Asymmetric Catalysis

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Facile and Efficient Enantioselective Hydroxyamination Reaction: Synthesis of 3-Hydroxyamino-2-Oxindoles Using Nitrosoarenes**

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Nitroso compounds are interesting reagents that are used in synthetic organic chemistry mainly because of their application in functional group transformations.[1–2] Nitrosoarenes have been widely recognized as an attractive electrophile in catalytic asymmetric nitroso aldol reactions. Organocatalysts having hydrogen-bond donors such as amide or hydroxy groups were used to control the regioselectivity of the nitroso aldol reaction through hydrogen bonding to nitrogen or oxygen atoms of the nitrosoarene.[2] Usually, the aminoxylation reaction of carbonyl compounds proceeds to give α-oxygenated compounds as the major products because of the higher basicity of the hydrogen bond between the nitrogen and the hydrogen atoms compared with that between the oxygen and hydrogen atoms.[3] In contrast, only a few contributions on the enantioselective hydroxyamination reaction through the electrophilic attack on the nitrogen group of the nitrosoarene have been reported to give α-amino compounds; the reports focused on α-branched aliphatic aldehydes,[4] enolates,[5a] cyclic ketones,[5b] and α-cyanopropionates.[6] However, it is still a challenge to control the chemo- and enantioselectivity of the products by other methods, owing to the high reactivity of nitrosoarene.

Oxindoles constitute an important structural motif in the library of natural products and biologically active drugs. Recently, Barbas and co-workers developed an asymmetric aminoxylation reaction of N-protected 3-substituted-2-oxindoles, thus delivering the desired O adducts (Figure 1a).[3b] The hydroxyamination reaction of oxindoles would provide access to optically active 3-amino oxindole derivatives,[7–8] which present common structural motifs in a variety of bioactive molecules such as NITD609 and SSR-149415, the drug candidates for the treatment of malaria and stress-related disorders, respectively.[9] In view of this, a highly enantioselective synthesis of 3-hydroxyamino-2-oxindole is therefore considered to be in high demand. Such a reaction has been recently reported as being promoted by a cinchona alkaloid catalyst, but there is room for improvement in terms of enantioselectivity and efficiency.[7]

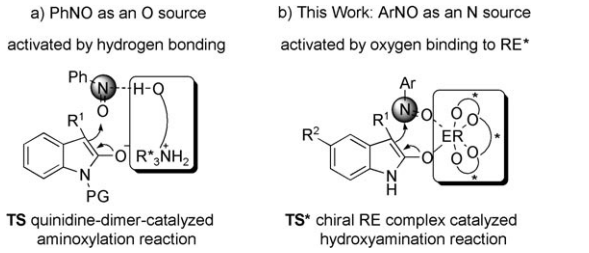

Figure 1. Projected synthesis of chiral hydroxyamino oxindoles. The aminoxylation (a) versus the hydroxyamination (b) reaction of 2-oxindoles. RE = rare-earth metal, PG = protecting group, TS = transition state.

Given our long-standing work in the development of catalysts derived from rare-earth metal/*N*,*N*′-dioxide complexes,[10] we envisioned that a rare-earth metal might coordinate with the oxygen atom of a nitrosoarene as a result of its strong oxygen affinity. The enolate would then preferentially attack the nitrogen atom of the nitroso group to provide direct access to enantioenriched hydroxyamino oxindoles (Figure 1b). Herein, we address these issues and describe a general, practical, and highly enantioselective hydroxyamination of N-unprotected 3-substituted-2-oxindoles with nitrosoarenes in up to 98% yield with 98% *ee* using a Sc^{III}/*N*,*N*′-dioxide complex.

Initially, owing to the importance of protecting-group-free synthetic strategies,[9d,11] we probed the optimal reaction conditions using commercially available 3-methyl-2-oxindole (**1a**) and nitrosobenzene as model substrates. The hydroxyamination reaction was effectively promoted by a 1:1 $Sc(OTf)_3$/**L1** complex in CH_3CCl_3 at 30°C, thus giving the N-nitroso aldol product **2aa** in 88% yield with 90% *ee* and trace amounts of the O-adduct **3** (Table 1, entry 1).[12] The absolute configuration of **2aa** was unambiguously determined to be *R* by comparision of the optical rotation with that of the known compound (Scheme 1). Ligands **L2** and **L3**, which have less sterically hindered substituents at the phenyl ring, afforded less satisfactory results (Table 1, entries 2 and 3). Other rare-earth-metal sources, such as $La(OTf)_3$, $Lu(OTf)_3$, and $Sm(OTf)_3$ only resulted in trace amounts of products. This phenomenon could be attributed to the smallest ionic radius and strongest Lewis acidity that Sc^{III} possesses among the rare-earth metals. When *N*,*N*′-dioxide **L4** (derived from L-proline) and **L5** (derived from L-ramipril) were used instead of **L1** (L-pipecolic acid derived), the enantioselectivities

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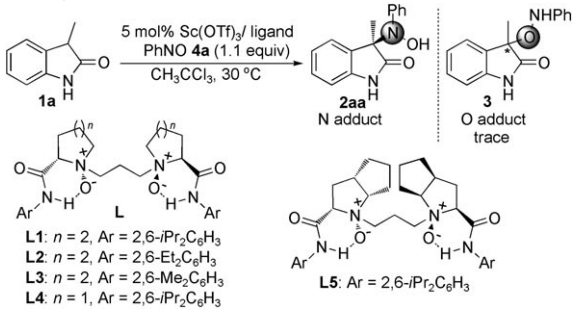
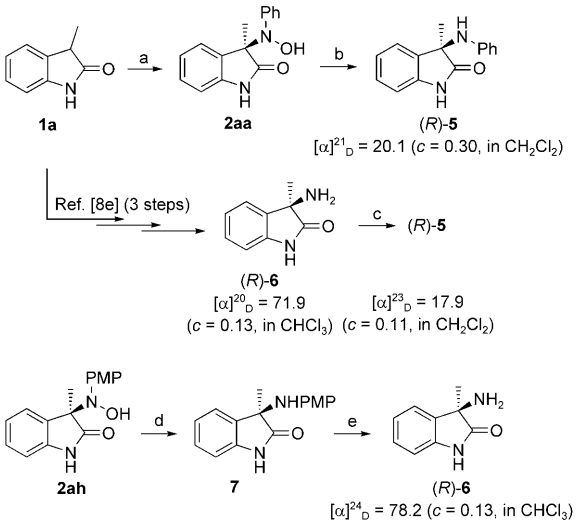
Table 1: Optimization of the reaction conditions.[a]



Entry	Ligand	Ratio of $Sc(OTf)_3$/**L**	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**L1**	1:1	24	88	90 (*R*)
2	**L2**	1:1	24	65	67
3	**L3**	1:1	24	44	54
4	**L4**	1:1	24	90	50
5	**L5**	1:1	24	82	62
6	**L1**	2:1	0.2	93	94
7[d]	**L1**	**1:1.5**	**0.3**	**92**	**95**
8[d,e]	**L1**	1:1.5	3	88	94
9	**L1**	1.5:1	36	61	30
10[f]	–	1:0	72	trace	–
11[d,g]	**L1**	1:1.5	24	95	85
12[d,g,h]	**L1**	1:1.5	24	92	90

[a] Reaction conditions (unless noted otherwise): 0.1 mmol scale with respect to **1**, catalyst (5 mol%), CH_3CCl_3 (1.0 mL). [b] Yield of isolated **2aa**. [c] Determined by HPLC on a chiral stationary phase. [d] Used 3.3 mol% catalyst. [e] The reaction mixture was not stirred. [f] The reaction was performed without **L1**. [g] At 0°C. [h] In 3.0 mL CH_3CCl_3.



Scheme 1. Synthetic utility of this hydroxyamination reaction. Reagents and conditions: a) **1a** (1.47 g, 10 mmol), $Sc(OTf)_3$/**L1** (3.3 mol%), PhNO (1.18 g, 11 mmol), CH_3CCl_3 (40 mL), 30°C, 1.5 h, 82% yield, 94% *ee*; b) **2aa** (2.08 g, 8.2 mmol) 10% Pd/C (0.2 g), $NaBH_4$ (0.912 g, 24 mmol), H_2, MeOH (20 mL), RT, 3 h, 95% yield, 94% *ee*; c) (*R*)-**6** (0.49 g, 3 mmol) Cu_2O (0.014 g, 0.1 mmol), NMP (2 mL), PhI (0.61 g, 3 mmol), 140°C, 72 h, 10% yield, 85% *ee*,; d) **2ah** (28.4 g, 0.1 mmol) 10% Pd/C (3 mg), $NaBH_4$ (11.3 g, 0.3 mmol), H_2, MeOH (5 mL), RT, 3 h; e) CAN (164 mg, 0.3 mmol), aq. CH_3CN (3 mL), 0°C, 10 min, 64% yield in two steps from **2ah**, 92% *ee*. CAN = ammonium cerium nitrate, DMF = *N*,*N*′-dimethylformamaide, NMP = *N*-methylpyrrolidinone, PMP = *p*-methoxyphenyl.

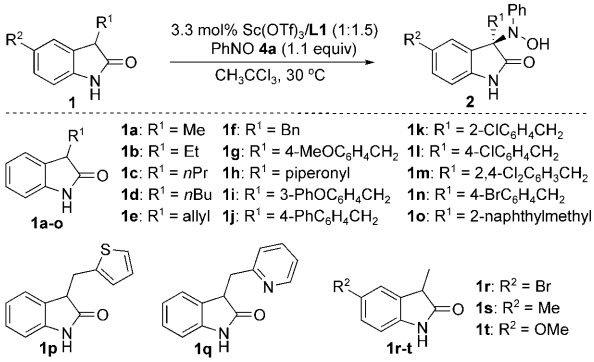
decreased to 50% and 62% *ee*, respectively (Table 1, entries 4 and 5 versus entry 1).

The molar ratio of ligand **L1** to the central metal ion Sc^{III} was found to be another important factor for reactivity (Table 1, entries 6–10). To our delight, the reaction was completed in 20 minutes when a small excess of **L1** was employed (Table 1, entry 6). The optimal ratio of $Sc(OTf)_3$ to **L1** was determined to be 1:1.5 to meet the requirements of atom economy and efficiency (Table 1, entry 7). In contrast, **2aa** was not detected in the absence of **L1** (Table 1, entry 10). Thus, according to the remarkable enhancement on reactivity, the enantioselective addition in the presence of $Sc(OTf)_3$/**L1** should be a ligand-accelerated process.[13] Excess $Sc(OTf)_3$ significantly reduced the *ee* value of **2aa** (Table 1, entry 9). Surprisingly, even without stirring, the corresponding product was isolated in good yield with an excellent *ee* value (Table 1, entry 8). Lowering the temperature resulted in a longer reaction time and diminished enantiocontrol (Table 1, entry 11 versus 7). However, lowering the reaction temperature and diluting the reaction mixture caused a slight improvement in enantioselectivity (Table 1, entry 12 versus 11). Judging from these phenomena, the actual source N should be the nitrosobenzene monomer, which was dissociated from the azodioxy dimer.[1b] Combined with the ligand-acceleration catalysis, the introduction of an excess of **L1** might suppress the coordination between scandium and the azodioxy dimer. Notably, the reaction process could be monitored by the naked eye since the reaction mixture quickly changed from clear green solution to yellowish suspension upon completion.

Encouraged by these initial results, we further explored the scope of the transformations with a series of N-unprotected oxindoles under the same reaction conditions. In each case, the reaction was complete in only 20 to 60 minutes. Evaluation of the substrate scope revealed that a high level of regio- and enantioselectivity could be achieved (Table 2).[14] The length of a linear saturated alkyl group at C3 of the oxindoles had little effect upon the enantioselectivity (Table 2, entries 1–4). With the 3-allyl-substituted oxindole **1e**, the enantiomeric excess of the desired N adduct was still excellent (Table 2, entry 5); this result is meaningful as the unsaturated alkyl group is a useful handle for additional functional group manipulation. 3-Benzyloxindole could be consumed rapidly to deliver the corresponding adduct **2fa** with 95% *ee* (Table 2, entry 6). The aromatic ring of R^1 with both electron-donating groups (Table 2, entries 7–10) and electron-withdrawing groups (Table 2, entries 11–14) afforded products in 90–94% yield with 90–97% *ee*. The oxindole **1o** bearing a bulky naphthylmethyl group reacted quickly with nitrosobenzene, thus giving the desired products with excellent enantioselectivity (up to 98% *ee*; Table 2, entry 15). Remarkably, more challenging heterocyclic groups containing **1p** and **1q** were also tolerated (Table 2, entries 16–17). In addition, this method was compatible with the modification of the benzo moiety of oxindole core (Table 2, entries 18–20).

A broad spectrum of nitrosoarenes could be employed in the reaction to afford the desired N-addition products in excellent yields and high enantioselectivities (Table 3) with

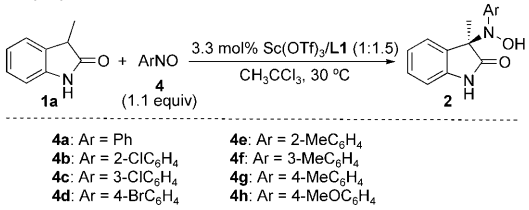
Table 2: Catalytic asymmetric hydroxyamination reaction of oxindoles **1** with nitrosobenzene **4a**.[a]



Entry	**1**	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	**2aa**	0.3	92	95
2	**1b**	**2ba**	1	91	92
3	**1c**	**2ca**	0.5	92	90
4	**1d**	**2da**	0.5	89	92
5	**1e**	**2ea**	0.5	98	94
6	**1f**	**2fa**	1	97	95
7	**1g**	**2ga**	1	94	97
8	**1h**	**2ha**	1	93	94
9	**1i**	**2ia**	1	95	95
10	**1j**	**2ja**	1	90	90
11	**1k**	**2ka**	0.5	92	90
12	**1l**	**2la**	0.5	93	94
13	**1m**	**2ma**	0.5	91	95
14	**1n**	**2na**	0.5	93	97
15	**1o**	**2oa**	1	95	98
16	**1p**	**2pa**	1	89	92
17	**1q**	**2qa**	1	93	92
18	**1r**	**2ra**	0.5	98	90
19	**1s**	**2sa**	0.3	92	91
20	**1t**	**2ta**	0.3	90	91

[a] For details, see the Supporting Information. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase.

Table 3: Catalytic asymmetric hydroxyamination reaction of 3-methyl-2-oxindole (**1a**) with nitrosoarenes **4**.[a]



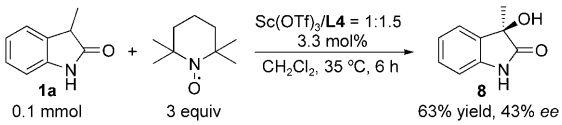
Entry	**4**	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**4a**	**2aa**	0.3	92	95
2	**4b**	**2ab**	0.5	88	90
3	**4c**	**2ac**	1	92	94
4	**4d**	**2ad**	0.5	90	92
5	**4e**	**2ae**	0.5	66	92
6	**4f**	**2af**	1	90	88
7	**4g**	**2ag**	1	85	89
8	**4h**	**2ah**	3	95	92

[a] For details, see the Supporting Information. [b] Yield of the isolated product. [c] Determined by HPLC on a chiral stationary phase.

the exception of 2-methyl-nitrosobenzene (Table 3, entry 5), wherein by-products were observed. A prolonged reaction time was required for consumption of 4-methoxyl-2-nitrosobenzene to deliver the stable nitrogen-selective product **2ah** (Table 3, entry 8).

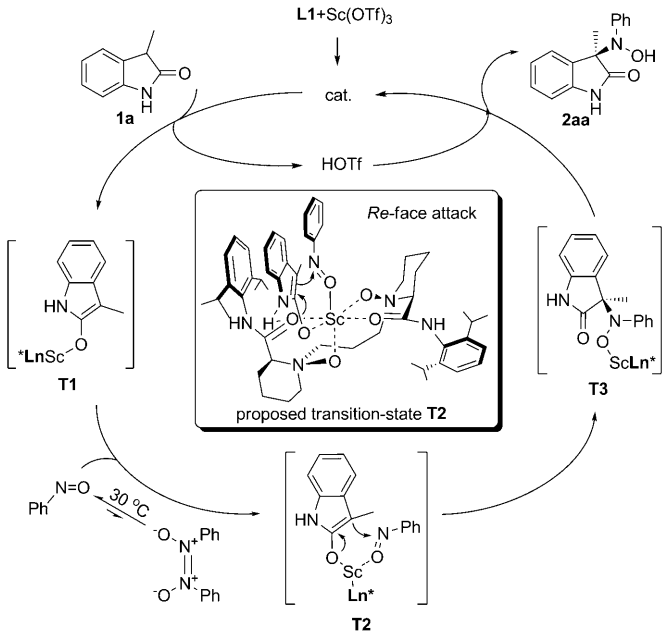
To further evaluate the synthetic potential of the catalytic system, the reaction was conducted on a gram scale with no loss in the *ee* value (Scheme 1). The oxindole **1a** reacted with dibenzyl azodicarboxylate in the presence of $Sc(OTf)_3$/**L1** with the subsequent sequential reduction using Pd/C and raney nickel under a hydrogen atmosphere to generate (*R*)-**6** in a 30% yield with 85% *ee*.[8e] The known compound (*R*)-**6** was transformed into (*R*)-**5** by the reported method[15] (not optimized). In contrast, product **2aa** (94% *ee*) could be readily transformed into the corresponding amine (*R*)-**5** in 95% yield with retention of enantiopurity using 10% Pd/C and three equivalents of sodium borohydride under mild reaction conditions (Scheme 1). The N–O cleavage procedure[16] was a modification to the existing reduction methods, and was more convenient than the direct C–N coupling method to deliver 3-arylamino-2-oxindole. Moreover, this transformation further validated the formation of the N-selective product. Removal of the OH group of **2ah** and removal of the *p*-methoxyphenyl (PMP) group[17] were carried out under conventional conditions to give 3-amino-3-methyloxindole (*R*)-**6** in good yield without loss of enantioselectivity (Scheme 1).

Recently, Sibi and Hasegawa,[18a] and Maruoka and coworkers[18b] reported the asymmetric α-aminoxylation of aldehydes using the stable radical 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (TEMPO). To the best of our knowledge, there have been no reports of the addition reaction of TEMPO involving amides such as 2-oxindole. As a special nitroso reagent in the preparation of α-hydroxy carbonyl compounds, we did some preliminary investigations. Pleasingly, the $Sc(OTf)_3$/**L4** complex was effective for this reaction, thus delivering 3-hydroxy-3-methyl-2-oxindole with a moderate *ee* value (Scheme 2). The reason for the cleavage of the N–O bond was uncertain, but might be ascribed to the bulky quaternary carbon center at the 3 position of **8**. The absolute configuration of **8** was unambiguously determined to be *R* by comparision of the optical rotation with that that was previously described.[19]



Scheme 2. Catalytic asymmetric synthesis of 3-hydroxy-3-methyl-2-oxindole **8** using TEMPO as the O source.

While a detailed mechanism for this transformation is unknown, we propose that the $Sc(OTf)_3$/*N*,*N*′-dioxide complex[10b] allows activation of both the nucleophile and electrophile simultaneously, as shown in Scheme 3. The in-situ formed catalyst (real active species), which was generated from **L1** and $Sc(OTf)_3$, deprotonated the α position of **1a** to



Scheme 3. Proposed catalytic process.

give chiral scandium enolate **T1**.[10g] **T1** coordinates with the oxygen atom of nitrosobenzene monomer because of the oxygen affinity characteristic of scandium to form intermediate **T2**. The coordination between the chiral Sc(OTf)$_3$/*N*,*N*′-dioxide complex and the oxygen atoms of both the oxindole and nitrosobenzene serve not only to activate both the nucleophile and electrophile at the same time, but also force the two substrates to be in closer proximity to one another. Coupled with the possible hydrogen-bonding interactions between the N–H group of the oxindole and the carbonyl moiety of the ligand, the observed unprecedented enantioselectivity can be rationalized. The zwitterionic enolate proposed by Barbas and co-workers might react with nitrosobezene in an O-selective fashion, presumably as a result of the directing effect of the hydroxy group of the catalyst that makes the oxygen atom more electrophilic (Figure 1 a).[3b]

As revealed in Scheme 3, in this Sc(OTf)$_3$/**L1** catalyst system, the nucleophile attacks the *Re* face through a plausible six-membered cyclic transition state predominantly to give the *R*-configured N-addition intermediate **T3**, which was in accordance with the experimental results. Subsequent protonation by HOTf afforded the N-adduct **2aa**, and regenerated the catalyst.

In conclusion, we report a highly efficient enantioselective hydroxyamination of N-unprotected 3-substituted-2-oxindoles catalyzed by a chiral Sc(OTf)$_3$/*N*,*N*′-dioxide complex. This transformation utilizes readily available nitrosoarenes as nitrogen sources. A series of N-selective products are obtained in good to excellent yields with excellent enantioselectivities within a very short reaction time. We are currently working on the improvement of the synthesis of chiral 3-hydroxy-2-oxindole using TEMPO, and ascertaining the mechanistic details of the hydroxyamination reaction of oxindoles as well.

Experimental Section

A mixture of **L1** (5 mol%), Sc(OTf)$_3$ (3.3 mol%), and oxindole **1a** (0.1 mmol) was stirred in CH_3CCl_3 (0.5 mL) at 35 °C for 1 h. Nitrosobenzene (1.1 equiv) and additional CH_3CCl_3 (0.5 mL) were added to the reaction mixture at 0 °C. Then the reaction was stirred at 30 °C for 20 min. The crude reaction mixture was dissolved in 0.3 mL of THF to get a clear solution before purification by chromatography on silica gel (petroleum ether/EtOAc 2:1) to afford product **2aa** in 92% yield with 95% *ee*. $[\alpha]_D^{20} = -60.2$ ($c = 0.28$, in THF). ^{1}H NMR (400 MHz, DMSO): $\delta = 10.27$ (s, 1H), 8.93 (s, 1H), 7.14 (dt, $J = 12.3$, 7.9 Hz, 3H), 7.10–7.04 (m, 3H), 6.99 (t, $J = 7.1$ Hz, 1H), 6.87 (t, $J = 7.5$ Hz, 1H), 6.69 (d, $J = 7.7$ Hz, 1H), 1.48 ppm (s, 3H). ^{13}C NMR (100 MHz, DMSO): $\delta = 185.10$, 150.44, 141.88, 130.95, 128.85, 127.96, 125.24, 124.54, 122.71, 121.49, 109.74, 70.72, 23.69 ppm. IR ν_{max} (KBr, film): $\tilde{\nu} = 3197$, 3088, 1715, 1332, 1211 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{14}N_2O_2$ [M+Na$^+$] 277.0947, found 277.0954.

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