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α,β-Unsaturated Amides as Dipolarophiles: Catalytic Asymmetric *Exo*-selective 1,3-Dipolar Cycloaddition with Nitrones

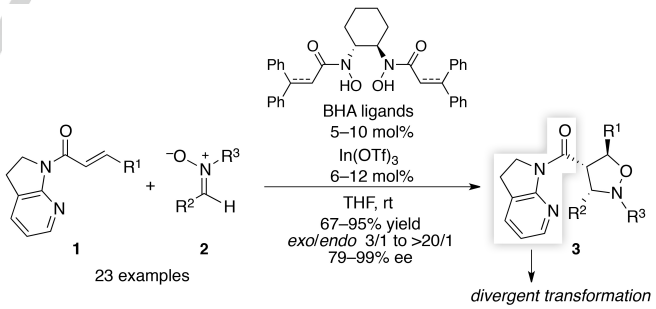
Ming Zhang,[a] Naoya Kumagai,*[a] and Masakatsu Shibasaki*[a]

Dedication ((optional))

Abstract: 1,3-Dipolar cycloaddition is a commonly exploited method to access 5-membered chemical entities with a variety of peripheral functionalities and their stereochemical arrangements. Nitrones are isolable 1,3-dipoles that exhibit sufficient reactivity toward electron-deficient olefins in the presence of Lewis acids to deliver highly substituted isoxazolidines. Herein we document that α,β-unsaturated amides, generally regarded as barely reactive in a 1,3-dipolar reaction manifold, were effectively activated using the designed 7-azaindoline auxiliary in an $In(OTf)_3$/bishydroxamic acid catalytic system. The broad substrate scope and clean removal of the 7-azaindoline auxiliary from the product highlight the synthetic utility of the present catalysis.

Introduction

Given the inherent nature of cycloaddition reactions to forge two bonds in one event, they are extensively utilized to construct molecular architectures of interest.[1] The 1,3-dipolar cycloaddition (1,3-DC) reaction is a cycloaddition reaction variant that couples 1,3-dipoles and dipolarophiles to produce 5-membered ring systems.[1c,2] Nitrones are an archetypal 1,3-dipole commonly used in 1,3-DC reactions with dipolarophiles having multiple bonds, allowing for expeditious access of multi-substituted isoxazolidines. The 1,3-DC reaction was first rendered catalytic and asymmetric by Jørgensen et al., in which a Ti(IV)/TADDOL complex promoted the reaction with oxazolidinone-based electron-deficient olefin as a dipolarophile in an *exo*-selective manner.[2b,3] This discovery triggered the development of catalytic asymmetric 1,3-DC reactions of alkenoyl oxazolidinones,[4] including highly *endo*-selective and enantioselective examples.[5] Palomo et al. and Evans et al. reported that different dipolarophiles with chelating characteristics, e.g., α'-hydroxy enones[6] and 2-alkenoyl imidazoles,[7] are potential substrates. Further exploration of bidentate dipolarophiles revealed that α'-phosphoric enones,[8] alkenoylpyridine *N*-oxides,[9] alkenoyl pyrazoles,[10] and alkenyl 2-pyridylsulfones[11] are also compatible in catalytic asymmetric 1,3-DC reactions. In contrast to the prior reports of the above-mentioned bidentate dipolarophiles exhibiting *endo*-selectivity, except for Jørgensen's pioneering work, Sibi et al. reported that 2-alkenoyl-3-pyrazolidinones[12] and α,β-disubstituted alkenyl imides[13] preferentially produce *exo*-cycloadducts with high enantioselectivity under Cu(II)/bisoxazoline catalysis. Alkylidene malonates[14] and 1,3-thiazolidine-2-thiones[15] were later revealed to exhibit *exo*-selectivity. Although more reactive monodentate enals are also incorporated in the catalytic asymmetric 1,3-DC reaction manifold with a variety of organocatalytic and metal-based catalytic systems, the majority of them are *endo*-selective reactions,[16] with some exceptions in which ketonitrones are employed.[16p,16s] While organocatalytic 1,3-DC of nitroalkenes provide *exo*-cycloadducts,[17] the number of examples of *exo*-selective 1,3-DC reactions remains limited despite extensive research spanning more than two decades.[10, 18] [19] Herein we document our exploration of *exo*-selective 1,3-DC reactions using α,β-unsaturated 7-azaindoline amides **1**. α,β-Unsaturated amides are generally less electrophilic than other classes of α,β-unsaturated carbonyl compounds and nitroolefins, and thus barely act as dipolarophiles except for aromatic amides[10] and imides.[3-5,15] α,β-Unsaturated 7-azaindoline amides engaged in 1,3-DC reactions with both aromatic and aliphatic nitrones **2** by the actions of a catalyst comprising $In(OTf)_3$ and modified Yamamoto's bishydroxamic acid (BHA) ligands,[20] affording *exo*-cycloadducts in a highly enantioselective manner. Divergent conversion of the amide functional group highlights the synthetic utility of the present catalysis.



Scheme 1. *Exo*-selective catalytic asymmetric 1,3-DC reaction of 7-azaindoline amides **1** and nitrones **2**.

Results and Discussion

In the course of our ongoing research, we reasoned that α,β-unsaturated 7-azaindoline amides **1** are viable dipolarophiles in catalytic asymmetric 1,3-DC reactions. The 7-azaindoline amides are characterized by their intrinsic stability and acquired reactivity in the presence of suitable Lewis acids, which is ascribed to a conformational change in the amide

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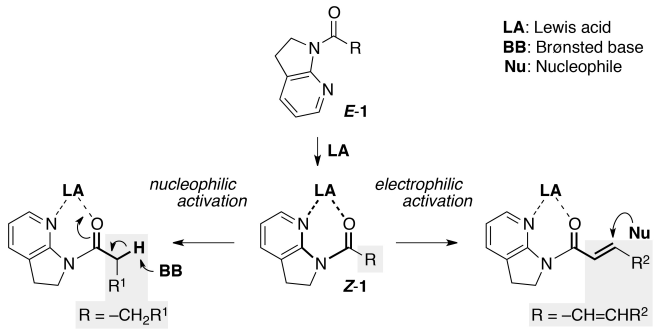
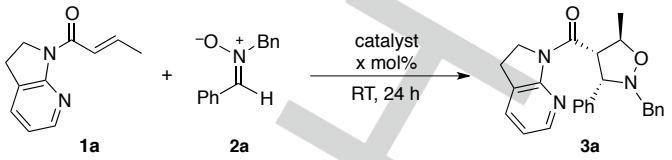


Figure 1. Utility of 7-azaindoline amides **1** as pronucleophiles and electrophiles.

geometry; the stable *E*-conformer is switched to a *Z*-conformer via bidentate coordination (Figure 1). The activated *Z*-conformer elicits masked reactivity to allow for catalytic enolization (nucleophilic activation)[21] and also serves as a Michael acceptor when conjugated with a double bond (electrophilic activation).[22] Given the electrophilic activation mode of the α,β-unsaturated amide by Lewis acids, we began screening chirally decorated Lewis acidic catalysts for a 1,3-DC reaction of amide **1a** and nitrone **2a** (Table 1). A Cu(II) and In(III) complex of *t*Bu-PyBox ligand **L1** preferentially delivered *exo*-cycloadduct **3a,** albeit in low yield and with low enantioselectivity (Entries 1,2). BHA-type ligands with $In(OTf)_3$ exhibited generally higher catalytic activity, and **BHA-2** with 3,3-diphenylpropionic hydroxamic acid units significantly outperformed other structurally similar BHA ligands, e.g., **BHA-1** and **BHA-3** (Entries 3–5). **BHA-2** was uniquely effective with $In(OTf)_3$ and the use of other metal salts, e.g., $Cu(OTf)_2$ and $Ni(OTf)_2$, gave significantly lower stereoselectivity (Entries 4,6,7). The ligand substantially accelerated the reaction, which barely proceeded in the absence of the ligand (Entry 8). A brief survey of solvents identified THF as optimal and the reaction reached completion with 5 mol% of catalyst at a higher concentration (Entries 9–13).

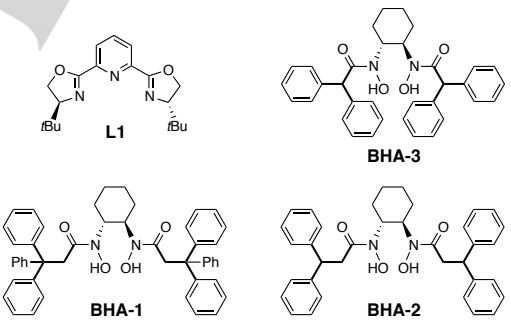
The electrophilic activation mode proposed in Figure 1 was supported by NMR analysis of **1a** in the absence and presence of the $In(OTf)_3$/**BHA-2** complex (Figure 2). The α-proton ($\mathbf{H_a}$) of **1a** was abnormally downfielded close to 8 ppm, which is indicative of *E*-conformation and intramolecular hydrogen bonding with the pyridyl nitrogen of the azaindoline (Figure 2a). Addition of the $In(OTf)_3$/**BHA-2** complex to **1a** resulted in a significant upfield shift of H_a (> 1 ppm), suggesting that the hydrogen bonding was abandoned to render bidentate coordination to the In(III) complex in a *Z*-conformation (Figure 2b). The observed NOE between the α-proton ($\mathbf{H_a}$) and $\mathbf{H_c}$ on the azaindoline provided further support for *Z*-conformation.[23] The downfield shift of the β-proton ($\mathbf{H_b}$) implied that electrophilic activation was manifested for the subsequent 1,3-DC reaction with incoming nitrones. In contrast to explicit peaks of **1a**, NMR signals derived from $In(OTf)_3$/**BHA-2** were very broad, giving little information. This observation is assumed to indicate that the mixture of $In(OTf)_3$ and **BHA-2** did not form a discrete complex and gave the oligomeric species in equilibrium.[24] The

Table 1. Optimization of catalytic asymmetric 1,3-DC reaction of α,β-unsaturated 7-azaindoline amide **1a** and nitrone **2a**.[a]



Entry	Catalyst	x	Solvent	Yield[b] [%]	*exo*/*endo*[b]	*ee*[c] [%]
1	$Cu(OTf)_2$/**L1**	10	CH_2Cl_2	26	7/1	17
2	$In(OTf)_3$/**L1**	10	CH_2Cl_2	18	2/1	26
3	$In(OTf)_3$/**BHA-1**	10	CH_2Cl_2	39	7/1	36
4	$In(OTf)_3$/**BHA-2**	10	CH_2Cl_2	94	>20/1	95
5	$In(OTf)_3$/**BHA-3**	10	CH_2Cl_2	21	4/1	65
6	$Cu(OTf)_2$/**BHA-2**	10	CH_2Cl_2	99	2/1	19
7	$Ni(OTf)_2$/**BHA-2**	10	CH_2Cl_2	12	10/1	19
8	$In(OTf)_3$	10	CH_2Cl_2	7	—	0
9	$In(OTf)_3$/**BHA-2**	10	$CHCl_3$	86	>20/1	96
10	$In(OTf)_3$/**BHA-2**	10	toluene	12	2/1	—
11	$In(OTf)_3$/**BHA-2**	10	THF	95	>20/1	97
12	$In(OTf)_3$/**BHA-2**	5	THF	60	>20/1	97
13[d]	$In(OTf)_3$/**BHA-2**	5	THF	93	>20/1	98

[a] **1a**: 0.1 mmol, **2a**: 0.12 mmol, 0.2 M. 1.2 equiv of ligand was used relative metal salts. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPL analysis. [d] Run on 0.5 M with 2 equiv of **2a** (0.2 mmol).



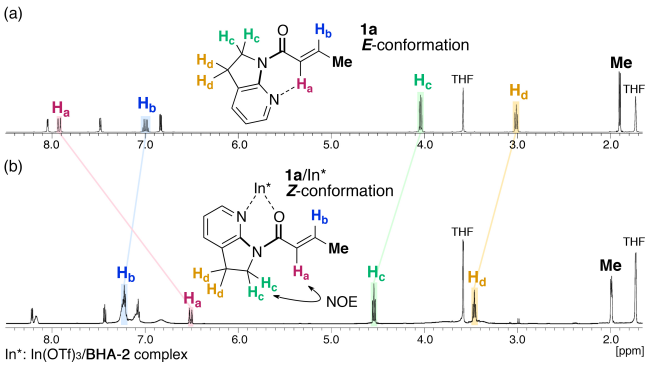


Figure 2. ^{1}H NMR analysis of amide **1a** in the absence and presence of the In(III)/**BHA-2** complex. (a) **1a** in THF-d_8. (b) **1a** : $In(OTf)_3$/**BHA-2** = 1:1 in THF-d_8.

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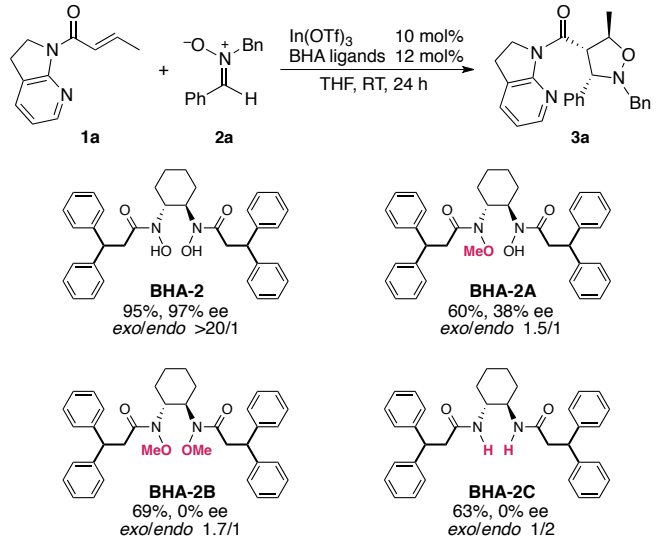
Table 2. Catalytic asymmetric 1,3-DC reaction of **1a** and **2a** with **BHA-2** and its derivatives.[a]



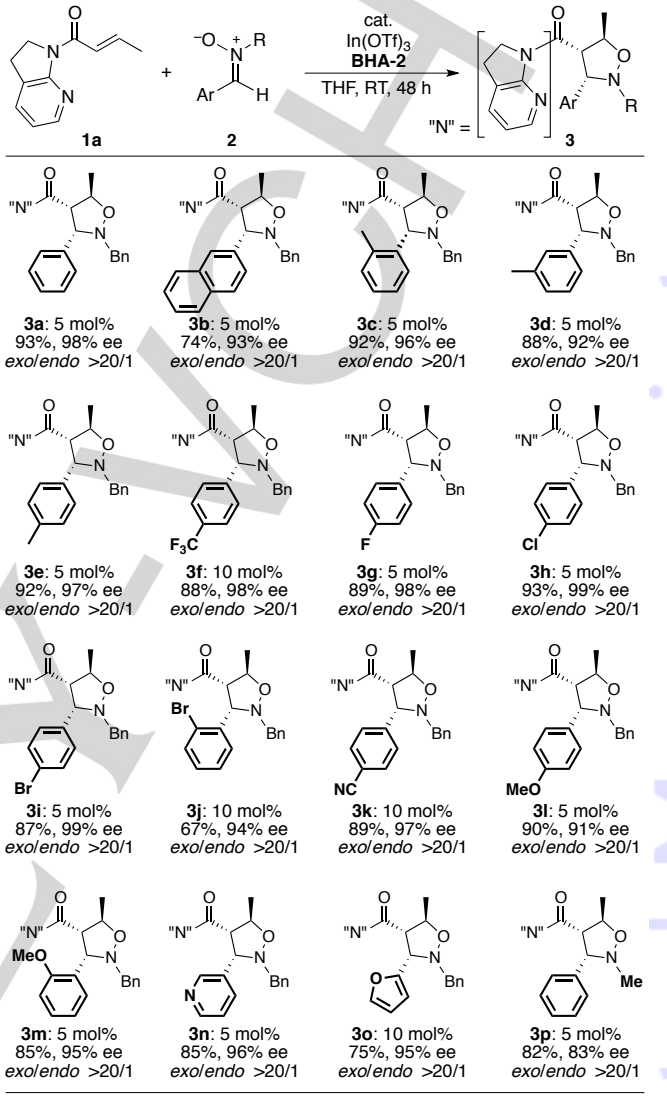
[a] **1a**: 0.1 mmol, **2a**: 0.12 mmol, 0.2 M. Yield and *exo*/*endo* ratio were determined by ^{1}H NMR analysis of the crude mixture. Enantioselectivity of the major diastereomers is shown.

bishydroxamic acid units proved essential for both efficient reaction progress and high stereoselectivity (Table 2). In the identical substrate set in Table 1, the reactions with modified ligands mono-*O*-methylated **BHA-2A** and di-*O*-methylated **BHA-2B** gave product **3a** in lower yield and substantially decreased stereoselectivity; and the latter gave a virtually racemic product. Together with the lack of enantiodiscrimination observed for the bisamide analog **BHA-2C**, bishydroxamic acid units in a suitable spatial arrangement were critical for the present *exo*-selective 1,3-DC reaction, although the three-dimensional structure of the complex remained elusive.

The optimized conditions using the In(OTf)$_3$/**BHA-2** catalyst could be generalized for the reactions of various nitrones **2** derived from aromatic aldehydes and 7-azaindoline (*E*)-crotonoylamide **1a** (Table 3).[25] Only *exo*-adducts **3** were obtained in all cases, and the reactions could be conducted at room temperature.[26] High yield and enantioselectivity were observed, irrespective of the substitution pattern of the non-polar substituents (**3b**–**e**). Electron-withdrawing (**3f**–**k**) and -donating groups (**3l**,**m**) were tolerated, but the reaction with *o*-Br substituted nitrone proceeded sluggishly even with 10 mol% of catalyst loading, likely due to steric factors (**3j**). Nitrones bearing a potentially Lewis basic heteroaromatic functional group were applicable (**3n**,**o**), albeit with lower conversion of the 2-furyl substituted product (**3o**). *N*-Me nitrone was accommodated with a marginal loss of enantioselectivity (**3p**).

Unexpectedly, nitrones bearing an aliphatic substituent gave poor results with **BHA-2**, prompting us to further screen BHA-type ligands in the *exo*-selective 1,3-DC reactions (Table 4). Specifically for nitrone **2q**, derived from hexanal, BHA-type ligands in the previous screening set were re-evaluated; **BHA-2,** optimal for aromatic nitrones, exhibited inferior performance compared with **BHA-3**, whose hydroxamic acid units are 1

Table 3. Substrate generality of nitrones in catalytic asymmetric 1,3-DC reaction of α,β-unsaturated 7-azaindoline amide **1a**.[a]

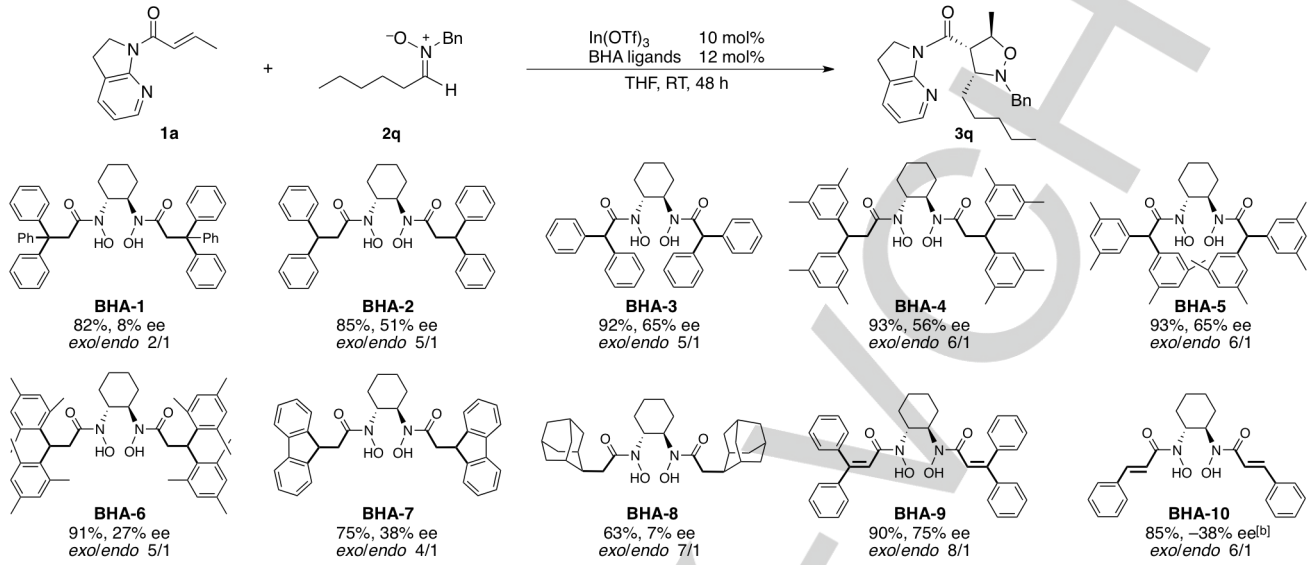


[a] **1a**: 0.1 mmol, **2a**: 0.12 mmol, 0.2 M. 1.2 equiv of **BHA-2** was used relative to In(OTf)$_3$. Isolated yield and ee of *exo*-adducts are shown.

methylene shorter. A similar tendency was observed for 3,5-xylyl analogs **BHA-4** and **BHA-5**. Based on **BHA-2**, a bulkier mesitylene analog (**BHA-6**), linked analog (**BHA-7**), and aliphatic analog (**BHA-8**) were synthesized, but none of them afforded better stereoselectivity than **BHA-2**. Gratifyingly, the rigidified analog **BHA-9** afforded **3q** with reasonably high *exo*/*endo* selectivity (8/1) and enantioselectivity (75% ee for *exo*-isomer). Less demanding cinnamoyl analog **BHA-10** exhibited inferior selectivity.

BHA-9 was useful for *exo*-selective 1,3-DC reactions of aliphatic nitrones **2q**–**s** and α,β-unsaturated amides **1b**–**e** with other β-substituents (Table 5).[27] Nitrones with an α-branched structure afforded slightly better enantioselectivity, reaching 90%

Table 4. Screening of BHA ligands for aliphatic nitrone **2q**.[a]



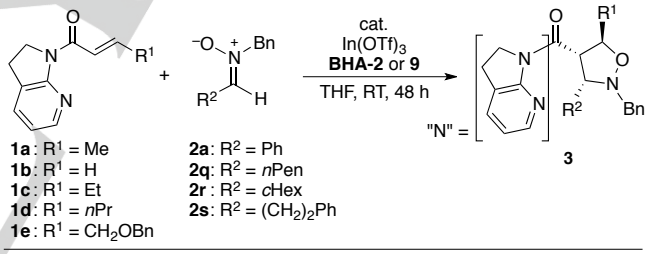
[a] **1a**: 0.1 mmol, **2a**: 0.12 mmol, 0.2 M. Yield and *exo*/*endo* ratio were determined by ^{1}H NMR analysis of the crude mixture. Enantioselectivity of *exo*-**3q** is shown. [b] *ent*-**3q** was obtained as major enantiomer.

ee (**3r**). Amide **1b** without any substituent at the β-position had lower enantioselectivity, and moderate *exo* selectivity and enantioselectivity were observed even with **BHA-9**. Amide **1c**,**d** with longer alkyl chains benefited from the use of **BHA-9**, delivering the desired products **3u,v** in decent yield and with moderate stereoselectivity. In the specific case of amide **1e** possessing an ether-type substituent, **BHA-2** was superior to **BHA-9** and **3w** was obtained with excellent stereoselectivity.

Figure 3 highlights the exclusive utility of the α,β-unsaturated 7-azaindoline amide as a competent dipolarophile in the present catalytic system. In the reaction of nitrone **2a** promoted by the In(OTf)$_3$/**BHA-2** catalyst, a series of α,β-unsaturated amides **4**–**7** was tested. Structurally-related amides **4** and **5** sharing the indoline architecture failed in the reaction, indicating that the nitrogen atom at the 7-position is crucial and supports the the activation mode shown in Figure 2. While a similar activation mode via bidentate coordination to the In(III) complex is possible, amide **6** having a 2-pyridyl group showed no reactivity in the present catalytic system. In general, α,β-unsaturated amides and esters are poor Michael acceptors and dipolarophiles, and simple dimethyl amide **7** and methyl ester **8** remained unchanged as expected.

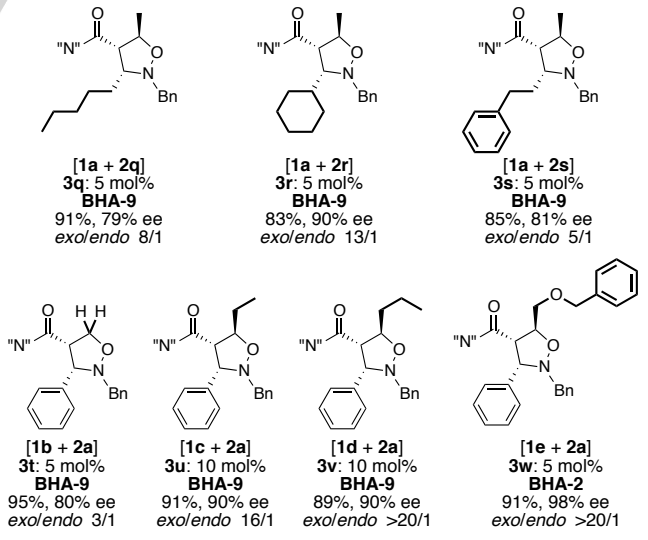
It is important to note the two advantages of the 7-azaindoline unit; it not only enabled the *exo*-selective catalytic activation of 1,3-DC reactions, but also served as a handle for divergent transformation (Scheme 2). The 7-azaindoline amide is bench-stable and easy-to handle, but readily hydrolyzed by treatment with 2M HCl/MeOH at 80 °C to give the corresponding carboxylic acid **9** in quantitative yield. Upon nucleophilic addition of a metallated carbanion or hydride, the transient tetrahedral intermediate was fairly stable to prevent over-alkylation or over-reduction, affording ketone **10** and aldehyde **11** in high yield.

Table 5. Utility of **BHA-9** in catalytic asymmetric 1,3-DC reaction of aliphatic nitrones and differently substituted α,β-unsaturated 7-azaindoline amides **1**.[a]



1a: R^1 = Me
1b: R^1 = H
1c: R^1 = Et
1d: R^1 = *n*Pr
1e: R^1 = CH_2OBn

2a: R^2 = Ph
2q: R^2 = *n*Pen
2r: R^2 = *c*Hex
2s: R^2 = $(CH_2)_2Ph$



[**1a** + **2q**]
3q: 5 mol%
BHA-9
91%, 79% ee
exo/*endo* 8/1

[**1a** + **2r**]
3r: 5 mol%
BHA-9
83%, 90% ee
exo/*endo* 13/1

[**1a** + **2s**]
3s: 5 mol%
BHA-9
85%, 81% ee
exo/*endo* 5/1

[**1b** + **2a**]
3t: 5 mol%
BHA-9
95%, 80% ee
exo/*endo* 3/1

[**1c** + **2a**]
3u: 10 mol%
BHA-9
91%, 90% ee
exo/*endo* 16/1

[**1d** + **2a**]
3v: 10 mol%
BHA-9
89%, 90% ee
exo/*endo* >20/1

[**1e** + **2a**]
3w: 5 mol%
BHA-2
91%, 98% ee
exo/*endo* >20/1

[a] **1**: 0.1 mmol, **2**: 0.12 mmol, 0.2 M. 1.2 equiv of BHA ligand was used relative to In(OTf)$_3$. Isolated yield and enantioselectivity of *exo*-adducts are shown.

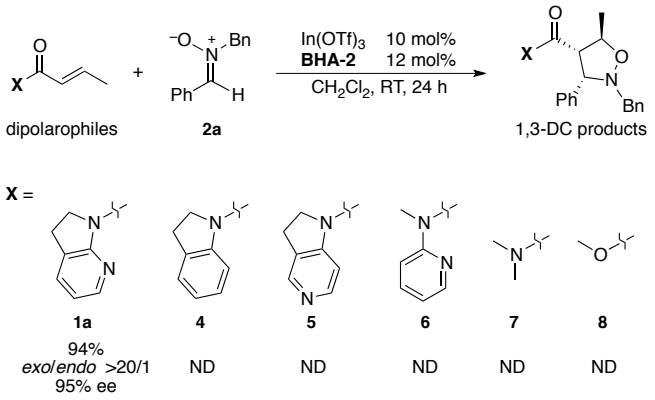
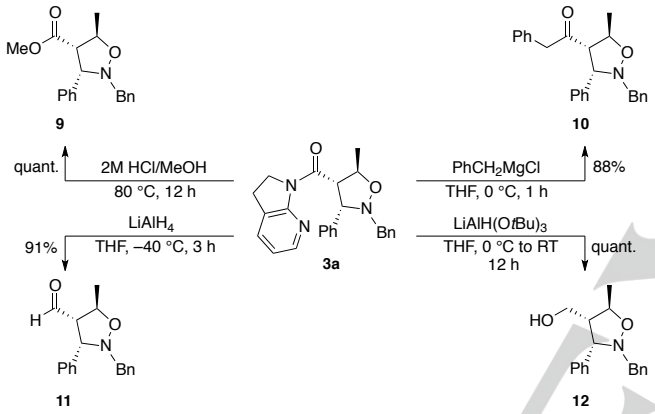


Figure 3. Exclusive reactivity of 7-azaindoline amide **1a** in the present 1,3-DC reaction.



Scheme 2. Divergent transformation of the 7-azaindoline amide moiety of 1,3-DC adduct **3a**.

One-step conversion to primary alcohol **12** was attained with $LiAlH(OtBu)_3$ at room temperature.

Conclusion

We developed an *exo*-selective 1,3-DC reaction of α,β-unsaturated amides and/aliphatic nitrones. The use of 7-azaindoline amide was crucial to elicit both high reactivity and high stereoselectivity. Screening of the BHA ligand in combination with $In(OTf)_3$ identified an optimal In(III)-based catalytic system. Although the structure of the In(III) complex was unclear, the activation mode of α,β-unsaturated 7-azaindoline amide was demonstrated by ^1H NMR analysis. The synthetic utility associated with broad substrate generality was leveraged by divergent transformation of a 7-azaindoline moiety.

Acknowledgements

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Keywords: cycloaddition • asymmetric catalysis • indium • isoxazolidine • bishydroxamic acid

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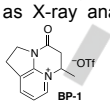
[23] See Supporting Information.

[24] DOSY spectrum of $In(OTf)_3$/**BHA-2** suggested the formation of oligomeric species. See Supporting Information for details.

[25] In some cases, byproduct **BP-1** was associated in ca. 5%, which was formed by intramolecular cyclization of **1a**. Spectroscopic data as well as X-ray analysis of **BP-1** are presented in Supporting Information.



BP-1

[26] Absolute configuration of **3a** was unequivocally determined by X-ray crystallographic analysis. Stereochemistry of other products was deduced by analogy.

[27] β-Aryl α,β-unsaturated 7-azaindoline amides exhibited low reactivity under optimized conditions and reactions barely proceeded at room temperature.

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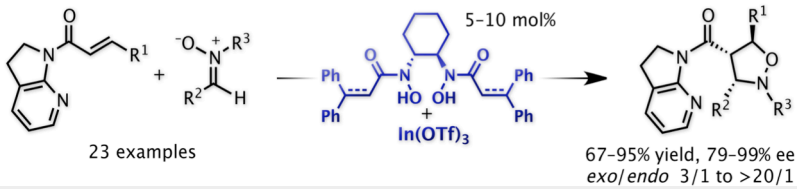

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α,β-Unsaturated Amides as Dipolarophiles; Catalytic Asymmetric *Exo*-selective 1,3-Dipolar Cycloaddition with Nitrones

Text for Table of Contents 1,3-Dipolar cycloaddition is a commonly exploited method to access 5-membered chemical entities with a variety of peripheral functionalities and their stereochemical arrangements. Nitrones are isolable 1,3-dipoles that exhibit sufficient reactivity toward electron-deficient olefins in the presence of Lewis acids to deliver highly substituted isoxazolidines. Herein we document that α,β-unsaturated amides, generally regarded as barely reactive in a 1,3-dipolar reaction manifold, were effectively activated using the designed 7-azaindoline auxiliary in an $In(OTf)_3$/bishydroxamic acid catalytic system. The broad substrate scope and clean removal of the 7-azaindoline auxiliary from the product highlight the synthetic utility of the present catalysis.