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Spiro Compounds

Asymmetric Tandem 1,5-Hydride Shift/Ring Closure for the Synthesis of Chiral Spirooxindole Tetrahydroquinolines

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Abstract: The direct functionalization of sp^3 C–H bonds through a tandem 1,5-hydride shift/ring closure is described. Various optically active spirooxindole tetrahydroquinoline derivatives bearing contiguous quaternary or tertiary stereogenic carbon centers were readily synthesized. A chiral scandium complex of *N*,*N*′-dioxide promoted the reactions in good yields (up to 97%) with excellent diastereoselectivities (>20:1) and enantioselectivities (up to 94% *ee*). Kinetic isotope effect (KIE) experiments and internal redox reactions of chiral substrates were conducted, and the results provided intriguing information that helped clarify the mechanism of the reaction.

Introduction

The development of methodologies for the direct functionalization of relatively unreactive C–H bonds is of intense interest and represents a long-standing goal in chemistry because these reactions provide novel strategic approaches for synthesis.[1] In the past decades, some promising catalytic systems for the selective functionalization of C(sp^3)–H bonds have been developed. Since Reinhoudt et al.[2] provided an alternative method of cleavage of a C(sp^3)–H bond through an intramolecular tandem 1,5-hydride shift/ring closure process in 1984, variants of this rearrangement have been reported.[3–6] One challenge associated with this chemistry has been to render it enantioselective under mild reaction conditions. Chiral organocatalysts (e.g., chiral phosphoric acid and iminium) and chiral Lewis acids (e.g., Mg^{II}, Co^{II} and Au^{I} coordinating with chiral ligands) are general catalysts that are used for the asymmetric transitions. This concept has enabled the straightforward construction of tetrahydroquinoline,[6a–c,f–h] furan-fused benzazepines,[6d] cyclic aminals,[6e] spiroethers,[6i] and others.

The chiral spirocyclic-3,3′-oxindole unit is encountered in a large variety of natural products and several pharmaceutical candidates with a wide spectrum of biological activities.[7] Extensive investigation has led to the synthesis of a series of enantiomeric enriched spiro-fused 2-oxindole rings with different functionality. Recently, Yuan and co-workers realized an efficient $FeCl_3$-catalyzed 1,5-hydride shift/ring closure reaction to form spirooxindole tetrahydroquinolines with contiguous quaternary or tertiary stereogenic carbon centers. Nevertheless, asymmetric versions of the process have hitherto been far from satisfactory. The combination of chiral diamine, salen, diphosphine, and bisoxazoline ligands with a number of metal salts gave no more than 11% *ee*. Only moderate enantioselectivity of 54% *ee* was achieved by using chiral phosphoric acids as the catalysts.[8] Highly diastereo- and enantioselective aspects of the reaction have remained elusive. Our group showed that chiral *N*,*N*′-dioxide–Co^{II} complexes could be exploited in the asymmetric formation of tetrahydroquinolines through an internal redox reaction.[6f] Furthermore, access to the set of stereoisomers of 2-oxindole-based compounds has also been realized through a number of strategies.[7] In this context, we envisaged that this privileged type of chiral Lewis acid could enable the highly stereoselective synthesis of spirooxindole tetrahydroquinolines by lowering the activation barriers of 1,5-hydride shift and controlling the stereoselectivity of the H-transfer and subsequent ring closure. We herein present our achievement of this goal (Figure 1).

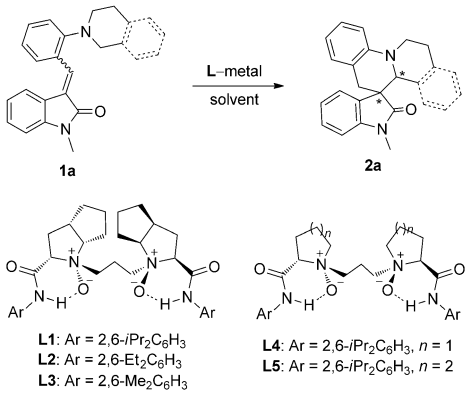

Figure 1. The synthesis of spirooxindole tetrahydroquinolines catalyzed by *N*,*N*′-dioxide–metal complexes.

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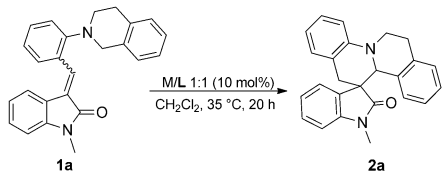
Results and Discussion

We selected oxindole derivative **1a** as a representative substrate to examine the intramolecular tandem 1,5-hydride shift/ring closure reaction. Initial efforts focused on the metal precursors. A series of metal salts such as Mg^{II}, Zn^{II}, Cu^{II} Co^{II}, and Sc^{III} chelated with L-ramipril derived *N*,*N*′-dioxide **L1** were used to catalyze the reaction in CH_2Cl_2 at 35 °C (Table 1, entries 1–5).[9] Scandium(III) triflate proved to be competent for the formation of the desired spirooxindole tetrahydroquinoline **2a**, with 95% yield, 89% *ee* and >20:1 d.r. (Table 1, entry 5), whereas the others were found to be ineffective Lewis acid mediators for the transformation. Other lanthanide metal salts could furnish the product in a range of yields and enantioselectivities, all of which were inferior to that obtained with scandium(III) triflate (Table 1, entries 6–9). The structure of the *N*,*N*′-dioxide ligands had a large effect on the enantioselectivity. Neither ligand **L4** derived from L-proline nor ligand **L5** derived from L-pipecolic acid were superior to L-ramipril derived **L1** (Table 1, entries 12 and 13 vs. entry 5). Altering the amide substitutions from 2,6-diisopropylaniline to 2,6-diethylaniline or 2,6-dimethylaninline allowed for the formation of the products in high yields but seriously decreased the enantioselectivity (Table 1, entries 10–11).

Table 1. Optimization of chiral *N*,*N*′-dioxide–metal complexes.



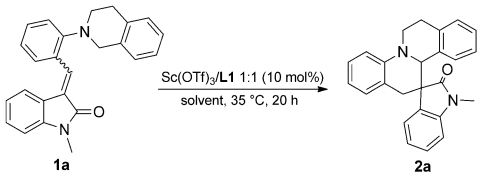
1a 2a

Entry[a]	Metal	Ligand	Yield [%][b]	*ee* [%][c,d]
1	$Mg(OTf)_2$	**L1**	NR	–
2	$Zn(OTf)_2$	**L1**	NR	–
3	$Cu(OTf)_2$	**L1**	NR	–
4	$Co(BF_4)_2{\cdot}6H_2O$	**L1**	trace	–
5	$Sc(OTf)_3$	**L1**	95	89
6	$La(OTf)_3$	**L1**	17	64
7	$Y(OTf)_3$	**L1**	25	73
8	$Yb(OTf)_3$	**L1**	75	77
9	$Sm(OTf)_3$	**L1**	25	70
10	$Sc(OTf)_3$	**L2**	93	61
11	$Sc(OTf)_3$	**L3**	91	29
12	$Sc(OTf)_3$	**L4**	97	85
13	$Sc(OTf)_3$	**L5**	97	83

[a] Reaction conditions (unless otherwise noted): **L**–metal (10 mol%, 1:1), **1a** (0.10 mmol), CH_2Cl_2 (1.0 mL), 35 °C, 20 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Up to 20:1 d.r. was obtained in all cases determined by ^{1}H NMR analysis. NR = no reaction.

Encouraged by the initial results, a range of solvents were tested in the presence of **L1**–$Sc(OTf)_3$ (10 mol%). The results indicated that the reaction solvent played an important role in governing the activity of the reaction. Low yields were obtained in coordinating solvents (Table 2, entries 1–2). No reaction took place in CH_3CN, presumably due to the poor solubility (Table 2, entry 4). Given that CH_2Cl_2 was initially found to be the optimal solvent, other chlorinated alkanes were then investigated, and 91% *ee* could be obtained in the medium of CH_2ClCH_2Cl (Table 2, entries 5–9). Molecular sieves were then added to this reaction, but no better results were obtained (Table 2, entries 10–12). Therefore, the optimal conditions were established as: **L1**–$Sc(OTf)_3$ complex (10 mol%; 1:1) and oxindole derivative **1** (0.1 mmol) in CH_2ClCH_2Cl (1.0 mL) at 35 °C (Table 2, entry 7).

Table 2. Optimization of the reaction conditions.

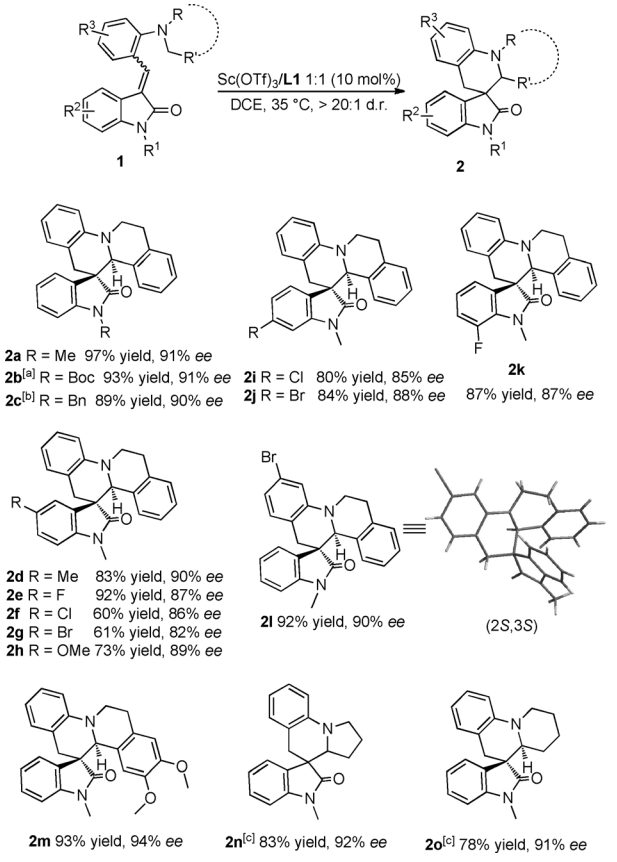


1a 2a

Entry[a]	Solvent	Additive	Yield [%][b]	*ee* [%][c,d]
1	THF	–	27	90
2	EtOAc	–	19	88
3	toluene	–	22	87
4	CH_3CN	–	NR	–
5	CH_2Cl_2	–	95	89
6	$CHCl_3$	–	93	89
7	CH_2ClCH_2Cl	–	97	91
8	$CHCl_2CHCl_2$	–	91	87
9	PhCl	–	90	88
10[e]	CH_2ClCH_2Cl	3 Å MS	93	91
11[e]	CH_2ClCH_2Cl	4 Å MS	91	91
12[e]	CH_2ClCH_2Cl	5 Å MS	92	91

[a] Reaction conditions (unless otherwise noted): **L1**–$Sc(OTf)_3$ (10 mol%, 1:1), **1a** (0.10 mmol), solvent (1.0 mL), 35 °C, 20 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Up to 20:1 d.r. was obtained in all cases determined by ^{1}H NMR analysis. [e] Molecular sieves (10 mg) were used.

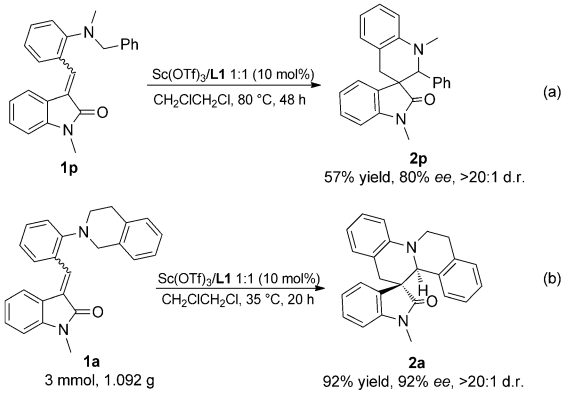
With the optimal conditions identified, we examined the substrate scope of the reaction (Scheme 1). In all cases, the reaction occurred smoothly to afford the products exclusively in up to 20:1 d.r. values. Oxindole derivatives **1b** and **1c** with *N*-Boc and *N*-Bn protecting groups were tolerated with no influence on the diastereo- and enantioselectivity, although the yields decreased slightly (Scheme 1, **2a**–**c**). We found that a range of substrates **1d**–**k**, with substituents at the oxindole framework, participated effectively in the internal redox reactions to yield the corresponding spirooxindole tetrahydroquinolines with extremely high diastereoselectivities (>20:1 d.r.). Compared with the 5-methyl or 5-methoxyl substituted oxindoles **1d** and **1h**, respectively, the electronically deficient halo-substituted oxindoles **1e**–**g** produced somewhat lower enantioselectivities (82–87% *ee*). Substrates **1i**–**k**, bearing halo-substituents at the 6- or 7-positions, served to generate the target products in 80–87% yields and 85–88% *ee*. Substituent at the extended aryl group of oxindole derivative **1l** was also compatible with the reaction conditions, generating **2l** in 92% yield and 90% *ee*. Substrate **1m**, containing the 6,7-dimethoxy-tetrahydroisoquinoline unit, was also tolerated (93% yield, 94% *ee*). The method was not limited to the $C(sp^3)$–H bond of tetrahydroisoquinoline, with both pyrrolidine and piperidine furnishing the desired products in high diastereo- and enantioselectivities (>20:1 d.r., 91–92% *ee*), which served to



Scheme 1. Substrate scope for spirooxindole tetrahydroquinoline derivatives. Unless otherwise noted, all reactions were performed with **L1**-$Sc(OTf)_3$ (10 mol%, 1:1), **1** (0.10 mmol) in CH_2ClH_2Cl (1.0 mL) at 35 °C for 20 h. Isolated yields based on the amount of total *E*/*Z* isomers are reported. The *ee* was determined by chiral HPLC analysis and the d.r. was determined by ^1H NMR analysis. Relative and absolute stereochemical configurations were determined by X-ray analysis of the product **2l** and on the circular dichroism spectrum. [a] $Mg(ClO_4)_2$ was used instead of $Sc(OTf)_3$. [b] $CHCl_3$ was used instead of CH_2ClCH_2Cl and **L4** was used instead of **L1**. [c] The reaction was performed at 60 °C.

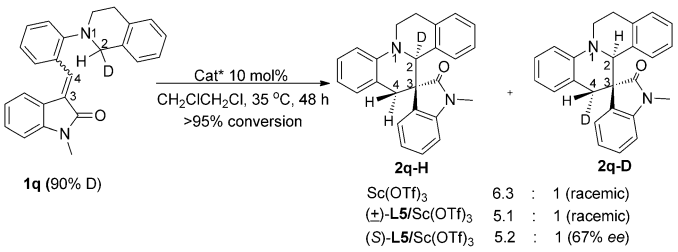
slow the rate of reaction and required a higher reaction temperature (60 °C) to drive the process. The absolute configuration of the product **2l** was determined to be (2*S*,3*S*) by X-ray analysis (see the Supporting Information). Notably, (*Z*)-substrates failed to be converted into the corresponding products.[10]

Subsequently, we turned our attention to broadening the substrate scope to include the acyclic tertiary amine unit and found that this substrate gave only trace amounts of the 1,5-hydride shift/ring closure product at 35 °C. Delightfully, applying the unique *N*,*N*′-dioxide-scandium(III)-mediated system at higher reaction temperature (80 °C) enabled the redox process to progress smoothly (57% yield, >20:1 d.r.), albeit with a slight drop in the enantioselectivity (80% *ee*; Scheme 2a). In addition, to show the synthetic utility of the catalyst system, a gram-scale reaction with **1a** was performed. As shown in Scheme 2b, the reaction proceeded smoothly to give the desired product **2a** in 92% yield with 92% *ee* and >20:1 d.r. Notably, significant self-disproportionation of enantiomers (SDE)[11] was observed during the silica column chromatography separation of the spirooxindole tetrahydroquinoline products (see the Supporting Information).



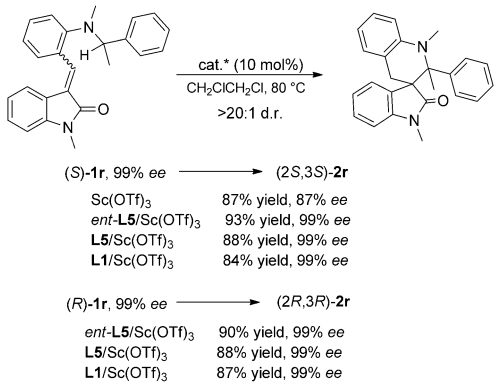
Scheme 2. a) Substrate for the catalytic asymmetric intramolecular 1,5-hydride transfer/closure of an acyclic compound. b) Gram-scale version of the reaction.

To clarify the detailed reaction course, a kinetic isotope effect (KIE) experiment[4f] was then conducted (Scheme 3). Racemic monodeuterated substrate **1q** was subjected to the intramolecular 1,5-hydride transfer/closure. The labeling experiments showed interesting results. H-transferred product **2q**-H and D-transferred product **2q**-D were obtained with k_H/k_D ratio as 6.3, 5.1 and 5.2, respectively, when $Sc(OTf)_3$, *rac*-**L5**/$Sc(OTf)_3$, and **L5**/$Sc(OTf)_3$ were used as catalysts, indicating that the 1,5-H transfer process in this reaction is the rate-determining step. The phenomenon is similar to $MgCl_2$-catalyzed *tert*-aminocyclization proven by Luo and co-workers.[6g] As mentioned in early reports,[2c,d] the *tert*-aminocyclization of 2-vinyl-*N*,*N*-dialkylanilines takes place in a suprafacial 1,5-H transfer manner, resulting in the formation of 2,4-*cis* configuration. In this case, based on the ^1H NMR spectrum of D-transferred product **2q**-D, the transferred H-2 and the bridgehead hydrogen H-1 was located at 3.81 and 4.86 ppm. Irradiation of the bridgehead hydrogen H-1 of **2a** gave a NOE of 0.73% at H-2, which indicated that two hydrogen atoms were located on the same face in **2a** (see the Supporting Information).



Scheme 3. Kinetic isotope effect experiments with monodeuterated substrate.

Control experiments were also conducted using chiral phenylethanamine derived substrate **1r** to clarify the origins of the stereocontrol of the internal redox reaction (Scheme 4). When optically pure oxindole derivative (*S*)-**1r** was employed in the reaction with $Sc(OTf)_3$ as the catalyst, the desired product was



Scheme 4. Control experiments of optically active substrate (*S*)-**1r** and (*R*)-**1r**.

afforded in 87% *ee* (Scheme 4). This is consistent with Akiyama's observation that the chiral information in optically active substrate did not completely disappear through the hydride shift process (Figure 2).[6c] Interestingly, in the presence of catalyst systems **L5**/$Sc(OTf)_3$, *ent*-**L5**/$Sc(OTf)_3$, or **L1**/$Sc(OTf)_3$, (*S*)-**1r** underwent the redox reaction to give the product in comparably high yields and identical configuration (Scheme 4). The absolute configuration was determined to be (2*S*,3*S*) by X-ray analysis (Figure 2). Consequently, (*R*)-**1r** furnished exclusively (2*R*,3*R*)-**2r** irrespective of which chiral catalyst was used (Scheme 4). The results differed from chiral phosphoric acid promoted internal redox reactions of chiral benzylidene malonates.[6c] One could speculate that the chiral memory effect is extremely strong in the presence of a chiral *N*,*N*′-dioxide–$Sc(OTf)_3$ complex catalyst, overwhelming the stereocontrol exerted by the chiral ligand (Figure 2, path 1). However, we have no means of ruling out an enantiofacial selection of the nucleophilic attack on the iminium cation when achiral substrates were used.

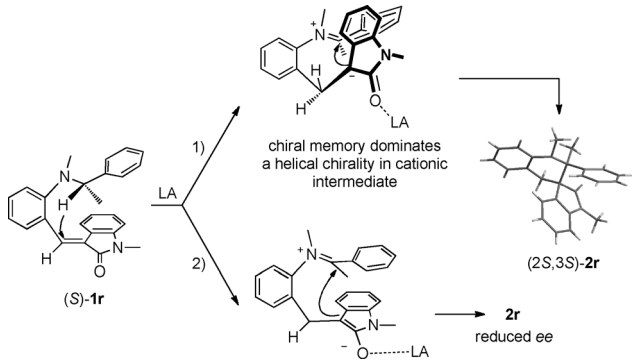


Figure 2. Possible reaction pathways.

Conclusion

We have presented a highly diastereo- and enantioselective 1,5-hydride shift/ring closure cascade. The identified optimal catalytic system of chiral *N*,*N*′-dioxide–$Sc(OTf)_3$ exhibits excellent performance. A range of optically active spirooxindole tetrahydroquinoline derivatives bearing quaternary or tertiary stereogenic carbon centers were obtained in high yields (up to 97%) with good *ee* values (up to 94% *ee*) and diastereoselectivities (>20:1 d.r.). Kinetic isotope effect (KIE) and control experiments were conducted. Strong chiral memory effect was found using a chiral substrate. Further investigations explaining the asymmetric mechanism of catalysis of the redox-neutral sp^3 C–H functionalization are underway in our group.

Experimental Section

Typical experimental procedure for the cyclic substrate

To a dry tube, **L1** (0.01 mmol, 7.1 mg), $Sc(OTf)_3$ (0.01 mmol, 4.9 mg), and CH_2ClCH_2Cl (1.0 mL) were added under a N_2 atmosphere and the mixture was stirred at 35 °C for 0.5 h. The substrate **1a** was added and the mixture was stirred at 35 °C for an additional 20 h. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O = 5:1) to afford the corresponding product **2a** (97% yield) as a white solid; m.p. 73–75 °C; 91% *ee*; >20:1 d.r.; $[\alpha]_D^{25}$ +201.96 (*c* = 0.56 in CH_2Cl_2). The *ee* was determined by HPLC analysis using a chiral ID column (hexane/*i*PrOH = 80:20, 1.0 mL min^{-1}, 254 nm): t_r = 11.39 (minor), 12.09 (major) min; the d.r. was determined by ^{1}H NMR analysis; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 7.2 Hz, 1H), 7.27–7.20 (m, 1H), 7.14–7.06 (m, 2H), 7.06–6.97 (m, 2H), 6.95–6.86 (m, 2H), 6.84–6.73 (m, 3H), 6.51 (d, *J* = 7.6 Hz, 1H), 4.86 (s, 1H), 7.04–3.95 (m, 1H), 3.81 (d, *J* = 16.8 Hz, 1H), 3.21 (td, *J* = 11.6, 3.2 Hz, 1H), 3.01 (s, 3H), 2.61–2.49 (m, 1H), 2.75 (d, *J* = 8.4 Hz, 1H), 2.46–2.38 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.69, 145.93, 143.10, 136.03, 132.51, 130.69, 129.85, 127.97, 127.77, 127.64, 127.16, 126.76, 125.55, 125.24, 121.84, 120.29, 117.36, 111.86, 107.10, 62.19, 52.34, 42.79, 36.09, 29.82, 26.07 ppm; HRMS (ESI-TOF): *m*/*z* calcd. for $C_{25}H_{22}N_2O$: 367.1810 [*M*+H$^+$]; found: 367.1808.

Typical experimental procedure for the acyclic substrate

To a dry tube, **L1** (0.01 mmol, 7.1 mg), $Sc(OTf)_3$ (0.01 mmol, 4.9 mg), and CH_2ClCH_2Cl (1.0 mL) were added under a N_2 atmosphere and the mixture was stirred at 35 °C for 0.5 h. The substrate **1p** was added and the mixture was stirred at 80 °C for an additional 48 h. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O = 5:1) to afford the corresponding product **2p** (57% yield) as a viscous oil; 80% *ee*; >20:1 d.r.; $[\alpha]_D^{25}$ +112.38 (*c* = 0.42 in CH_2Cl_2); the *ee* was determined by HPLC analysis using a chiral ID column (hexane/*i*PrOH = 80:20, 1.0 mL min^{-1}, 254 nm): t_r = 6.33 (major), 7.09 (minor) min; the d.r. was determined by ^{1}H NMR analysis; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.21 (m, 2H), 7.16–7.03 (m, 3H), 7.02–6.91 (m, 3H), 6.89–6.68 (m, 4H), 6.50 (d, *J* = 8.0 Hz, 1H), 4.71 (s, 1H), 3.64 (d, *J* = 15.6 Hz, 1H), 2.86 (s, 3H), 2.80 (s, 3H), 2.65 ppm (d, *J* = 15.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.43, 147.51, 143.17, 137.08, 129.60, 129.50, 127.97, 127.90, 127.56, 127.20, 125.75, 122.11, 120.45, 117.53, 113.14, 107.35, 68.29, 51.59, 38.17, 35.88, 25.89 ppm; HRMS (ESI-TOF): *m*/*z* calcd for $C_{24}H_{22}N_2O$: 377.1630 [*M*+Na$^+$]; found: 377.1634.

Procedure for the scale-up reaction

To a dry round-bottomed flask, **L1** (0.3 mmol, 213.0 mg), $Sc(OTf)_3$ (0.3 mmol, 147.0 mg), and CH_2ClCH_2Cl (30 mL) were added and the mixture was stirred at 35 °C for 2.5 h. **1a** (3.0 mmol) was added and the mixture was stirred at 35 °C for 20 h. The residue was puri-

fied by flash chromatography on silica gel to afford the product **2a** (92% yield); 92% *ee* and >20:1 d.r. It was notable that the product **2a** exhibited a clear self-disproportionation of enantiomers (SDE) effect.

General procedure for the kinetic isotope effect experiment with monodeuterated 1q

To a dry tube, *rac*-**5** (0.01 mmol, 6.5 mg), $Sc(OTf)_3$ (0.01 mmol, 4.9 mg), and CH_2ClCH_2Cl (1.0 mL) were added and the mixture was stirred at 35 °C for 0.5 h. **1q** (0.1 mmol) was added and the mixture was stirred at 35 °C for 20 h. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O = 5:1) to afford the corresponding product **2q** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 1H), 7.26–7.20 (m, 1H), 7.17–6.96 (m, 4H), 6.96–6.85 (m, 2H), 6.84–6.68 (m, 3H), 6.50 (d, J = 8.0 Hz, 1H), 4.85 (s, 0.23H), 4.02–3.96 (m, 1H), 3.81 (d, J = 16.8 Hz, 0.77H), 3.21 (td, J = 11.6, 3.2 Hz, 1H), 3.01 (s, 3H), 2.75 (d, J = 16.8 Hz, 1H), 2.61–2.49 (m, 1H), 2.47–2.37 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.62, 144.88, 142.05, 134.98, 131.38, 129.61, 128.76, 126.88, 126.68, 126.57, 126.08, 125.68, 124.47, 124.16, 120.75, 119.21, 116.26, 110.78, 106.01, 61.11, 51.26, 41.75, 35.00, 28.74, 24.98 ppm.

Crystallography

Details of the crystal structure determination are given in the Supporting Information. CCDC-994332 (**2l**) and -1012868 (**2r**) 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.

Acknowledgements

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Keywords: asymmetric catalysis · C–H functionalization · hydride shift · scandium · spirooxindoles

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