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Asymmetric Synthesis of Bicyclic Diol Derivatives through Metal and Enzyme Catalysis: Application to the Formal Synthesis of Sertraline

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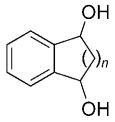
Abstract: Enzyme- and ruthenium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) of bicyclic diols to their diacetates was highly enantio- and diastereoselective to give the corresponding diacetates in high yield with high enantioselectivity (99.9% *ee*). The enantiomerically pure diols are accessible by simple hydrolysis (NaOH, MeOH), but an alternative enzyme-catalyzed ester cleavage was also used to give the *trans*-diol (*R*,*R*)-**1b** in extremely high diastereomeric purity (*trans*/*cis* = 99.9:0.1, > 99.9% *ee*). It was demonstrated that the diols can be selectively oxidized to the ketoalcohols in a ruthenium-catalyzed Oppenauer-type reaction. A formal enantioselective synthesis of sertraline from a simple racemic *cis*/*trans* diol **1b** was demonstrated.

Keywords: alcohols · asymmetric catalysis · dynamic resolution · enzyme catalysis · metal catalysis

Introduction

Chiral bicyclic diols of type **1** are potentially important synthetic intermediates.[1,2] For example, diol **1b** and derivatives thereof are useful precursors in the synthesis of sertraline, its analogues,[1] and other biologically active 1,4-disubstituted tetralins.[2]



1a (*n*=1)
b (*n*=2)
c (*n*=3)

Recently, Kündig et al. reported a procedure for the enantioselective reduction of tetralin-1,4-dione to give (*R*,*R*)-tetralin-1,4-diol ((*R*,*R*)-**1b**) in 72% yield with 99% *ee*.[3]

During the past decade dynamic kinetic resolution (DKR) has evolved as an efficient method in catalytic asymmetric synthesis[4] for the preparation of enantiomerically pure secondary alcohols[5] and primary amines.[6] Our group has recently been involved in combined enzyme- and transition-metal-catalyzed DKR of secondary alcohols,[5a] primary amines,[6b,c] and primary alcohols[7] as well as the dynamic kinetic asymmetric transformation (DYKAT)[8] of acyclic diols.[9] In the DYKAT of acyclic diols, coupled resolution and epimerization of a DL/*meso* mixture of the diol occur in situ, thus resulting in one enantiomer of the diol diacetate. The DYKAT of cyclic diols has been less studied and previous attempts to obtain enantiomerically pure diol diacetates from 1,3-cyclohexanediol were moderately successful.[10] It occurred to us that bicyclic diols **1** may be more suitable substrates for enzymatic transesterification, and we therefore decided to study them in DYKAT reactions.

Mixtures of *cis*- and racemic *trans*-diols **1** are readily accessible from the corresponding diones. Subsequent DYKAT reactions of these diols would be an efficient route toward enantiomerically pure diols **1**. Herein, we report the DYKAT reactions of diols **1** in high yield with 99.9% *ee* and apply diol **1b** to the formal synthesis of sertraline.

Results and Discussion

Many transition-metal catalysts have been developed for the racemization of alcohols. Our group has successfully employed racemization catalysts **2** and **3** (Scheme 1)[11] in DKR and DYKAT processes, and ruthenium complex **2** is one of the best catalysts known today in dynamic processes with alcohols. Many catalysts have been shown to racemize alcohols quickly, but only a few are compatible with enzymes.

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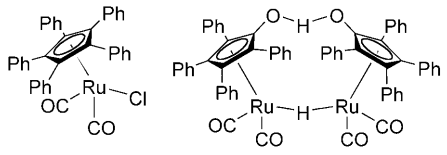
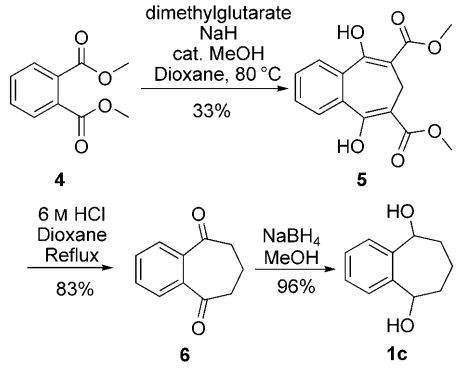


2 3

Scheme 1. Ruthenium racemization catalysts **2** and **3**.

Catalyst **2** in combination with *Candida antarctica* lipase B (CALB) often provides efficient routes to enantio- and diastereomerically pure alcohols. In this study, DYKAT processes of diols **1a–c** have been developed by using the combination of catalyst **2** and CALB.

The chemistry and synthesis of diols **1a–c** have not been very well studied. However, they are readily accessible from the reduction of the corresponding diketones. Diol **1a** was prepared in high yield, as previously described, by using Ru-catalyzed transfer hydrogenation.[12,13] Diol **1b** was prepared from the corresponding diketone according to a procedure developed by Enriquez-Garcia and Kündig.[14] Diol **1c** is known,[15] but has not been explored to any great extent. We chose a new route for the preparation of **1c** involving a reduction ($NaBH_4$/MeOH) of the corresponding diketone, which in turn was prepared from dimethylphthalate (**4**; Scheme 2).



4 5 6 1c

Scheme 2. Synthesis of diol **1c**.

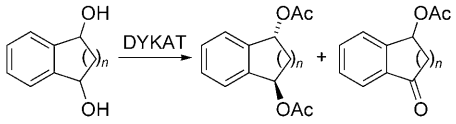
The condensation of dimethylglutarate and **4** gave dicarboxylate **5** according to a known procedure,[16] and subsequent decarboxylation of diester **5** afforded diketone **6** in 83% yield.[17]

Diols **1a–c** are all hygroscopic, so the diols were dried over P_2O_5 under vacuum and then stored over P_2O_5 in a desiccator because the DKR and DYKAT reactions involving Ru-catalyst **2** are water sensitive.

A kinetic asymmetric transformation (KAT) of a 1:1 *cis*/*trans* mixture of symmetric diols **1** by using a highly selective lipase and isopropenyl acetate for the transesterification should result in diacetate, monoacetate, and diol products in yields of 25, 50, and 25%, respectively, all of which are enantiopure. Indeed, this outcome was obtained when carrying out the KAT reaction with diol **1b** with CALB as the lipase at ambient temperature for 24 hours. Prolonged reaction times produced a small amount of *meso*-diacetate.

Because the KAT of diol **1b** was very selective at ambient temperature, DYKAT with CALB and Ru catalyst **2** was tested at this temperature. However, epimerization catalyzed by **2** was too slow at ambient temperatures, which has previously been observed for diols.[9c–e] Diols **1a**,**b** gave excellent results at 50°C with high yields of around 90% (Table 1, entries 2–5). Diol **1a** reached full conversion between 24 and 48 hours (Table 1, entry 1; 94 versus >99% conversion), whereas diol **1b** took at least 48 h. A by-product in the DYKAT of diols **1a–c** corresponds to acetoxy ketones **8a–c**, which are difficult to remove by column chromatography. The yields stated in Table 1 include both **8** and *cis* diastereomer *cis*-**7**.

Table 1. DYKAT of diols **1a–c**.[a]



n = 1 (**1a**) *n* = 2 (**1b**) *n* = 3 (**1c**)
1 ((*R*,*R*)-**7a**) *n* = 2 ((*R*,*R*)-**7b**) 3 ((*R*,*R*)-**7c**)
1 (**8a**) *n* = 2 (**8b**) 3 (**8c**)

Entry	Diol **1**	Time [h]	Conv. [%]	Yield[b] [%]	**8** [%]	*ee* [%]	d.r.
1	**1a**	24	94	85	**8a** (9)	n.d.	97:3
2	**1a**	48	>99	94	**8a** (10)	99.9	97:3
3[c]	**1a**	96	>99	98	**8a** (9)	99.9	95:5
4	**1b**	48	98	96	**8b** (9)	99.9	97:3
5[c]	**1b**	96	98	98	**8b** (8)	99.9	97:3
6[d]	**1c**	60	>99	88	**8c** (29)	99.9	99:1
7[e]	**1c**	120	83	n.d.	**8c** (3)	n.d.	98:2
8[e]	**1c**	168	>99	91	**8c** (4)	99.9	98:2

[a] Unless otherwise stated the reactions were carried out under the following conditions: ruthenium catalyst **2** (5 mol%), *t*BuOK (5 mol%), isopropenyl acetate (4 equiv), Na_2CO_3 (0.2 equiv), CALB (12.5 mg mmol of substrate^{-1}, toluene (0.5 M), 50°C. [b] Yields of the isolated products, including acetoxy ketone **8**. [c] Toluene was the solvent (0.2 M). [d] Conditions: Na_2CO_3 (1 equiv), CALB (25 mg mmol of substrate^{-1}), 0.1 M, 80°C. [e] Conditions: Na_2CO_3 (1 equiv), CALB (25 mg mmol substrate^{-1}), 0.13 M, 50°C.

Diol **1c** is a more troublesome substrate than **1a**,**b**. The temperature of the reaction had to be increased to 80°C to obtain a reasonable reaction time. At this temperature, the reaction is complete after 60 hours (Table 1, entry 6). The drawback with such high temperatures is that a large amount of **8c** is formed (29%). The reaction can be run at 50°C to avoid ketone formation, but in this case the reaction has to be stirred for at least 7 days (Table 1, entry 8). Under these conditions, **1c** afforded the product (*R*,*R*)-**7c** in high yield with excellent stereoselectivity (>99.9% *ee*, d.r. >98:2). Furthermore, only 4% of ketone **8c** was observed in the crude product.

With a working protocol in hand, we decided to scale up the DYKAT reactions of **1a**,**b** (Table 2). The loading of the Ru-catalyst **2** and *t*BuOK was decreased from 5 to 1 mol%.

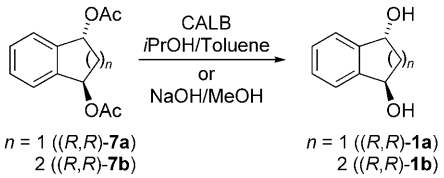
Table 2. DYKAT of diols **1a**-**b** on a preparative scale.[a]

Entry	1	Time [h]	Conv. [%]	Yield[b] [%]	8 [%]	*ee* [%]	d.r.
1[c]	**1a**	67	>99	95	**8a** (4)	99.9	92:8
2[d]	**1b**	72	88	n.d.	**8b** (6)	n.d.	96:4
3[d]	**1b**	96	99	94	**8b** (5)	99.9	95:5

[a] The reactions were run under the following conditions: ruthenium catalyst **2** (1 mol%), *t*BuOK (1 mol%), isopropenyl acetate (4 equiv), Na_2CO_3 (0.2 equiv), CALB (12.5 mg mmol of substrate^{-1}), toluene (0.5 M), 50 °C. [b] Yields of the isolated products, including acetoxy ketone **8**. [c] Scale = 8 mmol. [d] Scale = 10 mmol.

As a consequence of the decrease in catalyst loading, the reaction time had to be extended to ensure complete conversion. The yields in the scaled-up reactions of **1a**,**b** (95 and 94%, respectively) were in the same range as in the case of the small-scale reactions (see Table 1). In both cases the d.r. value slightly decreased, probably due to slower epimerization as a consequence of the lower catalyst loading. However, the decrease in catalyst loading also gave a lower amount of acetoxy ketone **8**.

Hydrolysis of diacetates **7a**,**b** (Scheme 3) can be performed in a solution of NaOH in methanol (1 M) to afford enantiopure and diastereoenriched diols (*R*,*R*)-**1a** and

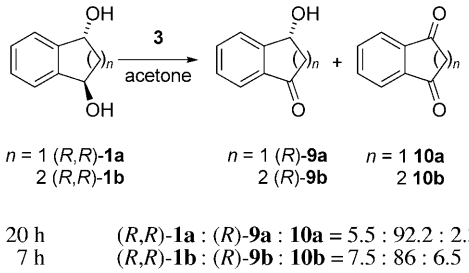


Scheme 3. Ester cleavage of diacetates **7a**,**b**.

(*R*,*R*)-**1b**. Because it is difficult to remove the *cis*-diacetate, present in a small percentage, from the product, the diol will have the same d.r. value as the diacetate. In an effort to improve the d.r. value of diols **1a**,**b**, we carried out the ester cleavage with CALB. In this case, only the acetate group with the *R* configuration will be cleaved, and because the *cis*-diacetate has an *R*,*S* configuration it will only be transformed into a monoacetate by the enzyme and is easily separated from the diol product. In this way, the d.r. value should be dramatically increased. To our surprise, the CALB-catalyzed hydrolysis of **7b** was more difficult than we had expected. Very low conversions were achieved in phosphate buffers of pH 7.0–7.9 under different concentrations and at different temperatures. The addition of organic solvents such as acetone and methanol to improve the solubility of **7b** did not improve the reaction. Instead, a method developed by Kim and co-workers[18] was employed in which CALB is used to catalyze the transesterification of **7b** in an organic solvent. Kim and co-workers[18] used THF as the solvent, whereas we found that toluene gave the best result. Also, the loading of CALB could be decreased from 377 to only 25 mg mmol^{-1}.

This reaction was sensitive to the amount of *i*PrOH added. The reaction was severely slowed down with 16 equivalents of *i*PrOH; therefore, a suitable amount was 8 equivalents with respect to the diacetate. By using this method, pure (*R*,*R*)-**1b** was obtained in 76% overall yield from racemic **1b** in a two-step procedure (preparative scale) with d.r. = 99.9:0.1 and >99.9% *ee*. The enzymatic hydrolysis of diacetate **7a** was less efficient, and the classical hydrolysis reaction (NaOH, MeOH) was employed, thus affording (*R*,*R*)-**1a** with d.r. = 97:3 and >99.9% *ee*.

During our investigations, we found that oxidation of diols **1a**,**b** to hydroxy ketones **9a**[19a] and **9b**,[14,19] respectively, through Ru-catalyzed hydrogen transfer with catalyst **3**[20] in acetone (transfer dehydrogenation)[21] is much faster than the corresponding oxidation of the hydroxy ketones to diketones **10a**,**b**, respectively (Scheme 4). We decided to take



Scheme 4. Mono-oxidation of diol (*R*,*R*)-**1a**,**b** catalyzed by **3**.

advantage of the difference in rate between the two oxidation steps for the preparation of enantioenriched hydroxy ketones (*R*)-**9a** and (*R*)-**9b**. Complex **3** is also known to catalyze the racemization of *sec*-alcohols. However, we argued that because acetone is in large excess there should be little or no racemization.

The oxidation of diols (*R*,*R*)-**1a** and (*R*,*R*)-**1b** was carried out at 35 °C. At higher temperatures (i.e., ≥50 °C), the mono-oxidation is fast (i.e., ~1 h); therefore, it is difficult to stop the reaction without overoxidation to a diketone. Oxidation of enantio- and diastereomerically pure diol (*R*,*R*)-**1a** (99.9% *ee*, >99% *trans*)[22] gave the corresponding hydroxy ketone (*R*)-**9a** in 85% yield with 98% *ee* after 20 h at 35 °C. This outcome indicates that only a small amount of racemization takes place in the mono-oxidation of (*R*,*R*)-**1a**, which makes it an attractive method to obtain enantioenriched (*R*)-**9a**. Compound (*R*)-**9a** should be a potential precursor for the synthesis of indatralin.[23]

In the mono-oxidation of diol (*R*,*R*)-**1b**, which starts from 99.9% *ee* and d.r. = 99.9:0.1, the reaction yields the maximum amount of hydroxy ketone (*R*)-**9b** after around 7 hours (86% according to ^{1}H NMR spectroscopic analysis). Compound (*R*)-**9b** was isolated by chromatography on silica gel in 82% yield with 97% *ee*. Hydroxy ketone (*R*)-**9b** should be a useful starting material for the synthesis of ser-

tralin,[1] as also pointed out by Enriquez-Garcia and Kündig.[14] The reaction profiles of the oxidation of (*R*,*R*)-**1a** and (*R*,*R*)-**1b** are given in Figures 1 and 2, respectively. These data were recorded with ^{1}H NMR spectroscopy; the concentration in the experiments was 0.1 M in [D$_6$]acetone for solubility reasons. Hydroxy ketone (*R*)-**9b** has been prepared before,[14,19] although the present method gives a higher *ee* value than previous methods and compares very well with the best of those approaches.[14]

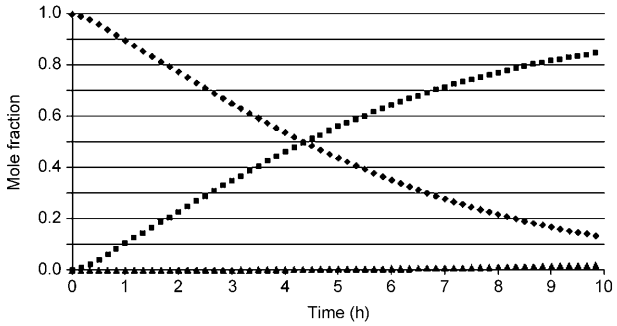


Figure 1. Reaction profile for the oxidation of diol (*R*)-**1a**. ◆: **1a**; ■: **9a**; ▲: **10a**. Conditions: catalyst **2** (0.02 equiv), [D$_6$]acetone (0.1 M), 35 °C.

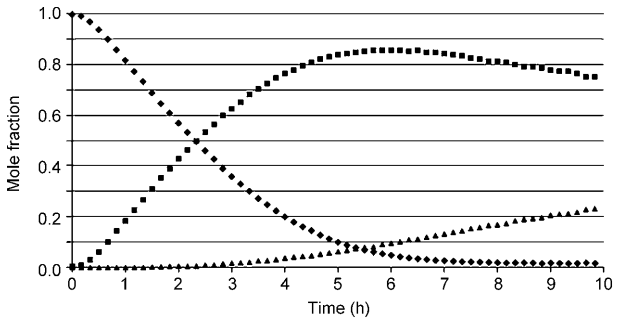
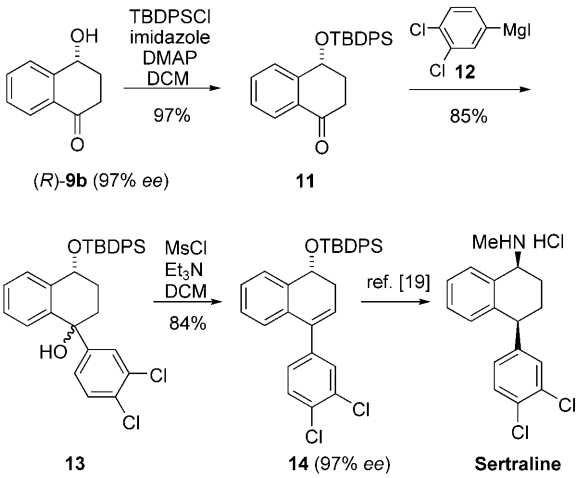


Figure 2. Reaction profile for the oxidation of diol (*R*)-**1b**. ◆: **1b**; ■: **9b**; ▲: **10b**. Conditions: Catalyst **2** (0.02 equiv), [D$_6$]acetone (0.1 M), 35 °C.

The enantiomerically pure bicyclic diols (*R*,*R*)-**1**, their acetate derivatives (*R*,*R*)-**7**, and, in particular, chiral hydroxy ketones (*R*)-**9** should be useful synthetic intermediates for the preparation of various biologically active compounds. Compound **14** is an important precursor for the synthesis of sertraline and has been transformed into sertraline in a few steps.[24,25] We now demonstrate that (*R*)-**9b** can be transformed into **14** in three steps in high yield (Scheme 5), thus constituting a formal total synthesis of sertraline.

The alcohol group in (*R*)-**9b** was protected with a TBDPS group in high yield (97%) followed by a Grignard addition to the ketone. The competing reaction to the addition reaction is deprotonation at the α-position, which gives back the ketone in the workup. However, the selectivity is 85:15, thus favoring addition to the ketone. The remaining ketone **11** is also easily recycled in the final elimination step. The addition product **13** is a diastereomeric mixture of 4:1, presumably with the aryl group *trans* to the silyl ether moiety as the



Scheme 5. Formal total synthesis of sertraline. DCM = dichloromethane, DMAP = 4-dimethylaminopyridine, MsCl = methanesulfonyl chloride, TBDPS = *tert*-butyldiphenylsilyl.

major isomer. The isolated yield of **13** was 85%. Due to separation problems of **11** and the major diastereomer of **13**, the mixture of **11** and **13** was used in the consecutive elimination step to give **14**. It has been observed that silyl ether **14** is labile,[24a] which was also noted during our investigations. All attempts to use acidic dehydration failed,[26] thus leading to an aromatized product, presumably through desilylation and elimination of H_2O. Therefore, alcohol **13** was transformed into its mesylate, which undergoes an elimination reaction in situ at room temperature if excess triethylamine is added. This method gave **14** in 84% yield (97% yield based on 86% conversion) with 97% *ee*. After the elimination reaction, **11** can be recycled after separation from **14** by using column chromatography.

Conclusions

In summary, we have developed a DYKAT protocol for diols **1a–c** that give high enantio- and diastereoselectivities. These procedures could also be used on 8- and 10-mmol scales for diols **1a**,**b**, respectively. We have also demonstrated that the hydrolysis of (*R*,*R*)-**7b** catalyzed by CALB gave enantio- and diastereomerically pure diols. The optically pure diols (*R*,*R*)-**1a** and (*R*,*R*)-**1b** were transformed into hydroxy ketones (*R*)-**9a**,**b** with high selectivity and in high yield. This mono-oxidation was catalyzed by **3** with only a small amount of racemization. Finally, (*R*)-**9b** was used in a formal total synthesis of sertraline without loss of enantiomeric excess.

Experimental Section

Procedure for the DYKAT of diols 1a,b: Base *t*BuOK (0.5 M, 0.05 mmol) in THF (100 μL) was added to a flame-dried Schlenk flask under argon. THF was removed under vacuum and the flask refilled with argon. Ru

catalyst **2** (32 mg, 0.05 mmol) and toluene (2 mL) were added to the reaction mixture, which was stirred for 3 min at 50 °C before the diol (1 mmol) was added. After the mixture had been stirred at 50 °C for a further 30 min, CALB (12.5 mg), Na_2CO_3 (21 mg, 0.2 mmol), and isopropenyl acetate (440 μL, 4 mmol) were charged to the flask. The reaction mixture was stirred at 50 °C until no more diol or monoacetate remained (the conversion was checked by ^{1}H NMR spectroscopic analysis with CD_3OD as the solvent). The reaction mixture was allowed to reach ambient temperature before filtration through a short plug of silica gel (eluated with EtOAc) to remove the inorganic material and the enzyme. The solvent was evaporated and the crude product was purified by chromatography on silica gel (eluent: CH_2Cl_2). (For yields see Table 1): An analytical sample of (*R*,*R*)-**7a** was obtained by refined chromatography. (*R*,*R*)-**7a**: $[\alpha]_D^{20} = +131.4$ ($c = 1.1$, EtOAc; ≥99.9% *ee*, 99% d.r.); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.44$–7.33 (4H, m), 6.28 (2H, app t, $J = 5.4$ Hz), 2.47 (2H, app t, $J = 5.4$ Hz), 2.04 ppm (6H, s); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 172.7$, 143.0, 130.5, 126.6, 77.4, 40.9, 21.0 ppm; the analytical data for **7b** was in accordance with those previously reported.[27]

Procedure for the DYKAT of diol 1c: Base *t*BuOK (0.5 M, 0.02 mmol) in THF (40 μL) was added to a flame-dried Schlenk flask under argon. THF was removed under vacuum and the flask refilled with argon. Ru catalyst **2** (13 mg, 0.02 mmol) and toluene (3 mL) were added to the reaction mixture, which was stirred for 3 min at 50 °C before the diol (0.4 mmol) was added. After the mixture had been stirred at 50 °C for a further 30 min, CALB (10 mg), Na_2CO_3 (42 mg, 0.4 mmol), and isopropenyl acetate (176 μL, 1.6 mmol) were charged into the flask. The reaction mixture was stirred at 50 °C for 7 days. The reaction mixture was allowed to reach ambient temperature before filtration through a short plug of silica gel (eluated with EtOAc) to remove the inorganic material and the enzyme. The solvent was evaporated and the crude product was purified by chromatography on silica gel (eluent: CH_2Cl_2). (For yields see Table 1): An analytical sample of (*R*,*R*)-**7c** was obtained by refined chromatography. (*R*,*R*)-**7c**. $[\alpha]_D^{20} = +100.6$ ($c = 1.1$, EtOAc; ≥99.9% *ee*, >99.9% d.r.); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38$–7.31 (m, 2H), 7.29–7.22 (2H, m), 6.19–6.09 (2H, m), 2–16 (6H, s), 2.07–1.94 (4H, m), 1.94–1.81 ppm (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.0$, 138.5, 127.8, 127.0, 75.3, 32.8, 22.0, 21.3 ppm.

(1*R*,4*R*)-1,2,3,4-Tetrahydronaphthalene-1,4-diol ((*R*,*R*)-1b): Compound (*R*,*R*)-**7b** from the large-scale DYKAT reaction of **1a** (1.0 g, 4 mmol; 99.9% *ee*, dr = 95:5; 5% ketone **8b**) and CALB (100 mg) were suspended in dry toluene (16 mL) in an argon atmosphere. *i*PrOH (HPLC grade from a freshly opened bottle; 2.45 mL, 32 mmol) was added to the reaction mixture, which was stirred 3.5 days at 50 °C. The solvent was evaporated, the residue was added to MeOH to make a slurry, and the solids were removed by filtration. The product was evaporated onto silica gel and purified by chromatography (CH_2Cl_2/EtOAc 1:1) to yield a white solid (535 mg, 81%, 99.9% *ee*, d.r. = 99.9:0.1). The *ee* value was determined according to method B (see the Supporting Information) and the d.r. value was measured by using ^{1}H NMR spectroscopic analysis.

(*R*)-4-Hydroxy-3,4-dihydronaphthalen-1(2*H*)-one ((*R*)-9b): Compound (*R*,*R*)-**1b** (246 mg, 1 mmol, ≥99.9% *ee*, d.r. = ≥99.9:0.1) and the Shvo catalyst **3** (32 mg, 0.02 mmol) were suspended in acetone (PA grade; 7.5 mL) in an atmosphere of air and stirred at 35 °C for 7 h. The solvent was removed under vacuum ($T \leq 35$ °C). Purification by chromatography on silica gel (CH_2Cl_2/EtOAc 4:1) yielded the desired product (201 mg, 82%, 97% *ee*). The analytical data were in accordance with previously reported data.[14,19] The *ee* value was determined according to method B (see the Supporting Information).

(*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3,4-dihydronaphthalen-1(2*H*)-one (11): Compound (*R*)-**9b** (122 mg, 0.75 mmol), imidazole (128 mg, 1.88 mmol), and DMAP (6.5 mg, 0.05 mmol) were dissolved in CH_2Cl_2 (3.75 mL, 0.2 M with respect to (*R*)-**9b**). *t*-Butyldiphenylchlorosilane (212 μL, 0.83 mmol) was added to the reaction mixture, which was stirred 2 h at ambient temperature. The reaction mixture was diluted with CH_2Cl_2, silica gel was added, and the solvent was removed under vacuum. Chromatography on silica gel (pentane/ethyl acetate 98:2) afforded product (293 mg, 97%, 98% *ee*). The *ee* value was measured according to method D (see the Supporting Information). $[\alpha]_D^{20} = +42.5$ ($c = 0.8$, EtOAc; 98% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.00$ (1H, dd, $J = 7.7$, 1.5 Hz), 7.76–7.72 (2H, m), 7.62–7.58 (2H, m), 7.50–7.32 (8H, m), 7.29–7.24 (1H, m), 4.96 (1H, dd, $J = 7.2$, 3.5 Hz), 2.97 (1H, ddd, $J = 17.6$, 8.3, 4.7 Hz), 2.45 (1H, ddd, $J = 17.6$, 8.1, 4.8 Hz), 2.23–2.13 (1H, m), 2.12–2.03 (1H, m), 1.08 ppm (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.0$, 145.6, 136.0, 136.0, 134.0, 133.7, 133.4, 131.4, 130.1, 130.0, 128.1, 127.9, 127.8, 127.6, 127.1, 69.6, 34.9, 32.2, 27.1, 19.6 ppm.

4-(*tert*-Butyldiphenylsilyloxy)-1-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (13): A solution of **12** (0.4 M) was prepared by slowly adding a solution of 3,4-dichloroiodobenzene (1.1 g, 4 mmol) in dry Et_2O (10 mL) to Mg turnings (144 mg, 6 mmol), which was stirred for 2 h at room temperature under argon. The Grignard solution of **12** (3.3 mL, 1.32 mmol) was charged into a solution of **11** in Et_2O (0.2 M, 241 mg, 0.6 mmol). The reaction mixture was stirred for 17 h at room temperature before quenching the reaction with saturated aqueous NH_4Cl. The aqueous layer was acidified with HCl (1 M) to pH ~1 and extracted with Et_2O (3×20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvents yielded a yellow sticky solid (348 mg). The crude mixture contained **11** and product **13** in a ratio of 15:85. Compound **13** was obtained as a diastereomeric mixture of 4:1. Chromatography on silica gel (pentane/ethyl acetate 96:4) easily separated **11** from the minor diastereomer, but it was difficult to fully separate the major diastereomer from **11**. For practical purposes, the 15:85 mixture of **11** and **13** was employed in the subsequent reaction. The combined fractions from the chromatography on silica gel yielded a colourless sticky solid (313 mg). Based on NMR spectroscopic analysis, the amount of **13** was estimated to be 277 mg (85%). For detailed analysis, a small amount of product was purified by chromatography on silica gel (pentane/ethyl acetate 96:4). Major diastereomer of **13**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$ (4H, m), 7.58–7.54 (1H, m), 7.50–7.36 (7H, m), 7.30 (1H, d, $J = 8.3$ Hz), 7.29 (1H, app td, $J = 7.6$, 1.5 Hz), 7.20 (1H, app td, $J = 3.8$, 1.4 Hz), 7.02 (1H, dd, $J = 8.4$, 2.2 Hz), 6.96 (1H, dd, $J = 7.8$, 1.3 Hz), 4.90 (1H, dd, $J = 8.3$, 4.8 Hz), 2.38 (1H, bs), 2.14–2.01 (1H, m), 2.19 (1H, ddd, $J = 13.8$, 6.9, 3.0 Hz), 1.88 (1H, ddd, $J = 13.8$, 10.6, 3.2 Hz), 1.83–1.73 (1H, m), 1.13 ppm (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.8$, 140.8, 140.5, 136.1, 134.3, 133.6, 132.1, 130.8, 130.0, 129.9, 129.8, 128.6, 128.6, 128.4, 128.3, 127.9, 127.8, 127.8, 126.1, 74.7, 70.7, 38.2, 29.5, 27.3, 19.6 ppm. Minor diastereomer of **13**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$–7.70 (2H, m), 7.65 (1H, d, $J = 2.2$ Hz), 7.63–7.59 (2H, m), 7.49–7.33 (7H, m), 7.22 (1H, dd, $J = 8.4$, 2.2 Hz), 7.19 (1H, app td, $J = 3.8$, 1.5 Hz), 7.11 (1H, app td, $J = 3.7$, 1.5 Hz), 6.94 (2H, ddd, $J = 9.4$, 7.7, 1.5 Hz), 4.84 (1H, app t, $J = 3.7$ Hz), 2.67 (1H, ddd, $J = 14.2$, 12.3, 3.0 Hz), 2.06–1.83 (4H, m), 1.06 ppm (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 149.8$, 141.0, 138.6, 136.2, 136.1, 134.1, 134.0, 132.2, 130.8, 130.0, 129.9, 129.9, 129.7, 128.9, 128.8, 128.6, 128.2, 127.9, 127.7, 126.1, 74.7, 69.2, 36.3, 28.6, 27.1, 19.6 ppm.

(*R*)-*tert*-Butyl(4-(3,4-dichlorophenyl)-1,2-dihydronaphthalen-1-yloxy)diphenylsilane (14): Compound **13** (65 mg mixture of **13** and **11** (85:15); 0.1 mmol with respect to **13**), DMAP (0.6 mg, 0.005 mmol), and Et_3N (84 μL, 0.6 mmol) were dissolved in CH_2Cl_2 (1 mL) at ambient temperature. MsCl (23 μL, 0.3 mmol) was added to the reaction mixture, which was stirred for 4 h. The reaction mixture was put directly onto a preprepared column of silica gel and chromatography (pentane/EtOAc 99:1), which yielded the pure product **14** (44.5 mg, 84%, 97% *ee*; see method E in the Supporting Information). The NMR spectroscopic data were slightly different from those reported previously.[24] The major differences in the ^{1}H NMR spectra were that the reported shift at $\delta = 7.38$ (1H, m) was not found by us.[28] The control experiments given below confirmed that we have the correct product **14**. First, desilylation of **14** with the same desilylation protocol as described in ref. [24] yielded the alcohol (compound **10** in ref. [24]), which had spectral data identical to those reported in ref. [24]. We also quenched the Grignard reagent **12** (prepared in the synthesis of **13**) with CO_2 to yield 3,4-dichlorobenzoic acid to ensure that the Grignard position or any of the chlorine atoms did move on the ring. ^{1}H NMR (400 MHz, [D$_6$]DMSO) of 3,4-dichlorobenzoic acid: $\delta = 8.06$ (1H, d, $J = 2.0$ Hz), 7.88 (1H, dd, $J = 8.3$, 2.0 Hz), 7.78 ppm (1H, d, $J = 8.3$ Hz). The coupling pattern of 3,4-dichlorobenzoic acid is difficult to find in **14** if the ^{1}H NMR spectra is recorded in C_6D_6; however, the pat-

tern can be found if $CDCl_3$ is used instead (see the attached COSY spectra: $\delta = 7.43$ (1H, d, $J = 8.3$ Hz), 7.43 (1H, d, $J = 2.0$ Hz), 7.16 ppm (1H, dd, $J = 8.3$, 2.0 Hz)). Additionally, the ^{13}C NMR spectrum is easier interpreted if it is recorded in $CDCl_3$ due to the lack of overlap in the aromatic region (relative to C_6D_6). Therefore, we chose to report our spectra recorded in $CDCl_3$, although the spectra recorded in C_6D_6 are attached for comparison purposes. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.77$ (2H, m), 7.70–7.63 (2H, m), 7.50–7.33 (7H, m), 7.43 (1H, d, $J = 8.3$ Hz), 7.43 (1H, d, $J = 2.0$ Hz), 7.25 (1H, app td, $J = 7.5$, 1.3 Hz), 7.20 (1H, app td, $J = 7.5$, 1.6 Hz), 7.16 (1H, dd, $J = 8.3$, 2.0 Hz), 6.96 (1H, dd, $J = 7.5$, 1.3 Hz), 5.86 (1H, dd, $J = 5.3$, 4.0 Hz), 4.99 (1H, dd, $J = 9.9$, 5.5 Hz), 2.49 (1H, ddd, $J =$ 16.5, 9.9, 4.0 Hz), 2.26 (1H, app dt, $J = 16.5$, Hz), 1.11 ppm (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 140.5$, 138.9, 137.8, 136.1, 135.9, 134.6, 133.7, 133.5, 132.5, 131.3, 130.6, 130.4, 129.9, 129.9, 128.2, 127.9, 127.8, 127.8, 127.5, 125.9, 125.8, 125.3, 69.8, 33.0, 27.2, 19.6 ppm.

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