 13).

Table 1. Optimization of the Reaction Conditions[a]



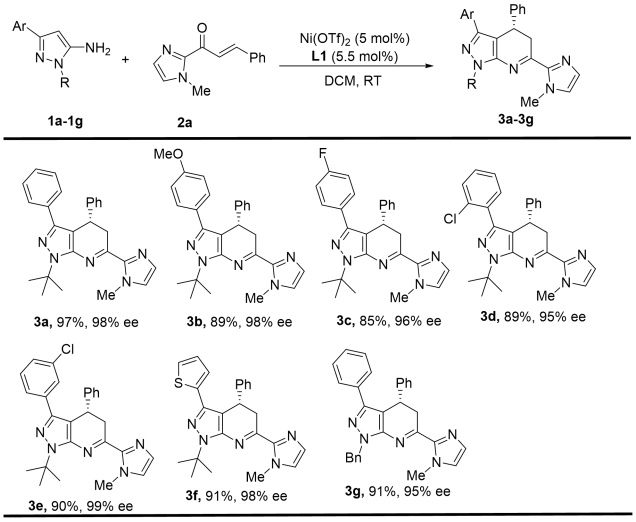


entry	Ligand	solvent	time(h)	yield (%)[b]	ee(%)[c]
1	L1	DCM	24	97	98
2	L2	DCM	24	95	98
3	L3	DCM	24	95	98
4	L4	DCM	24	96	95
5	L5	DCM	24	94	72
6[d]	L1	DCM	24	93	86
7[e]	L1	DCM	24	95	2
8[f]	L1	DCM	24	92	58
9	L1	$CHCl_3$	24	96	30
10	L1	DCE	24	95	96
11	L1	THF	24	95	97
12	L1	CH_3CN	24	92	97
13[g]	L1	DCM	26	97	98

[a]Reaction conditions: $Ni(OTf)_2$ (10 mol %), **L1-L5** (11 mol %), **1a** (0.12 mmol), and **2a** (0.10 mmol) in 1.0 mL of CH_2Cl_2 at 25 °C. [b]Isolated yield after flash chromatography. [c]Determined by HPLC analysis.[d]$Ni(ClO_4)_2{\cdot}6H_2O$ (10 mol %), **L1** (11 mol %). [e]$Cu(OTf)_2$ (10 mol %), **L1** (11 mol %). [f]$Zn(OTf)_2$ (10 mol %), **L1** (11 mol %). [g]$Ni(OTf)_2$ (5 mol %), **L1** (5.5 mol %).

With the optimized reaction conditions in hand, a variety of 5-aminopyrazoles **1** were employed to test the generality of this asymmetric Michael addition/Cyclization process (Scheme 2). Initially, 5-aminopyrazoles with electron-donating substituted phenyl ring were evaluated, such as methoxyl, and **3b** in good yield (89%) with excellent enantioselectivity (98%) was achieved. The introduction of electron-withdrawing groups such as F and Cl substituents on the phenyl rings also afforded the corresponding products (**3c-3e**) in 85-90% yields with 95-99% ee values. 5-aminopyrazole bearing hetero-aromatic substituent could afford the desired products **3f** with excellent enantioselectivity (98% ee). Furthermore, the replacement of N-^{t}Bu with Bn of 5-aminopyrazole has no influence on the outcome of the reaction, affording the corresponding product **3g** in excellent yield with excellent enantioselectivity (Scheme 2, **3g**, 91%, 95% ee).

Scheme 2. Substrate Scope: 5-aminopyrazoles 1.[a]

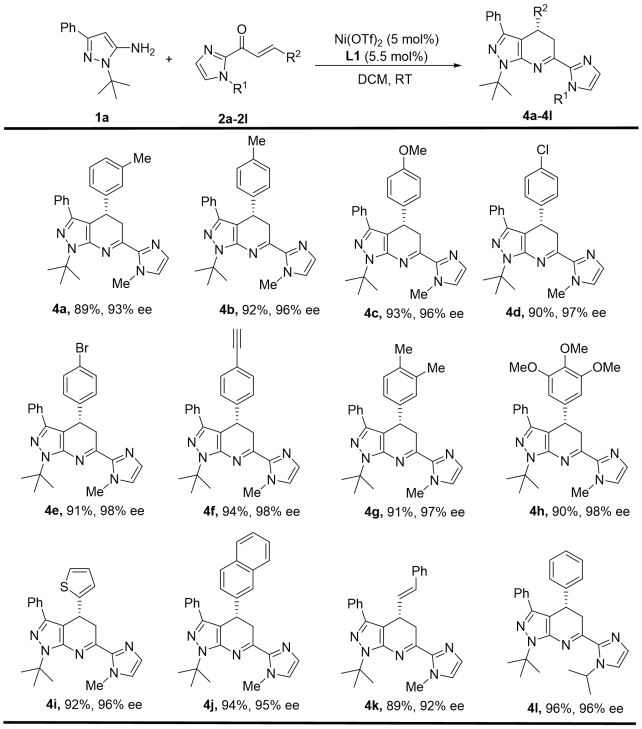


[a]Reaction conditions: $Ni(OTf)_2$ (5 mol %), **L1**(5.5 mol %), **1** (0.12 mmol), and **2a** (0.10 mmol) in 1.0 mL of CH_2Cl_2 at 25 °C.

Further examination of the substrate scope of all sorts of α,β-unsaturated 2-acyl imidazoles, which were employed to test the generality of this asymmetric Michael addition/Cyclization process (Scheme 3). Initially, α,β-unsaturated 2-acyl imidazoles with electron-donating substituted phenyl ring were evaluated, and in all case (**4a-4c**, **4g-4h**), high yields (89-93%) with excellent enantioselectivities (93-98%) were achieved. The absolute stereochemistry of **4c** was assigned unambiguously by single-crystal X-ray diffraction analysis and that of the other derivatives were assigned by analogy (for details see the supporting information).[10] The introduction of electron-withdrawing groups such as Cl and Br substituents on the phenyl rings also afforded the cooresponding products (**4d-4e**) in 90-91% yields with 97-98% ee values. The introduction of ethynyl group on the phenyl rings also afforded the corresponding product (**4f**) in 94% yield with 98% ee values. The substrates with 2-naphthyl or hetero-aromatic substituents worked well, affording **4i-4j** in 92-94% yields with up to 96% ee. In addition to aromatic substituents, alkyl substituents such as styryl-substituted α,β-unsaturated 2-acyl imidazoles were also tolerated, delivering the desired product (**4k**) in 89% yield with 92% enantiomeric excess. In addition, the replacement of N-Me with ^{i}Pr of α,β-unsaturated 2-acyl imidazoles has no influence on the outcome of the reaction, affording the

corresponding product in good yield with excellent enantioselectivity (Scheme 3, **4l**).

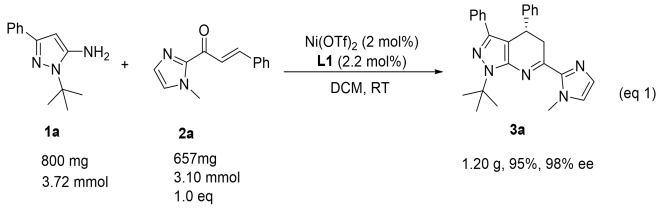
Scheme 3. Substrate Scope: α,β-Unsaturated 2-Acyl Imidazoles.[a]



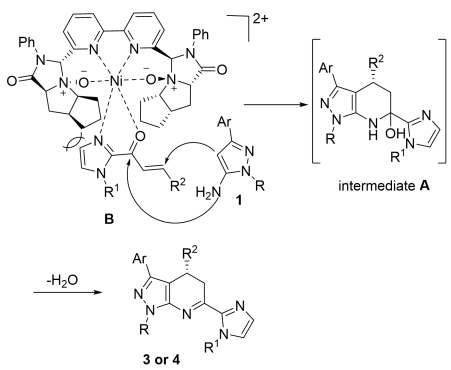
[a]Reaction conditions: $Ni(OTf)_2$ (5 mol %), **L1**(5.5 mol %), **1a** (0.12 mmol), and **2** (0.10 mmol) in 1.0 mL of CH_2Cl_2 at 25 °C.

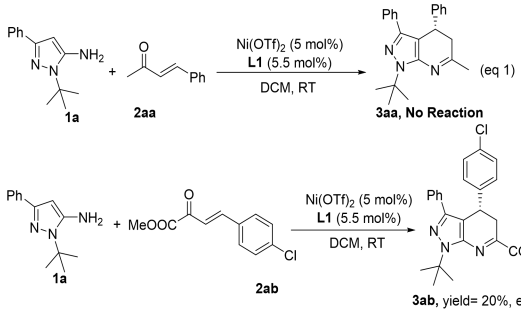
To evaluate the synthetic potential of this catalytic system, a gram-scale reaction of α,β-unsaturated 2-acyl imidazole **2a** (657 mg/3.10 mmol) with 5-aminopyrazole 1a (800 mg/3.72 mmol) was conducted in the presence of 2.2 mol % of **L1** and 2.0 mol % of $Ni(OTf)_2$ in DCM at room temperature. Gratifyingly, the reaction proceeded smoothly to afford 3a in 95% yield with 98% ee (eq 1, Scheme 4).

Scheme 4. Gram-scale experiments of product **3a**.



Scheme 5. Proposed mechanism and control experiments.





The proposed mechanism was shown in **Scheme 5**. Firstly, the α,β-unsaturated 2-acyl imidazoles **2a** was activated by nickel catalyst through bidentate N,O-coordination to acquire **B**. Simultaneously, 5-amino pyrazoles **1** attacks **B** to provide intermediate **A** with high regioselectivity controlled by the nickel catalyst. Then intermediate **A** generate desired product **3** or **4** by releasing H_2O. To study the coordination between nickel catalyst and α,β-unsaturated 2-acyl imidazoles **2**, a series of control experiments were carried out. Firstly, replaced the starting material **2a** with **2aa** or β,γ-unsaturated ketoesters **2ab**, the reaction did not react or proceed smoothly, which indicated the importance of 2-acyl imidazole group.

To sum up, we have developed a newly prepared C2-symmetric chiral bipyridine-N,N'-dioxides from optically pure (1S,3S,5S)-2-Azabicyclo[3,3,0]octane-3-carborylic acid benzyl ester hydrochloride and successfully applied them to synthesize chiral pyrazolo[3,4-b]pyridine analogues. In the presence of 5.5 mol % of **L1** and 5.0 mol % of $Ni(OTf)_2$ in DCM at room temperature, the corresponding products were obtained in good to excellent yields (85-97%) with excellent enantioselectivities (up to 99%). Remarkably, this protocol exhibits extraordinary advantages in terms of reactivity and enantioselectivity, given the fact that as low as 2.2 mol % of L1 and 2.0 mol % of $Ni(OTf)_2$ can promote the title reaction on gram scale to afford desired product with excellent enantioselectivity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and spectroscopic data (PDF)

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Notes

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(10) CCDC 2313276 (for **4c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.