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Lipase-catalyzed dynamic kinetic resolution giving optically active cyanohydrins: use of silica-supported ammonium hydroxide and porous ceramic-immobilized lipase

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Abstract

Synthetically useful cyanohydrin acetates, ArCH(OAc)CN (Ar=C_6H_5, 3,4-methylenedioxyphenyl, 4-Me−C_6H_4, 4-Cl−C_6H_4, 4-F−C_6H_4, 4-CF_3−C_6H_4), were successfully synthesized in high enantiomeric purities (79−93% ee) via the lipase-catalyzed dynamic kinetic resolution (DKR) of cyanohydrins synthesized in situ from the corresponding aldehydes and acetone cyanohydrin. The combined use of silica-supported BTAH (benzyltrimethylammonium hydroxide) and porous ceramic-immobilized lipase under the optimized reaction conditions enabled the remarkable acceleration of the enantioselective DKR reactions.

Keywords: Lipase; Dynamic kinetic resolution; Cyanohydrin

1. Introduction

Optically active cyanohydrins are versatile intermediates for the synthesis of a wide variety of useful compounds including amino acids,[1a] hydroxy acids,[1b] and others;[1c,d] and therefore chemical[2] and enzymatic[3] synthetic methods for optically active cyanohydrins have been developed extensively. The enzymatic methods are especially attractive because high enantioselectivity can be attained easily with commercially available enzymes. The enzymatic methods reported so far can be classified into three categories: (a) the hydrocyanation of aldehydes with HCN using oxynitrilases;[3] (b) the lipase-catalyzed kinetic resolution of racemic cyanohydrins;[4] and (c) the dynamic kinetic resolution (DKR) of cyanohydrins.[4,5] The last method is attractive for the preparative-scale synthesis because a single enantiomer can be obtained via a simple and safe experimental procedure. Here we developed a more practical DKR system for the cyanohydrin synthesis using silica-supported ammonium hydroxide (or acetate) as a base for racemization and a porous ceramic-immobilized lipase as a biocatalyst.

Enzymatic DKR systems have attracted much attention as an interdisciplinary technology for green sustainable chemistry.[6] Among them, the lipase-catalyzed DKR using aromatic aldehydes and acetone cyanohydrin was pioneered by Oda and co-workers in 1992,[5a] where the less reactive enantiomer of cyanohydrin was racemized by a basic anion-exchange resin (Amberlite IRA-904, OH^- form). A variety of aromatic cyanohydrin acetates with a functional group can be obtained in high yields with high enantiomeric purities (70−91% ee) in a simple one-pot reaction. However, there are still problems to be solved: (a) the instability of the basic anion-exchange resin, which gradually decomposes, giving off an unpleasant smell, and which causes a problem of disposal; (b) the prolonged reaction time (2−8 days), which can result in the racemization of cyanohydrin acetates produced; and (c) optically unstable aromatic cyanohydrin acetates substituted with an electron-withdrawing group have not yet been prepared by

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this method.[5a] Although Hanefeld[5b] and Kanerva et al.[4] have recently reported the DKR method, the difficult-to-handle resin was still used.

Here, we report that the combined use of silica-supported benzyltrimethylammonium hydroxide (BTAH, **5a**) (or its acetate **5b**) and a *Burkholderia cepacia* lipase immobilized on a porous ceramic support called Toyonite[7] (lipase PS-C II[7b,8]) led to the highly accelerated DKR reaction, making the reaction applicable even to optically unstable cyanohydrins bearing a fluorinated (4-F or 4-CF_3) phenyl group, which have never been obtained by the DKR reaction[5] or by the oxynitrilase-catalyzed hydrocyanation of aldehydes.[3]

2. Results and discussion

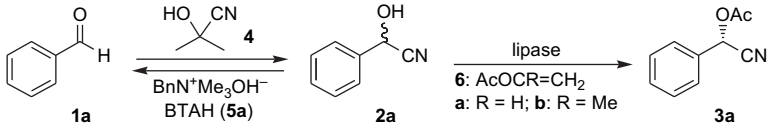
2.1. Optimization of the DKR reaction conditions

We initially employed Amberlyst A-27 (OH^- form) as a base for the racemization of cyanohydrin in the lipase-catalyzed DKR reaction; however, the reactions were accompanied with many impurities, and the resin was decomposed in a few weeks. Another attempt to covalently immobilize ammonium hydroxide to a porous ceramic support, Toyonite, was unsuccessful. We therefore examined the possibility of readily available BTAH (**5a**) (0.13 equiv with respect to **1a**). The reaction was conducted with the porous ceramic-immobilized lipase called lipase PS-C II, **1a**, acetone cyanohydrin (**4**), BTAH (**5a**), and vinyl acetate (**6a**) or isopropenyl acetate (**6b**) in *i*-Pr_2O. The results are summarized in Table 1.

As shown in Table 1, the reaction with **6a** at room temperature (entry 1) gave cyanohydrin acetate **3a** with only 62% ee, while the use of **6b** gave **3a** with a much improved enantiomeric purity (86% ee) although considerable amounts of **1a** (4%) and **2a** (53%) were also obtained (entry 2). These results indicate that just a simple kinetic resolution took place and that, unfortunately, BTAH (**5a**) was not effective for the in situ racemization of **2a**. The reaction with **6a** at 50 °C gave **3a** in a moderate yield but with little or no enantiomeric excess (entry 3), while no acceleration was observed with **6b** even at 50 °C (entry 4). As a result of the screening of enzymes, lipase PS-C II was found to be the best biocatalyst showing high catalytic activity in the presence of the base, BTAH (**5a**). A few examples are listed in Table 1. Lipase AK and LIP-300, both of which showed comparable activity and enantioselectivity (entries 5 and 6), are inferior to lipase PS-C II (entry 2). Novozym 435 exhibited a much lower activity with a large amount of **2a** accumulated (entry 7), partly because the resin support was dissolved by BTAH (**5a**). The solvent effect was briefly investigated for the lipase PS-C II mediated reactions at room temperature (entries 8–11). The use of acetone resulted in the base-catalyzed aldol reaction, giving a trace amount of product (entry 8). The DKR in THF gave only 17% conversion, while the reactions in *t*-BuOMe and cyclopentyl methyl ether (CPME) afforded moderate conversions (entries 9–11). These results indicated that *i*-Pr_2O is the best solvent for this system.

In the above reactions, BTAH (**5a**) is insoluble in *i*-Pr_2O, which might hamper its racemizing power. In order to solve this problem, we examined silica-supported BTAH and, to our delight, found that it is a quite effective racemizing agent as shown in Table 2. To prepare an active agent, silica-supported BTAH, silica was added to a methanolic solution of **5a**, and MeOH was then evaporated thoroughly to dryness under vacuum. Silica-supported BTAH thus prepared is considered to be dispersed on the silica surface, allowing **5a** on silica to

Table 1
Lipase-catalyzed DKR of cyanohydrin **2a** using BTAH (**5a**) as a racemizing agent in the absence of silica[a]



Entry	Lipase	**6**	Solvent	*T* (°C)	Time (h)	Ratio[b] (%)			**3a**
						1a	**2a**	**3a**	% Yield[c] (% ee)[d]
1	PS-C II	**6a**	*i*-Pr_2O	rt	24	15	60	25	23 (62)
2	PS-C II	**6b**	*i*-Pr_2O	rt	15	4	53	43	32 (86)
3	PS-C II	**6a**	*i*-Pr_2O	50	24	18	16	66	60 (2)
4	PS-C II	**6b**	*i*-Pr_2O	50	24	38	26	36	34 (1)
5	AK	**6b**	*i*-Pr_2O	rt	39	10	60	30	26 (74)
6	LIP-300	**6b**	*i*-Pr_2O	rt	39	5	62	33	31 (80)
7	Novozym 435	**6b**	*i*-Pr_2O	rt	39	12	83	5	—[e]
8	PS-C II	**6b**	Acetone	rt	5	Trace	Trace	Trace	—[e]
9	PS-C II	**6b**	THF	rt	24	5	78	17	16 (85)
10	PS-C II	**6b**	*t*-BuOMe	rt	24	9	65	26	24 (81)
11	PS-C II	**6b**	CPME	rt	24	9	61	30	27 (90)

[a] Conditions: **1a** (1.0 mmol), **4** (5.0 mmol), **5a** (0.13 mmol), **6** (10 mmol), lipase (125 mg), molecular sieves 3 Å (several pieces), dry solvent (10 mL).
[b] Determined by ^1H NMR.
[c] Isolated yield.
[d] Determined by capillary GC with a CP-cyclodextrin-β-2,3,6-M-19 column (Chrompack, ϕ 0.25 mm×25 m).
[e] Not isolated.

Table 2
Optimization of the lipase-catalyzed DKR of cyanohydrin **2a** using silica-supported BTAH as a racemizing agent[a]

Entry	Lipase (mg)	Silica (mg)	**5a** (equiv)	**6b** (equiv)	Time (h)	Ratio (%)			% Yield (% ee)
						1a	**2a**	**3a**	
1	125	50	0.13	10	19	0	36	64	52 (83)
2	125	80	0.20	3	22	Trace	30	70	60 (85)
3	125	80	0.20	3	41	Trace	18	82	75 (82)
4	237	80	0.20	3	44	0	13	87	80 (75)
5	300	80	0.20	3	26	5	3	92	80 (79)

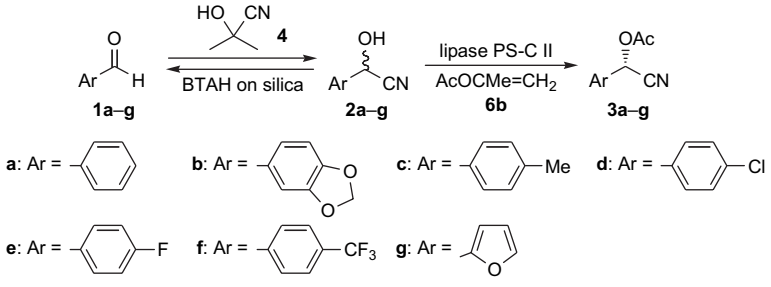
[a] Conditions: **1a** (1.0 mmol), **4** (5.0 mmol), **5a** (indicated above), **6** (indicated above), lipase PS-C II (indicated above), molecular sieves 3 Å (several pieces), dry *i*-Pr_2O (10 mL for entries 1 and 2 and 8 mL for entries 3–5), rt.

effectively exert its ability as a base. Table 2 shows that the use of silica (entry 1) greatly accelerated the reaction, giving a higher yield in a shorter reaction time. Obviously, the DKR process proceeded. When larger amounts of silica and **5a** were used, the amount of acylating agent **6b** could be decreased (entry 2). The DKR in a longer reaction time afforded the product **3a** in a higher yield (entry 3). These results show that silica-supported BTAH is a readily available, stable, and effective racemizing agent useful for the DKR reaction. Finally, the amount of lipase PS-C II was optimized (entries 4 and 5). An increased amount of lipase (300 mg) gave the best result with 92% conversion and 79% ee in a short reaction time of 26 h (entry 5). Thus, the combined use of lipase PS-C II and silica-supported BTAH resulted in the considerable acceleration of the reaction. The DKR under the optimized reaction conditions is now a convenient and readily accessible method for the laboratory-scale preparation of **3a**.

2.2. Synthesis of a variety of cyanohydrin acetates

The optimized conditions (Table 2, entry 5) were next applied to the synthesis of a variety of cyanohydrin derivatives. The results are shown in Table 3. Cyanohydrin acetates with a methylenedioxy or methyl group, **3b** and **3c**, were obtained in good yields with high enantiomeric purities in shorter reaction times (entries 2 and 3). The longer reaction time gave an improvement in the conversion, with high enantioselectivity retained (entry 4). The advantage of the present method over the previously reported method[5a] is that the former could be applied successfully even to cyanohydrins with an electron-withdrawing group (Cl or F) on the phenyl group; for example, **3d** and **3e** were obtained in 82% ee within 25 h (entries 5 and 6). The shortened reaction time as compared with that in the literature[5a] may have led to the high enantiomeric purities. However, the application of the optimized reaction conditions to 4-(trifluoromethyl)benzaldehyde (**1f**) furnished **3f** with only 10% ee at 75% conversion, which is probably due to its optical instability (entry 7). Although furyl-substituted cyanohydrin acetate **3g** was obtained in 53% ee (entry 8), which is close to the previous value (47% ee), the reaction was faster than that reported previously (73% conversion in 6 days).[5a] Except for **3e** and **3f**, for which no lipase-mediated DKR has been reported, all the cyanohydrin acetates

Table 3
Lipase-catalyzed DKR of cyanohydrins **2a–f** using silica-supported BTAH as a racemizing agent[a]



Entry	Ar	Time (h)	Ratio (%)			**3**	
			1	**2**	**3**	% Yield[b] (% ee)[c]	*R*/*S*
1	**a**	26	5	3	92	80 (79)	*S*
2	**b**	15	10	0	90	84 (87)	*S*
3	**c**	25	5	22	73	63 (93)	*S*
4	**c**	45	0	11	89	79 (91)	*S*
5	**d**	25	1	11	88	71 (82)	*S*
6	**e**	24	0	13	87	74 (82)	*S*
7	**f**	28	0	25	75	55 (10)	*S*
8	**g**	71	0	4	96	90 (53)	*R*

[a] Conditions: **1** (1.0 mmol), **4** (5.0 mmol), silica-supported BTAH (0.2 mmol, silica 80–90 mg), **6** (3.0 mmol), lipase PS-C II (300 mg), molecular sieves 3 Å (several pieces), dry *i*-Pr_2O (8 mL), rt.
[b] Isolated yield.
[c] Determined by capillary GC with a CP-cyclodextrin-β-2,3,6-M-19 column (Chrompack, ϕ 0.25 mm×25 m).

Table 4
Lipase-catalyzed DKR of cyanohydrin **2f** using benzyltrimethylammonium acetate (**5b**) or benzoate (**5c**) on alumina or silica as a racemizing agent[a]

Entry	**5** (mmol)	Support (mg)	Time (h)	Ratio (%)			**3f**
				1f	**2f**	**3f**	% Yield (% ee)
1	None (—)	A (90)	69	26	36	38	19 (91)
2	**5b** (0.057)	A (100)	21	0	0	100	81 (21)
3	**5b** (0.012)	A (100)	38	0	42	58	53 (87)
4	**5b** (0.030)	A (100)	23	5	17	78	62 (65)
5	**5b** (0.072)	S (70)	29	0	31	69	48 (90)
6	**5b** (0.072)	S (60)	42	0	15	85	75 (81)
7	**5c** (0.072)	S (60)	42	0	20	80	65 (72)

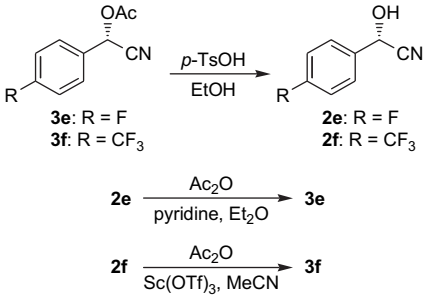
[a] Conditions: **1f** (1.0 mmol), **4** (5.0 mmol), **5b** on alumina (A) or silica (S) (indicated above), **6** (3.0 mmol), lipase PS-C II (400 mg), molecular sieves 3 Å (several pieces), dry *i*-Pr_2O (8 mL), rt.

in Table 3 had the same enantiopreferences as those reported previously.[5a]

To improve the % ee value of compound **3f**, the basicity of the ammonium salt **5** was tuned by anion exchange from OH^- to OAc^- or benzoate and by choosing either silica or alumina as an inorganic support (Table 4). When basic alumina was used in the absence of the organic base, only kinetic resolution of **2f** took place (entry 1), which indicates that the basicity of basic alumina used in this study is too weak to bring about the racemization of **2f**. We therefore employed benzyltrimethylammonium acetate (**5b**), which is a weaker base as compared with **5a**. The use of 0.057 equiv of **5b** resulted in 100% conversion but with only 21% ee (entry 2). Obviously, product **3f** was racemized by **5b**. The use of 0.012 equiv of **5b** made the reaction too slow (entry 3), while the addition of 0.03 equiv of **5b** hampered the enantioselectivity (entry 4). On the other hand, the combination of **5b** and silica gel produced better results. For example, **3f** with 90% ee was obtained at 69% conversion (entry 5). A slight decrease in the amount of silica yielded the best result, giving **3f** in 81% ee at 85% conversion (entry 6). The replacement of the counter anion to benzoate resulted in a lower conversion with a reduced % ee value (entry 6). Thus, we could optimize the reaction conditions for the DKR of the optically unstable cyanohydrin **2f**.

2.3. Determination of the absolute configurations

The absolute configurations of compounds **3a**–**3d** and **3g** were determined by comparing the signs of their specific rotations with those of the reported values, and those of the fluorinated compounds **3e** and **3f** were determined in the same way after conversion to the corresponding cyanohydrins **2e** and **2f**, respectively. As shown in Scheme 1, **3e** and **3f** were converted, respectively, to **2e** and **2f** by the treatment with *p*-TsOH in EtOH. The retention of the enantiomeric purity of **3e** during the transesterification was confirmed by the conversion of **2e** back to **3e** by the treatment with Ac_2O and pyridine in Et_2O and the subsequent determination of the % ee value of **3e**. On the other hand, because cyanohydrin **2f** with a high enantiomeric purity had never been reported and because **2f** is a crystalline compound, we decided to purify **2f**, derived from **3f** with 81% ee, by recrystallization. Recrystallization of **2f** from hexane/Et_2O gave white needles, and the enantiomeric purity of **2f** was determined to be >99% ee by converting **2f** to **3f** by the treatment with Ac_2O and $Sc(OTf)_3$ in MeCN. The Lewis acid, $Sc(OTf)_3$, was found to be essential because cyanohydrin **2f** and acetate **3f** were readily racemized under basic conditions, for example, with Ac_2O and pyridine, which were used in the synthesis of 4-fluoro derivative **3e**.



Scheme 1. Conversion of **3e**–**f** to **2e**–**f** to determine the absolute configurations and conversion of **2e**–**f** back to **3e**–**f** to determine the enantiomeric purities.

3. Conclusion

Silica-supported BTAH (benzyltrimethylammonium hydroxide), prepared very easily, is a quite effective racemizing agent. Moreover, it does not give off a bad smell as ion-exchange resins do, and it is easy to handle. Using silica-supported BTAH (or its acetate) together with porous ceramic-immobilized lipase (lipase PS-C II), efficient lipase-catalyzed DKR of cyanohydrins, prepared from aldehydes and acetone cyanohydrin in one pot, have been carried out. The DKR under the optimized conditions gave cyanohydrin acetates, ArCH(OAc)CN (Ar= C_6H_5, 3,4-methylenedioxyphenyl, 4-Me–C_6H_4, 4-Cl–C_6H_4, 4-F–C_6H_4, 4-CF_3–C_6H_4, 2-furyl), with high enantiomeric purities in short reaction times. Because the present DKR system is efficient, practical, and user-friendly, we expect that this system will be used widely for the synthesis of a variety of chiral cyanohydrin derivatives.

4. Experimental

4.1. General

Silica gel (BW-127ZH, 100–270 mesh) was purchased from Fuji Silysia Chemical, Ltd, and used for column chromatography and for supporting the ammonium salts. Aluminum oxide 90 active basic was purchased from Merck and used as a support. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254}. Lipase PS-C 'Amano' II (Amano Enzyme Inc.) and LIP-300 were purchased from Wako Pure Chemical Industries, Ltd and Toyobo Co., Ltd, respectively. Lipase AK and Novozym 435 were provided by Amano Enzyme Inc. and Novozymes Japan Ltd, respectively. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 200 and

50 MHz, respectively. Capillary GC was performed with a CP-cyclodextrin-β-2,3,6-M-19 (Chrompack, ϕ 0.25 mm×25 m) column (Inj. 250 °C, Det. 220 °C).

4.2. Typical procedure for the one-pot synthesis of optically active cyanohydrin acetates **3** from aldehydes **1**

Silica (80 mg) and benzyltrimethylammonium hydroxide (BTAH, **5a**) (40% in MeOH, 90 μL, 0.2 mmol) were placed in a 25 mL round-bottomed flask, and concentrated in vacuo to remove MeOH. Then, lipase PS-C II (300 mg), molecular sieves 3 Å (several pieces), benzaldehyde (**1a**) (106 mg, 1.0 mmol), acetone cyanohydrin (**4**) (426 mg, 5.0 mmol), isopropenyl acetate (**6b**) (300 mg, 3.0 mmol), and *i*-Pr_2O (8 mL) were added successively. The mixture was stirred at room temperature for 26 h under N_2. The mixture was filtered through Celite, washed with brine (3 mL), and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residual oil was analyzed by ^{1}H NMR. Purification by silica gel column chromatography (hexane/EtOAc (12:1)) gave acetate (*S*)-**3a** as a colorless oil (141 mg, 80% yield, 79% ee); $[\alpha]_D^{25}$ −4.97 (*c* 0.905, $CHCl_3$), lit.[10] $[\alpha]_D^{21}$ −6.92 (*c* 2.20, $CHCl_3$) for (*S*)-**3a** with 95% ee; chiral GC: Col. 130 °C, (*R*) 27 min, (*S*) 30 min; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.17 (s, 3H), 6.41 (s, 1H), 7.44−7.52 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.4, 62.8, 116.0, 127.7, 129.1, 130.3, 131.6, 168.8.

4.2.1. (*S*)-(+)-1-Cyano-1-[3,4-(methylenedioxy)-phenyl]methyl acetate (**3b**)

Enantiomeric excess: 87%; $[\alpha]_D^{24}$ +12.4 (*c* 0.70, $CHCl_3$), lit.[5a] $[\alpha]_D^{25}$ +42.7 (*c* 1.53, C_6H_6) for (*S*)-**3b** with 91% ee; chiral GC: Col. 160 °C, (*R*) 50 min, (*S*) 54 min; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.15 (s, 3H), 6.03 (s, 2H), 6.31 (s, 1H), 6.84 (dd, *J*=0.7, 7.7 Hz, 1H), 6.98 (s, 1H), 7.0 (dd, *J*=0.7, 7.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.5, 62.6, 101.7, 108.2, 108.6, 116.1, 122.4, 125.2, 148.3, 149.3, 168.8.

4.2.2. (*S*)-(+)-1-Cyano-1-(4-methylphenyl)methyl acetate (**3c**)

Enantiomeric excess: 93%; $[\alpha]_D^{26}$ +6.31 (*c* 0.60, $CHCl_3$), lit.[5a] $[\alpha]_D^{25}$ +30.4 (*c* 1.41, C_6H_6) for (*S*)-**3c** with 91% ee; chiral GC: Col. 130 °C, (*R*) 39 min, (*S*) 45 min; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.38 (s, 3H), 6.37 (s, 1H), 7.25 (d, *J*=8.2 Hz, 2H), 7.41 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.4, 21.2, 62.7, 116.1, 127.7, 128.7, 129.7, 140.5, 168.8.

4.2.3. (*S*)-(+)-1-Cyano-1-(4-chlorophenyl)methyl acetate (**3d**)

Enantiomeric excess: 82%; $[\alpha]_D^{26}$ +9.03 (*c* 0.78, $CHCl_3$), lit.[11] $[\alpha]_D^{20}$ −14.1 (*c* 1, $CHCl_3$) for (*R*)-**3d** with 97% ee; chiral GC: Col. 130 °C, (*R*) 65 min, (*S*) 77 min; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.17 (s, 3H), 6.38 (s, 1H), 7.40−7.50 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.4, 62.1, 115.7, 129.2, 129.4, 130.1, 136.5, 168.6.

4.2.4. (*S*)-(−)-1-Cyano-1-(4-fluorophenyl)methyl acetate (**3e**)

Enantiomeric excess: 82%; $[\alpha]_D^{26}$ −1.98 (*c* 1.01, $CHCl_3$); chiral GC: Col. 130 °C, (*R*) 26 min, (*S*) 31 min; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.17 (s, 3H), 6.39 (s, 1H), 7.15 (t, *J*=8.7 Hz, 2H), 7.52 (dd, *J*=5.2, 8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.3, 62.1, 115.9, 116.2 (d, J_{CF}=21.9 Hz), 127.7 (d, J_{CF}=2.7 Hz), 129.9 (d, J_{CF}=8.2 Hz), 163.5 (d, J_{CF}=249.5 Hz), 168.7. For determination of the absolute configuration of **3e**, it was transformed into **2e**. To a solution of acetate (*S*)-**3e** (238 mg, 1.23 mmol, 80% ee) in EtOH (6 mL), *p*-TsOH·H_2O (234 mg, 1.23 mmol) was added, and the mixture was stirred at room temperature for 2 days. The mixture was concentrated under reduced pressure and extracted with EtOAc, and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a viscous oil. The product was purified by silica gel column chromatography (hexane/EtOAc (14:1)) to give (*S*)-**2e** as a colorless oil (178 mg, 96% yield); $[\alpha]_D^{26}$ −31.4 (*c* 0.69, $CHCl_3$), lit.[2b] $[\alpha]_D^{22}$ −36.4 (*c* 0.8, $CHCl_3$) for (*S*)-**2e** with 96% ee. Then, **2e** (16.0 mg, 0.104 mmol) was added into a solution of pyridine (25 μL), DMAP (1.3 mg, 0.01 mmol) and Ac_2O (19.6 μL, 0.208 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure and extracted with EtOAc, and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by silica gel column chromatography (hexane/EtOAc (12:1)) to give acetate (*S*)-**3e** as a colorless oil with a slightly reduced % ee value (17.4 mg, 87% yield, 79% ee).

4.2.5. (*S*)-(−)-1-Cyano-1-[4-(trifluoromethyl)phenyl]methyl acetate (**3f**)

Enantiomeric excess: 81%; $[\alpha]_D^{26}$ −3.41 (*c* 0.53, $CHCl_3$); chiral GC: Col. 130 °C, (*R*) 23 min, (*S*) 27 min; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.20 (s, 3H), 6.47 (s, 1H), 7.66 (d, *J*=8.7 Hz, 2H), 7.74 (d, *J*=8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.2, 62.1, 115.5, 120.7, 126.1 (q, J_{CF}=3.7 Hz), 128.1, 132.3 (q, J_{CF}=32.8 Hz), 135.4, 168.6. A solution of acetate (*S*)-**3f** (319 mg, 1.32 mmol, 81% ee) and *p*-TsOH·H_2O (250 mg, 1.32 mmol) in EtOH (8 mL) was stirred at room temperature for 2 days. The resulting solution was concentrated in vacuo, and the residual solid was purified by silica gel column chromatography (hexane/EtOAc (4:1)) to give (*S*)-**2f** as a white solid (264 mg, 98% yield); $[\alpha]_D^{29}$ −19.3 (*c* 0.64, $CHCl_3$). The product was further purified by recrystallization from hexane/Et_2O to give enantiomerically pure (*S*)-**2f**; $[\alpha]_D^{25}$ −25.8 (*c* 0.70, $CHCl_3$), lit.[9] $[\alpha]_D$ +19.0 (*c* 1.759, $CHCl_3$) for (*R*)-**2f** with 80% ee; mp 78 °C (67−69 °C for *rac*-**2f**[3d]). Cyanohydrin **2f** (40 mg, 0.2 mmol) in MeCN (2 mL) was added to a mixture of $Sc(OTf)_3$ (0.98 mg, 0.002 mmol) and Ac_2O (38 μL, 0.4 mmol). The mixture was stirred at room temperature for 1 h, and then concentrated under reduced pressure to give cyanohydrin acetate **3f**. Purification by silica gel column chromatography (hexane/EtOAc (21:1)) gave the desired product (*S*)-**3f** as a colorless oil (46 mg, 94% yield, with >99% ee); $[\alpha]_D^{25}$ −4.26 (*c* 0.94, $CHCl_3$).

*4.2.6. (R)-(+)-1-Cyano-1-(2-furyl)methyl acetate (**3g**)*

Enantiomeric excess: 53%; $[\alpha]_D^{20}$ +7.8 (*c* 1.09, $CHCl_3$), lit.[11] $[\alpha]_D^{22}$ −18.8 (*c* 1, $CHCl_3$) for (*S*)-**3g** with 98% ee; chiral GC: Col. 130 °C, (*S*) 9.6 min, (*R*) 10.2 min; ^1H NMR (200 MHz, $CDCl_3$) δ 2.17 (s, 3H), 6.45 (dd, *J*=1.9, 3.8 Hz, 1H), 6.47 (s, 1H), 6.69 (dd, *J*=0.8, 3.8 Hz, 1H), 7.51 (dd, *J*=0.8, 1.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.2, 55.6, 111.0, 112.5, 114.0, 143.9, 144.9, 168.6.

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References and notes

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