First Aromatic Amine Organocatalysed Activation of α,β-Unsaturated Ketones

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Supporting Information

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1. General Information

Starting materials **1a** and **2a-d**, as well as the amine catalysts **I-IX**, are commercially available and were employed as received without further treatment or purification. In case of solvent, commercial tetrahydrofuran (THF, HPLC grade) was transferred to a new recipient and molecular sieves (4 Å) were added.

All reactions were performed at room temperature under ambient conditions. The reactions were monitored by thin-layer chromatography (TLC) using aluminum sheets recoated with silica gel and a fluorescent indicator (60 F_{254}, 0.2 mm). The compounds were visualized at 254 nm by employment of UV light. The products **3** were isolated by flash chromatography using silica gel (0.06-0.2 nm) as stationary phase and mixtures of commercial dichloromethane/ethyl acetate as eluent.

The chiral HPLC analysis of products **3** was performed in a Waters 600 equipment, using a Daicel ChiralPak IC column as stationary phase and mixtures of commercial *n*-hexane/isopropyl alcohol as eluent. The specific rotation of products **3** was determined using a Jasco P-1020 polarimeter, in acetonitrile or tetrahydrofuran (both HPLC grade) as solvent. The absolute configuration of products **3a**[1] and **3d**[2] was assigned comparing their specific rotation with those reported in the literature. The same absolute configuration is assumed for the rest of products **3**.

The ^{1}H-NMR and ^{13}C-NMR (APT) spectra of reagents and products were recorded at 300 MHz (Bruker ARX300 spectrometer) or 400 MHz (Bruker AV400 spectrometer), in chloroform-*d* ($CDCl_3$) or dimethyl sulfoxide-d_6 ($(CD_3)_2SO$) as deuterated solvent. Infrared spectra of starting materials and products were obtained employing an attenuated total reflection infrared (ATR-FTIR) in a PerkinElmer FTIR spectrometer equipped with a universal ATR sampling accessory. The HRMS analysis of reagents and products was performed using a MicroTof-Q mass spectrometer and electrospray (ESI) as ionization method. Melting point of reagents and products was determined employing a Gallenkamp MPD 350 BM 2.5 device.

The spectroscopic data recorded for synthetized starting materials **1b**,[3] **1c**,[3] **1d**,[3] **1e**,[3] and **1f**,[3] as well as products obtained **3a**,[4] **3b**,[4] **3c**,[1b] **3e**,[1b] **3f**,[5] **3g**,[6] **3h**,[7] **3i**[6] and **3j**[6] are in agreement with values previously reported by other authors.

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[1] a) West, B. D.; Preis, S.; Schroeder, C. H.; Link, K. P. *J. Am. Chem. Soc.* **1961**, *83*, 2676-2679; b) Shi, T.; Guo, Z.; Yu, H.; Xie, J.; Zhong, Y.; Zhu, W. *Adv. Synth. Catal.* **2013**, *355*, 2538-2543.
[2] Dong, Z.; Wang, L.; Chen, X.; Liu, X.; Lin, L.; Feng, X. *Eur. J. Org. Chem.* **2009**, 5192-5197.
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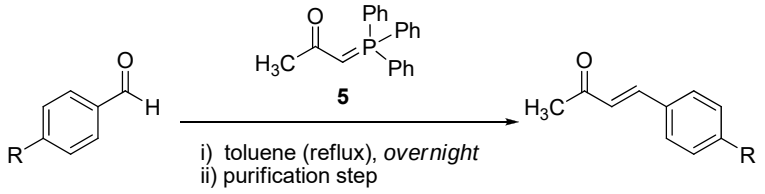
[5] Yang, H.-M.; Li, L.; Jiang, K.-Z.; Jiang, J.-X.; Lai, G.-Q.; Xu, L.-W. *Tetrahedron* **2010**, *66*, 9708-9713.
[6] Modrocká, V.; Veverková, E.; Mečiarová, M.; Šebesta, R. *J. Org. Chem.* **2018**, *83*, 13111-13120.
[7] Xie, J.-W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.-G.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 413-415.

2. Synthesis of benzylideneacetone derivatives 1b-f

The substrates **1b-f** were synthetized from the corresponding commercial aldehydes **4b-f** and the phosphonium ylide **5**, which was previously prepared following the procedure reported in the literature using commercially available reagents.[8] The respective yields after purification are collected in the Scheme S1. The ratio (E)/(Z) of products **1b-f** was determined by ^{1}H-RMN spectroscopy, using DMSO-d_6 as solvent.



4a-f

4b: R = Cl
4c: R = Br,
4d: R = CN
4e: R = Me,
4f: R = OMe

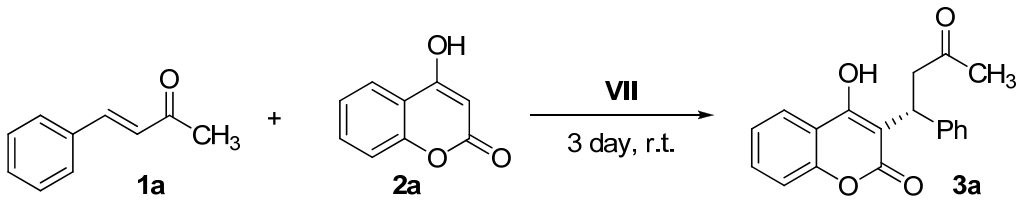
1b-g

1b: 71%
1c: 36%
1d: 54%
1e: 51%
1f: 43%

Scheme S1. Synthesis of electrophiles **1b-f**.

3. Screening of the reaction conditions

Table S1. Screening of the reaction conditions using catalyst VII.[a]



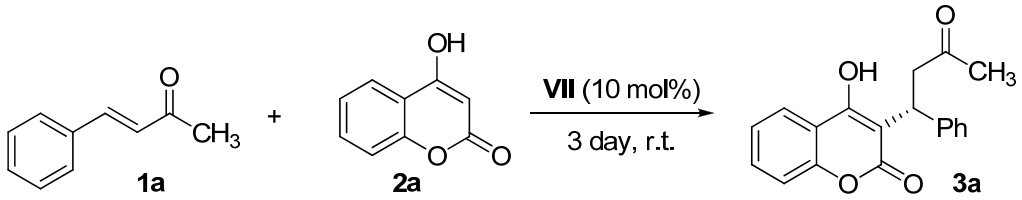
Entry	THF (μL)	Equiv. **1a**	Equiv. **2a**	**VII**	Yield (%)[b]	ee (%)[c]
1	200	1.2	1	20	19	68
2	200	1.2	1	10	10	68
3	200	1	1	10	13	70
4	200	1	1.2	10	15	68
5	200	1	1.5	10	20	68
6	200	1	2	10	22	67
7	200	1	1.5	20	58	66
8	200	1	2	20	30	68
9	100	1.2	1	20	12	66
10	100	1	1.5	20	66	63

[8] Vicente, J.; Chicote, M. T.; Saura-Llamas, I. *J. Chem. Ed.* **1993**, *70*, 163-164.

11	100	1	2	20	68	64
12	100	1	1.2	10	42	64

[a] To a mixture of catalyst **VII** (10-20 mol%) and coumarin **2a** (0.1-0.2 mmol) in THF (100-200 µL), benzylideneacetone **1a** (0.1-0.12 mmol) was added at room temperature. [b] After isolation by column chromatography. [c] Determined by chiral HPLC analysis (Chiralpak IC, Hex:*i*PrOH 80:20, 1ml/min).

Table S2. Screening of solvents.



Entry	Equiv. **1a**	Equiv. **2a**	Solvent (200 µL)	Yield (%)[a]	ee (%)[b]
1	1.0	1.2	Toluene	n.r	n.d.
2	1.0	1.2	Acetonitrile	n.r.	n.d.
3	1.0	1.2	H_2O	n.r.	n.d.
4	1.0	1.2	Hexane	≥23	40
5	1.0	1.2	CH_2Cl_2	traces	n.d.
6	1.0	1.2	1,2-DCE	traces	n.d.
7	1.0	1.2	$CHCl_3$	13	26
8	1.0	1.2	ClPh	traces	n.d.
9	1.0	1.2	1,2-$(Cl)_2$Ph	traces	n.d.
10	1.0	1.2	Diethyl ether	32	38
11	1.0	1.2	1,4-dioxane	traces	n.d.
12	1.0	1.2	AcOEt	traces	n.d.
13	1.0	1.2	DMF	≥5	44
14	1.0	1.2	iPrOH	36	44

[a] After isolation by column chromatography. [b] Determined by chiral HPLC analysis (Chiralpak IC, Hex:*i*PrOH 80:20, 1ml/min).

4. ^{1}H-NMR spectra of starting materials 1b-f

Figure S1. ^{1}H-NMR spectrum of compound **1b** (400 MHz, DMSO-d_6)

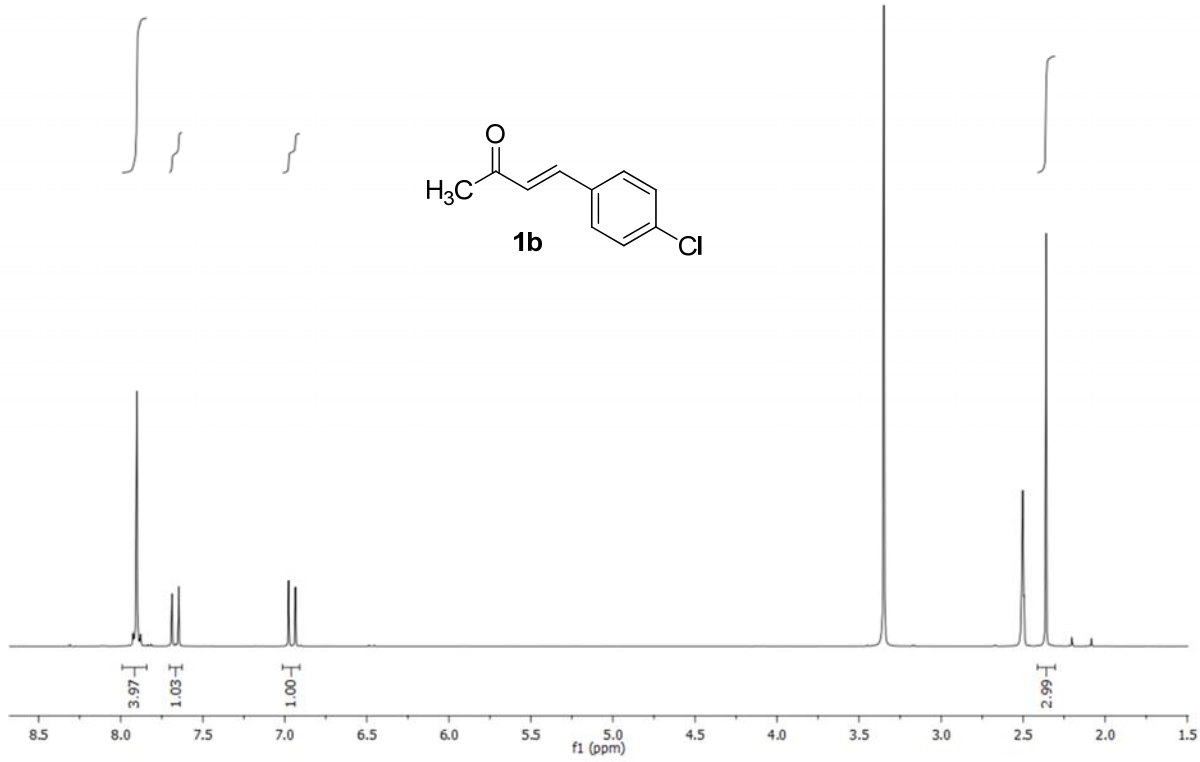


Figure S2. ^{1}H-NMR spectrum of compound **1c** (400 MHz, DMSO-d_6)

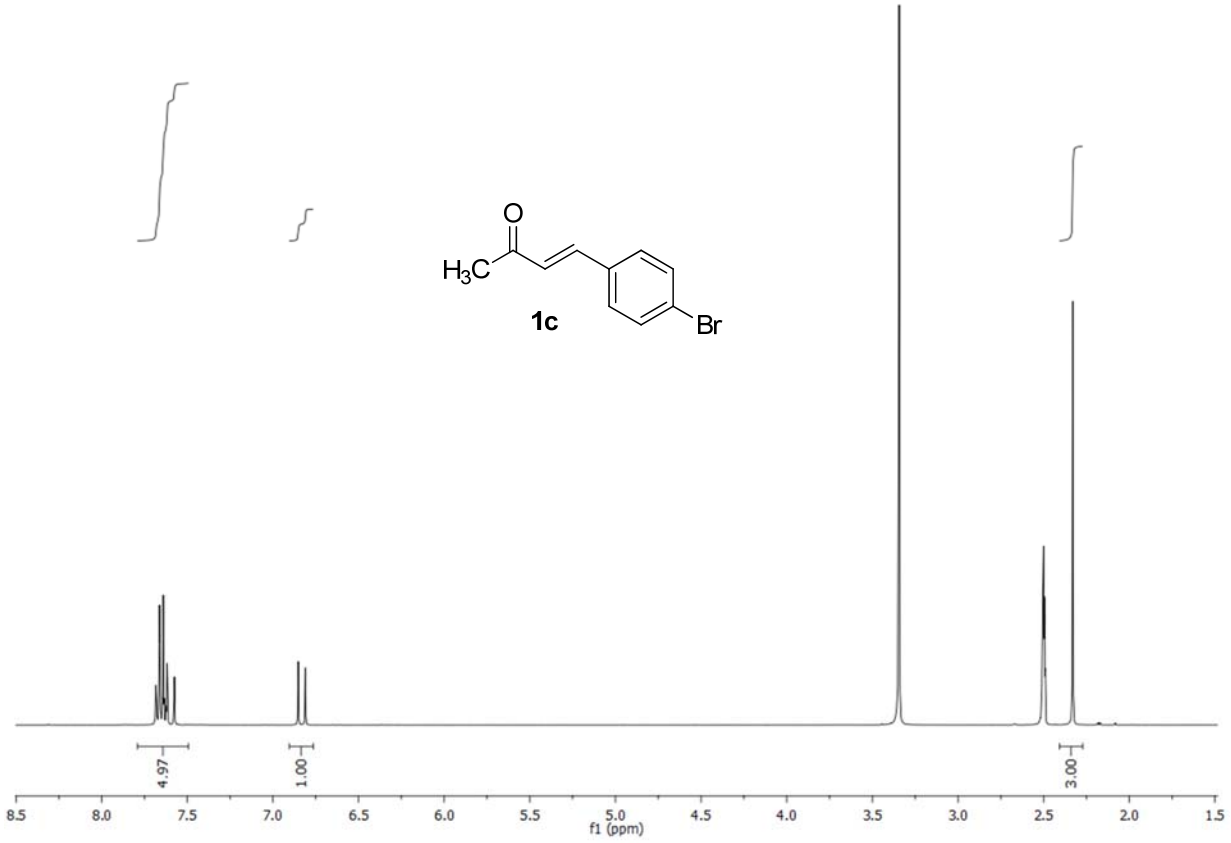


Figure S3. ^{1}H-NMR spectrum of compound **1d** (400 MHz, DMSO-d_6)

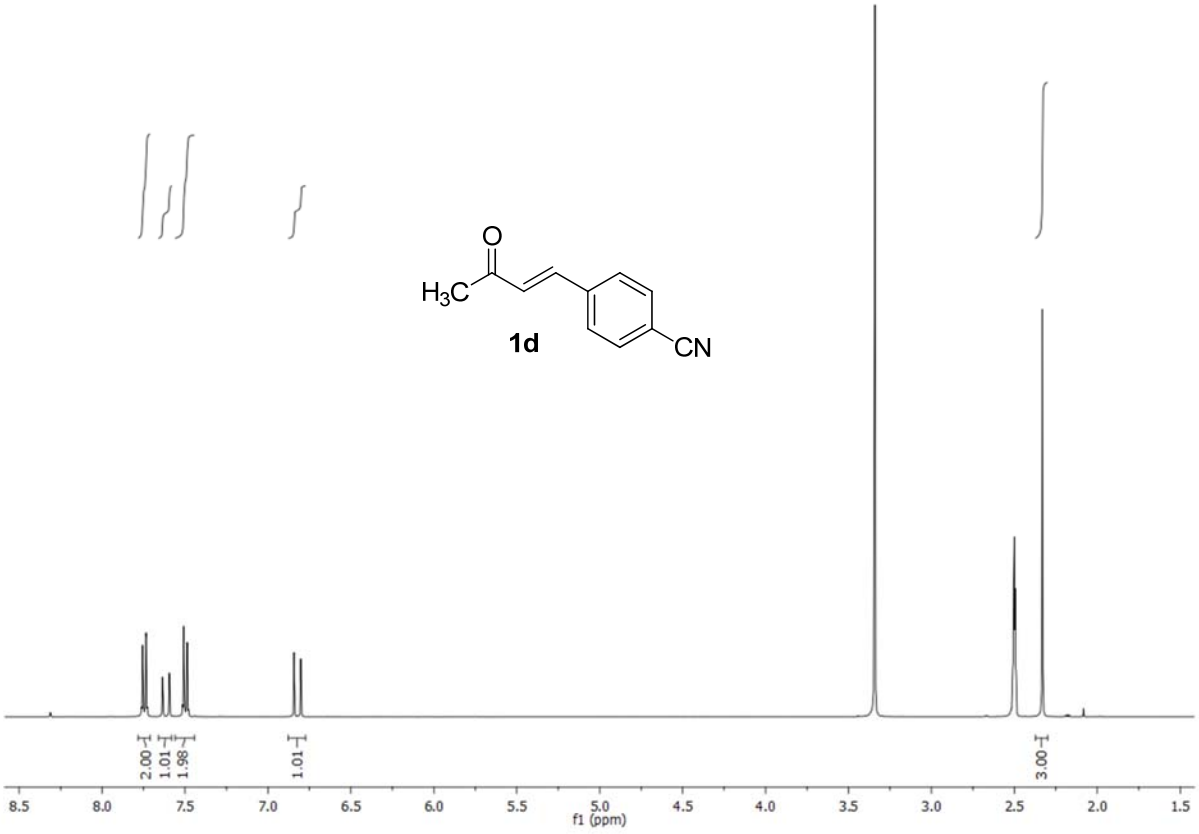


Figure S4. ^{1}H-NMR spectrum of compound **1e** (400 MHz, DMSO-d_6)

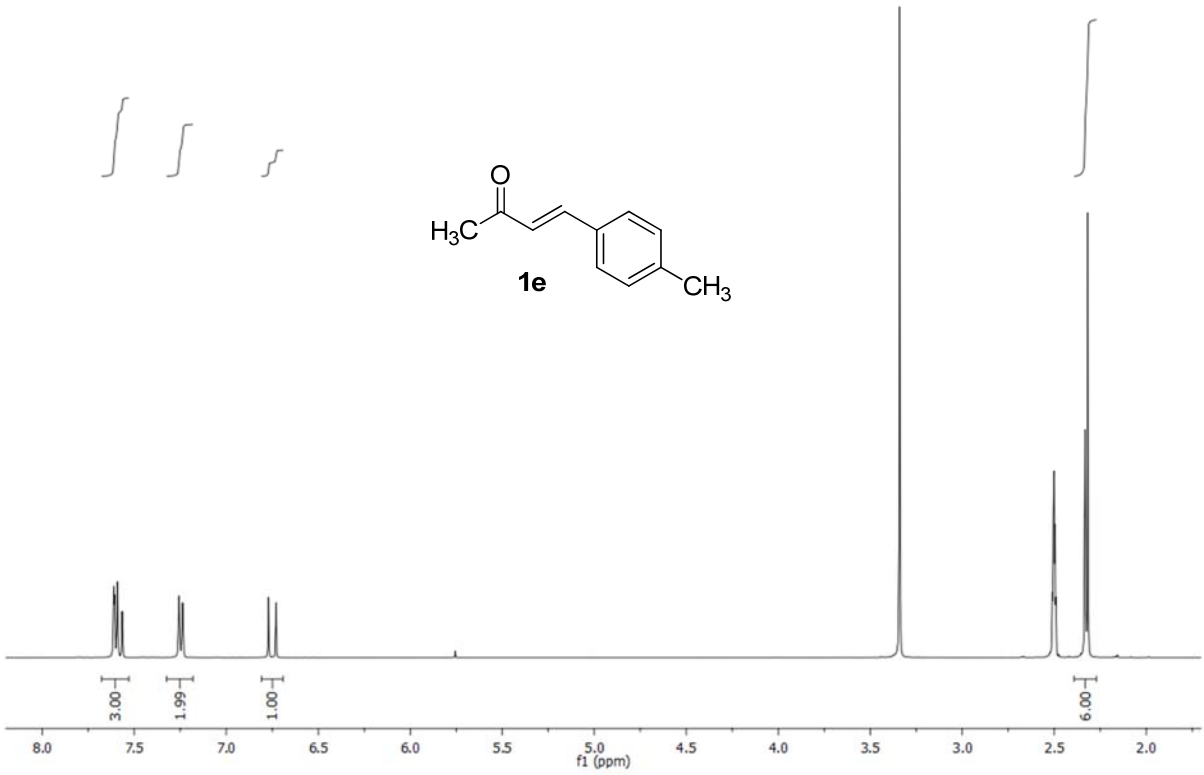
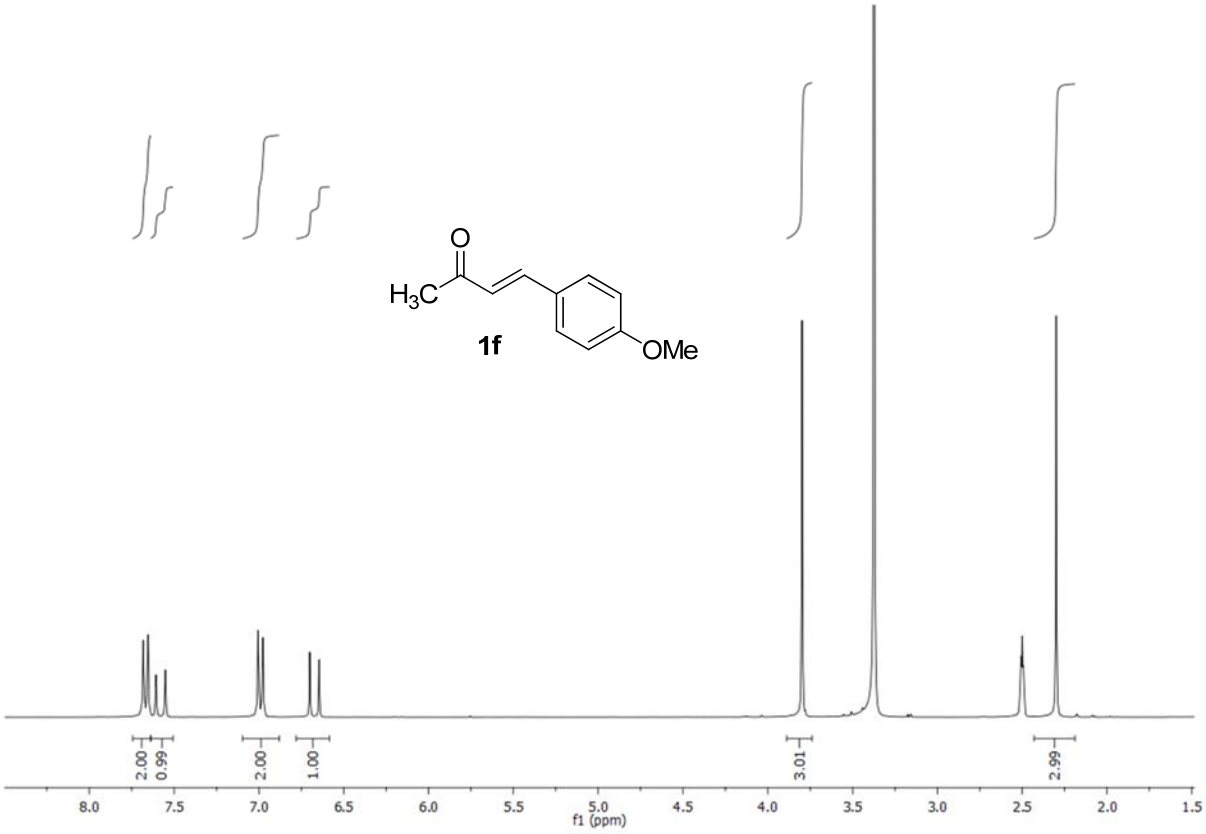


Figure S5. ^{1}H-NMR spectrum of compound **1f** (400 MHz, DMSO-d_6).



5. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of products 3d,k

Figure S6. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of compound **3d**.

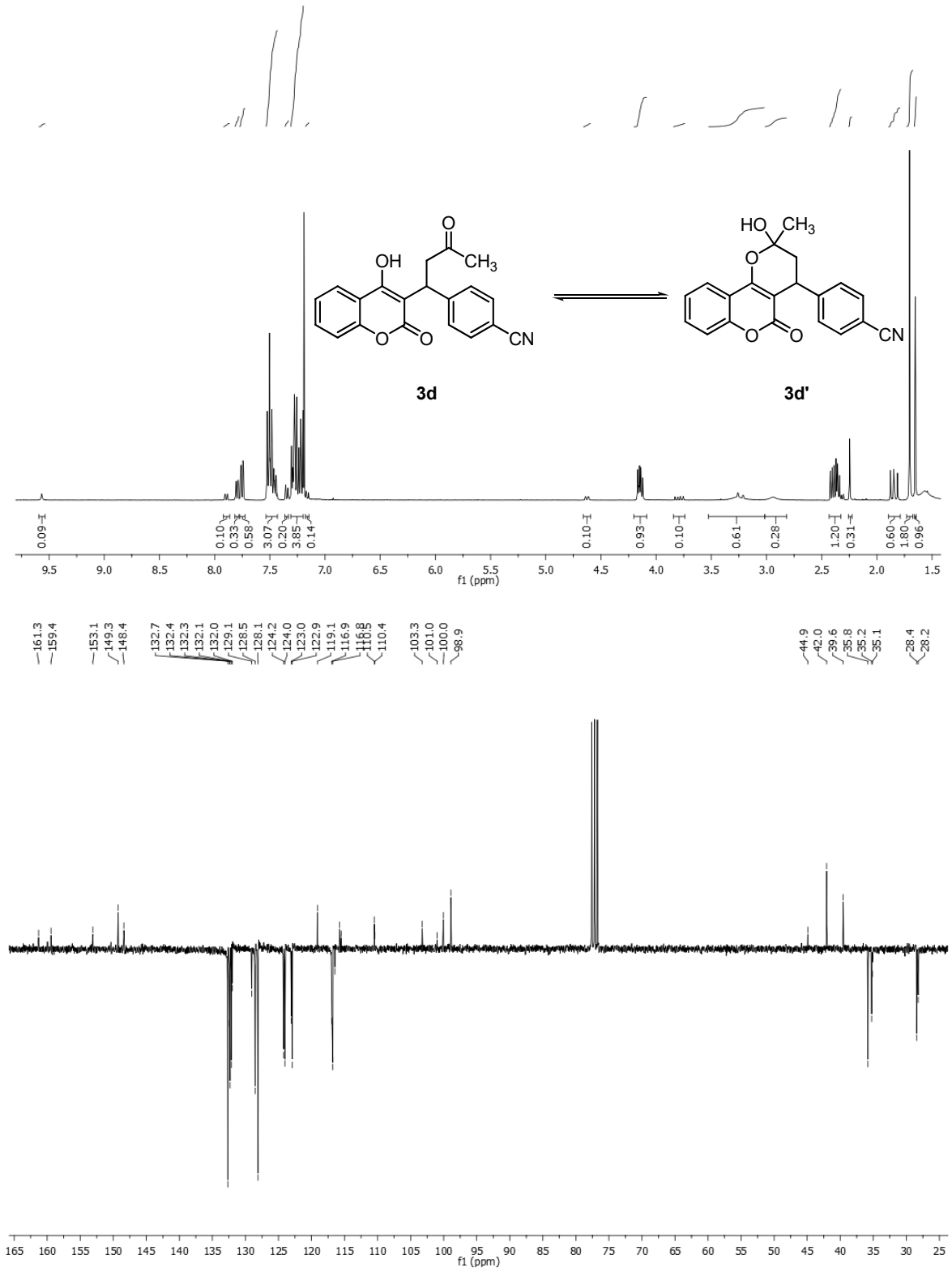
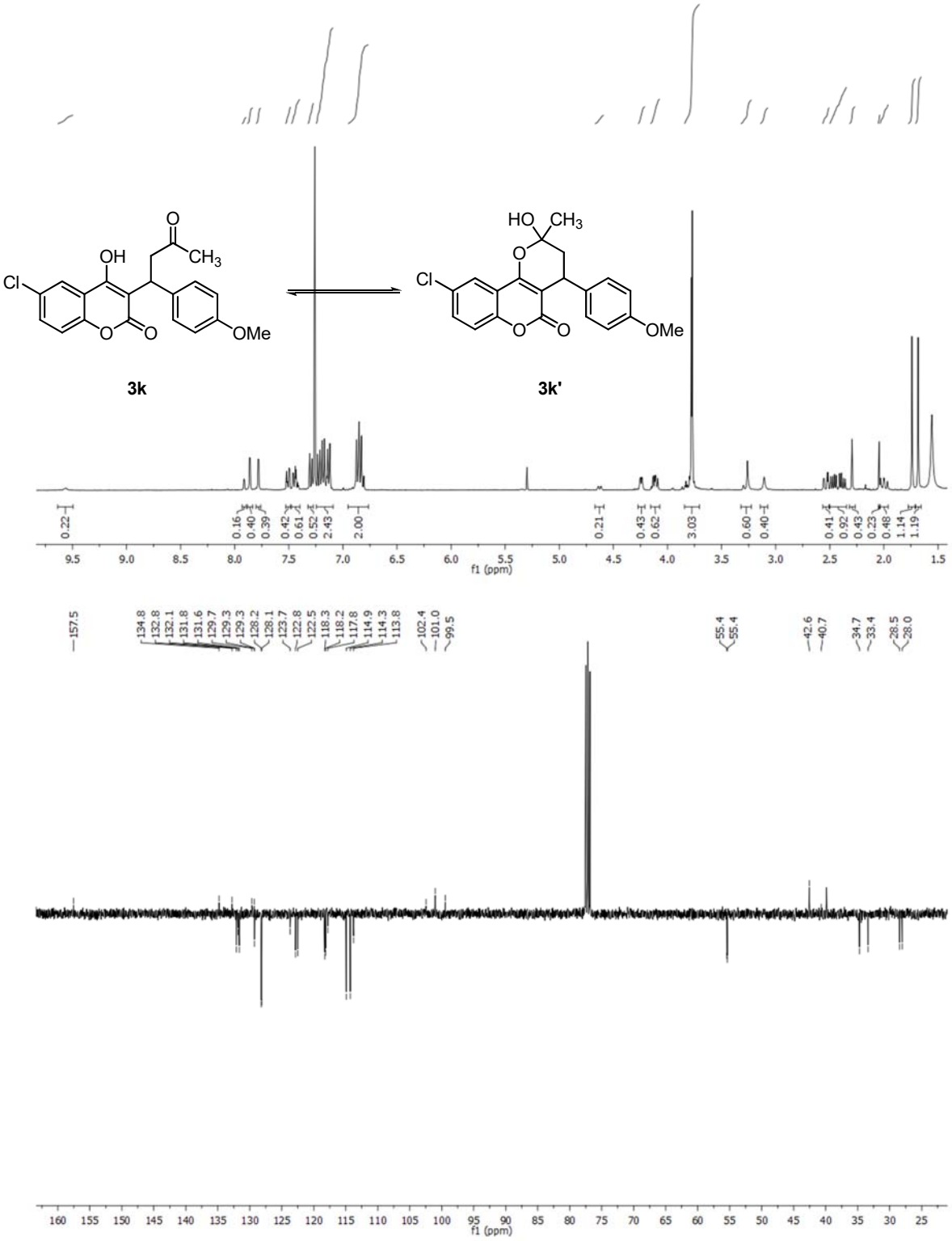
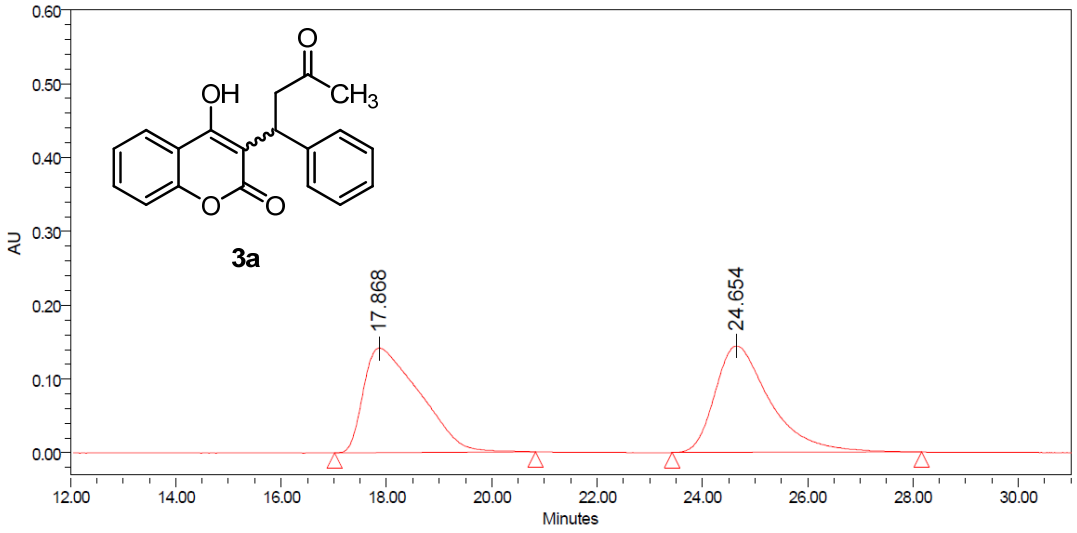


Figure S7. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of compound **3k**.



6. Chiral HPLC analysis of compounds 3a-l

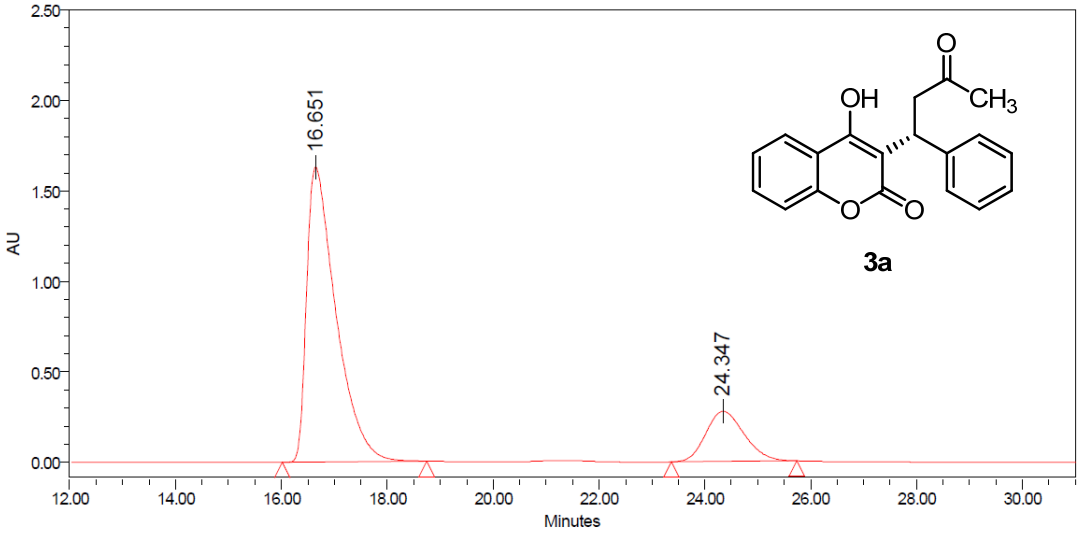
Figure S8. Racemic mixture of **3a**. Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 282.5 nm).



Processed Channel: PDA 282.5 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 282.5 nm	17.868	10508431	49.98	141912
2	PDA 282.5 nm	24.654	10518842	50.02	144596

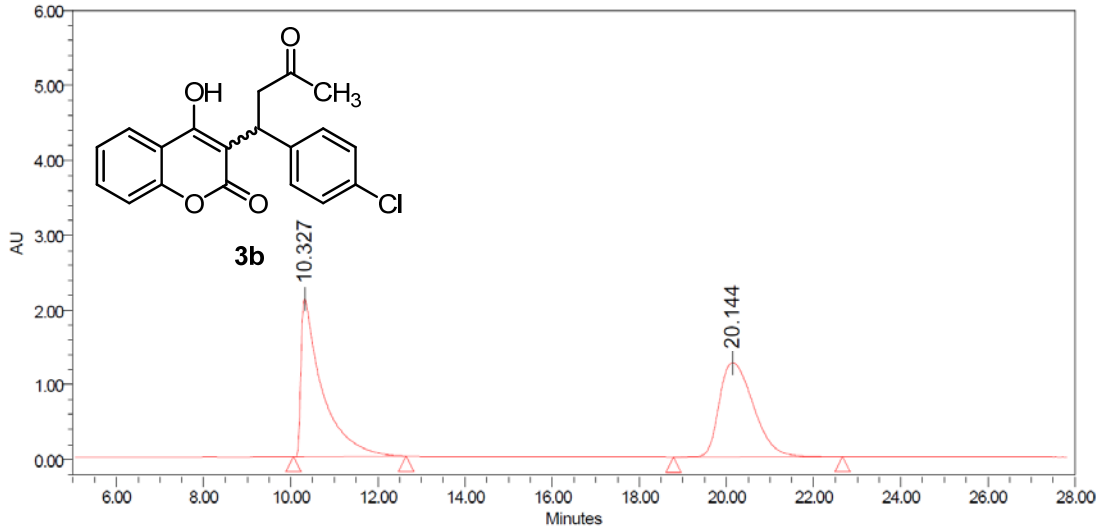
Figure S9. Enantioenriched mixture of **3a** (64% ee). Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 282.5 nm).



Processed Channel: PDA 282.5 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 282.5 nm	16.651	62871769	81.81	1630861
2	PDA 282.5 nm	24.347	13977288	18.19	277482

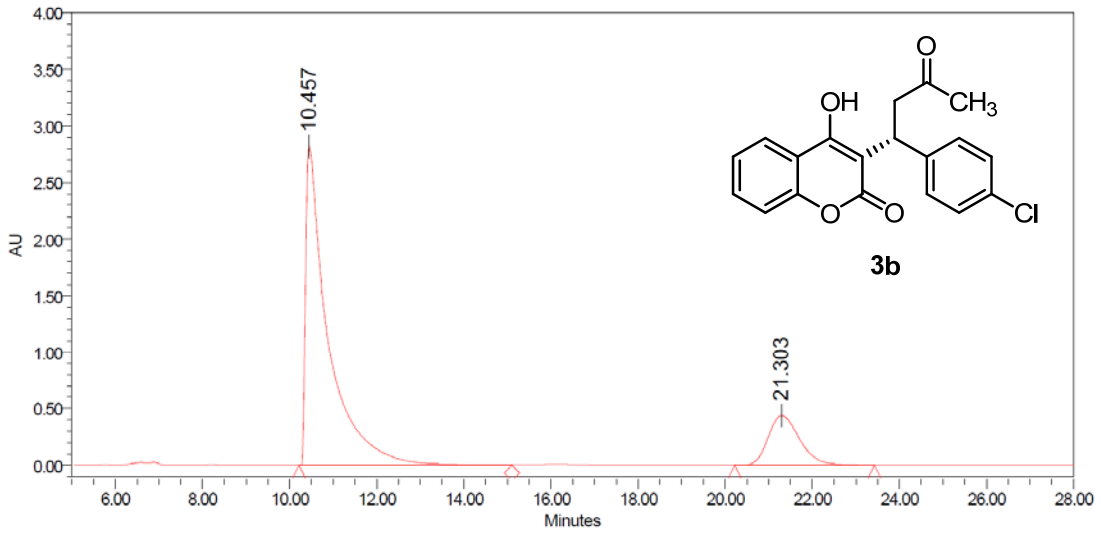
Figure S10. Racemic mixture of **3b**. Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 279.4 nm).



Processed Channel: PDA 279.4 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 279.4 nm	10.327	70618459	51.15	2116294
2	PDA 279.4 nm	20.144	67455943	48.85	1248455

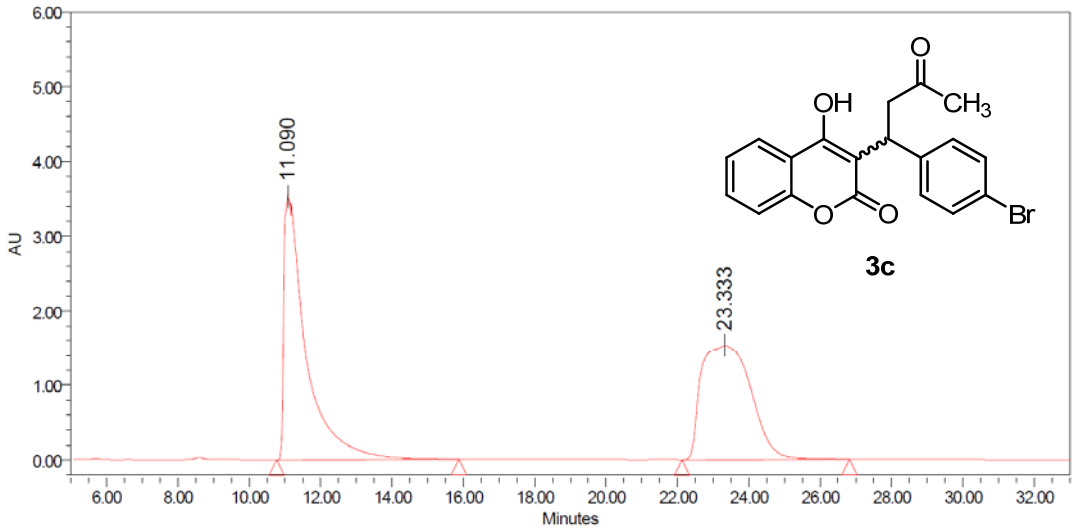
Figure S11. Enantioenriched mixture of **3b** (64% ee). Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 279.4 nm).



Processed Channel: PDA 279.4 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 279.4 nm	10.457	100487064	82.14	2821345
2	PDA 279.4 nm	21.303	21852131	17.86	436846

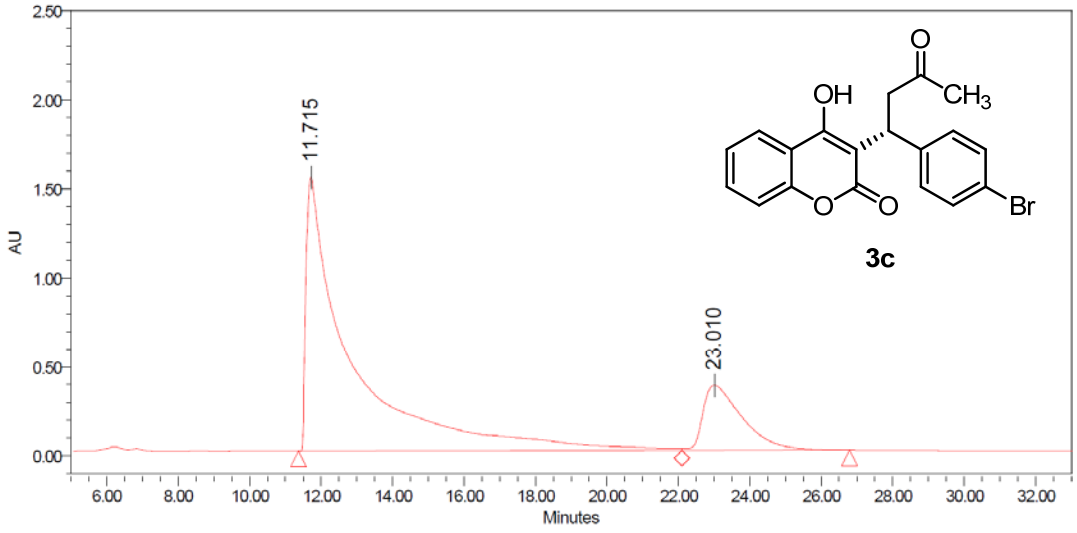
Figure S12. Racemic mixture of **3c**. Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 279.4 nm).



Processed Channel: PDA 279.4 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 279.4 nm	11.090	151429001	50.64	3521102
2	PDA 279.4 nm	23.333	147626932	49.36	1532173

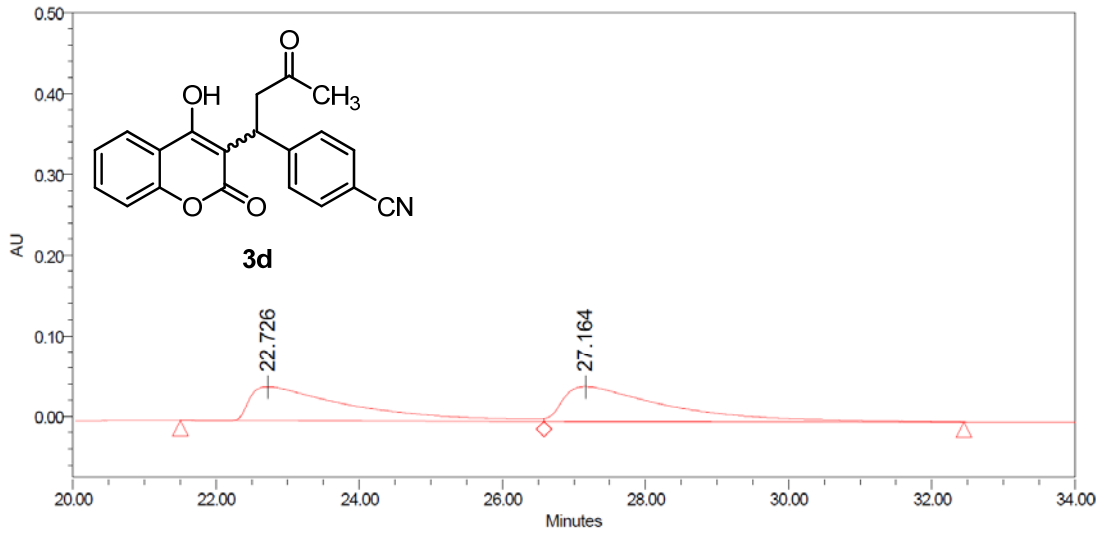
Figure S13. Enantioenriched mixture of **3c** (66% ee). Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 279.4 nm).



Processed Channel: PDA 279.4 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 279.4 nm	11.715	135539213	82.90	1537290
2	PDA 279.4 nm	23.010	27960604	17.10	365809

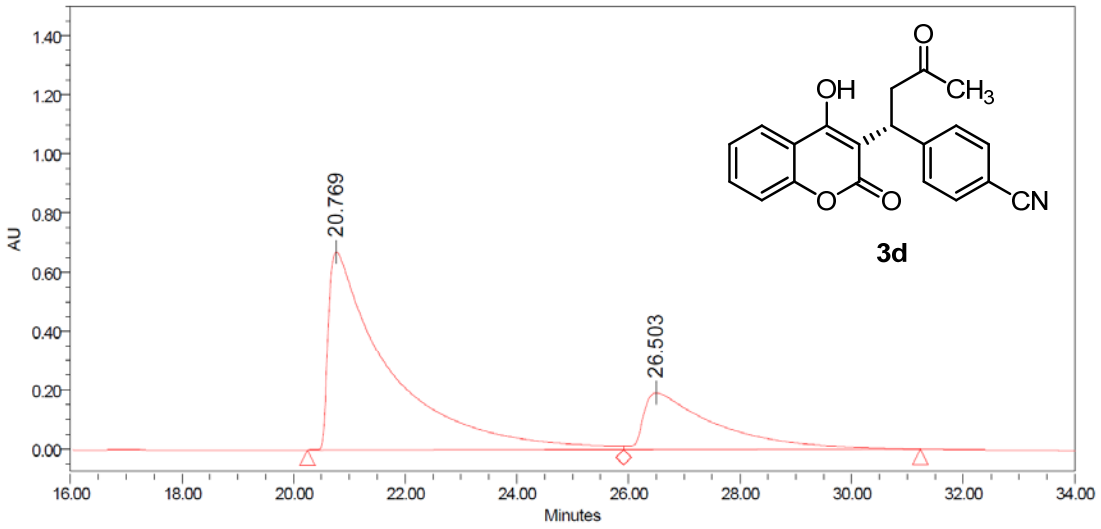
Figure S14. Racemic mixture of **3d**. Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 250.0 nm).



Processed Channel: PDA 250.0 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 250.0 nm	22.726	4081700	48.63	41799
2	PDA 250.0 nm	27.164	4312163	51.37	42798

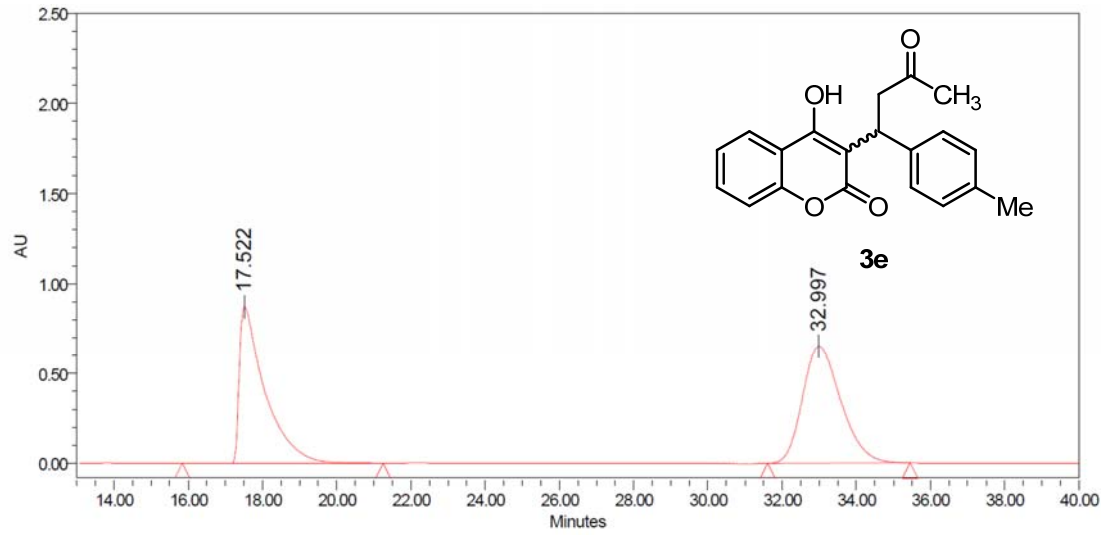
Figure S15. Enantioenriched mixture of **3d** (50% ee). Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 250.0 nm).



Processed Channel: PDA 250.0 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 250.0 nm	20.769	50779910	75.00	671849
2	PDA 250.0 nm	26.503	16926677	25.00	190616

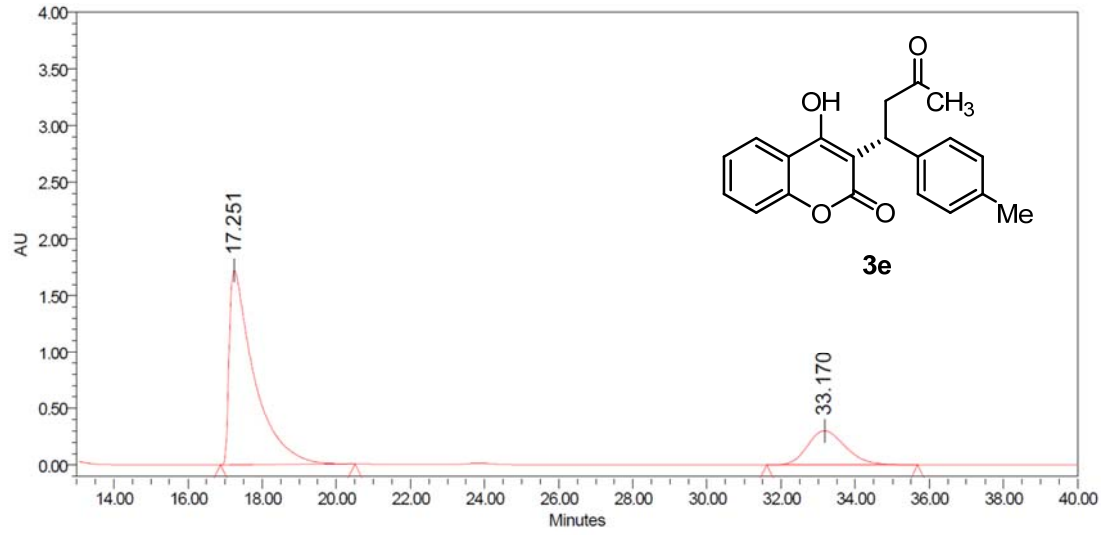
Figure S16. Racemic mixture of **3e**. Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 279.4 nm).



Processed Channel: PDA 279.4 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 279.4 nm	17.522	41570657	47.02	871881
2	PDA 279.4 nm	32.997	46836944	52.98	651692

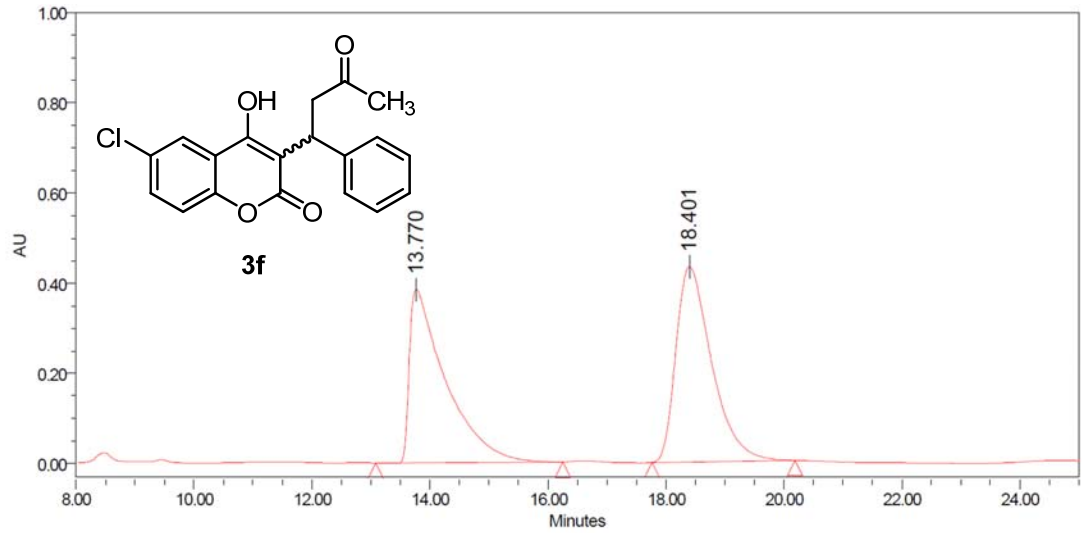
Figure S17. Enantioenriched mixture of **3e** (58% ee). Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 279.4 nm).



Processed Channel: PDA 279.4 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 279.4 nm	17.251	79986114	78.88	1721727
2	PDA 279.4 nm	33.170	21420841	21.12	300879

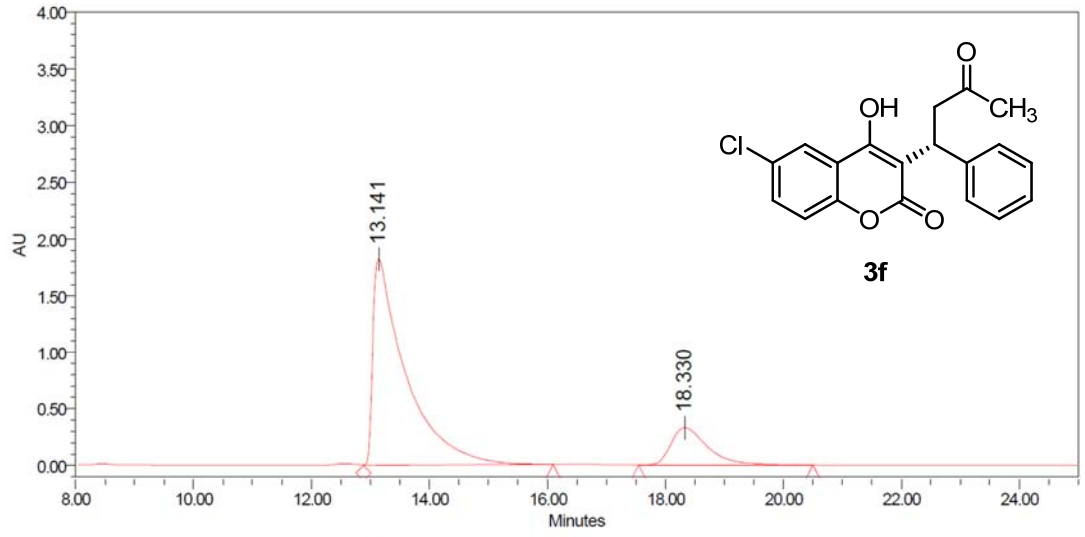
Figure S18. Racemic mixture of **3f**. Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 272.2 nm).



Processed Channel: PDA 272.2 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 272.2 nm	13.770	16404339	47.31	385959
2	PDA 272.2 nm	18.401	18267377	52.69	433442

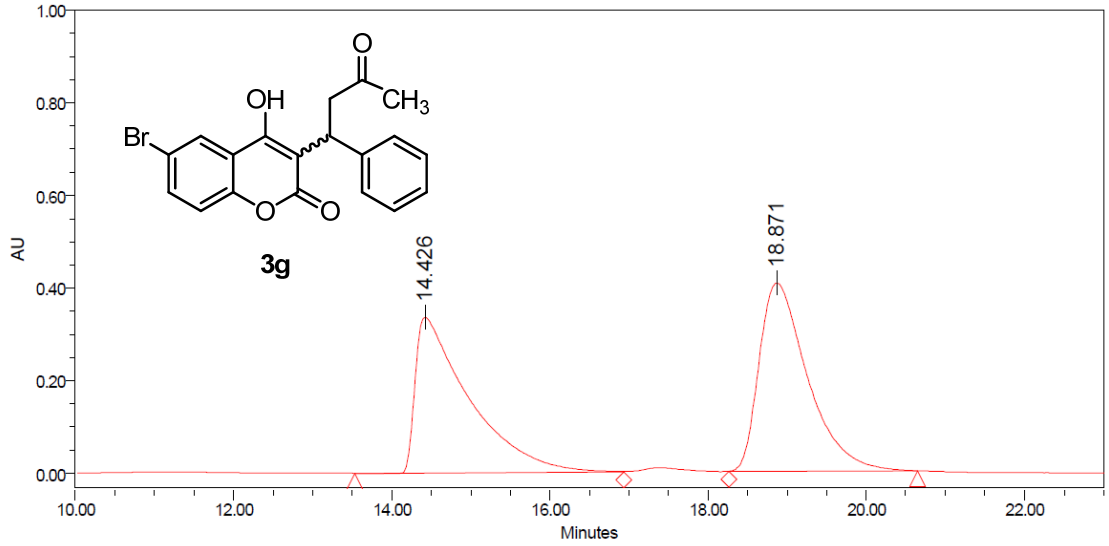
Figure S19. Enantioenriched mixture of **3f** (67% ee). Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 272.2 nm).



Processed Channel: PDA 272.2 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 272.2 nm	13.141	70400701	83.33	1825639
2	PDA 272.2 nm	18.330	14087249	16.67	327796

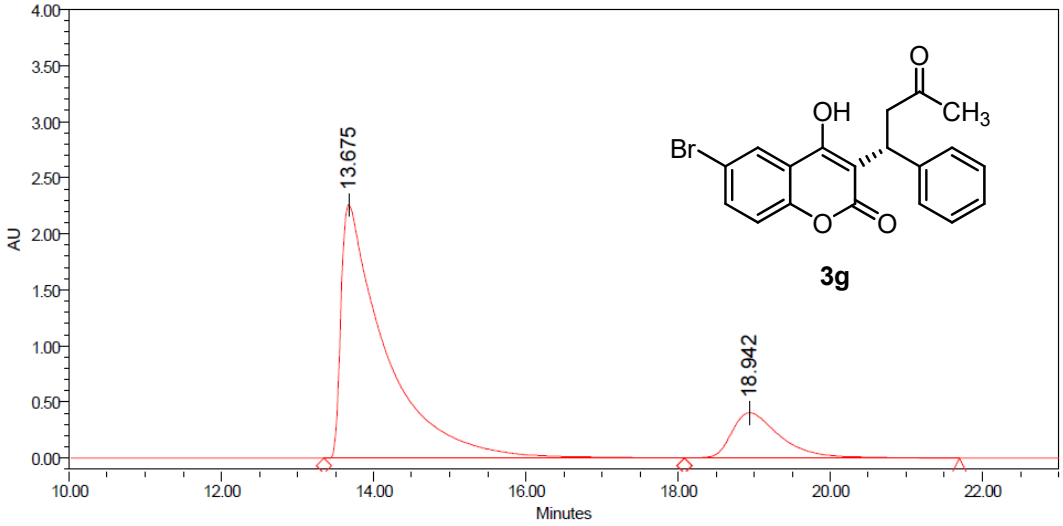
Figure S20. Racemic mixture of **3g**. Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 272.2 nm).



Processed Channel: PDA 272.2 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 272.2 nm	14.426	15901013	47.84	336429
2	PDA 272.2 nm	18.871	17339424	52.16	407055

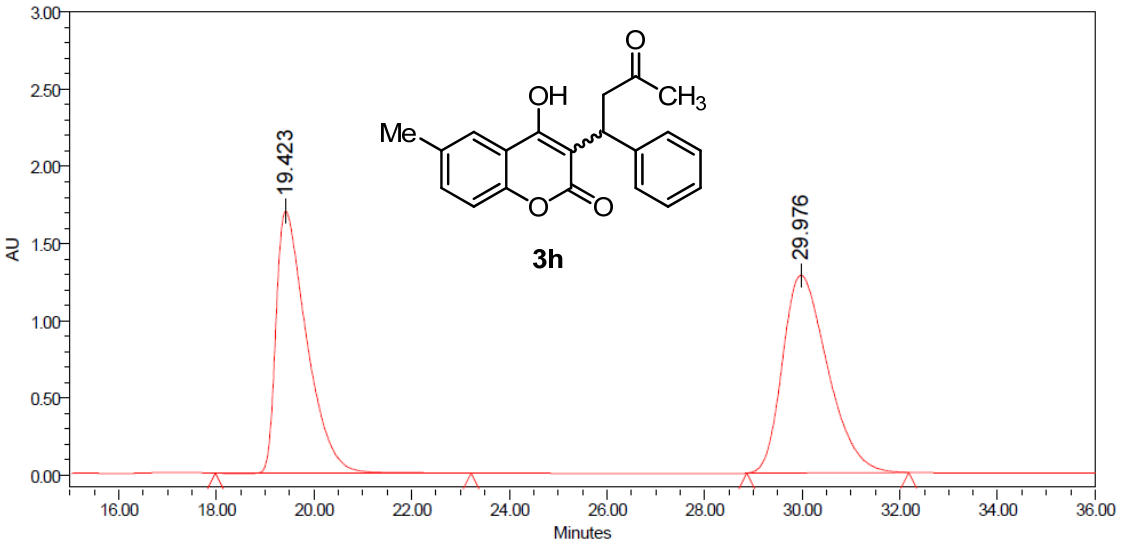
Figure S21. Enantioenriched mixture of **3g** (67% ee). Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 272.2 nm).



Processed Channel: PDA 272.2 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 272.2 nm	13.675	92408505	83.52	2266228
2	PDA 272.2 nm	18.942	18233692	16.48	405590

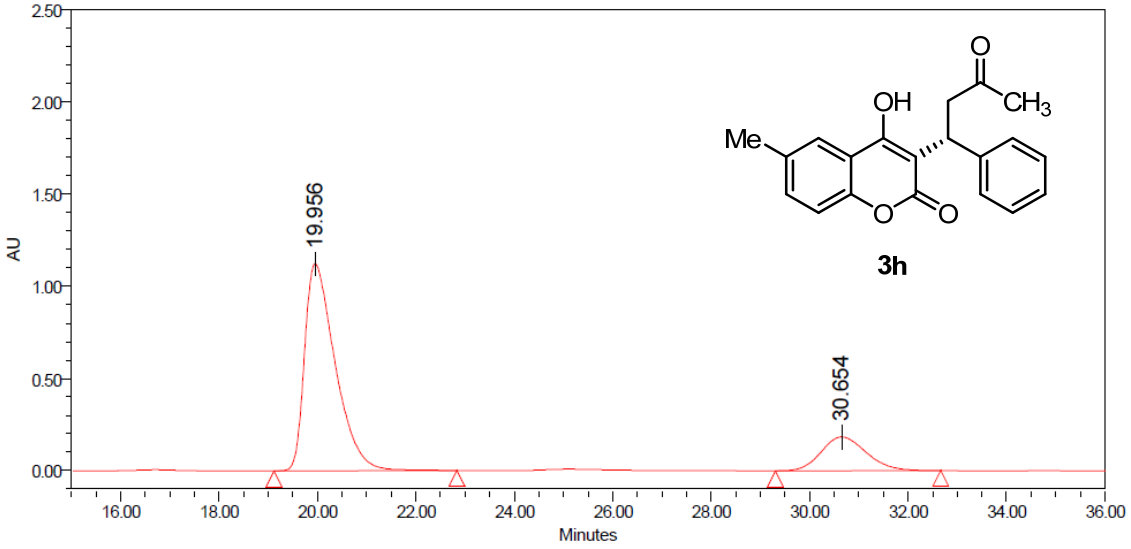
Figure S22. Racemic mixture of **3h**. Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 271.0 nm).



Processed Channel: PDA 271.0 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 271.0 nm	19.423	74071932	47.42	1698641
2	PDA 271.0 nm	29.976	82145423	52.58	1280434

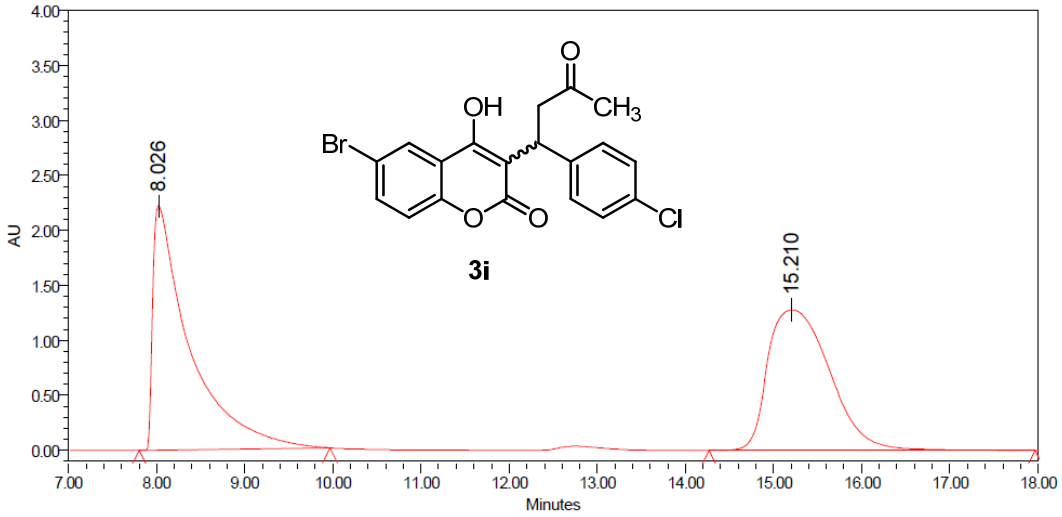
Figure S23. Enantioenriched mixture of **3h** (61% ee). Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 271.0 nm).



Processed Channel: PDA 271.0 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 271.0 nm	19.956	48489860	80.62	1122777
2	PDA 271.0 nm	30.654	11655126	19.38	183148

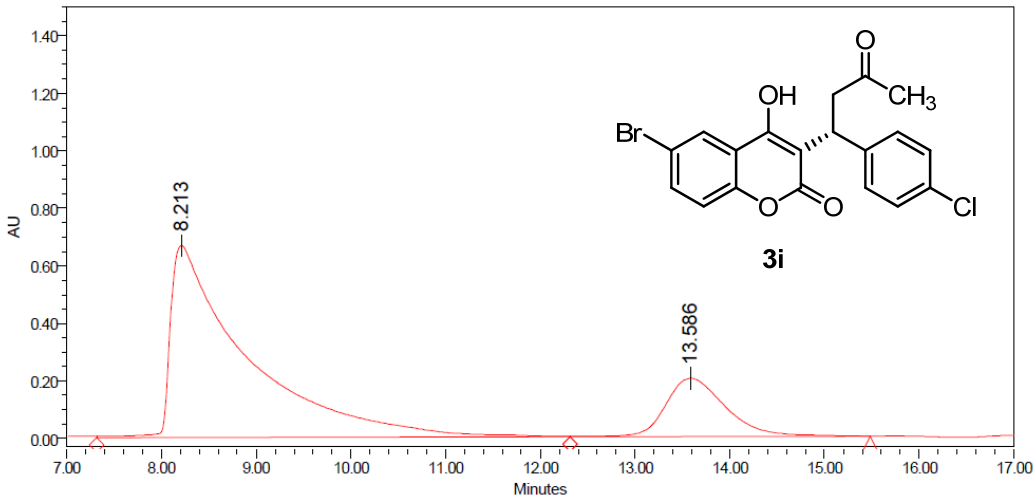
Figure S24. Racemic mixture of **3i**. Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 272.2 nm).



Processed Channel: PDA 272.2 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 272.2 nm	8.026	64255438	50.75	2233890
2	PDA 272.2 nm	15.210	62364144	49.25	1277353

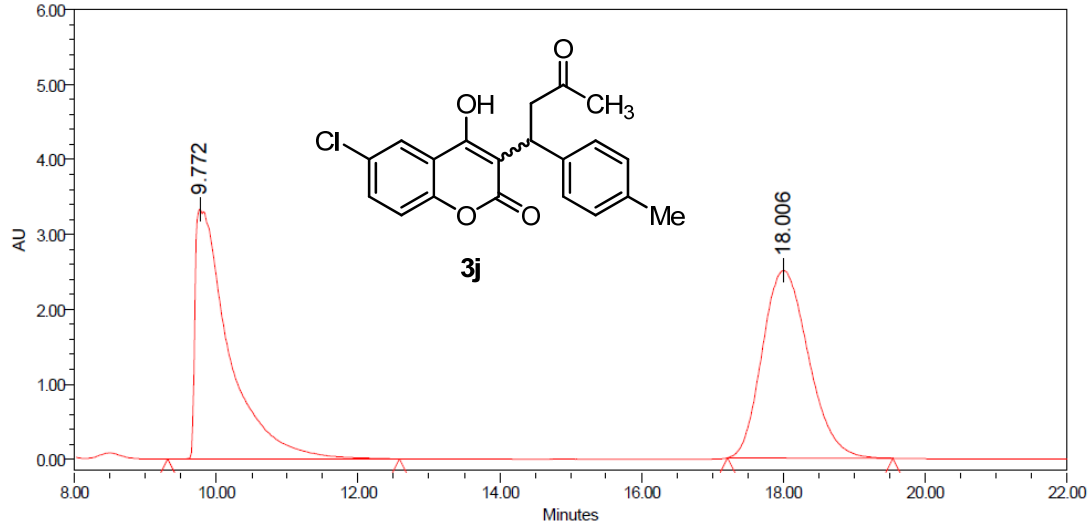
Figure S25 Enantioenriched mixture of **3i** (62% ee). Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 272.2 nm).



Processed Channel: PDA 272.2 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 272.2 nm	8.213	37159642	80.81	667403
2	PDA 272.2 nm	13.586	8824184	19.19	201837

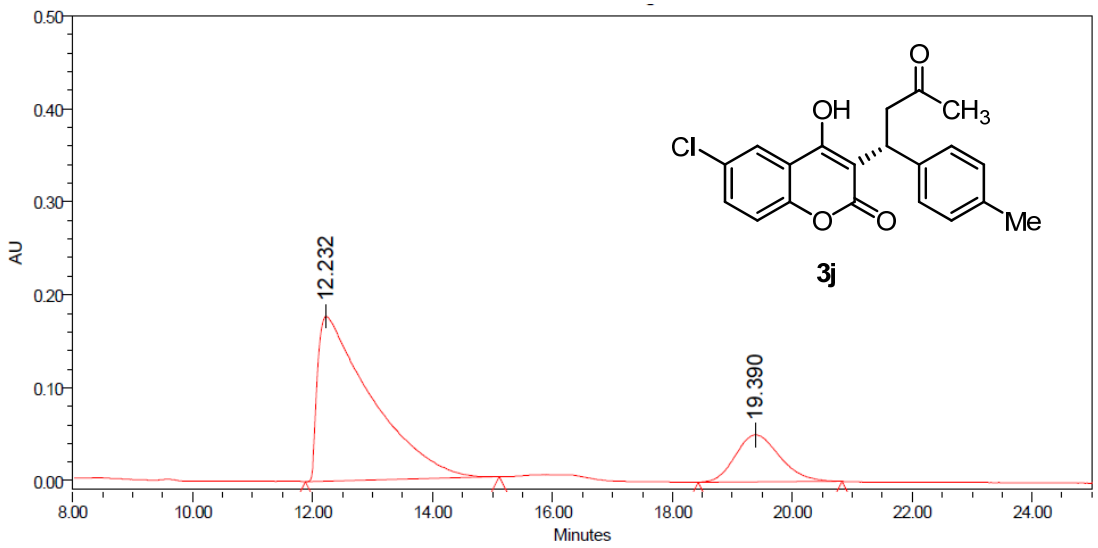
Figure S26. Racemic mixture of **3j**. Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 272.2 nm).



Processed Channel: PDA 272.2 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 272.2 nm	9.772	110780845	49.45	3340738
2	PDA 272.2 nm	18.006	113239874	50.55	2499085

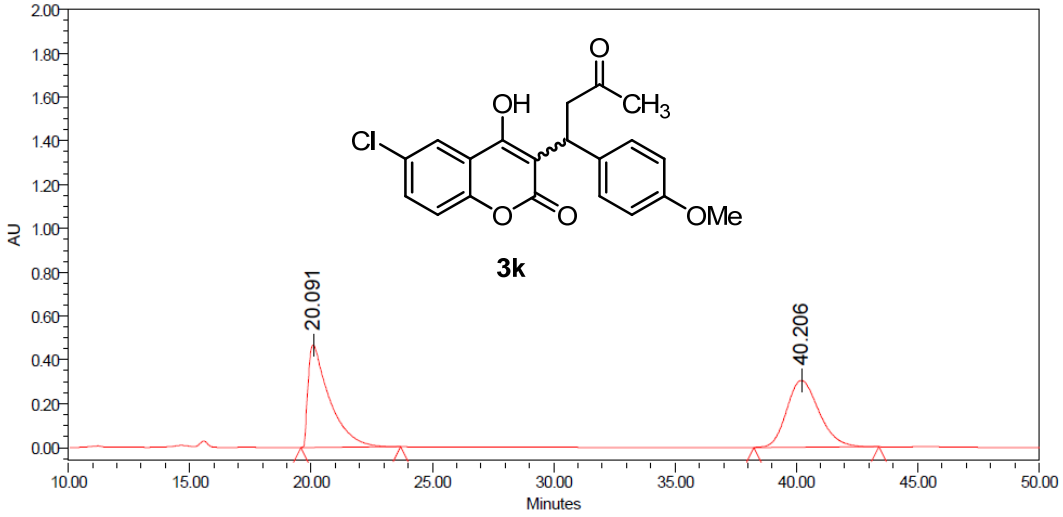
Figure S27. Enantioenriched mixture of **3j** (62% ee). Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 272.2 nm).



Processed Channel: PDA 272.2 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 272.2 nm	12.232	11088569	80.88	177431
2	PDA 272.2 nm	19.390	2620682	19.12	50765

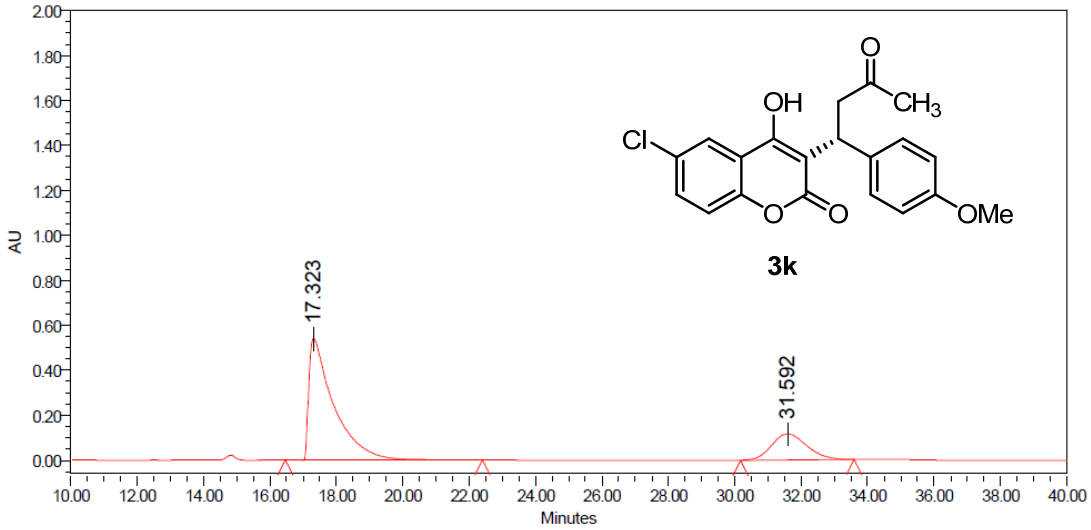
Figure S28. Racemic mixture of **3k**. Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 272.2 nm).



Processed Channel: PDA 272.2 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 272.2 nm	20.091	28654856	50.26	467592
2	PDA 272.2 nm	40.206	28356896	49.74	305324

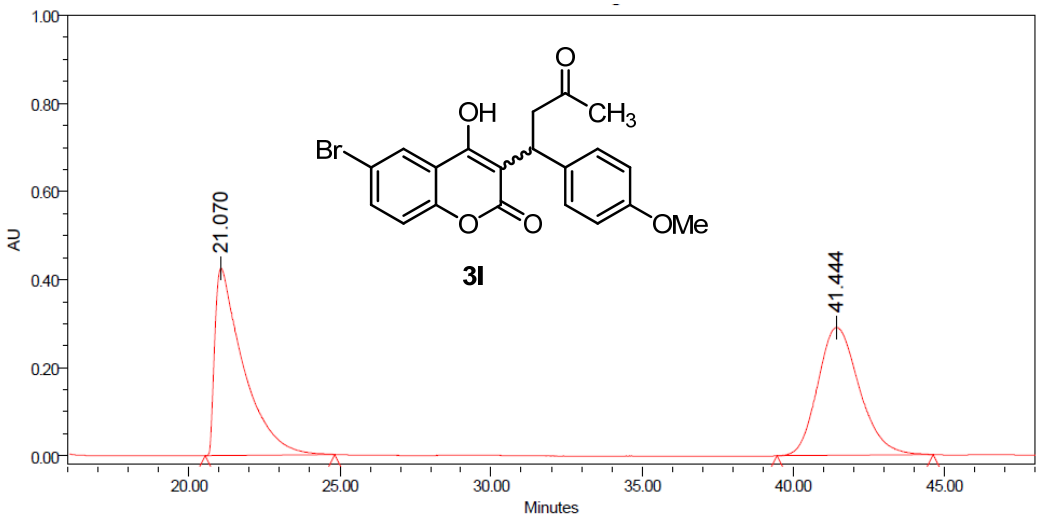
Figure S29. Enantioenriched mixture of **3k** (54% ee). Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 272.2 nm).



Processed Channel: PDA 272.2 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 272.2 nm	17.323	28009176	76.77	539533
2	PDA 272.2 nm	31.592	8474156	23.23	115542

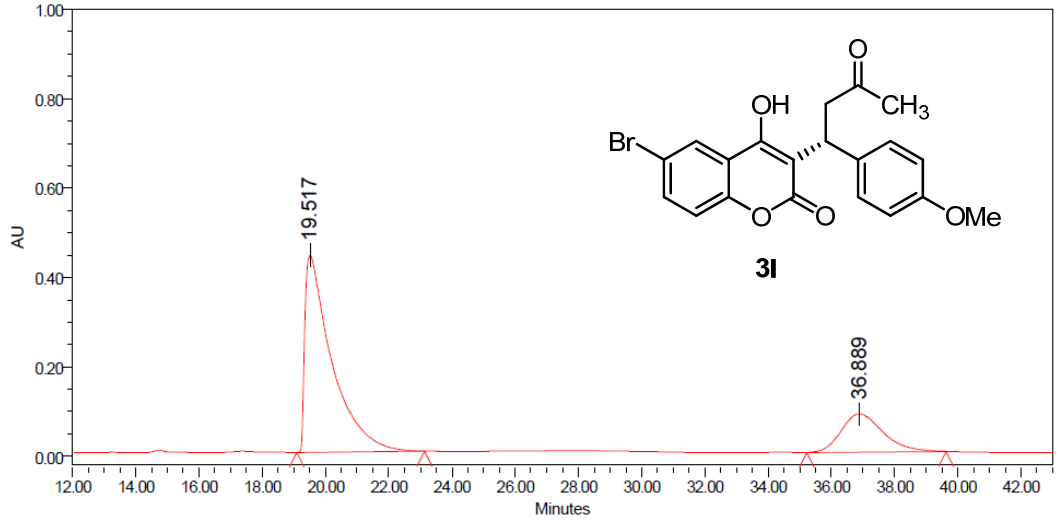
Figure S30. Racemic mixture of **3l**. Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 272.2 nm).



Processed Channel: PDA 272.2 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 272.2 nm	21.070	28057165	50.25	425860
2	PDA 272.2 nm	41.444	27774925	49.75	290366

Figure S31. Enantioenriched mixture of **3l** (54% ee). Daicel ChiralPak IC column (*n*-hexane/isopropyl alcohol = 80:20, 1 mL min^{-1}, λ = 272.2 nm).



Processed Channel: PDA 272.2 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 272.2 nm	19.517	25978463	76.86	440514
2	PDA 272.2 nm	36.889	7820214	23.14	85308