Synthetic Methods

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Catalytic Asymmetric Synthesis of Substituted 3-Hydroxy-2-Oxindoles**

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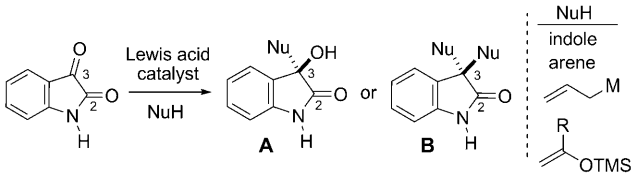
Substituted 3-hydroxy-2-oxindoles are important core structures found in many natural products[1] and pharmaceutical lead compounds.[2] Despite the prevalence of bioactive oxindole structures, there is not currently a general asymmetric method for the addition of a broad range of unactivated electron-rich π nucleophiles to isatins (indole-2,3-diones).[3,4] Although the development of an asymmetric reaction is the primary challenge, the addition of electron-rich arenes is further complicated by the competing formation of achiral 3,3-diaryl oxindole products (such as **B**, Scheme 1).[5,6]

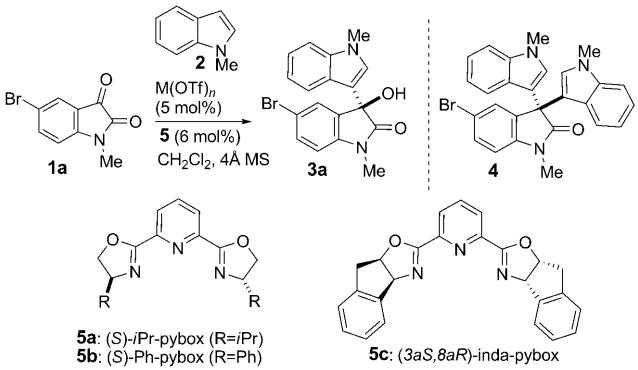


Scheme 1. Competing formation of monoaddition (**A**) and double-addition (**B**) oxindole products in the Lewis acid catalyzed addition of nucleophiles to isatin. TMS = trimethylsilyl.

Herein, we compare the activity and selectivity of diverse Lewis acid catalysts and show that chiral scandium(III) and indium(III) complexes offer a general method to control both the reactivity of the direct monoaddition of indole and arene nucleophiles to isatins and the absolute configuration of the product. Reactions involving catalytic asymmetric addition to isatins have been reported previously; however, this direct method is the first catalytic asymmetric addition of indole nucleophiles to an isatin.

We examined a series of Lewis acid catalysts (Pd^{II}, Cu^{II}, In^{III}, Sc^{III}, La^{III}, and Y^{III} complexes) capable of activating 1,2-dicarbonyl electrophiles to classify the effects of the metal, ligand, and temperature for addition reactions of nucleophiles to isatins. We used the addition of *N*-methylindole (**2**) to 5-bromo-*N*-methylisatin (**1a**) as a model reaction and evaluated three criteria: reactivity, selectivity for the monoaddition product **3**, and enantioselectivity (Table 1). Metal complexes with slower reaction rates were observed to be active for the addition reaction with limited (or no) formation of the 3,3′-bisindolyl product **4**; however, both the use of a low temperature and the presence of a chiral ligand also promoted the

Table 1: Metal and ligand effects for the addition of *N*-methylindole.[a]



$M(OTf)_n$	Ligand	*T* [°C]	*t* [h]	Yield [%][b] **3a**	**4**	*ee* [%][c]
$Sc(OTf)_3$	none	−20	0.25	40	58	0
$Sc(OTf)_3$	none	23	0.08	45	51	0
$ScCl_3$	none	23	18	99	0	0
$Y(OTf)_3$	none	23	4	67	25	0
$Y(OTf)_3$	none	−20	96	99	0	0
$In(OTf)_3$	none	−20	0.5	47	50	0
$Cu(OTf)_2$	none	−20	3	15	83	0
$Zn(OTf)_2$	none	23	72	95	0	0
$[Pd(MeCN)_4](BF_4)_2$	none	−20	24	62	0	0
$Sc(OTf)_3$	**5a**	−20	1	98	0	73 (*R*)
$Sc(OTf)_3$	**5b**	−20	1	95	0	73 (*S*)
$Sc(OTf)_3$	**5c**	−20	1	98	0	99 (*R*)
$Sc(OTf)_3$	**5c**	23	1	96	4	93 (*R*)
$ScCl_3$	**5c**	23	43	99	0	78 (*R*)
$Y(OTf)_3$	**5c**	23	50	84	14	52 (*R*)
$In(OTf)_3$	**5c**	−20	1	94	0	99 (*R*)
$Zn(OTf)_2$	**5c**	−20	72	23	0	0
$Cu(OTf)_2$	(*S*)-*i*Pr-box	−20	76	17	0	1 (*R*)
$Cu(OTf)_2$	**5c**	−20	73	17	0	5 (*R*)
$PdCl_2$	(*R*)-binap	−20	94	10	0	2 (*R*)
$PdCl_2/AgSbF_6$	(*R*)-binap	−20	76	58	0	1 (*R*)
$[Pd(MeCN)_4](BF_4)_2$	(*R*)-binap	−20	94	41	0	7 (*R*)

[a] All reactions were performed in CH_2Cl_2 (0.2 M) under argon with 3 equivalents of the indole **2** in the presence of 4 Å molecular sieves. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC analysis on a chiral phase with an AD-H column. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, Tf = trifluoromethanesulfonyl, *i*Pr-box = 2,2-bis((4*S*)-(—)-4-isopropyloxazoline)propane, pybox = bis(oxazolinyl)pyridine.

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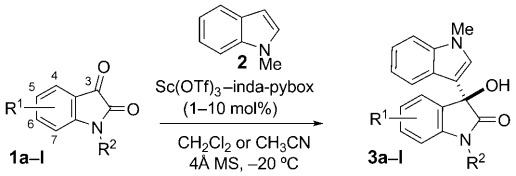
selective formation of the monoaddition product **3a**. The choice of the chiral metal complex proved to be important for yield and enantioselectivity, whereby the use of the inda-pybox ligand led to high enantioselectivity with several metal complexes.[7] In the presence of either the scandium(III)–inda-pybox or the indium(III)–inda-pybox catalyst, the addition of *N*-methylindole proceeded efficiently to give the 3-indolyl-3-hydroxyoxindole **3a** with superb enantioselectivity (99% *ee*) and complete suppression of the formation of the 3,3′-bisindolyl oxindole **4** at −20 °C.[8] These metal-catalyzed reactions overcome the competing formation of the 3,3-diaryl oxindole products and represent the first catalytic asymmetric addition of an indole to an isatin. This direct addition method complements the asymmetric addition of activated arenes and alkenes reported previously,[4] as well as asymmetric hydroxylation methods.[9]

We examined the scope of the reaction with respect to the isatin electrophile with both commercially available NH isatin reagents and isatins prepared in a single step by N-alkylation (Table 2). Owing to their prevalence in oxindole natural products and medicinal compounds, we focused primarily on halogenated and oxygenated isatins substituted in various positions. The scandium(III)-catalyzed reactions proceeded with excellent yield and enantioselectivity (87–99% *ee*) for the formation of 3-indolyl-3-hydroxy-2-oxindoles **3a–l**, with a catalyst loading as low as 1 mol% for activated isatins (Table 2, entries 1, 2, and 5). Initially, the reactions of unprotected NH isatins **1f–l** proceeded with low yield and enantioselectivity as a result of the limited solubility of the reagent in CH_2Cl_2; however, high yields and enantioselectivities were observed when CH_3CN was used as the solvent. The indium(III)–pybox complex also showed excellent reactivity and enantioselectivity with NH isatins (Table 2, entry 8). Notably, substituents at the C4 position do not hinder this reaction, and excellent enantioselectivity was observed even at room temperature (Table 2, entry 13).[4d] Furthermore, the scandium(III) and indium(III) complexes are among the very few catalyst systems with which addition to unprotected NH isatins is highly successful; thus, protecting-group manipulations can be avoided.

We investigated the scope of this methodology further and compared the effectiveness of scandium and indium catalysts by examining reactivity and selectivity for the addition of a series of electron-rich π nucleophiles (Table 3).[10] With both scandium and indium complexes, unprotected indoles were compatible with the reaction conditions, and the reaction proceeded with high enantioselectivity (Table 3, entries 1–3). Nucleophilic arenes, such as *m*-anisidine (**8**) and 2-methoxyfuran (**10**), also reacted rapidly and with excellent enantioselectivity, at least in the presence of the scandium complex; when the indium complex was used with **10**, the product was formed with 50% *ee* (Table 3, entries 4–7).[11] Under the same conditions with the scandium(III)–pybox catalyst, allylation[12] and aldol reactions[13] also proceeded with high yield and enantioselectivity (Table 3, entries 8–10). Although scandium and indium complexes are known to have similar reactivity profiles, herein we show that indium(III) complexes are less effective for allylation and aldol reactions.[14] Thus, it is particularly notable that a single scandium(III) catalyst system is suitable for the addition of this wide range of nucleophiles.

The stereoinduction observed for this reaction can be rationalized by an octahedral or pentagonal-bipyramidal model (Figure 1). When the amide carbonyl group of the isatin is bound in the apical position, the nucleophile approaches from the *Si* face,[7] consistent with the absolute configuration of the observed products. To investigate the isatin binding mode, we analyzed mixtures of the reaction components by NMR spectroscopy.[15] When $Sc(OTf)_3$ and the pybox ligand were dissolved in either CD_2Cl_2 or CD_3CN, substantial changes in the resonance signals indicated the formation of the scandium(III)–pybox complex; however, the isatin peaks were not shifted when the substrate was mixed with either $Sc(OTf)_3$ or the scandium(III)–pybox complex.[16]

Table 2: Scope of the addition to isatins under the catalysis of $Sc(OTf)_3$–inda-pybox.[a]



Entry	1	R^1	R^2	Catalyst loading [mol%]	*t* [h]	Solvent	Yield[b] [%]	*ee*[c] [%]
1	**1a**	5-Br	Me	1.0	18	CH_2Cl_2	98	99
2	**1b**	5-F	Me	1.0	46	CH_2Cl_2	98	99
3	**1c**	H	Ph	5.0	18	CH_2Cl_2	98	95
4[d]	**1d**	H	Me	5.0	1	CH_3CN	98	96
5	**1e**	7-Br, 5-Me	Me	1.0	18	CH_2Cl_2	90	99
6[d]	**1f**	H	H	5.0	8	CH_3CN	99	90
7	**1g**	5-Br	H	10.0	48	CH_3CN	93	94
8[e]	**1g**			5.0	72	CH_3CN	90	99
9	**1h**	5-F	H	10.0	24	CH_3CN	97	95
10	**1i**	7-F	H	10.0	19	CH_3CN	90	88
11	**1j**	5-OCF_3	H	10.0	22	CH_3CN	93	91
12[d]	**1k**	5-OCH_3	H	10.0	41	CH_3CN	73[f]	87
13[d]	**1l**	4-Cl	H	5.0	17	CH_3CN	97	94

[a] All reactions were performed under argon (0.2 M solution) with 3 equivalents of the indole **2** in the presence of 4 Å molecular sieves. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC analysis on a chiral phase with an AD-H column. [d] The reaction was performed at room temperature. [e] The reaction was performed with $In(OTf)_3$–inda-pybox. [f] The 3,3′-bisindolyl oxindole product was also isolated in 15% yield.[6]

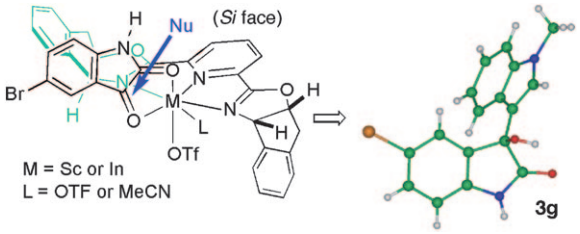
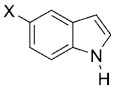
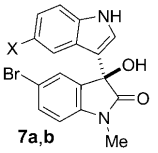
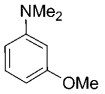
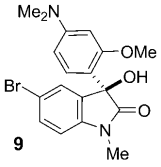
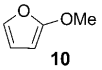
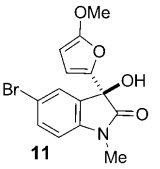
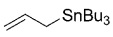
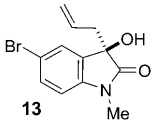
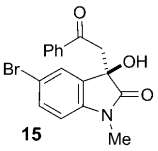


Figure 1. Stereochemical model for the addition reaction and X-ray crystal structure of **3g**.

Table 3: Nucleophilic addition to isatin **1a** and comparison of the $Sc(OTf)_3$–inda-pybox and $In(OTf)_3$–inda-pybox catalysts.[a]

Entry	Metal	*T* [°C]	*t* [h]	NuH	Product	Yield[b] [%]	*ee*[c] [%]
					 **7a,b**		
1	Sc	−20	1	**6a**, X = H	**7a**, X = H	80	99
2	Sc	−40	48	**6b**, X = OMe	**7b**, X = OMe	84	88
3	In	−40	2	**6b**	**7b**	77	89
4[d]	Sc	−20	48	 **8**	 **9**	87	97
5[d]	In	23	24			88	91
6	Sc	−20	0.08	 **10**	 **11**	82	94
7	In	−40	0.17			82	50
8	Sc	−20	2	 **12**	 **13**	90	80
9	In	−20	4			97	42
10	Sc	−40	18	 **14**	 **15**	84	95
11	In	−40	1			15	50

[a] Reactions were performed with 5 mol% of the catalyst and 3 equivalents of the nucleophile in CH_2Cl_2 (0.2 M) under argon in the presence of 4 Å molecular sieves. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC analysis on a chiral phase with an AD-H or AS-H column. [d] The reaction was performed with 10 mol% of the catalyst.

Further mechanistic insight was gained through the use of electrospray ionization mass spectrometry (ESIMS) for the analysis of dynamic intermediates.[17] We injected mixtures of isatin **1a**, $Sc(OTf)_3$, and the inda-pybox ligand **5c** into the mass spectrometer to observe isatin binding. Peaks were detected at *m*/*z* 736.5, 799.8, and 877.5, which correspond to the complexes $[Sc(OTf)_2(\text{inda-pybox})]^+$, $[Sc(OTf)_2(CH_3CN)(\text{inda-pybox})+Na]^+$, and $[Sc(OTf)(CH_3CN)(\text{inda-pybox})(\mathbf{1a})-CH_3+Na]^+$, respectively. Further structural and mechanistic studies are in progress.

In summary, we have evaluated various Lewis acid catalysts and identified chiral scandium(III) and indium(III) pybox complexes as efficient catalysts for the direct addition of indoles and electron-rich arenes to isatin electrophiles. This operationally simple method does not require the use of activated arenes or transmetalation conditions. High yields and high enantioselectivity were observed for substrates with various substitution patterns, including unprotected isatins and indoles, which are directly applicable to the synthesis of natural products and biologically active oxindoles. The most efficient scandium(III)–pybox complex also promoted allylation and aldol reactions. Because 1,2-dicarbonyl compounds are important electrophiles, this comparison of reactivity and selectivity with various Lewis acid complexes will help guide the selection of appropriate Lewis acids in reactions of other 1,2-dicarbonyl compounds.

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[8] The structure of the monoaddition product was confirmed by HRMS and the absolute configuration assigned on the basis of X-ray crystallography (anomalous dispersion method) of **3e**, **3g**, **3l**, **9**, and **13**. CCDC 749352 (**3e**), 749353 (**3g**), 749358 (**3l**), 749355 (**9**), and 749356 (**13**) 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.

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[16] When [D_6]DMSO was used, a 0.4 ppm shift in the signals of the aromatic hydrogen atoms of the isatin was observed upon mixing with either $Sc(OTf)_3$ or the $Sc(OTf)_3$–pybox complex.

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