Asymmetric Catalysis

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Chiral Scandium(III)-Catalyzed Enantioselective α-Arylation of N-Unprotected 3-Substituted Oxindoles with Diaryliodonium Salts**

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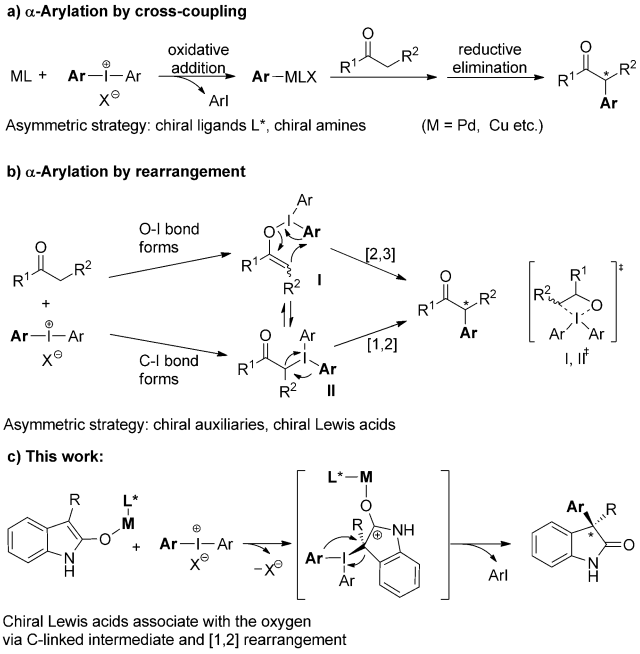
Dedicated to Professor Xiao-Zeng You on the occasion of his 80th birthday

The catalytic asymmetric α-arylation of carbonyl compounds is of high interest, because it provides an efficient access to optically active α-aryl compounds regarded as essential motifs in many biologically active natural products and pharmaceutically active compounds.[1] Significant efforts have been directed towards the development of metal-catalyzed α-arylation of carbonyl compounds with aryl halides, aryl triflates, or aryl organometallic reactants.[2] Diaryliodonium salts are mild, selective, and non-toxic reagents, and are alternative arylation partners for a variety of nucleophiles.[3] The MacMillan group[4] provided earily enantioselective enolate α-arylation employing diaryliodonium salts, such as a metal–organocatalysis merger for α-arylation of aldehydes,[4a] and chiral copper catalysis of silylkene acetals.[4b] The Gaunt group realized chiral copper-catalyzed α-arylation of *N*-acyloxazolidiones.[5] In these cases, a Cu^{III}–aryl process followed by reductive elimination was postulated (Scheme 1 a). Furthermore, the involvement of electrophilic addition and aryl moiety in rearrangement was also proposed.[6] A recent computational study by Olofsson and co-workers confirmed that the reaction could follow associative or dissociative ligand-exchange pathways.[6b] It suggests that the addition of diaryliodonium salts to the enolate results in almost isoenergetic oxygen–iodine and carbon–iodine bonded isomers. The [2,3]-rearrangement pathway was favored over the [1,2]-process (Scheme 1 b). An interesting perspective is that the asymmetric version could be obtained either based on covalently linked auxiliaries, or chiral Lewis acid catalysis.[6b] Chiral diaryliodonium salts,[7] such as Ochiai's salt,[7b] show the success of the former strategy. A direct asymmetric α-arylation of cyclohexanones by shifting the enantiodifferentiation away from the C–C bond-forming step was realized by Aggarwal.[7c] Nevertheless, the development of non-oxidative metal-participated or organocatalytic arylation is of considerable interest. If a chiral Lewis acid with strong oxygen affinity was introduced,[6b] the association would benefit the formation of C-linked intermediate enantiotopically, overwhelming incorporation of the O–I process (Scheme 1 c).



Scheme 1. Possible mechanism for α-arylation of carbonyl compounds.

Given our long-term endeavor in the development of chiral catalysts derived from rare-earth metal/*N*,*N*′-dioxide complexes,[8] we envision that this kind of useful catalyst could provide new route for the asymmetric α-arylation of carbonyl compounds. Herein, we present a chiral Lewis acid catalyzed asymmetric α-arylation of N-unprotected 3-substituted oxindoles with diaryliodonium salts. The scandium(III) complex of chiral *N*,*N*′-dioxide bearing tetrahydroisoquinoline backbones exhibited excellent performance under mild reaction conditions, generating oxindole derivatives with quaternary carbon centers in high enantioselectivity and reactivity (up to 99% *ee* and 99% yield). The process also facilitated the synthesis of an antiproliferative agent for the treatment of cancer.

We chose N-unprotected 3-substituted oxindoles as the model substrates, considering that oxindole derivatives are

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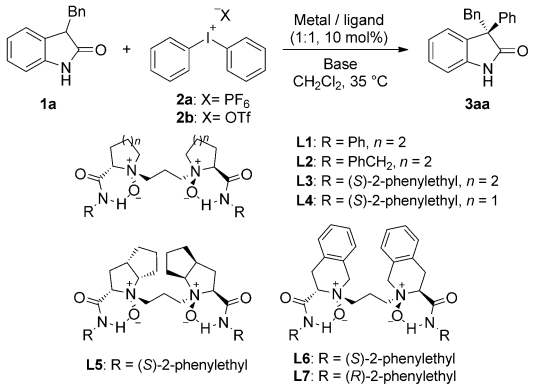
a ubiquitous structural motif in a variety of natural products and biologically active drug candidates.[9] The Buchwald group has utilized enantioselective Pd-catalyzed intermolecular coupling of *N*-Me oxindoles with aryl and vinyl bromides to construct 3-substituted oxindoles with chiral quaternary centers.[2f] Moreover, 3-substituted oxindole[10] is a acidic carbon nucleophile that could react well with electrophilic diaryliodonium salts. Initially, the study focused on the reaction of N-unprotected 3-benzyl-2-oxindole **1a** and commercially available diaryliodonium salt **2a** in the presence of chiral *N*,*N*′-dioxide–metal complex and K_2CO_3. Investigation of different Lewis acids coordinated to ligand **L1** derived from L-piperic acid showed that only $Sc(OTf)_3$ gave promising reactivity (Table 1, entry 4), while metal sources as CuBr, $Cu(OTf)_2$, and $Pd(OAc)_2$, which were popular in α-arylation, resulted in poor yields or complicated mixtures (Table 1, entries 1–3). Following the survey of ligands complexed with $Sc(OTf)_3$, we found that the ligands bearing (*S*)-phenylethanamine modifies exhibited superior results (18% yield, 30% *ee*; Table 1, entries 4–6). Interestingly, of all the ligands with various amino acid backbones and amide substituents screened, *N*,*N*′-dioxide **L6** bearing tetrahydroisoquinoline units and (*S*)-phenylethanamine modifies exhibited the best enantioselectivity (50% yield and 80% *ee*; Table 1, entry 9 versus entries 6–8). Chiral match among the subunits in the ligands was found. Using ligand **L7**, the diastereomer of the optimal ligand **L6**, resulted in dramatically reduced enantioselectivity and yield (Table 1, entry 10). Changing the anion of diaryliodonium salt from tetrafluoroborate to triflate made the reaction more applicable, and the desired α-arylation product **3aa** was given in 63% yield and 90% *ee* (Table 1, entry 11). A further survey of other bases (see the Supporting Information for details) showed that a slightly improved enantioselectivity (93% *ee*) was achieved using $NaHCO_3$ (Table 1, entry 12). Moreover, both the yield and the enantioselectivity increased by the addition of 3 Å molecular sieves (Table 1, entry 13). Gratifyingly, when the ratio of oxindole **1a**, diaryliodonium triflate **2b** and $NaHCO_3$ was fixed to 1:1.5:3, the desired 3-benzyl-3-phenylindolin-2-one **3aa** was generated in 89% yield and 95% *ee* (Table 1, entry 14). Attempts to decrease the catalyst loading resulted in lower yield, albeit with slightly decreased enantioselectivity (Table 1, entry 15).

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



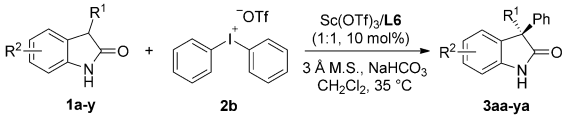
Entry	Ligand	Metal	Base	2	Yield [%][b]	*ee* [%][c]
1	**L1**	CuBr	K_2CO_3	**2a**	trace	–
2	**L1**	$Cu(OTf)_2$	K_2CO_3	**2a**	0[d]	–
3	**L1**	$Pd(OAc)_2$	K_2CO_3	**2a**	n.r.[e]	–
4	**L1**	$Sc(OTf)_3$	K_2CO_3	**2a**	18	5
5	**L2**	$Sc(OTf)_3$	K_2CO_3	**2a**	16	17
6	**L3**	$Sc(OTf)_3$	K_2CO_3	**2a**	18	30
7	**L4**	$Sc(OTf)_3$	K_2CO_3	**2a**	17	9
8	**L5**	$Sc(OTf)_3$	K_2CO_3	**2a**	10	17
9	**L6**	$Sc(OTf)_3$	K_2CO_3	**2a**	50	80
10	**L7**	$Sc(OTf)_3$	K_2CO_3	**2a**	25	17
11	**L6**	$Sc(OTf)_3$	K_2CO_3	**2b**	63	90
12	**L6**	$Sc(OTf)_3$	$NaHCO_3$	**2b**	55	93
13[f]	**L6**	$Sc(OTf)_3$	$NaHCO_3$	**2b**	67	94
14[f,g]	**L6**	$Sc(OTf)_3$	$NaHCO_3$	**2b**	89	95
15[f,h]	**L6**	$Sc(OTf)_3$	$NaHCO_3$	**2b**	75	91

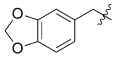
[a] Unless otherwise noted, all reactions were performed with metal/ligand (1:1, 10 mol%), base (0.11 mmol), **1a** (0.1 mmol), and diaryliodonium salt **2** (0.1 mmol) in CH_2Cl_2 (0.8 mL) under N_2 at 35 °C for 48 h. [b] Yield of isolated product. [c] Determined by HPLC analysis using a Chiralcel IA column. [d] A complicated mixture was observed. [e] n.r. = no reaction. [f] 3 Å M.S. (2.0 mg) was added. [g] The ratio of **1a**/**2b**/$NaHCO_3$ was 1:1.5:3. [h] **L6**-$Sc(OTf)_3$ (1:1, 5 mol%).

With the optimized reaction conditions in hand (Table 1, entry 14), the substrate scope of 3-substituted oxindoles was investigated (Table 2). The reactions performed well with a series of 3-benzyl substituted oxindoles, giving the corresponding α-arylated products in 80–99% yields with 91–99% *ee*, regardless of the electronic nature and the position of substituents on the aromatic ring of the benzyl group (Table 2, entries 1–18). In general, 3-benzyl oxindoles with a *meta*-substituent on the aromatic ring gave slightly higher enantioselectivities than those with *ortho*- or *para*-substituents (Table 2, entries 3, 6, 9, 11 and 13). 3-Benzyl oxindoles with two substituents also gave out satisfying results, of which the major product **3qa** was unambiguously determined to be *R* configuration by X-ray analysis[11] (Table 2, entries 17,18). Remarkably, substrates bearing a condensed ring or heteroaromatic ring in the R^1 substituents were also suitable substrates for the reaction, affording the corresponding products with good yields and excellent enantioselectivities (81–90% yields, 91–96% *ee*; Table 2, entries 19–21). The 3-*tert*-butyl-2-oxindole **2u** reacted smoothly under the optimal conditions (71% yield, 84% *ee*; Table 2, entry 22). Moreover, oxindole **2v** with an allyl group at the C3 position was compatible with this catalytic system, giving a moderate yield with 72% *ee* (Table 2, entry 23). Excellent results were achieved for 6-chloro-substituent on the oxindole structure, and the α-arylation of oxindole **2w** and **2x** generated the corresponding products in 89% yield, 90% *ee*, and 90% yield, 98% *ee*, repectively (Table 2, entries 24 and 25). Furthermore, 3,3-diaryloxindoles are widely used as effecient mineralocortocoid receptor antagonists[9e] and anticancer agents.[9f] However, there are limited asymmetric synthetic methods available. We achieved the asymmetric synthesis of 3,3-diaryloxindole **3ya**, albeit in moderate yield and enantioselectivity (Table 2, entry 26).

Next, a range of diaryliodonium triflates was employed. The symmetric diaryliodonium triflates[12] containing elec-

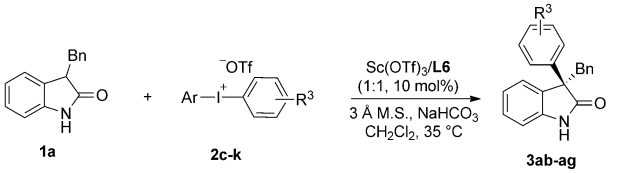
Table 2: Substrate scope of substituted oxindoles.[a]



Entry	R^1	R^2	Time [h]	Yield (**3**) [%][b]	*ee* [%][c]
1	$C_6H_5CH_2$	H	48	89 (**3 aa**)	95
2	2-$MeC_6H_4CH_2$	H	72	99 (**3 ba**)	91
3	3-$MeC_6H_4CH_2$	H	48	80 (**3 ca**)	95
4	4-$MeC_6H_4CH_2$	H	48	98 (**3 da**)	94
5	2-$ClC_6H_4CH_2$	H	48	93 (**3 ea**)	92
6	3-$ClC_6H_4CH_2$	H	24	99 (**3 fa**)	99
7[d]	3-$ClC_6H_4CH_2$	H	24	95 (**3 fa**)	96
8	4-$ClC_6H_4CH_2$	H	35	84 (**3 ga**)	96
9	3-$FC_6H_4CH_2$	H	48	95 (**3 ha**)	97
10	4-$FC_6H_4CH_2$	H	48	92 (**3 ia**)	95
11	3-$BrC_6H_4CH_2$	H	48	99 (**3 ja**)	99
12	4-$BrC_6H_4CH_2$	H	35	82 (**3 ka**)	97
13	3-$O_2NC_6H_4CH_2$	H	48	99 (**3 la**)	98
14	4-$O_2NC_6H_4CH_2$	H	48	98 (**3 ma**)	95
15	4-$NCC_6H_4CH_2$	H	48	97 (**3 na**)	97
16	4-$MeOC_6H_4CH_2$	H	48	95 (**3 oa**)	95
17	2,4-$Cl_2C_6H_3CH_2$	H	48	90 (**3 pa**)	95
18	2,6-$Cl_2C_6H_3CH_2$	H	48	89 (**3 qa**)	92 (*R*)
19		H	48	90 (**3 ra**)	96
20	2-naphthylmethyl	H	48	81 (**3 sa**)	96
21	2-thienylmethyl	H	48	82 (**3 ta**)	91
22	$tBuCH_2$	H	48	71 (**3 ua**)	84
23	allyl	H	120	60 (**3 va**)	72
24	$C_6H_5CH_2$	6-Cl	48	89 (**3 wa**)	90
25	3-$ClC_6H_4CH_2$	6-Cl	48	90 (**3 xa**)	98
26	4-ClC_6H_4	H	120	47 (**3 ya**)	57

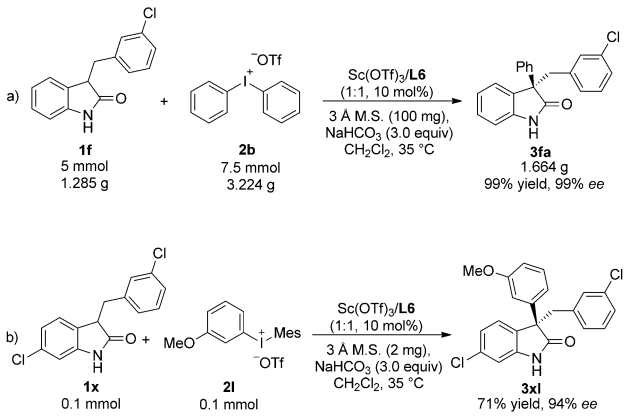
[a] Unless specified, the reactions were performed with **1** (0.1 mmol), **L6**-$Sc(OTf)_3$ (1:1, 10 mol%), 3 Å M.S. (2.0 mg), $NaHCO_3$ (0.3 mmol), and diaryliodonium salt **2b** (0.15 mmol) in CH_2Cl_2 (0.8 mL) at 35 °C for the indicated time. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] **L6**-$Sc(OTf)_3$ (1:1, 5 mol%).

Table 3: Substrate scope of diaryliodonium triflates.[a]



Entry	Ar	R^3	Time [h]	Yield (**3**) [%][b]	*ee* [%][c]
1	4-FC_6H_4	4-F	48	65 (**3 ab**)	94
2	4-ClC_6H_4	4-Cl	24	79 (**3 ac**)	96
3	4-BrC_6H_4	4-Br	48	82 (**3 ad**)	98
4	4-$tBuC_6H_4$	4-*t*Bu	72	80 (**3 ae**)	92
5	4-MeC_6H_4	4-Me	72	76 (**3 af**)	96
6	Mes	H	120	80 (**3 aa**)	92
7	Mes	4-Cl	120	79 (**3 ac**)	94
8	Mes	4-Br	120	65 (**3 ad**)	94
9	Mes	4-Ph	120	55 (**3 ag**)	90

[a] All reactions were performed with **1 a** (0.1 mmol), **L6**-$Sc(OTf)_3$ (1:1, 10 mol%), 3 Å M.S. (2.0 mg), $NaHCO_3$ (0.3 mmol), and diaryliodonium salt **2** (0.15 mmol) in CH_2Cl_2 (0.8 mL) at 35 °C for the indicated time. [b] Yield of isolated product. [c] Determined by HPLC analysis.



Scheme 2. a) Gram version of the reaction; b) asymmetric synthesis of the antiproliferative agent.

tron-rich or electron-deficient aryl groups could be successfully transferred to 3-benzyl-2-oxindole **1 a** with high enantioselective levels (92–98% *ee*), and moderate to good yields (65–82%; Table 3, entries 1–5). Pleasingly, the reaction of diaryliodonium triflate with *n*-butyl substituents performed well within a longer reaction time (80% yield, 92% *ee*; Table 3, entry 4). It is important to note that the unsymmetric salts[13] bearing nontransferring mesityl ligand could also be readily exploited, and the electron-poor aryl moiety is preferably transferred in enolate arylation. Aryl groups with halogen substituents on the phenyl substituents could be introduced in satisfying results under mild reaction conditions (Table 3, entries 7–9). Unfortunately, α-vinylation[2f] by using vinyliodonium salts failed.

To show the utility of the current method, a gram-scale synthesis of 3-benzyl-3-aryloxindole derivative was carried out with oxindole **1 f** and diaryliodonium triflate **2 b**. The reaction proceeded smoothly to give the product **3 fa** in 99% yield and 99% *ee* (Scheme 2 a). Oxindole derivative **3 xl** is used as a antiproliferative agent for the treatment of cancer. To date, there are few asymmetric methods for synthesizing **3 xl**.[14] The arylation process between oxindole **1 x** and unsymmetric salt **2 l** was conducted to afford the enantiomeric enriched product **3 xl** in 71% yield and 94% *ee* (Scheme 2 b). This provides a useful and concise route to construct such an important chiral molecules for the purposes of medicinal agent testing.

Preliminary studies of the mechanism were carried out by HRMS experiments. The coordination of *N*,*N*′-dioxide **L6** with $Sc(OTf)_3$ was confirmed by the ion peak at *m*/*z* 825.2388, corresponding to the intermediate $[Sc^{3+} + (\mathbf{L6}\text{-H})^- + TfO^-]^+$. Peaks at *m*/*z* 898.3812 and 1048.3442 were assigned to $[Sc^{3+} + \mathbf{L6} + \mathbf{1a}\text{-}2H^-]^+$ and $[Sc^{3+} + \mathbf{L6} + \mathbf{1a} + TfO^-\text{-H}]^+$, respectively, which indicated the association of oxindole to the metal center. Based on our previous study of chiral *N*,*N*′-dioxide-metal complex promoted asymmtric reaction of oxindoles, as well as the theoretical study of Olofsson, we postulated a possible catalytic model to elucidate the stereocontrol (see the Supporting Information). The formation of chiral scan-

dium enolate from oxindole **1** reduced the electric-charge density of oxygen, which was adverse to the electrophilic addition of diaryliodonium salts. Meanwhile, severe steric hindrance around the oxygen also hampered the generation of O–I bonded isomer and C–I to O–I isomerization (Scheme 1 b). The enantioselective arylation of enolate was obtained by differentiation of its enantiopotic faces through the shielding effect of the nearby amide moiety of the ligand. With easily dissociated triflate counterion, it was likely that cationic hypervalent iodine reagents prefered to attack the C3 atom of the enolate from the *Re*-face. The intermediate reapidly performed [1,2] rearrangement to give the desired (*R*)-product, which is in good agreement with the X-ray analysis of **3qa**.

In conclusion, we have developed a new asymmetric catalytic strategy for α-arylation of carbonyl compounds. Chiral Lewis acid catalysts of *N*,*N*′-dioxide-Sc(OTf)$_3$ complex performed well in the reaction of N-unprotected 3-substituted oxindoles with diaryliodonium triflates under mild reaction conditions. The desired oxindole derivatives with quaternary carbon centers were afforded in high enantioselectivity and reactivity (up to 99% *ee* and 99% yield). As one example, this new procedure has been successfully applied to the enantioselective synthesis of an antiproliferative agent. Of our study, this is the first example that *N*,*N*′-dioxide bearing tetrahydroisoquinoline backbones gave better enantiocontrol than these derived from other amino acids. Further application of C2-symmetric *N*,*N*′-dioxide amides to other asymmetric transformations, as well as the study of the relationship between the structure of the catalyst and its catalytic features in reactions, are ongoing in our laboratory.

Experimental Section

General procedure for the asymmetric α-arylation of 3-substituted oxindoles: A dry reaction tube was charged with **L6**-Sc(OTf)$_3$ (1:1, 10 mol%), 3 Å M.S. (2.0 mg, activated at 300 °C for 5 h before use), and oxindole **1** (0.1 mmol) under N_2 atmosphere. CH_2Cl_2 (0.5 mL) was added, and the mixture was stirred at 35 °C for 0.5 h. Then, diaryliodonium salt **2** (0.15 mmol), $NaHCO_3$ (0.3 mmol), and CH_2Cl_2 (0.3 mL) were added under stirring. The reaction mixture was stirred at 35 °C for 24–120 h. After complete consumption of the starting materials, the mixture was direct purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1 to 6:1) to afford **3** as a white solid.

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