CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200903471

Catalytic Asymmetric Synthesis of 3-(α-Hydroxy-β-carbonyl) Oxindoles by a Sc^{III}-Catalyzed Direct Aldol-Type Reaction

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Abstract: A direct catalytic asymmetric aldol-type reaction of 3-substituted-2-oxindoles with glyoxal derivatives and ethyl trifluoropyruvate, catalyzed by a chiral *N,N′*-dioxide–$Sc(OTf)_3$ (Tf = trifluoromethanesulfonyl) complex, has been developed that tolerates a wide range of substrates. The reaction proceeds in good yields and excellent enantioselectivities (up to 93% yield, 99:1 diastereomeric ratio (dr), and >99% enantiomeric excess (*ee*)) under mild conditions, to deliver 3-(α-hydroxy-β-carbonyl) oxindoles with vicinal quaternary–tertiary or quaternary–quaternary stereocenters. Even with 1 mol% catalyst loading or on scaleup (10 mmol of starting material), maintenance of *ee* was observed, which showed the potential value of the catalyst system. In studies probing the reaction mechanism, a positive nonlinear effect was observed and Sc^{III}-based enolate intermediates were detected by using ESIMS. On the basis of the experimental results and previous reports, a possible catalytic cycle was assumed.

Keywords: aldol reaction · asymmetric catalysis · enolates · oxindoles · scandium

Introduction

In recent years, great effort has been devoted to the asymmetric reactions of nucleophilic 3-substituted oxindoles[1–5] to construct oxindoles containing an asymmetric quaternary stereogenic center[6] at the C3 position. These compounds have potential medicinal interest, owing to the unique biological activities of such natural products.[7] Typically, construction of 3-(α-hydroxy-β-carbonyl) oxindoles is attractive and imperative because several pharmaceutical candidates, taking surugatoxin, for instance,[8] contain this structural motif. The direct catalytic asymmetric aldol reaction[9] is a powerful and atom-economical method for the synthesis of such oxindoles. However, the higher pK_a values of the α-proton of oxindoles relative to activated carbonyl compounds[10] and the inconvenience of creating contiguous, sterically hindered, chiral carbon stereocenters[11] made this catalytic asymmetric aldol reaction difficult. To date, there is only one successful transformation between oxindoles and ethyl trifluoropyruvate, disclosed by Shibata and co-workers, using a chiral amine base as a catalyst.[12] Although some progress has been made, demand for other practical processes remains in this area. Herein, we report our efforts to address these issues by employing a scandium–*N,N′*-dioxide complex to catalyze the direct asymmetric aldol-type reaction of 3-substituted-2-oxindoles **1** with dicarbonyl compounds **2** to produce 3-(α-hydroxy-β-carbonyl) oxindoles **3** with vicinal quaternary–tertiary or quaternary–quaternary stereocenters in up to >99% *ee* and 99:1 dr.

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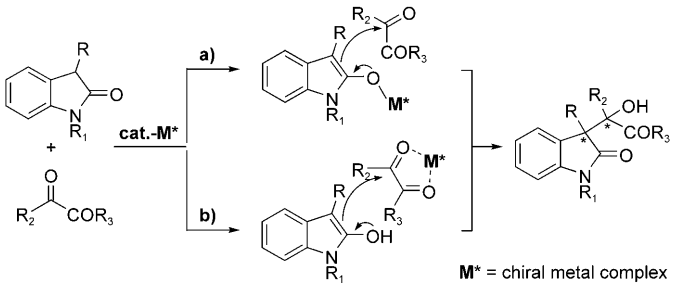
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200903471.

Results and Discussion

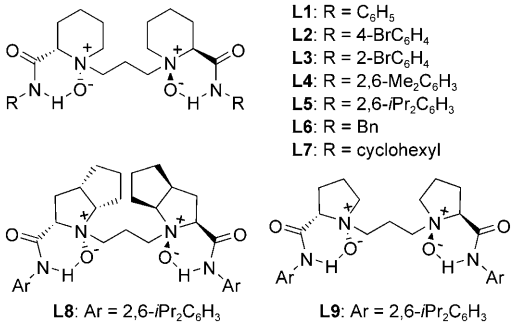
As revealed in Scheme 1, the aldol adduct from the reaction of an oxindole and a dicarbonyl compound was expected to be obtained by means of nucleophilic attack through two possible activation models: 1) the 3-substituted-2-oxindole could be activated through an in situ generated O–metal enolate,[13] or 2) the activation of the dicarbonyl substrate might be facilitated through bidentate chelation with a metal complex. Further work was directed toward a detailed examination of these models.

We probed the optimal reaction conditions using 3-methyl-2-oxindole (**1a**) and phenylglyoxal (**2a**) as model substrates. *N,N′*-Dioxides have been applied to many asymmetric procedures because they permit a tunable electronic



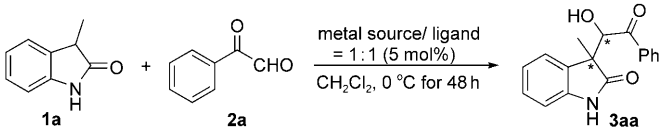
Scheme 1. Proposed activation models of the direct aldol-type reaction between 3-substituted-2-oxindoles and dicarbonyl compounds.

and steric chiral environment.[14] Our investigations began with screening several chiral Lewis acid catalysts that were generated in situ from metal salts and *N,N′*-dioxide **L1** to evaluate their ability to promote the addition of **1a** to **2a**. Inspiringly, $Sc(OTf)_3$ (Tf = trifluoromethanesulfonyl) gave the best results (Table 1, entry 1). Other metal sources, such as $Y(OTf)_3$, $La(OTf)_3$, $Ti(OiPr)_4$, and $Cu(OTf)_2$ resulted in poor reactivity and selectivity (Table 1, entries 2–5). Further optimization of the reaction conditions was aimed at exploring the efficiency of $Sc(OTf)_3$ paired with other *N,N′*-dioxide ligands **L**. We found that the amide moiety in the *N,N′*-dioxide ligands had a significant effect on the enantioselectivity (Table 1, entries 6–11). Significant enhancement of the reaction was observed upon addition of *N,N′*-dioxide **L5**. The aldol addition was effectively promoted by a 1:1 **L5**–$Sc(OTf)_3$ complex in CH_2Cl_2 at 0 °C and gave oxindole **3aa** in 52% yield, 75:25 dr, and 96% *ee* (Table 1, entry 9). Ligand **L4**, with dimethyl substituents on the phenyl ring rather than isopropyl substituents, afforded much less satisfactory results (36% *ee*; Table 1, entry 8). When the amide moiety was replaced by an aliphatic ring, both the enantioselectivity and the yield decreased dramatically (Table 1, entry 11). When *N,N′*-dioxide **L8** (derived from L-ramipril) and **L9** (derived from L-proline) were used instead of L-pipecolic acid derived ligand **L5**, the enantioselectivities decreased to 83 and 57%, *ee* respectively (Table 1, entries 12 and 13 versus entry 9). Therefore, the **L5**–$Sc(OTf)_3$ system was chosen to assess other reaction parameters.



Encouraged by the initial results, various solvents were tested in the presence of **L5**–$Sc(OTf)_3$ (5 mol%). The results indicated that the reaction solvent played an important role in governing the rate and enantioselectivity of the reaction. Chlorinated alkanes were investigated because CH_2Cl_2 was initially found to be the optimal solvent, however, no superior result was obtained (Table 2, entry 1 versus entries 2–5). Other solvents, such as ethyl acetate, THF, diethyl ether, and toluene, also gave less satisfactory results (Table 2, en-

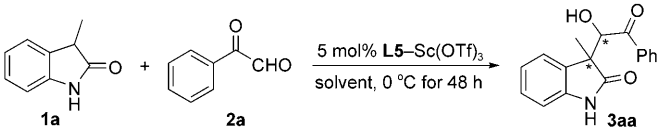
Table 1. Central metal and ligand effects on the catalytic asymmetric aldol-type reaction of 3-methyl-2-oxindole (**1a**) and phenylglyoxal (**2a**) under the indicated conditions.[a]



Entry	Metal	L	Yield [%][b]	dr	*ee* [%][c]
1	$Sc(OTf)_3$	**L1**	20	74:26	23
2	$Y(OTf)_3$	**L1**	12	70:30	−2
3	$La(OTf)_3$	**L1**	8	72:28	5
4	$Ti(OiPr)_4$	**L1**	7	73:27	−5
5	$Cu(OTf)_2$	**L1**	9	84:16	race.
6	$Sc(OTf)_3$	**L2**	17	69:31	12
7	$Sc(OTf)_3$	**L3**	12	60:40	race.
8	$Sc(OTf)_3$	**L4**	36	73:27	36
9	$Sc(OTf)_3$	**L5**	52	75:25	96
10	$Sc(OTf)_3$	**L6**	23	65:35	33
11	$Sc(OTf)_3$	**L7**	20	84:16	4
12	$Sc(OTf)_3$	**L8**	57	50:50	83
13	$Sc(OTf)_3$	**L9**	55	72:28	57

[a] Unless noted otherwise, the reactions were conducted on a 0.1 mmol scale at 0.1 M, using equimolar amounts of **1a** and **2a**, in CH_2Cl_2, under Ar, at 0 °C. [b] Isolated yield. [c] The *ee* value of the major diastereomer is given, determined by chiral HPLC analysis. Race. = racemic mixture.

Table 2. Solvent and concentration effects on the catalytic asymmetric aldol-type reaction of 3-methyl-2-oxindole (**1a**) and phenylglyoxal (**2a**).[a]



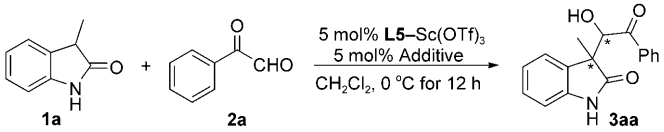
Entry	Solvent	Yield [%][b]	dr	*ee* [%][c]
1	CH_2Cl_2	52	75:25	96
2	$CHCl_3$	50	83:17	80
3	$Cl_2CHCHCl_2$	30	86:14	97
4	$ClCH_2CHCl_2$	40	91:9	87
5	CH_3CCl_3	36	86:14	95
6	ethyl acetate	72	68:32	55
7	THF	70	60:40	36
8	Et_2O	77	55:45	70
9	toluene	71	55:45	75
10[d]	CH_2Cl_2	55	74:26	95
11[e]	CH_2Cl_2	79	83:17	98

[a] Unless noted otherwise, the reactions were conducted on a 0.1 mmol scale at 0.1 M, using equimolar amounts of **1a** and **2a**, in CH_2Cl_2, under Ar, at 0 °C. [b] Isolated yield. [c] The *ee* value of the major diastereomer is given, determined by chiral HPLC analysis. [d] CH_2Cl_2 was used without prior distillation. [e] The reaction was carried out in CH_2Cl_2 (2.0 mL) for 24 h.

tries 6–9, respectively). It should be noted that this process tolerated the presence of moisture. When CH_2Cl_2 was used without prior distillation, no clear decrease in *ee* value was observed in this case (Table 2, entry 10). Dilution was also a key factor and it was found that the reactivity was increased by reducing the reaction concentration to 0.05 M (Table 1, entry 11).

Subsequently, the effect of additives and catalyst loading was examined and the results are presented in Table 3. Introduction of 3 Å molecular sieves could further shorten the

Table 3. Effect of additives and catalyst loading on the catalytic asymmetric aldol-type reaction of 3-methyl-2-oxindole (**1a**) and phenylglyoxal (**2a**).[a]



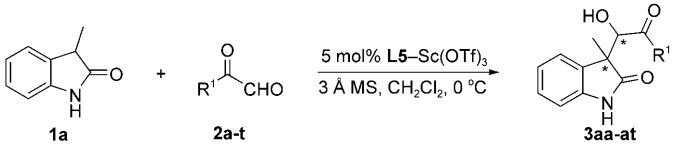
Entry	Additive	Yield [%][b]	dr	*ee* [%][c]
1	3 Å MS (2 mg)	79	86:14	98
2	4 Å MS (2 mg)	82	78:24	85
3	5 Å MS (2 mg)	80	79:21	98
4	Mg_2SO_4 (2 mg)	83	80:20	98
5	H_2O (20 μL)	77	82:18	96
6	*i*PrOH	67	77:23	51
7	phenol	38	75:25	77
8	HCOOH	n.r.[d]	–	–
9[e]	3 Å MS (2 mg)	70	81:19	96

[a] Unless noted otherwise, the reactions were conducted on a 0.1 mmol scale at 0.05 M, using equimolar amounts of **1a** and **2a**, in CH_2Cl_2, under Ar, at 0 °C. [b] Isolated yield. [c] The *ee* value of the major diastereomer is given, determined by chiral HPLC analysis. [d] No reaction. [e] 1 mol % catalyst loading was used (0.5 mmol scale).

reaction time to 12 h (Table 3, entry 1). To our surprise, the reaction was not sensitive to additional water (Table 3, entry 5). Acidic additive, formic acid, shut down the catalytic ability of the **L5**–$Sc(OTf)_3$ complex (Table 3, entry 8). The catalyst loading was then evaluated. Even with 1 mol % catalyst loading, maintenance of the *ee* value, although a slight decrease in dr, was observed (Table 3, entry 9). Extensive screening showed that the optimal conditions were as follows: **L5**–$Sc(OTf)_3$ complex (5 mol %; 1:1 molar ratio of **L5**–$Sc(OTf)_3$), **1a** (0.1 mmol), and **2a** (0.1 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C. These conditions were subsequently used to determine the generality of this process.

Evaluation of the reaction scope revealed that high levels of enantioselectivity could be achieved for a wide range of glyoxal derivatives **2** (92–>99 % *ee*; Table 4). Aromatic rings substituted with both electron-donating and -withdrawing groups (Table 4, entries 2–15) afforded products in 75–92 % yield, 62:38–97:3 dr, and 94–>99 % *ee*. The naphthyl glyoxals **2p** and **2q** reacted smoothly with **1a** and gave the desired products with excellent diastereo- and enantioselectivity (up to 99:1 dr, 99 % *ee*; Table 4, entries 16 and 17). The catalyst system was also applicable to heteroaryl glyoxals, which delivered the corresponding adducts in up to 97

Table 4. Direct catalytic asymmetric aldol-type reaction of oxindole **1a** with glyoxal derivatives **2**.[a]



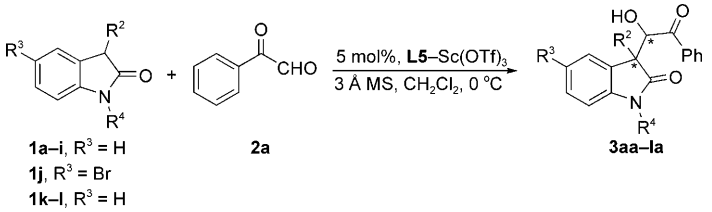
Entry	R^1	Product	*t* [h]	Yield [%][b]	dr	*ee* [%][c]
1	C_6H_5	**3aa**	12	79	86:14	98
2	2-MeC_6H_4	**3ab**	12	82	90:10	99
3	3-MeC_6H_4	**3ac**	12	89	85:15	>99
4	4-MeC_6H_4	**3ad**	12	90	91:9	97
5	3-$MeOC_6H_4$	**3ae**	16	89	96:4	98
6	4-$MeOC_6H_4$	**3af**	16	88	96:4	97
7	3,4-$(MeO)_2C_6H_3$	**3ag**	16	82	95:5	95
8	2-FC_6H_4	**3ah**	24	75	73:27	95
9[d]	4-FC_6H_4	**3ai**	24	88	83:17	99
10	3-ClC_6H_4	**3aj**	24	85	79:21	95
11[d]	4-ClC_6H_4	**3ak**	24	88	97:3	99
12	3,4-$Cl_2C_6H_3$	**3al**	24	92	62:38	94
13[d]	4-BrC_6H_4	**3am**	24	85	96:4	98
14	3-$NO_2C_6H_4$	**3an**	24	77	63:37	94
15	4-$NO_2C_6H_4$	**3ao**	24	83	85:15	95
16	1-naphthyl	**3ap**	36	83	94:6	99
17	2-naphthyl	**3aq**	36	80	99:1	99
18	2-furyl	**3ar**	36	75	56:44	97
19	2-thienyl	**3as**	36	78	65:35	99
20[e]	Me	**3at**	24	75	79:21	92

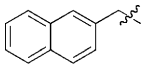
[a] For details, see the Supporting Information. [b] Isolated yield. [c] The *ee* value of the major diastereomer is given, determined by chiral HPLC analysis. [d] The reaction was carried out in CH_2Cl_2 and $Cl_2CHCHCl_2$ (2.0 mL; 1:1 v/v). [e] The reaction was carried out in $ClCH_2CHCl_2$ and toluene (2.0 mL; 1:1 v/v).

and 99 % *ee*, respectively (Table 4, entries 18 and 19). Aliphatic glyoxal **2t** resulted in poor yield and dr when the reaction was performed in CH_2Cl_2 (40 % yield, 49:50 dr). Modification of the solvent was effective in improving the results to 75 % yield, 79:21 dr, and 92 % *ee* (Table 4, entry 20).

Moreover, the scope of the aldol-type reaction was extended successfully to a variety of 3-substituted-2-oxindoles **1a–j**. Oxindoles with saturated aliphatic substituents at the C3 position generally provided the corresponding products in excellent *ee* (98–>99 %, Table 5, entries 1–4).[15] With a 3-allyl substituent on the oxindole, the enantiomeric excess of the desired product was still excellent (Table 5, entry 5), which is meaningful because the ally group in compound **3ea** is a useful handle for further functional group manipulation.[2c,3b,c] Variation of the C3-substituent to benzyl or 2-naphthylmethyl was also possible to give the expected products **3fa** and **3ga** in >98 % *ee* (Table 5, entries 6–7). Significantly, oxindole **1h**, which has a 2-thienylmethyl group at C3, also afforded an excellent *ee* (>99 %, Table 5, entry 8). To our delight, 3-phenyl-2-oxindole (**1i**) was also a suitable substrate for this reaction (98 % *ee*, Table 5, entry 9). The catalytic system was also effective for electron-deficient 5-bromo-2-oxindole (Table 5, entry 10). The effect of *N*-substitution of the 2-oxindole on the reaction was further examined. For *N*-Boc-2-oxindole **1k** and *N*-methyl-2-oxindole **1l**,

Table 5. Direct catalytic asymmetric aldol-type reaction of oxindoles **1** with phenylglyoxal (**2a**).[a]



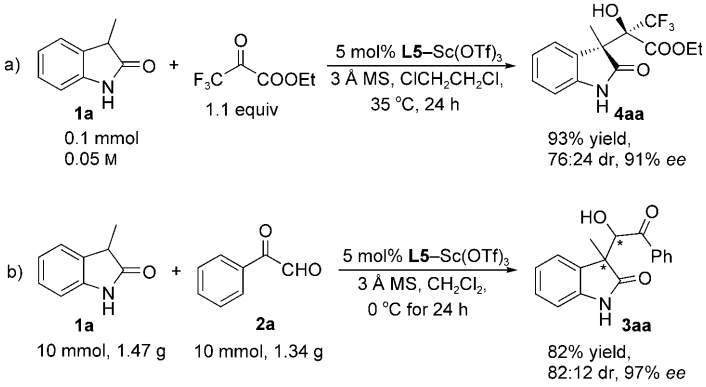
Entry	R^2	R^4	Prod.	*t* [h]	Yield [%][b]	dr	*ee* [%][c]
1	Me	H	**3aa**	12	79	86:14	98
2	Et	H	**3ba**	12	81	87:13	99
3	*n*Pr	H	**3ca**	12	82	89:11	>99
4	*n*Bu	H	**3da**	16	82	83:17	99
5	Allyl	H	**3ea**	16	80	86:14	99
6	Bn	H	**3fa**	24	72	64:36	99
7	 **1j**	H	**3ga**	24	75	77:23	98
8	 **1h**	H	**3ha**	24	88	70:30	>99
9	Ph	H	**3ia**	24	62	80:20	98
10	Me	H	**3ja**	16	90	75:25	82
11	Me	Boc[d]	**3ka**	12	trace	–	–
12	Me	Me	**3la**	12	<10	–	–

[a] For details, see the Supporting Information. [b] Isolated yield. [c] The *ee* value of the major diastereomer is given, determined by chiral HPLC analysis. [d] Boc = *tert*-butyloxycarbonyl.

To gain insight into the reaction mechanism, control experiments were carried out and the results are summarized in Table 6. Initially, product **3aa** was obtained in less than 10% yield using $Sc(OTf)_3$ as a Lewis acid catalyst (Table 6, entry 2). In contrast, significant improvement was observed upon addition of *N,N′*-dioxide **L5** (Table 6, entry 4 versus 2). In view of this phenomenon, the enantioselective addition with **L5**–$Sc(OTf)_3$ should be a ligand-accelerated process.[17] This result demonstrated that **L5** works well as a Brønsted base, adjusting the Lewis acidity of the scandium. The experimental procedure also had a great effect on the reaction. When **2a** was added prior to **1a** (procedure B), enantioselectivity decreased from 98 to 69% *ee* (Table 1, entry 5 versus entry 4). The inferior result caused by procedure B might be ascribed to the strong bidentate coordination of **2a** to **L5**–$Sc(OTf)_3$, which could develop a different chiral environment prior to the formation of the chiral Sc^{III}–enolate. Hence, the key step to accomplish this reaction should be the preferential formation of the enolate, induced by **L5**–$Sc(OTf)_3$, and the activation pathway a in Scheme 1 is favorable.

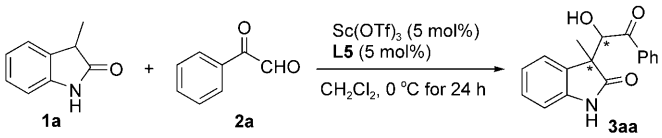
low product levels were detected in the reaction with **2a** (Table 5, entries 11 and 12), which indicated that the NH subunit of the oxindole was necessary for this reaction.

Inspiringly, the **L5**–$Sc(OTf)_3$ complex was also effective for reaction with ethyl trifluoropyruvate (Scheme 2a). Oxindole **4a** was isolated, which bore a tertiary α-trifluoromethyl alcohol moiety,[1a] and could provide access to novel drug candidates.[16] To exploit the potential of the current catalyst system, the reaction was scaled up to 10 mmol of starting material (1.47 g of **1a** and 1.34 g of **2a**) in the presence of 5 mol% of **L5**–$Sc(OTf)_3$ as the catalyst. Encouragingly, the reaction proceeded smoothly and good yield, dr, and excellent *ee* were maintained (Scheme 2b).



Scheme 2. a) Aldol-type reaction of **1a** with ethyl trifluoropyruvate under the catalysis of **L5**–$Sc(OTf)_3$ complex; b) Scaleup of the asymmetric catalytic direct aldol-type reaction of **1a** with **2a**.

Table 6. Control experiments.[a]



Entry	$Sc(OTf)_3$ [mol%]	**L5** [mol%]	Procedure	Yield [%][b]	dr	*ee* [%][c]
1	none	none	A	n.r.[d]	–	–
2	5	none	A	<10	–	–
3	none	5	A	<5	–	race.[e]
4	5	5	A	79	86:14	98
5	5	5	B	45	77:23	69
6	5	5	C	80	84:16	97

[a] Unless noted otherwise, the reactions were conducted on a 0.1 mmol scale at 0.05 M, using equimolar amounts of **1a** and **2a**, in CH_2Cl_2. Procedure A: **1a** and **2a** were added sequentially at 0°C. Procedure B: **2a** was stirred with the catalyst for 1 h at 0°C before **1a** was added. Procedure C: **1a** was stirred with the catalyst for 1 h at 0°C before **2a** was added. [b] Isolated yield. [c] The *ee* value of the major diastereomer is given, determined by chiral HPLC analysis. [d] No reaction. [e] Racemic mixture.

For direct proof of the rationality of the proposed Sc^{III}-based enolate activation, we investigated the aldol-type reaction using ESIMS, which enabled us to identify the critical intermediates in the reaction mixture. The sample was prepared from $Sc(OTf)_3$ and **L5** in a 1:1 ratio, in the presence of **1a** (2.0 equiv relative to the catalyst) in CH_2Cl_2. The spectrum of the sample obtained from the reaction mixture after stirring for 1 h revealed ions at *m*/*z* 1138.3318 and 2277.5900, which correspond to enolate intermediates $[\mathbf{5}+H]^+$ and $[\mathbf{6}+H]^+$ (Figure 1). Moreover, characteristic signals at *m*/*z* 1122.3566 and 1272.3114 were observed in the ESIMS spectrum of ions $[\mathbf{7}-OTf]^+$ and $[\mathbf{7}+H]^+$ (Figure 2). These signals were consistent with the fragmentation of the aldol-type adduct before scission with the **L5**–Sc^{III} complex, which indicated that these signals should correspond to the intermediacy of the aldol adduct. The above MS results confirmed our proposed activation models, which involved a metal–enolate intermediate in the aldol-type reaction mechanism, as shown in Scheme 1.

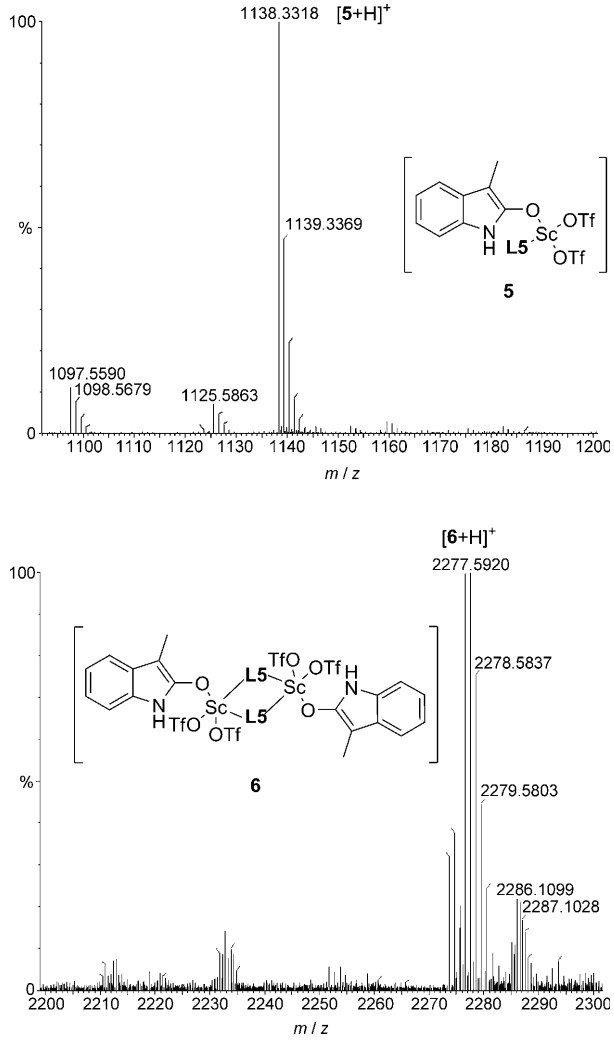


Figure 1. ESIMS spectrum of the aldol-type reaction 1 h after stirring **1a** with **L5**–$Sc(OTf)_3$ in CH_2Cl_2. HRMS: *m*/*z* calcd: 1138.3893 $[\mathbf{5}+H]^+$, 2277.7714 $[\mathbf{6}+H]^+$; found: 1138.3318, 2277.5900.

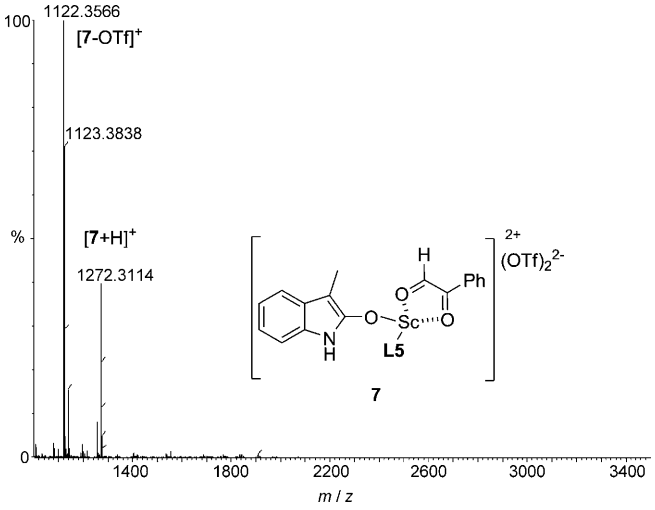


Figure 2. ESIMS spectrum of the aldol-type reaction 3 h after stirring **2a** with **L5**–$Sc(OTf)_3$ and **1a** in CH_2Cl_2. HRMS: *m*/*z* calcd: 1122.4668 $[\mathbf{7}-OTf]^+$, 1272.4261 $[\mathbf{7}+H]^+$; found: 1122.3566, 1272.3114.

As a result of the detected dimer species **6** (Figure 1), a nonlinear effects (NLE) study[18] was carried out. Asymmetric amplification leading to both diastereomers was observed (Figure 3). The (+)-NLE should be a consequence of the

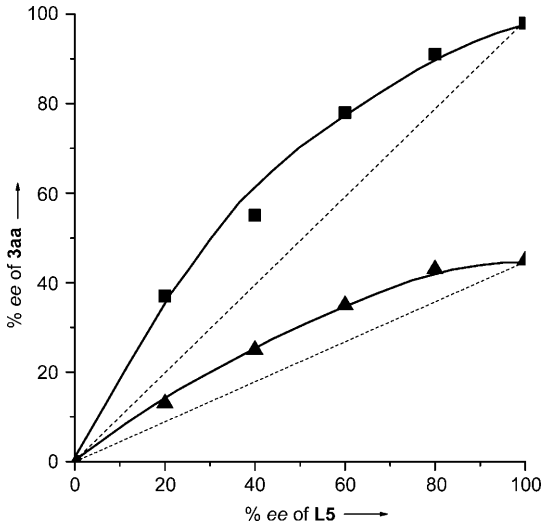
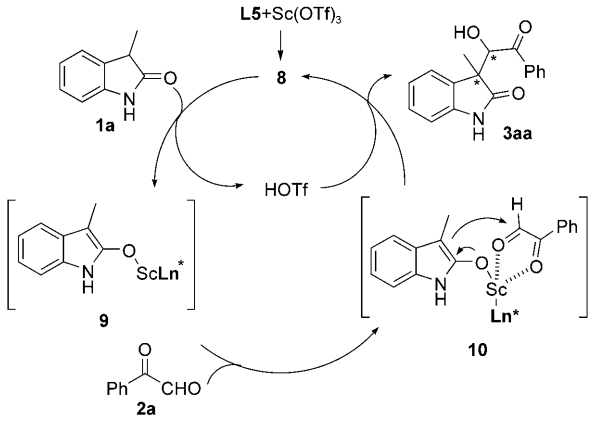


Figure 3. Chiral amplification in the direct aldol-type reaction of **1a** with **2a**, catalyzed by 5 mol% **L5**–$Sc(OTf)_3$. ■: major diastereomer, ▲: minor diastereomer.

formation of an oligomeric species of the **L5**–$Sc(OTf)_3$ catalyst, rather than a unique monomeric structure. This observation was also consistent with the results of the ESIMS study above. Thus, it was considered that the active catalytic species was a less-stable homochiral complex. When the concentration was decreased from 0.1 to 0.05 M, higher yield could be obtained (Table 2, entry 11 versus 1), which might be ascribed to the shift in equilibrium between oligomeric and monomeric species.

In light of the above experimental results, we assumed that a catalytic cycle was operating for this reaction (Scheme 3). The in situ formed catalyst **8** (real active species), which was generated from **L5** and $Sc(OTf)_3$, deprotonated the α-position of **1a** to give chiral scandium enolate **9** in situ. Thus formed, the chiral scandium enolate reacted with phenylglyoxal (**2a**) through a bidentate chelation to form intermediate **10**. Subsequent nucleophilic attack and protonation by HOTf afforded the aldol adduct **3aa** and the regenerated catalyst.



Scheme 3. Proposed catalytic cycle.

Conclusion

The direct catalytic asymmetric aldol-type reaction of 3-substituted-2-oxindoles with glyoxal derivatives and ethyl trifluoropyruvate was successfully established through Sc^{III}-based enolate activation. The **L5**–$Sc(OTf)_3$ complex efficiently promoted the aldol addition, and resulted in 3-(α-hydroxy-β-carbonyl) oxindoles with vicinal quaternary–tertiary or quaternary–quaternary stereocenters, in up to 93% yield, 99:1 dr, and >99% *ee* under mild conditions. Application of *N,N′*-dioxide–metal complexes to other reactions involving oxindoles as nucleophiles is ongoing in our laboratory.

Experimental Section

Typical experimental procedure for the reaction of oxindoles 1 with glyoxal derivatives 2: A mixture of **L5** (5 mol%), $Sc(OTf)_3$ (5 mol%), and 3 Å molecular sieves (2 mg) was stirred in CH_2Cl_2 (1.0 mL) at 35°C under Ar for 1 h. Oxindole **1a** (0.1 mmol) and phenylglyoxal **2a** (0.1 mmol) were then added sequentially at 0°C, followed by the addition of CH_2Cl_2 (1.0 mL). The reaction was stirred at 0°C and monitored by TLC. The crude product was purified by flash chromatography directly (petroleum ether/ethyl acetate, 2:1) to afford **3aa** as a colorless gel, as an inseparable diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 1H), 7.42–7.50 (m, 4H), 7.27–7.31 (m, 2H), 6.95–7.02 (m, 1H), 6.91–6.94 (m, 1H), 6.63–6.65 (d, J = 7.6 Hz, 1H), 5.37–5.39 (d, J = 6.4 Hz, 1H), 4.19–4.21 (d, J = 6.4 Hz, 1H), 1.62 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.9, 179.9, 139.7, 135.0, 134.0, 128.8, 128.6, 128.5, 128.4, 128.1, 124.5, 122.7, 109.6, 53.1, 21.1 ppm; HRMS (EI): *m/z* calcd for $C_{17}H_{15}NO_3$+Na^+: 304.0944 $[M+Na]^+$; found: 304.0947. The *ee* was determined by HPLC analysis by using a chiralcel OD-H column, hexane/2-propanol (90:10), flow rate = 1.0 mL min^{-1}, 254 nm. Retention time (t_R) (major diastereomer, 98% *ee*) = 10.20 min (major enantiomer), t_R = 12.03 min (minor enantiomer); t_R (minor diastereomer) = 15.64 min (major enantiomer), t_R = 17.08 min (minor enantiomer).

Typical experimental procedure for the reaction of oxindole 1 with ethyl trifluoropyruvate: A mixture of **L5** (5 mol%), $Sc(OTf)_3$ (5 mol%), 3 Å molecular sieves (2 mg), and oxindole **1a** (0.1 mmol) was stirred in $ClCH_2CH_2Cl$ (2.0 mL) at 35°C under Ar for 1 h. Ethyl trifluoropyruvate (0.11 mmol) was then added at 35°C. The reaction mixture was stirred at 35°C and monitored by TLC. The crude product was purified by flash chromatography directly (petroleum ether/ethyl acetate, 3:1) to afford **4a** as a white solid,[1a] as an inseparable diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (s, 1H), 7.44–7.46 (d, J = 7.6 Hz, 1H), 7.25–7.29 (t, J = 7.7 Hz, 1H), 7.05–7.09 (t, J = 7.6 Hz, 1H), 6.91–6.93 (d, J = 7.6 Hz, 1H), 5.38 (s, 1H), 4.39–4.44 (q, J = 7.2 Hz, 1H), 4.14–4.29 (m, 1H), 1.58 (s, 3H), 1.10–1.12 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.3, 167.9, 139.9, 129.7, 129.0, 126.2, 125.8, 124.5, 123.0, 110.1, 63.5, 51.6, 19.7, 13.7 ppm. The *ee* was determined by HPLC analysis using a chiralcel OJ-H column, hexane/2-propanol (93:7), flow rate = 1.0 mL min^{-1}, 254 nm. t_R (major diastereomer, 91% *ee*) = 11.62 min (major enantiomer), t_R = 25.31 min (minor enantiomer); t_R (minor diastereomer) = 11.66 min (major enantiomer), t_R = 15.99 min (minor enantiomer).

Acknowledgements

We appreciate the National Natural Science Foundation of China (no. 20732003), PCSIRT (no. IRT0846), and the Major State Basic Research and Development Program (no. 2010CB833300) for financial support. We also thank Sichuan University Analytical & Testing Center for NMR spectroscopy analysis and the State Key Laboratory of Biotherapy for HRMS analysis.

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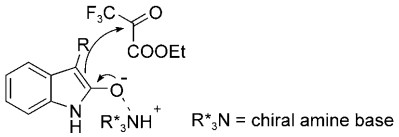

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Received: December 18, 2009
Published online: February 19, 2010

