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Asymmetric Synthesis of Tetrahydroquinolines with Quaternary Stereocenters through the Povarov Reaction

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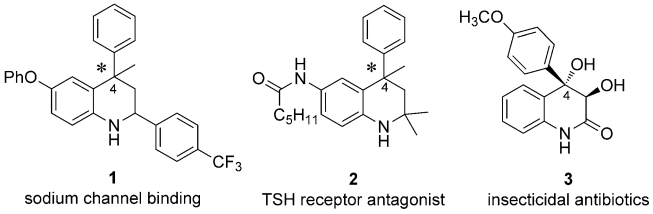
Abstract: The asymmetric Povarov reaction with α-alkyl styrenes as dienophiles was catalyzed by an *N*,*N*′-dioxide **L4**–$Sc(OTf)_3$ complex. Enantiopure tetrahydroquinoline derivatives with a quaternary stereocenter at the C4 position were synthesized for the first time. A wide variety of α-alkyl styrenes and *N*-aryl aldimines were tolerated in the reaction, to give excellent diastereo- (up to 99:1 d.r.) and enantioselectivities (92 to >99% *ee*). In addition, the reaction could be performed on the gram scale without any loss of yield, diastereoselectivity, or enantioselectivity. An intermolecular hydrogen-shift reaction was found to be a side reaction, which offered a method to synthesize the corresponding quinoline derivatives with chiral quaternary sterocenters.

Keywords: asymmetric catalysis · dioxides · Povarov reaction · scandium · tetrahydroquinolines

Introduction

The asymmetric construction of molecules with quaternary carbon stereocenters represents a highly challenging area in organic synthesis.[1] Tetrahydroquinoline derivatives bearing a quaternary carbon center at the C4 position exhibit potential biological activities. Representative examples[2] are shown in Scheme 1. The Povarov reaction,[3] an inverse electron-demand aza Diels–Alder reaction[4–7] of *N*-aryl imines (2-azadienes) with electron-rich alkenes (dienophiles), is one of the most efficient routes to construct this kind of privileged backbone. In 1996, Ishitani and Kobayashi developed the first catalytic asymmetric Povarov reaction with cyclopentadiene and vinyl ethers as dienophiles by using chiral binaphthol–ytterbium complexes.[8] Subsequently, great endeavors have been devoted toward asymmetric Povarov reactions with various dienophiles.[9] In 2006, Akiyama and coworkers reported the reaction with vinyl ethers as dienophiles promoted by a chiral phosphoric acid.[9b] Later, enecarbamates and vinylindoles were used as dienophiles in reactions with chiral phosphoric acids as catalysts by Zhu and Masson's group[9c] and Bernardi and Ricci's group,[9d] respectively. In 2010, Jacobsen's group reported the Povarov reaction with vinyl ethers, enecarbamates and enamides as dienophiles through cooperative catalysis of strong Brønsted acids with chiral ureas.[9e] Very recently, Jørgensen and coworkers developed an intramolecular Povarov reaction catalyzed by a prolinol silyl ether.[9h] However, the previous studies could only afford chiral tetrahydroquinolines with a tertiary stereocenter at the C4 position, and the construction of chiral tetrahydroquinolines with a quaternary stereocenter at the C4 position remains unreported.[10]



Scheme 1. Examples of biologically active tetrahydroquinoline derivatives bearing a quaternary carbon center at the C4 position.

With α-alkyl styrenes as dienophiles, the corresponding tetrahydroquinoline adducts can be oxidized into quinoline-3-one derivatives with the quaternary carbon center maintained;[11] comparatively, tetrahydroquinolines with the C4 position as a tertiary stereocenter would be converted into quinolines[12] (Scheme 2). With the consideration that tetrahydroquinolines with the C4 position as a quaternary stereocenter potentially exhibit biological activities, an effective catalyst for this Povarov reaction is highly desirable. As excellent chiral scaffolds, *N*,*N*′-dioxide ligands[13] can coordinate with various metals and have shown strong asymmetry-inducing capability for many reactions, including the Povarov reaction of cyclopentadiene.[9f] In an effort to develop a practical approach toward the structural class of tetrahydroquinolines, we have expanded the scope of the asymmetric Povarov reaction of α-alkyl styrenes. Herein, we report the asymmetric synthesis of optically active tetrahydroquinoline

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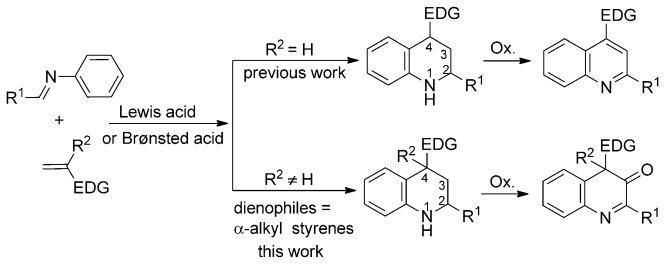


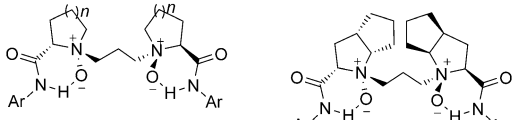
EDG = electron-donating group, Ox. = oxidation reaction

Scheme 2. The Povarov reaction and the oxidation of the products.

derivatives with a quaternary stereocenter catalyzed by an *N*,*N*′-dioxide–$Sc(OTf)_3$ complex[14] in good yields and with excellent diastereoselectivities (up to 99:1 d.r.) and enantioselectivities (92 to >99% *ee*). The side reactions occurring in the process were also studied in detail.

Results and Discussion

Initially, L-pipecolic acid derived *N*,*N*′-dioxide **L1** (Scheme 3) was complexed with various metal salts to catalyze the Povarov reaction of *N*-aryl imine **4a** with α-methyl-



L1: Ar = Ph, *n* = 2
L2: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, *n* = 2
L3: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, *n* = 1
L4: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$

Scheme 3. Chiral ligands employed for the Povarov reaction.

styrene (**5a**) in CH_2Cl_2 at 30°C. The central metal ion was found to significantly affect the enantioselectivity of the reaction. As shown in Table 1, when $Mg(OTf)_2$ or $Cu(OTf)_2$ were tested, trace amounts of tetrahydroquinoline **6a** were obtained (Table 1, entries 1 and 2). $Yb(OTf)_3$, $Y(OTf)_3$, and $La(OTf)_3$ gave the racemic tetrahydroquinoline **6a** in poor yields with the *cis* isomer as the major product (Table 1, entries 3–5). When $Sc(OTf)_3$ was tested as the metal salt, nearly equal amounts of the *cis* and *trans* isomers were obtained with 37% yield of the total products **6a** and 30% *ee* for the *trans* isomer (Table 1, entry 6). In addition, the counterion also affected the reactivity greatly, and $Sc(OiPr)_3$ gave trace amounts of tetrahydroquinoline **6a** (Table 1, entry 7 versus entry 6). Other lanthanide metal salts were also employed, but no better results were obtained (Table 1, entries 8–10). As a result, $Sc(OTf)_3$ was selected as the metal salt for the further examination.

Further optimization of the reaction conditions was aimed at exploring the effect of complexes of other *N*,*N*′-dioxide ligands with $Sc(OTf)_3$ (Table 2). An increase in the steric hindrance of the amide subunits of the *N*,*N*′-dioxide, such as in

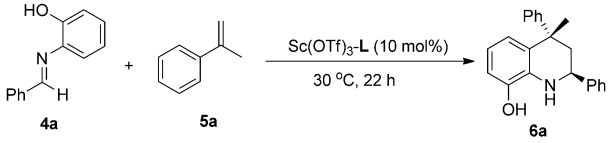
Table 1. Screening of central metal ions in the asymmetric Povarov reaction of *N*-aryl imine **4a** and α-methylstyrene (**5a**).[a]

4a **5a** **6a**

Entry	Metal salt	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][c]
1	$Mg(OTf)_2$	trace		
2	$Cu(OTf)_2$	trace		
3	$Yb(OTf)_3$	5	25/75	0
4	$Y(OTf)_3$	16	26/74	0
5	$La(OTf)_3$	5	26/74	0
6	$Sc(OTf)_3$	37	49/51	30
7	$Sc(OiPr)_3$	trace		
8	$Ce(OTf)_3$	20	26/74	0
9	$Pr(OTf)_3$	6	27/73	0
10	$Nd(OTf)_3$	trace		

[a] Unless otherwise noted, all reactions were carried out with 10 mol% of **L1**/metal (1/1), **4a** (0.2 mmol), and **5a** (7.5 equiv, 200 μL) in CH_2Cl_2 (1.0 mL) under N_2 at 30°C for 22 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis; the *trans* isomer was confirmed by ^{1}H NMR spectroscopy; the *ee* value refers to the *trans* isomer.

Table 2. Screening of ligand and solvent effects in the asymmetric Povarov reaction of *N*-aryl imine **4a** and α-methylstyrene (**5a**).[a]



4a **5a** **6a**

Entry	L	Solvent	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][c]
1	**L1**	CH_2Cl_2	37	49/51	30
2	**L2**	CH_2Cl_2	27	74/26	80
3	**L3**	CH_2Cl_2	32	73/27	89
4	**L4**	CH_2Cl_2	39	95/5	96
5	**L4**	THF	trace		
6	**L4**	$CHCl_3$	10	93/7	86
7	**L4**	$ClCH_2CH_2Cl$	18	91/9	91
8	**L4**	Cl_2CHCH_2Cl	17	89/11	83

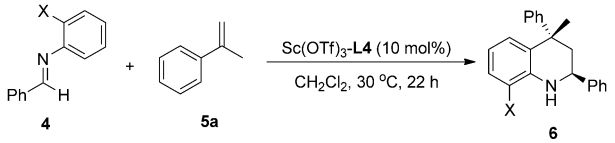
[a] Unless otherwise noted, all reactions were carried out with 10 mol% of **L**/$Sc(OTf)_3$ (1/1), **4a** (0.2 mmol), and **5a** (7.5 equiv, 200 μL) in solvent (1.0 mL) under N_2 at 30°C for 22 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis; the *trans* isomer was confirmed by ^{1}H NMR spectroscopy; the *ee* value refers to the *trans* isomer.

L2 with bulkier isopropyl groups, could raise the diastereoselectivity and enantioselectivity of the *trans* product (74:26 d.r. and 80% *ee*; Table 2, entry 2 versus entry 1). Furthermore, the L-ramipril derived *N*,*N*′-dioxide **L4** exhibited superior stereoselectivity (95:5 d.r. and 96% *ee*) compared with the L-proline and L-pipecolic acid derived ones, and it afforded the best results (Table 2, entry 4 versus entries 2 and 3). On the encouraging basis of these initial results, various solvents were tested in the presence of **L4**–$Sc(OTf)_3$ (Table 2, entries 5–8). Tetrahydrofuran reduced the catalytic activity greatly, and only traces of product **6a** were observed (Table 2, entry 5). When chloroform, 1,2-dichloroethane,

and 1,1,2-trichloroethane were used as solvents, excellent diastereoselectivities and enantioselectivities could also be obtained, but the yields were low (Table 2, entries 6–8). Therefore, CH_2Cl_2 was established as the best solvent for the further optimization.

With CH_2Cl_2 as the solvent and the **L4**–$Sc(OTf)_3$ complex as the catalyst, however, the isolated yield of **6a** is only 39% (Table 3, entry 1) and a large amounts of 2-aminophenol was detected. It is possible that the cause is decomposition of imine **4a** in the presence of a Lewis acid. In order to decrease the decomposition of imine **4a**, benzaldehyde and $MgSO_4$ were added, which greatly improved the yield (62% yield; Table 3, entries 2 and 3). Extensive screening of the reaction conditions, including the concentrations in the reaction system, a three-component version, and the catalyst loading, showed that the optimal conditions were 10 mol% of the **L4**–$Sc(OTf)_3$ complex, 0.2 mmol of *N*-aryl imine **4a**, and benzaldehyde and $MgSO_4$ as additives in 0.6 mL CH_2Cl_2 at 30°C (Table 3, entries 4–6). If the reaction was performed under air and moisture, the diastereo- and enantioselectivity could be maintained, although the yield was slightly decreased (Table 3, entry 7). It is also worth pointing out that only racemic tetrahydroquinolines were obtained if *N*-aryl imines derived from aniline or 2-methoxyaniline were tested, which indicates the crucial role of the hydroxy group of *N*-aryl imine **4a** in the stereorecognition process (Table 3, entries 8 and 9).

Table 3. Screening of the effects of additives and the hydroxy group in *N*-aryl imine **4a** in the asymmetric Povarov reaction of *N*-aryl imine **4a** and α-methylstyrene (**5a**).[a]



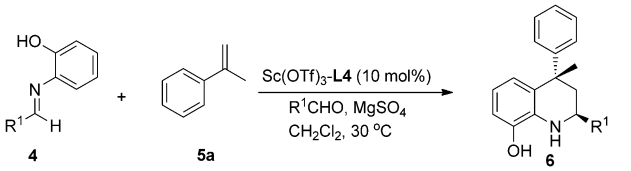
4a: X = OH
4aa: X = H
4ab: X= OMe

6a: X = OH

Entry	**4a**	Additive	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][c]
1	**4a**	–	39	95/5	96
2	**4a**	PhCHO	58	96/4	97
3[d]	**4a**	PhCHO, $MgSO_4$	62	95/5	97
4[d,e]	**4a**	PhCHO, $MgSO_4$	75	94/6	96
5[d,e,f]	**4a**	PhCHO, $MgSO_4$	69	94/6	96
6[d,e,g]	**4a**	PhCHO, $MgSO_4$	65	91/9	93
7[d,e,h]	**4a**	PhCHO, $MgSO_4$	65	95/5	97
8[d,e]	**4aa**	PhCHO, $MgSO_4$	40	21/79	0
9[d,e]	**4ab**	PhCHO, $MgSO_4$	72	10/90	0

[a] Unless otherwise noted, all reactions were carried out with 10 mol% of **L4**/$Sc(OTf)_3$ (1/1), **4** (0.2 mmol), **5a** (7.5 equiv, 200 μL), and PhCHO (0.5 equiv, 11.5 μL) in CH_2Cl_2 (1.0 mL) under N_2 at 30°C for 22 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis; the *trans* isomer was confirmed by ^{1}H NMR spectroscopy; the *ee* value refers to the *trans* isomer. [d] $MgSO_4$ (10.0 mg) was added. [e] CH_2Cl_2 (0.6 mL) was used and the reaction time was 38 h. [f] Imine formed in situ. [g] 5 mol% of the catalyst was used. [h] Reaction was performed under air and moisture.

Table 4. The scope of 2-azadienes **4** tolerated in the asymmetric Povarov reactions.[a]



Entry	R^1	*t* [h]	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][c]
1	Ph	38	75 (**6a**)	94/6	96
2	2-ClC_6H_4	18	93 (**6b**)	93/7	92
3	3-ClC_6H_4	44	76 (**6c**)	95/5	95
4	4-ClC_6H_4	69	82 (**6d**)	96/4	>99
5	3,4-$Cl_2C_6H_3$	21	84 (**6e**)	94/6	94
6	3-BrC_6H_4	45	88 (**6f**)	94/6	94
7[d]	4-BrC_6H_4	42	92 (**6g**)	96/4	>99
8	4-FC_6H_4	42	85 (**6h**)	95/5	98
9	4-$CF_3C_6H_4$	69	81 (**6i**)	93/7	99
10	2-MeC_6H_4	69	88 (**6j**)	95/5	94
11[e]	3-MeC_6H_4	69	66 (**6k**)	94/6	97
12	4-MeC_6H_4	69	51 (**6l**)	95/5	99
13	4-$MeOC_6H_4$	93	22 (**6m**)	91/9	98
14	2-naphthyl	95	67 (**6n**)	96/4	>99
15	2-thienyl	93	35 (**6o**)	89/11	96
16[e,f]	cyclohexyl	46	33 (**6p**)	61/39	95

[a] Unless otherwise noted, all reactions were carried out with 10 mol% of **L4**/$Sc(OTf)_3$ (1/1), **4** (0.2 mmol), **5a** (7.5 equiv, 200 μL), the aldehyde (0.5 equiv) from which the *N*-aryl imine **4** was derived, and $MgSO_4$ (10.0 mg) in CH_2Cl_2 (0.6 mL) under N_2 at 30°C. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis; the *trans* isomer was confirmed by ^{1}H NMR spectroscopy; the *ee* value refers to the *trans* isomer. [d] The absolute configuration of adduct **6g** was determined to be (2*S*,4*S*) by X-ray diffraction analysis. [e] The imine was formed in situ from aldehyde (1.5 equiv) and 2-aminophenol (0.2 mmol). [f] 20 mol% of **L4**/$Sc(OTf)_3$ (2:1) was used at 0°C.

Under the optimized conditions (Table 3, entry 4), the substrate scope of 2-azadienes in the Povarov reaction was examined (Table 4). Regardless of the steric hindrance of the substituents on the electron-deficient imines, tetrahydroquinolines with a quaternary stereocenter were obtained in high yields with excellent diastereo- and enantioselectivities (92 to >99% *ee*; Table 4, entries 1–9). It would appear that the electron-donating substituent on the aromatic imine enriches the electron density and thus decreases the reactivity. In the case of imines derived from methyl-substituted benzaldehydes, moderate to good yields with excellent diastereo- and enantioselectivities (94–99% *ee*) could also be obtained (Table 4, entries 10–12). When an electron-donating 4-methoxy-substituted imine was used, excellent enantioselectivity (98% *ee*) was observed, but the yield was substantially reduced (Table 4, entry 13). In addition, the 2-naphthaldehyde-derived imine served as a good 2-azadiene component to form the tetrahydroquinoline **6n** with >99% *ee* (Table 4, entry 14). Meanwhile, imines derived from heteroaromatic and aliphatic aldehydes were also suitable substrates to afford the desired adducts with high enantioselectivities (95–96% *ee*) but low yields (Table 4, entries 15 and 16). The absolute configuration of tetrahydroquinoline **6g**

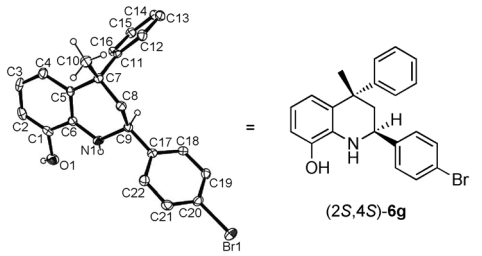
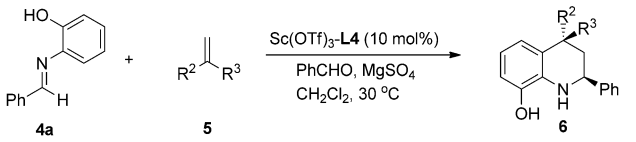


Figure 1. The structure of (2*S*,4*S*)-**6g** determined by X-ray analysis.

was unambiguously determined to be (2*S*,4*S*) by single-crystal X-ray diffraction analysis (Figure 1).[15]

Subsequently, the substrate scope of the α-alkyl styrenes was tested. Both electron-rich and electron-poor dienophiles were applied and resulted in excellent diastereoselectivities and enantioselectivities (93/7–99/1 *trans*/*cis*, 93–98% *ee*; Table 5, entries 1–6). Comparatively, an electron-deficient

Table 5. The scope of dienophiles **5** tolerated in the asymmetric Povarov reactions.[a]



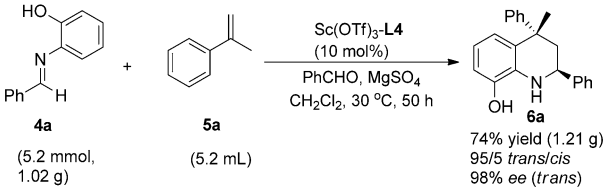
Entry	R^2	R^3	*t* [h]	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][c]
1	Ph	Me	38	75 (**6a**)	94/6	96
2	3-MeC_6H_4	Me	27	83 (**6q**)	95/5	96
3	4-MeC_6H_4	Me	33	81 (**6r**)	99/1	98
4	3,4-$Me_2C_6H_3$	Me	27	89 (**6s**)	97/3	96
5	3,4-$(MeO)_2C_6H_3$	Me	41	63 (**6t**)	95/5	93
6	4-FC_6H_4	Me	41	70 (**6u**)	97/3	98
7	2-naphthyl	Me	27	85 (**6v**)	99/1	96
8	Ph	Et	48	40 (**6w**)	93/7	96
9	Ph	H	35	54 (**6x**)	95/5	95

[a] Reaction conditions: 10 mol% of **L4**/$Sc(OTf)_3$ (1/1), **4a** (0.2 mmol), **5** (200 μL or 7.5 equiv for solid), PhCHO (0.5 equiv), and $MgSO_4$ (10.0 mg) in CH_2Cl_2 (0.6 mL) under N_2 at 30°C. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis; the *trans* isomer was confirmed by ^1H NMR spectroscopy; the *ee* value refers to the *trans* isomer.

styrene gave a slightly lower yield than the others (Table 5, entry 6 versus entries 1–4). In addition, 2-(2-naphthyl)-propene was tolerated well to give the adduct **6v** with excellent results (Table 5, entry 7). The reactions with α-ethylstyrene and styrene as dienophiles also afforded the desired tetrahydroquinolines with 96 and 95% *ee* values, respectively (Table 5, entries 8 and 9).

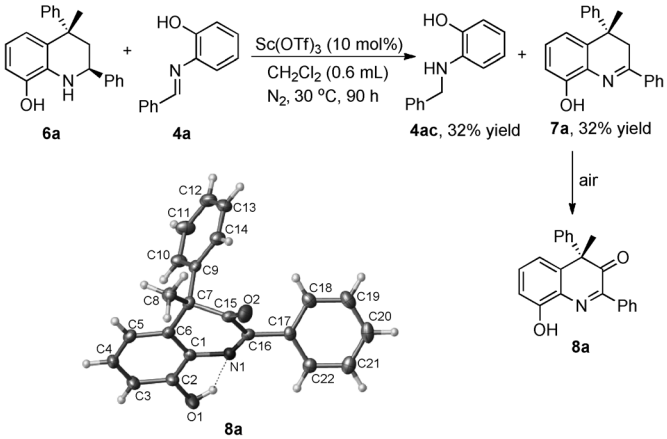
For the purpose of examining the utility of the catalytic system, gram scale quantities of 2-azadiene **4a** were treated with **5a** under the optimized reaction conditions. The tetrahydroquinoline **6a** was obtained without any loss of yield, diastereoselectivity, or enantioselectivity (Scheme 4).

In some cases shown in Tables 4 and 5, the low yield of the product is a partial consequence of the generation of by-products.[16] Under the catalytic reaction conditions, aniline



Scheme 4. The gram scale synthesis of tetrahydroquinoline **6a**.

4ac was generated from the reduction of the substrate imine **4a**. Comparative experiments were performed to investigate the real reductive reagent. Equivalent amounts of pure tetrahydroquinoline **6a** and imine **4a** in the presence of $Sc(OTf)_3$ under an N_2 atmosphere yielded quinoline derivative **7a** and aniline **4ac** with the same yield (Scheme 5). No-



Scheme 5. The intermolecular hydrogen-shift reaction and the crystal structure of **8a** determined by X-ray analysis.

tably, quinoline derivative **7a** could be easily oxidized into the quinoline-3-one under air. The quaternary carbon center was maintained in product **8a**, which was confirmed by single-crystal X-ray diffraction analysis (Scheme 5).[15] It is reasonable to conclude that $Sc(OTf)_3$ could promote hydrogen transfer from the tetrahydroquinoline to the imine, which offers a method to synthesize the corresponding quinoline derivatives with quaternary stereocenters.[17]

Conclusion

In summary, we have developed an efficient asymmetric Povarov reaction with α-alkyl styrenes as the dienophiles catalyzed by an *N*,*N*′-dioxide **L4**–$Sc(OTf)_3$ complex. A wide variety of tetrahydroquinolines with a quaternary stereocenter at the C4 position were obtained with excellent diastereo- and enantioselectivities (up to >99:1 d.r. and 92 to >99% *ee*). In addition, the reaction could be performed on the gram scale without any loss of yield, diastereoselectivity, or enantioselectivity. The intermolecular hydrogen-shift re-

action was found to be a side reaction, which offers a method to synthesize the corresponding quinoline derivatives with quaternary stereocenters. Further studies about the intermolecular hydrogen-shift reaction and the application of the catalyst to other reactions are underway.

Experimental Section

Typical experimental procedure for the asymmetric Povarov reaction with *N*-aryl imine 4a and α-alkyl styrene 5a: $Sc(OTf)_3$ (9.8 mg, 0.02 mmol), *N*,*N*′-dioxide ligand **L4** (14.0 mg, 0.02 mmol), *N*-aryl imine **4a** (39.4 mg, 0.2 mmol), and dried $MgSO_4$ (10.0 mg) were stirred in CH_2Cl_2 (0.5 mL) under nitrogen. Subsequently, PhCHO (10.5 μL, 0.1 mmol) and CH_2Cl_2 (0.1 mL) were added, and the reaction was stirred at 30 °C. After 0.5 h, α-methylstyrene (**5a**; 200 μL) was added. The reaction mixture was stirred at 30 °C for 38 h and then directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 8/1) to afford the desired product **6a** as a yellow amorphous solid in an inseparable diastereomeric mixture: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 5H), 7.25 (m, 2H), 7.18 (t, J = 7.2 Hz, 1H), 7.11 (d, J = 7.2 Hz, 2H), 7.10–6.10 (m, 3H), 4.59 (s, 1H), 4.48–4.18 (brs, 1H), 4.02 (brs, 1H), 2.27 (m, 1H), 2.17 (t, J = 12.0 Hz, 1H), 1.76 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.46, 128.58, 128.19, 128.01, 127.56, 127.35, 127.16, 126.77, 125.84, 116.28, 48.13, 41.80, 29.76 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{21}NO$ [M+H$^+$]: 316.1696; found: 316.1696; the *ee* value was determined by chiral HPLC analysis on an Daicel Chiralcel IB column by comparison with authentic racemates: eluent: *n*-hexane/2-propanol, 90/10; flow rate: 1.0 mL min^{-1}; λ = 254 nm; retention times: 5.62 (*trans*, minor), 6.06 (*cis*), 6.94 (*cis*), 7.80 min (*trans*, major).

Typical experimental procedure for the intermolecular hydrogen-shift reaction of tetrahydroquinoline 6a and *N*-aryl imine 4a: $Sc(OTf)_3$ (9.8 mg, 0.02 mmol), tetrahydroquinoline **6a** (63.0 mg, 0.2 mmol), and *N*-aryl imine **4a** (39.4 mg, 0.2 mmol) were stirred under nitrogen, then CH_2Cl_2 (0.6 mL) was added, and the reaction was stirred at 30 °C under nitrogen for 65 h. The residue was then purified by flash chromatography on silica gel (petroleum ether/ethyl ether, 100/1) to afford the quinoline derivative **7a** as a yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.93 (m, 2H), 7.62 (m, 1H), 7.44–7.38 (m, 3H), 7.25–7.15 (m, 4H), 7.10 (t, J = 7.6 Hz, 1H), 6.92 (dd, J = 7.6, 1.2 Hz, 1H), 6.63 (dd, J = 7.6, 1.2 Hz, 1H), 3.41 (d, J = 16.8 Hz, 1H), 2.94 (d, J = 16.4 Hz, 1H), 1.67 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.44, 152.05, 146.20, 138.22, 135.44, 130.92, 130.69, 128.50, 128.48, 128.20, 126.67, 126.64, 126.50, 116.86, 112.81, 40.79, 40.21, 26.99 ppm.

The quinoline derivative **7a** could be easily oxidized into the quinoline-3-one **8a** under air: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.77 (m, 2H), 7.63 (s, 1H), 7.47–7.34 (m, 3H), 7.32 (t, J = 8.0 Hz, 1H), 7.29–7.26 (m, 1H), 7.23 (m, 2H), 7.10–6.97 (m, 3H), 6.87 (d, J = 7.6 Hz, 1H), 1.91 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.53, 155.78, 153.96, 139.21, 137.47, 133.74, 131.12, 130.99, 129.01, 128.74, 128.41, 128.35, 128.02, 127.16, 118.77, 114.43, 55.41, 21.81 ppm; the oxidation reaction of tetrahydroquinoline **7a** under air could be detected with chiral HPLC analysis on a Daicel Chiralcel IA column: *n*-hexane/2-propanol, 95/5; flow rate: 1.0 mL min^{-1}; λ = 254 nm; retention times: 8.28 (**8a**), 11.21 (**7a**), 12.31 (**8a**), 14.10 min (**7a**).

The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 8/1) to afford the reduced aniline **4ac** as a yellow viscous liquid: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.36 (m, 5H), 6.99–6.90 (m, 1H), 6.81 (d, J = 7.7 Hz, 1H), 6.77–6.66 (m, 2H), 5.18 (s, 2H), 4.43 ppm (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.73, 139.46, 137.15, 128.74, 127.74, 127.34, 121.65, 118.13, 114.73, 112.63, 48.69 ppm; HRMS (ESI-TOF): calcd for $C_{13}H_{13}NO$ [M+H$^+$]: 200.1070; found: 200.1077.

Typical experimental procedure for the scaled-up reaction: $Sc(OTf)_3$ (255.8 mg, 0.52 mmol), *N*,*N*′-dioxide ligand **L4** (364.5 mg, 0.52 mmol), *N*-aryl imine **4a** (1.02 g, 5.2 mmol), and dried $MgSO_4$ (260 mg) were stirred in CH_2Cl_2 (13 mL) in a 50 mL dried flask under nitrogen. Subsequently, benzaldehyde (2.6 mmol, 263.5 μL) and CH_2Cl_2 (2.6 mL) were added, and the reaction was stirred at 30 °C. After 0.5 h, α-methylstyrene (**5a**; 5.2 mL) was added, and the reaction mixture was stirred at 30 °C for 50 h. The residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether, 1/8) to afford **6a** (1.21 g, 74% yield, 95:5 d.r., 98% *ee*).

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[1] For reviews on the construction of chiral tetrasubstituted carbon centers, see: a) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037–2066; b) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; c) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725–4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597; d) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367; e) D. J. Ramón, M. Yus, *Curr. Org. Chem.* **2004**, *8*, 149–183; f) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482; g) B. M. Trost, C. H. Jiang, *Synthesis* **2006**, 369–396; h) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969–5994; i) O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5*, 873–888; j) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583–1614.

[2] a) H.-H. Hennies, C. Maul, M. Przewosny, B. Sundermann, DE 10236910, **2004**; b) R. Uchida, R. Imasato, K. Shiomi, H. Tomoda, S. Ōmura, *Org. Lett.* **2005**, *7*, 5701–5704; c) R. Uchida, R. Imasato, Y. Yamaguchi, R. Masuma, K. Shiomi, H. Tomoda, S. Ōmura, *J. Antibiot.* **2006**, *59*, 646–651; d) W. F. J. Karstens, P. G. M. Conti, C. M. Timmers, R. Plate, C. J. Van Koppen, WO 2009027482, **2009**.

[3] L. S. Povarov, *Russ. Chem. Rev.* **1967**, *36*, 656–670.

[4] For a recent review of normal-electron-demand aza Diels–Alder reactions, see: K. A. Jørgensen, *Angew. Chem.* **2000**, *112*, 3702–3733; *Angew. Chem. Int. Ed.* **2000**, *39*, 3558–3588.

[5] For selected examples of asymmetric normal-electron-demand aza Diels–Alder reactions, see: a) S. Kobayashi, S. Komiyama, H. Ishitani, *Angew. Chem.* **1998**, *110*, 1026–1028; *Angew. Chem. Int. Ed.* **1998**, *37*, 979–981; b) S. Yao, M. Johannsen, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **1998**, *110*, 3318–3321; *Angew. Chem. Int. Ed.* **1998**, *37*, 3121–3124; c) S. Yao, S. Saaby, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.* **2000**, *6*, 2435–2448; d) N. S. Josephsohn, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, 4018–4019; e) O. G. Mancheño, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2004**, *126*, 456–457; f) H. Sundén, I. Ibrahem, L. Eriksson, A. Córdova, *Angew. Chem.* **2005**, *117*, 4955–4958; *Angew. Chem. Int. Ed.* **2005**, *44*, 4877–4880; g) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2006**, *118*, 4914–4916; *Angew. Chem. Int. Ed.* **2006**, *45*, 4796–4798; h) D. J. Shang, J. G. Xin, Y. L. Liu, X. Zhou, X. H. Liu, X. M. Feng, *J. Org. Chem.* **2008**, *73*, 630–637; i) H. Mandai, K. Mandai, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 17961–17969.

[6] For reviews of inverse-electron-demand aza Diels–Alder reactions, see: a) A. R. Katritzky, S. Rachwal, B. Rachwal, *Tetrahedron* **1996**, *52*, 15031–15070; b) P. Buonora, J.-C. Olsen, T. Oh, *Tetrahedron* **2001**, *57*, 6099–6138; c) V. V. Kouznetsov, *Tetrahedron* **2009**, *65*, 2721–2750.

[7] For selected racemic examples of inverse-electron-demand aza Diels–Alder reactions, see: a) P. A. Grieco, A. Bahsas, *Tetrahedron Lett.* **1988**, *29*, 5855–5858; b) S. Kobayashi, H. Ishitani, S. Nagayama, *Synthesis* **1995**, 1195–1202; c) S. Kobayashi, H. Ishitani, S. Nagayama, *Chem. Lett.* **1995**, 423–424; d) J. S. Yadav, B. V. Subba Red-

dy, R. Srinivas, C. Madhuri, T. Ramalingam, *Synlett* **2001**, 0240–0242; e) A. A. Kudale, J. Kendall, D. O. Miller, J. L. Collins, G. J. Bodwell, *J. Org. Chem.* **2008**, *73*, 8437–8447.

[8] H. Ishitani, S. Kobayashi, *Tetrahedron Lett.* **1996**, *37*, 7357–7360.

[9] a) G. Sundararajan, N. Prabagaran, B. Varghese, *Org. Lett.* **2001**, *3*, 1973–1976; b) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070–13071; c) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. P. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598–4599; d) G. Bergonzini, L. Gramigna, A. Mazzanti, M. Fochi, L. Bernardi, A. Ricci, *Chem. Commun.* **2010**, *46*, 327–329; e) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science* **2010**, *327*, 986–990; f) M. S. Xie, X. H. Chen, Y. Zhu, B. Gao, L. L. Lin, X. H. Liu, X. M. Feng, *Angew. Chem.* **2010**, *122*, 3887–3890; *Angew. Chem. Int. Ed.* **2010**, *49*, 3799–3802; g) L. Bernardi, M. Comes-Franchini, M. Fochi, V. Leo, A. Mazzanti, A. Ricci, *Adv. Synth. Catal.* **2010**, *352*, 3399–3406; h) G. Dickmeiss, K. L. Jensen, D. Worgull, P. T. Franke, K. A. Jørgensen, *Angew. Chem.* **2011**, *123*, 1618–1621; *Angew. Chem. Int. Ed.* **2011**, *50*, 1580–1583.

[10] For selected racemic examples with styrene or α-methylstyrene as dienophiles: a) T. Kametani, H. Takeda, Y. Suzuki, T. Honda, *Heterocycles* **1984**, *22*, 275–276; b) J. M. Mellor, G. D. Merriman, *Tetrahedron* **1995**, *51*, 6115–6132; c) S. Kobayashi, S. Nagayama, *J. Am. Chem. Soc.* **1996**, *118*, 8977–8978; d) F. Linkert, S. Laschat, S. Kotila, T. Fox, *Tetrahedron* **1996**, *52*, 955–970; e) W. Zhang, X. D. Jia, L. Yang, Z.-L. Liu, *Tetrahedron Lett.* **2002**, *43*, 9433–9436; f) X. D. Jia, H. C. Lin, C. D. Huo, W. Zhang, J. M. Lü, L. Yang, G. Y. Zhao, Z.-L. Liu, *Synlett* **2003**, 1707–1709.

[11] H. Miyamura, K. Maehata, S. Kobayashi, *Chem. Commun.* **2010**, *46*, 8052–8054.

[12] a) B. Crousse, J.-P. Bégué, D. Bonnet-Delpon, *J. Org. Chem.* **2000**, *65*, 5009–5013; b) V. V. Kouznetsov, C. Ochoa Puentes, A. R. Romero Bohórquez, S. A. Zacchino, M. Sortino, M. Gupta, Y. Vázquez, A. Bahsas, J. Amaro-Luis, *Lett. Org. Chem.* **2006**, *3*, 300–304; c) V. V. Kouznetsov, C. M. Meléndez Gómez, J. H. Bermúdez Jaimes, *J. Heterocycl. Chem.* **2010**, *47*, 1148–1152.

[13] For a recent review on chiral *N*,*N*′-dioxides as ligands and organocatalysts in catalytic asymmetric reactions, see: a) X. H. Liu, L. L. Lin, X. M. Feng, *Acc. Chem. Res.*, **2011**, *44*, 547–587; for recent examples, see: b) Z. P. Yu, X. H. Liu, Z. H. Dong, M. S. Xie, X. M. Feng, *Angew. Chem.* **2008**, *120*, 1328–1331; *Angew. Chem. Int. Ed.* **2008**, *47*, 1308–1311; c) K. Zheng, J. Shi, X. H. Liu, X. M. Feng, *J. Am. Chem. Soc.* **2008**, *130*, 15770–15771; d) M. Kokubo, C. Ogawa, S. Kobayashi, *Angew. Chem.* **2008**, *120*, 7015–7017; *Angew. Chem. Int. Ed.* **2008**, *47*, 6909–6911; e) Y. L. Liu, D. J. Shang, X. Zhou, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2009**, *15*, 2055–2058; f) Y. Zhu, X. H. Chen, M. S. Xie, S. X. Dong, Z. Qiao, L. L. Lin, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2010**, *16*, 11963–11968; g) Y. F. Cai, X. H. Liu, Y. H. Hui, J. Jiang, W. T. Wang, W. L. Chen, L. L. Lin, X. M. Feng, *Angew. Chem.* **2010**, *122*, 6296–6300; *Angew. Chem. Int. Ed.* **2010**, *49*, 6160–6164; h) W. Li, J. Wang, X. L. Hu, K. Shen, W. T. Wang, Y. Y. Chu, L. L. Lin, X. H. Liu, X. M. Feng, *J. Am. Chem. Soc.* **2010**, *132*, 8532–8533; i) Y. Zhu, M. S. Xie, S. X. Dong, X. H. Zhao, L. L. Lin, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2011**, *17*, 8202–8208; j) W. D. Cao, X. H. Liu, W. T. Wang, L. L. Lin, X. M. Feng, *Org. Lett.* **2011**, *13*, 600–603; k) K. Zheng, C. K. Yin, X. H. Liu, L. L. Lin, X. M. Feng, *Angew. Chem.* **2011**, *123*, 2621–2625; *Angew. Chem. Int. Ed.* **2011**, *50*, 2573–2577; l) K. Shen, X. H. Liu, G. Wang, L. L. Lin, X. M. Feng, *Angew. Chem.* **2011**, *123*, 4780–4784; *Angew. Chem. Int. Ed.* **2011**, *50*, 4684–4688; m) Z. Wang, Z. G. Yang, D. H. Chen, X. H. Liu, L. L. Lin, X. M. Feng, *Angew. Chem.* **2011**, *123*, 5030–5034; *Angew. Chem. Int. Ed.* **2011**, *50*, 4928–4932; n) Y. F. Cai, X. H. Liu, J. Jiang, W. L. Chen, L. L. Lin, X. M. Feng, *J. Am. Chem. Soc.* **2011**, *133*, 5636–5639.

[14] For a recent review on chiral scandium complexes in catalytic asymmetric reactions, see: X. M. Feng, X. H. Liu in *Scandium: Compounds, Productions and Applications* (Ed.: V. A. Greene), Nova Science, New York, **2011**, pp. 1–48.

[15] CCDC-807702 (**6g**) and 825022 (**8a**) 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.

[16] A trace amount of byproduct was observed with an HRMS signal of 719.3610; for more details, see the Supporting Information.

[17] For a cascade Povarov/hydrogen-transfer reaction providing quinolines, see: a) R. Leardini, D. Nanni, A. Tundo, G. Zanardi, F. Ruggieri, *J. Org. Chem.* **1992**, *57*, 1842–1848; b) N. Shindoh, H. Tokuyama, K. Takasu, *Tetrahedron Lett.* **2007**, *48*, 4749–4753; c) N. Shindoh, H. Tokuyama, Y. Takemoto, K. Takasu, *J. Org. Chem.* **2008**, *73*, 7451–7456.

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