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Catalytic Enantioselective Protonation of Enol Trifluoroacetates by Means of Hydrogenocarbonates and Cinchona Alkaloids

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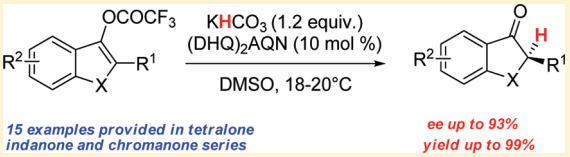
Supporting Information

ABSTRACT: Herein is disclosed an efficient catalytic enantioselective protonation of enol acetates by means of a readily implementable transition-metal-free chemical process. By making use of simple hydrogenocarbonates as the proton source and hydroquinine anthraquinone-1,4-diyl diether as the chiral proton shuttle, a series of cyclic enol trifluoroacetates are protonated under mild conditions to yield the corresponding ketones in up to 93% ee.



Enantioselective protonation (EP) of prostereogenic enol derivatives has become a method of choice for the preparation of enantioenriched α-substituted carbonyl compounds.[1] Ever since the first reports by Duhamel and Plaquevent in the late 1970s,[2,3] great advances have been accomplished making EP an attractive and useful tool in asymmetric synthesis.

In particular, much effort has been devoted to developing efficient catalytic processes with metal enolates derived from ketones[4−6] and amides[7] as well as with a large variety of latent enolates, including mainly silyl enolates,[8−17] ketenes,[18−24] ketene disilyl acetals,[25] malonate derivatives,[26,27] and unsaturated carbonyl compounds.[28] Somewhat surprisingly, enol esters remain one of the last important classes of latent enolates almost unexplored in catalytic EP,[29] although asymmetric biocatalytic protonation has already been successfully reported by means of esterases.[30] As an extension of our efforts directed toward the development of new catalytic EP strategies, we report herein an efficient nonenzymatic catalytic EP of enol esters under mild and transition-metal-free conditions. Our approach is based on the simple use of hydrogenocarbonates not only providing the protonating agent but also serving as a nucleophilic activator to release the transient enolate (Figure 1b). A chiral Brønsted base is expected to act as a chiral proton shuttle to ensure the asymmetric proton transfer. One can draw some parallels between this approach and enzymatic hydrolysis of enol esters illustrated in Figure 1a.

To probe the feasibility of this biomimetic approach, we first investigated the reactivity of various enol esters **1aa**−**1ac** derived from 2-methyltetralone in the presence of 1.2 equiv of $KHCO_3$ and 10 mol % hydroquinine anthraquinone-1,4-diyl diether [$(DHQ)_2AQN$], a readily commercially available ligand commonly used in Sharpless's enantioselective dihydroxylation reactions.[31] Although enol acetate **1aa** was recovered quantitatively under these initial conditions (Table 1, entry 1), enol trichloroacetate **1ab** afforded the desired tetralone **2a** in 54% yield and 28% ee (Table 1, entry 2). The use of the more reactive

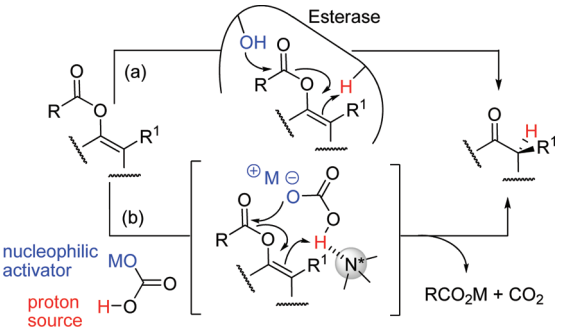


Figure 1. (a) Biocatalytic hydrolysis of enol esters by esterases. (b) Proposed biomimetic approach using $MHCO_3$ as both the nucleophilic activator and proton source combined with a chiral Brønsted base.

enol trifluoroacetate **1ac** eventually resulted in a substantial increase in both the yield and the enantioselectivity, providing **2a** in 80% yield and 43% ee within 5 h (Table 1, entry 3).

Encouraged by these initial results, we then examined the impact of the most relevant reaction parameters during protonation of enol trifluoroacetate **1ac** (Table 2). Attempts to use nonpolar solvents such as toluene or dichloromethane afforded lower enantioselectivities compared to those initially obtained in acetonitrile (Table 2, entries 1−3). Although the more polar *N*-methylpyrrolidone (NMP) did not exhibit better results (Table 2, entry 4), we were delighted to find that the reaction performed in DMF and DMSO proceeded with significantly higher enantioselectivities of 77% and 86%, respectively (Table 2, entries 5 and 6).

The reaction temperature was also found to have a significant effect on the stereoinduction. Whereas a noticeable drop in enantioselectivity was recorded when the reaction temperature

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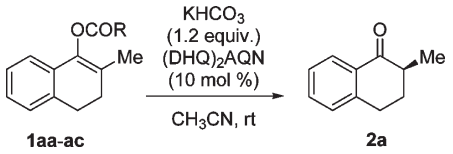
Table 1. Evaluation of Various Enol Esters 1aa−ac[a]



1aa-ac 2a

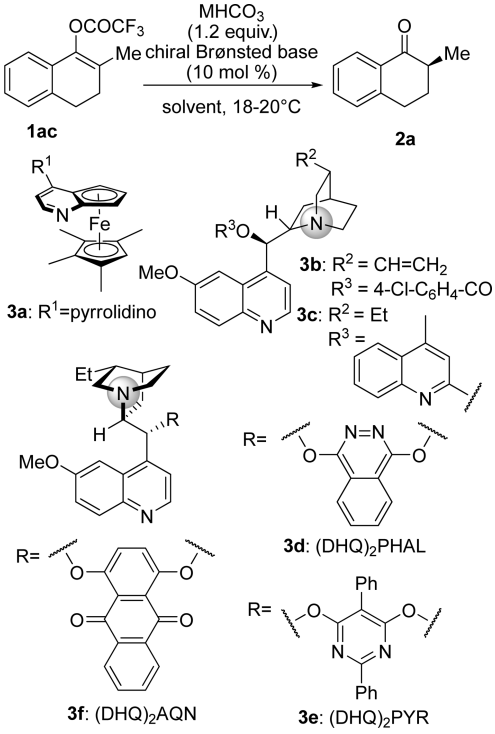
entry	R	enol ester **1a**	time (h)	yield[b] (%)	ee[d] (%)
1	Me	**1aa**	72	0	
2	CCl_3	**1ab**	72	54[c]	28 (*S*)
3	CF_3	**1ac**	5	85	43 (*S*)

[a] Reactions performed with 1.0 equiv of enol esters **1aa−ac** (1 mmol), 1.2 equiv of $KHCO_3$, and 0.1 equiv of $(DHQ)_2AQN$ in acetonitrile. [b] Isolated yields. [c] Protonation of enol trichloroacetate **1ab** gave rise to the desired tetralone **2a** along with 2-chloro-2-methyltetralone in 30% yield. [d] Determined by chiral HPLC analysis. The absolute configuration was determined by comparison with literature data.

was increased from 20 to 30 °C (Table 2, entry 6), against all odds, a deleterious impact on the level of stereoinduction was also observed when the reaction was conducted at 0 °C (Table 2, entry 5). Consequently, stringent control of the temperature was essential to achieve optimal enantioselectivity.[32] We next studied the efficiency of this EP process with regard to the catalytic amount of the Brønsted base. The reaction conducted in the presence of 20 mol % $(DHQ)_2AQN$ did not lead to any further increase in the enantioselectivity (Table 2, entry 7), whereas a slight erosion of the level of stereoinduction was observed by using 5 mol % $(DHQ)_2AQN$ (Table 2, entry 8). While changing the protonating agent from $KHCO_3$ to $NaHCO_3$ did not alter the performance of the process (Table 2, entries 6 and 9), the use of $CsHCO_3$ resulted in a somewhat lower enantioselectivity (Table 2, entry 10). From the outset of this investigation, we focused our attention on $(DHQ)_2AQN$ mainly owing to its good performance previously reported during catalytic EP of silyl enolates.[14] Surprisingly, when we screened other cinchona alkaloids, including biscinchona alkaloids such as hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQ)_2PYR$, **3e**] and hydroquinine 1,4-phthalazinediyl diether [$(DHQ)_2PHAL$, **3d**], structurally close to $(DHQ)_2AQN$ (**3f**), tetralone **2a** was obtained as a racemic mixture in all cases (Table 2, entries 11−14). Among all other chiral Brønsted bases tested, only Fu's DMAP **3a** furnished a modest 18% ee (Table 2, entry 15). On the basis of these screening results, $(DHQ)_2AQN$ turned out to be the sole candidate capable of acting as an effective chiral proton shuttle in this enantioselective process.

The scope of the reaction was then explored under the previously optimized reaction conditions with various enol trifluoroacetates **1ac−o** in the tetralone, indanone, and chromanone series (Table 3). Generally speaking, one can notice that, in all cases, ketones **2a−o** were isolated in high yields and enantioselectivities ranging from fair to excellent. With the exception of enol trifluoroacetate **1k** affording tetralone **2k** in 55% ee (Table 3, entry 11), the highest levels of selectivity were obtained in the tetralone series, reaching 93% ee with enol trifluoroacetate **1f** (Table 3, entries 1−10). In the chromanone and indanone series, while the level of stereoinduction was found to be somewhat lower, it still remained acceptable, giving rise to the corresponding ketones **2l−o** in enantioselectivities ranging from 69% to 80% ee (Table 3, entries 12−15).

Table 2. Optimization of Reaction Parameters during EP of Enol Trifluoroacetate 1ac[a]



entry	solvent	chiral base	$MHCO_3$	yield[b] (%)	ee[c] (%)
1	MeCN	**3f**	$KHCO_3$	85	43
2	toluene	**3f**	$KHCO_3$	90	29
3	DCM	**3f**	$KHCO_3$	88	24
4	NMP	**3f**	$KHCO_3$	95	45
5	DMF	**3f**	$KHCO_3$	84	77 (40)[d]
6	DMSO	**3f**	$KHCO_3$	96	86 (78)[e]
7	DMSO	**3f**[f]	$KHCO_3$	94	85
8	DMSO	**3f**[g]	$KHCO_3$	88	81
9	DMSO	**3f**	$NaHCO_3$	88	85
10	DMSO	**3f**	$CsHCO_3$	88	70
11	DMSO	**3b**	$KHCO_3$	81	0
12	DMSO	**3c**	$KHCO_3$	83	0
13	DMSO	**3d**	$KHCO_3$	87	0
14	DMSO	**3e**	$KHCO_3$	92	0
15	DMSO	**3a**	$KHCO_3$	98	18

[a] Reactions were conducted on a 0.5 mmol scale at 18−20 °C unless otherwise stated. [b] Isolated yields. [c] Determined by chiral HPLC. The absolute configuration was assigned as *S* in all cases by comparison with literature data. [d] Reaction performed at 0 °C. [e] Reaction performed at 30 °C. [f] A 20 mol % concentration was used. [g] A 5 mol % concentration was used.

Although the mechanism of asymmetric induction is not fully understood at present, some experimental observations that we have made helped to shed some light on the broad outline of this EP process (Scheme 1). First and foremost, it is worth noting that comparable protonation rates could be observed without any addition of $(DHQ)_2AQN$. This raises the question of how good levels of enantioselectivity can be reached with catalytic use of $(DHQ)_2AQN$, whereas no acceleration effect induced by this

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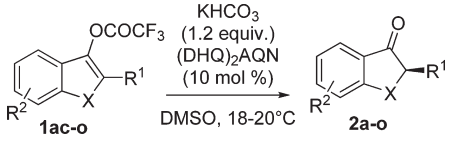
Table 3. Substrate Scope of the Reaction[a]



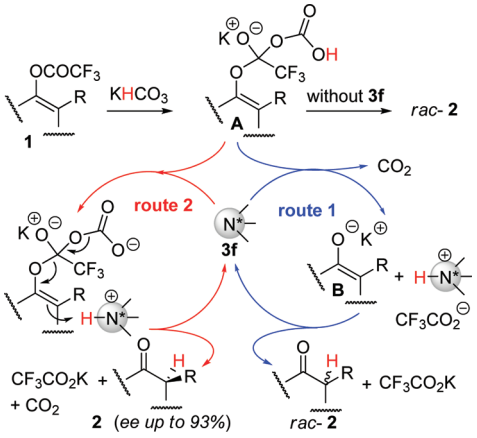
entry	X	R^2	R^1	1	yield[b] (%)	ee[c] (%)
1	$(CH_2)_2$	H	Me	**1ac**	85	86 (*S*)
2		H	Et	**1b**	95	81 (*S*)
3		H	Bn	**1c**	99	86 (*R*)
4		H	F	**1d**	80	85 (*S*)
5		5-OMe	Me	**1e**	99	89 (nd)
6		5-OMe	Bn	**1f**	98	93 (nd)
7		5-OMe	*o*-tol	**1g**	88	83 (nd)
8		6-OMe	Me	**1h**	78	72 (nd)
9		6-OMe	Bn	**1i**	89	82 (nd)
10		6-OMe	allyl	**1j**	95	76 (nd)
11		7-OMe	Bn	**1k**	83	55 (nd)
12	OCH_2	H	Me	**1l**	83	73 (nd)
13		H	Bn	**1m**	75	80 (nd)
14	CH_2	H	Me	**1n**	84	69 (*S*)
15		H	Et	**1o**	91	73 (*S*)

[a] Reactions carried out with 1.0 equiv of enol esters **1** (0.5 mmol), 1.2 equiv of $KHCO_3$, and 0.1 equiv of $(DHQ)_2AQN$ in DMSO (1 mL) at 18−20 °C. [b] Isolated yields. [c] Determined by chiral HPLC analysis. The absolute configuration was assigned from literature data.

chiral Brønsted base has been highlighted. This is likely made possible thanks to the poor solubility of hydrogenocarbonates in most organic solvents, allowing the process to take place under heterogeneous liquid−solid reaction conditions.[33] One can assume that the first step involves the reaction between $KHCO_3$ and the enol trifluoroacetate **1** to afford the tetrahedral intermediate **A**. This is supported by the fact that any interaction between either $(DHQ)_2AQN$ and $KHCO_3$ or $(DHQ)_2AQN$ and enol trifluoroacetate **1a** could be detected from ^1H NMR experiments conducted in DMSO-d_6, suggesting that $(DHQ)_2AQN$ is presumably not involved at an early stage of the reaction pathway. On the other hand, a control experiment revealed that the protonation of a preformed potassium enolate, **B**, prepared from enol acetate **1aa** in DMSO, with a full equivalent of ammonium trifluoroacetate salt **3f**·CF_3COOH or **3f**·$2CF_3COOH$ afforded **2a** as a racemic mixture in both cases.[34] This result seems to rule out any mechanism involving late protonation of the free enolate **B** by the mono- or diprotonated $(DHQ)_2AQN$ salts (Scheme 1, route 1). In light of these initial data, we currently favor an alternative mechanism wherein the putative tetrahedral intermediate **A** would protonate $(DHQ)_2AQN$ while triggering a concerted decarboxylation−protonation sequence to give the enantioenriched ketone **2** together with the regeneration of the chiral inducer **3f** (Scheme 1, route 2).

In conclusion, we have developed an efficient catalytic EP process of a new class of latent enolates, i.e., enol trifluoroacetates. Good to high enantioselectivities and excellent yields were obtained under mild and straightforward reaction conditions from a large range of cyclic enol trifluoroacetates. This work represents a significant contribution in this field by expanding the panel of valuable latent enolates successfully subjected to a catalytic EP process. Further studies to gain insight into the mechanism of this enantioselective process and to explain the exceptional performances of $(DHQ)_2AQN$ are under way in our laboratory.

Scheme 1. Plausible Reaction Pathway for the EP of Enol Trifluoroacetates 1 with $KHCO_3$ in the Presence of $(DHQ)_2AQN$ (3f)



EXPERIMENTAL SECTION

General Experimental Information. CH_2Cl_2, CH_3CN, DMF, DMSO, and toluene were distilled from CaH_2. THF and Et_2O were distilled from Na/benzophenone. All reagents were used as received from commercial sources unless otherwise indicated. The following compounds were prepared according to published procedures: **1aa**,[35] **1ab**,[36] **1ac**,[29] **2a,b,c,e,f,n,o**,[14] **2d,m**,[15] and **2h,i,j,k**.[17] All these compounds gave satisfactory ^1H and ^{13}C NMR analyses. The potassium enolate of 2-methyl-1-tetralone (**2a**) was prepared from 1-acetoxy-2-methyltetral-1-ene (**1aa**) according to the literature procedure.[34] The NMR spectra were recorded at 300 MHz (^1H), 75 MHz (^{13}C), and 282 MHz (^{19}F) using $CDCl_3$ as the solvent and the residual solvent (δ 7.26, ^1H; δ 77.16, ^{13}C) as the internal standard unless otherwise indicated. Melting points are uncorrected, and analytical thin layer chromatography (TLC) was performed on a precoated silica on aluminum and visualized by UV fluorescence quenching, vanillin, $KMnO_4$, or PMA staining. Flash chromatography was performed with silica gel (70−230 μm) unless otherwise indicated. HPLC analyses were performed on chiral columns (4.6 mm × 25 cm) with heptane/2-propanol solvent mixtures and visualization at 254 nm (UV detector) unless otherwise stated. Gas chromatography was performed on a 30 m × 0.25 mm × 25 μm column. All experiments were conducted under a nitrogen atmosphere in oven-dried glassware with magnetic stirring using standard Schlenk techniques.

Enol Acetate ***1aa***. **2a** (5 mmol, 750 μL) and acetic anhydride (50 mmol, 4.2 mL) were dissolved in CCl_4 (3.3 mL) at 0 °C. Some drops of concentrated $HClO_4$ were added, and the stirred mixture was allowed to warm to rt. After 1.5 h, the mixture was diluted in precooled saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water and dried over $MgSO_4$ and the solvents removed in vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/AcOEt, 95/5) to afford **1aa** as a colorless solid (0.780 g, 77%). Mp: 50−51 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.84 (s, 3H), 2.37 (s, 3H), 2.46 (t, 2H, J = 8.0 Hz), 2.93 (t, 2H, J = 8.1 Hz), 7.09−7.11 (m, 1H), 7.12−7.21 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.7, 20.3, 27.3, 28.7, 120.0, 123.9, 126.2, 126.8, 127.2, 130.9, 135.1, 140.0, 168.6. IR (KBr, cm^{-1}): 779, 1206, 1748, 1673, 2937.

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Enol Trichloroacetetate ***1ab***. **2a** (5 mmol, 750 μL) in trichloroacetic anhydride (27 mmol, 5 mL) was treated with *p*-toluenesulfonic acid (2.9 mmol, 0.5 g). The reaction mixture was heated for 6 h at 130−135 °C until no **2a** remained (TLC control). The reaction mixture was cooled to room temperature and poured into a saturated cold $NaHCO_3$ solution (10 mL). The reaction mixture was stirred until the evolution of CO_2 release, extracted with Et_2O (3 × 15 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O, 96/4) to afford **1ab** (1.2 g, 80%) as a glassy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 3H), 2.47 (t, 2H, *J* = 7.8 Hz), 2.9 (t, 2H, *J* = 7.8 Hz), 7.18 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 27.4, 29.1, 99.9, 119.8, 125.5, 126.7, 127.6, 127.7, 129.8, 135.3, 140.5, 159.9. IR (KBr, cm^{-1}): 634, 672, 725, 756, 794, 1063, 1126, 1156, 1604, 1675, 1906, 1942, 2835, 2893, 2927, 3025, 3074. HRMS (EI, *m*/*z*): calcd for $C_{13}H_{11}Cl_3O_2$, 303.9825; found, 303.9820.

General Procedures for Synthesis of Enol Trifluoroacetates 1ac−o. *Procedure I*. A solution of racemic ketones **2a**−**m** (5 mmol) in dichloromethane (7.5 mL) was added at 0 °C and under an inert atmosphere to a solution of 2,6-di-*tert*-butyl-4-methylpyridine (5 mmol) and trifluoroacetyl triflate (10 mmol) in dichloromethane (7.5 mL). After being stirred for 16 h at the same temperature, the mixture was concentrated in vacuum and the residue was diluted with Et_2O. The resulting precipitate was filtered, and the filtrate was washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum to afford enol trifluoroacetates **1ac**−**m**, which could be used in enantioselective protonation reaction without further purification.

Procedure II. A solution of racemic ketones **2n**,**o** (1.5 mmol) and trifluororacetic anhydride (40 mmol, 6 mL) was refluxed until complete consumption of the starting material (monitored by GC). The volatile compounds were removed under vacuum to afford enol trifluoroacetates **1n**,**o**, which could be used in enantioselective protonation reaction without further purification.

*2-Methyl-1-(trifluoroacetoxy)tetral-1-ene (**1ac**)*. This compound was prepared according to procedure I from **2a** (801 mg, 5 mmol) as a dark red oil (1.18 g, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.81 (s, 3H), 2.46 (t, 2H, *J* = 7.8 Hz), 2.90 (t, 2H, *J* = 7.8 Hz), 6.98−7.14 (m, 1H), 7.13−7.26 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.7, 27.3, 29.0, 114.9 (q, *J* = 284 Hz), 119.7, 125.5, 126.8, 127.7, 127.8, 129.3, 135.3, 139.5, 155.4 (q, *J* = 42 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.50. IR (KBr, cm^{-1}): 748, 765, 1136, 1170, 1225, 1276, 1681, 1799, 2936. HRMS (EI, *m*/*z*): calcd for $C_{13}H_{11}F_3O_2$, 256.0711; found, 256.0714.

*2-Ethyl-1-(trifluoroacetoxy)tetral-1-ene (**1b**)*. This compound was prepared according to procedure I from **2b** (871 mg, 5 mmol) as an orange oil (1.26 g, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (t, 3H, *J* = 7.5 Hz), 2.18 (q, 2H, *J* = 7.5 Hz), 2.46 (t, 2H, *J* = 7.8 Hz), 2.90 (t, 2H, *J* = 7.8 Hz), 6.98−6.99 (m, 1H), 7.15−7.21 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9, 23.9, 26.59, 27.8, 115.2 (q, *J* = 284 Hz), 120.1, 127.0, 127.9, 128.1, 129.6, 131.2, 135.7, 139.0, 156.0 (q, *J* = 43 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.49. IR (KBr, cm^{-1}): 748, 1135, 1168, 1225, 1668, 1799, 2881, 2940, 2974. HRMS (EI, *m*/*z*): calcd for $C_{14}H_{13}F_3O_2$, 270.0868; found, 270.0872.

*2-Benzyl-1-(trifluoroacetoxy)tetral-1-ene (**1c**)*. This compound was prepared according to procedure I from **2c** (1.18 g, 5 mmol) as an orange oil (1.58 g, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (t, 2H, *J* = 8.1 Hz), 2.86 (t, 2H, *J* = 8.1 Hz), 3.51 (s, 2H), 7.03−7.06 (m, 1H), 7.13−7.34 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 27.5, 36.5, 111.2 (q, *J* = 284 Hz), 120.2, 126.8, 126.9, 127.8, 128.2, 128.2, 128.8 (2C), 129.0 (2C), 129.1, 135.7, 137.8, 140.2, 155.9 (q, *J* = 43 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.34. IR (KBr, cm^{-1}): 702, 748, 766, 1133, 1170, 1226, 1668, 1799, 2935, 3028, 3064. HRMS (EI, *m*/*z*): calcd for $C_{19}H_{15}F_3O_2$, 332.1024; found, 332.1023.

*2-Fluoro-1-(trifluoroacetoxy)tetral-1-ene (**1d**)*. This compound was prepared according to procedure I from **2d** (821 mg, 5 mmol) as a brown oil (1.08 g, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.73−2.80 (m, 2H), 3.09 (td, 2H, *J* = 8.1 Hz, *J* = 2.4 Hz), 7.05−7.08 (m, 1H), 7.14−7.23 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.3 (d, *J* = 3.4 Hz), 27.6 (d, *J* = 6.8), 114.8 (q, *J* = 284 Hz), 120.3 (d, *J* = 6.8 Hz), 126.3 (d, *J* = 12.8 Hz), 127.2, 127.9, 128.1 (d, *J* = 2.3 Hz), 128.3, 132.4, 151.6 (d, *J* = 273 Hz), 155.6 (q, *J* = 44 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.26, −115.3. IR (KBr, cm^{-1}): 750, 1169, 1229, 1707, 1806, 2952, 3074. HRMS (EI, *m*/*z*): calcd for $C_{12}H_8F_4O_2$, 260.0460; found, 260.0479.

*5-Methoxy-2-methyl-1-(trifluoroacetoxy)tetral-1-ene (**1e**)*. This compound was prepared according to procedure I from **2e** (951 mg, 5 mmol) as a red oil (1.16 g, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (s, 3H), 2.44 (t, 2H, *J* = 8.4 Hz), 2.90 (t, 2H, *J* = 8.4 Hz), 3.84 (s, 3H), 6.66 (d, 1H, *J* = 7.8 Hz), 6.81 (d, 1H, *J* = 8.4 Hz), 7.13−7.19 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 19.7, 28.5, 55.6, 110.4, 112.5, 114.9 (q, *J* = 284 Hz), 123.1, 125.6, 127.2, 130.4, 139.4, 155.5 (q, *J* = 42 Hz), 156.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.52. IR (KBr, cm^{-1}): 740, 1054, 1140, 1175, 1225, 1265, 1682, 1798, 2921, 3048. HRMS (CI^+, *m*/*z*): calcd for $C_{14}H_{14}F_3O_2$ $[M + H]^+$, 287.0895; found, 287.0911.

*2-Benzyl-5-methoxy-1-(trifluoroacetoxy)tetral-1-ene (**1f**)*. This compound was prepared according to procedure I from **2f** (1.33 g, 5 mmol) as a red oil (1.79 g, 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (t, 2H, *J* = 8.4 Hz), 2.82 (t, 2H, *J* = 8.4 Hz), 3.48 (s, 2H), 3.78 (s, 3H), 6.69 (d, 1H, *J* = 7.8 Hz), 7.01 (d, 1H, *J* = 8.4 Hz), 7.13−7.31 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8, 26.2, 36.5, 55.6, 110.8, 113.0, 114.9 (q, *J* = 284 Hz), 123.6, 126.8, 127.3, 128.1, 128.8 (2C), 129.0 (2C), 130.2, 137.8, 140.1, 155.9 (q, *J* = 43 Hz), 156.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.33. IR (KBr, cm^{-1}): 700, 718, 744, 770, 788, 1046, 1115, 1136, 1169, 1225, 1263, 1582, 1601, 1681, 1798, 2838, 2935, 3028. HRMS (CI^+, *m*/*z*): calcd for $C_{20}H_{18}F_3O_3$ $[M + H]^+$, 363.1208; found, 363.1205.

*5-Methoxy-2-(2-methylbenzyl)-1-(trifluoroacetoxy)tetral-1-ene (**1g**)*. This compound was prepared according to procedure I from **2g** (1.40 g, 5 mmol) as a glassy solid (1.77 g, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (t, 2H, *J* = 8.1 Hz), 2.31 (s, 3H), 2.85 (t, 2H, *J* = 8.4 Hz), 3.52 (s, 2H), 3.84 (s, 3H), 6.72 (d, 1H, *J* = 7.8 Hz), 6.84 (d, 1H, *J* = 8.1 Hz), 7.15−7.23 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.6, 19.8, 26.0, 34.0, 55.6, 110.8, 112.9, 115.1 (q, *J* = 284 Hz), 123.5, 126.2, 126.9, 127.2, 127.5, 129.6, 130.2, 130.4, 135.7, 136.9, 140.0, 155.9 (q, *J* = 42 Hz), 156,5. ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.37. IR (KBr, cm^{-1}): 723, 743, 760, 781, 1041, 1141, 1170, 1224, 1579, 1682, 1796, 2840, 2895, 2934, 3011, 3079. HRMS (CI^+, *m*/*z*): calcd for $C_{21}H_{20}F_3O_3$ $[M + H]^+$, 377.1364; found, 377.1354.

*6-Methoxy-2-methyl-1-(trifluoroacetoxy)tetral-1-ene (**1h**)*. This compound was prepared according to procedure I from **2h** (951 mg, 5 mmol) as a glassy solid (1.39 g, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.79 (s, 3H), 2.43 (t, 2H, *J* = 8.4 Hz), 2.87 (t, 2H, *J* = 8.1 Hz), 3.79 (s, 3H), 6.70−6.73 (m, 2H), 6.92−6.95 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4, 27.3, 28.9, 55.3, 111.1, 114.1, 114.9 (q, *J* = 284 Hz), 120.9, 122.3, 122.4, 137.2, 139.3, 155.4 (q, *J* = 43 Hz), 159.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.53. IR (KBr, cm^{-1}): 770, 1037, 1137, 1226, 1256, 1606, 1681, 1798, 2935. HRMS (CI^+, *m*/*z*): calcd for $C_{14}H_{14}F_3O_3$ $[M + H]^+$, 287.0895; found, 287.0897.

*2-Benzyl-6-methoxy-1-(trifluoroacetoxy)tetral-1-ene (**1i**)*. This compound was prepared according to procedure I from **2i** (1.33 g, 5 mmol) as a brown oil (1.76 g, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (t, 2H, *J* = 8.1 Hz), 2.86 (t, 2H, *J* = 8.1 Hz), 3.54 (s, 2H), 3.84 (s, 3H), 6.79 (d, 2H, *J* = 7.8 Hz), 7.034 (d, 1H, *J* = 8.1 Hz), 7.28−7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.5, 28.0, 36.3, 55.3, 111.3, 114.2, 114.9 (q, *J* = 284 Hz), 121.5, 122.0, 125.1, 126.7, 128.7 (2C), 128.9 (2C), 137.6, 138.0, 140.0, 156.9 (q, *J* = 43 Hz), 159.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.32. IR (KBr, cm^{-1}): 705, 752, 1141, 1177, 1220, 1255, 1602, 1673, 1794, 2838, 2940, 3028, 3066. HRMS (CI^+, *m*/*z*): calcd for $C_{20}H_{18}F_3O_3$ $[M + H]^+$, 363.1208; found, 363.1210.

*2-Allyl-6-methoxy-1-(trifluoroacetoxy)tetral-1-ene (**1j**)*. This compound was prepared according to procedure I from **2j** (1.08 g, 5 mmol) as a brown oil (1.48 g, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (t, 2H, *J* = 8.1 Hz), 2.88 (t, 4H, *J* = 8.4 Hz), 3.82 (s, 3H), 5.10−5.20

(m, 2H), 5.71−5.89 (m, 1H), 6.72−6.75 (m, 2H), 6.94−6.96 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.7, 28.0, 34.9, 55.4, 111.3, 113.0, 114.9 (q, J = 284 Hz), 117.2, 121.4, 122.3, 124.1, 133.7, 137.6, 149.9, 155.7 (q, J = 42 Hz), 155.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.51. IR (KBr, cm^{-1}): 768, 1134, 1168, 1126, 1255, 1602, 1638, 1674, 1799, 2838, 2937, 3079. HRMS (CI^-, m/z): calcd for $C_{16}H_{15}F_3O_3$, 312.0973; found, 312.0952.

*2-Benzyl-7-methoxy-1-(trifluoroacetoxy)tetral-1-ene (**1k**).* This compound was prepared according to procedure I from **2k** (1.33 g, 5 mmol) as a brown oil (1.58 g, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (t, 2H, J = 8.1 Hz), 2.78 (t, 4H, J = 8.1 Hz), 3.52 (s, 2H), 3.80 (s, 3H), 6.63 (d, 1H, J = 2.7 Hz), 6.74−6.77 (m, 1H), 7.05−7.20 (m, 1H), 7.20−7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.7, 27.1, 36.6, 55.4, 106.7, 113.0, 115.1 (q, J = 287 Hz), 126.8, 127.8, 128.6, 128.8, 128.9 (2C), 129.0 (2C), 130.2, 137.8, 140.0, 155.8 (q, J = 42 Hz), 158.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.36. IR (KBr, cm^{-1}): 702, 755, 1038, 1135, 1171, 1223, 1609, 1790, 1681, 2936. HRMS (CI^+, m/z): calcd for $C_{20}H_{18}F_3O_3$ $[M + H]^+$, 363.1208; found, 363.1221.

*3-Methyl-4-(trifluoroacetoxy)-(2H)-chromene (**1l**).* This compound was prepared according to procedure I from **2l** (811 mg, 5 mmol) as an orange oil (1.02 g, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (s, 3H), 4.86 (s, 2H), 6.82−6.84 (m, 1H), 6.90−6.91 (m, 2H), 7.12−7.20 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6, 69.4, 114.8 (q, J = 284 Hz), 116.1, 117.8, 119.0, 120.2, 121.6, 130.0, 136.6, 154.0, 155.0 (q, J = 43 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.37. IR (KBr, cm^{-1}): 759, 1037, 1148, 1609, 1636, 2925, 3383. HRMS (EI, m/z): calcd for $C_{12}H_9F_3O_3$, 258.0504; found, 258.0489.

*3-Benzyl-4-(trifluoroacetoxy)-(2H)-chromene (**1m**).* This compound was prepared according to procedure I from **2m** (1.19 g, 5 mmol) as a yellow oil (1.54 g, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.44, (s, 2H), 4.74 (s, 2H), 6.81−6.84 (m, 1H), 6.92−6.96 (m, 2H), 7.15−7.34 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.5, 67.9, 114.7 (q, J = 284 Hz), 116.3, 117.8, 120.7, 121.4, 121.8, 127.3, 128.8 (2C), 129.1 (2C), 130.4, 135.9, 137.4, 154.2, 155.4 (q, J = 44 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.20. IR (KBr, cm^{-1}): 700, 757, 1032, 1133, 1170, 1224, 1606, 1636, 1687, 1802, 2920, 3030, 3068. HRMS (CI^-, m/z): calcd for $C_{18}H_{13}F_3O_3$, 334.08178; found, 334.0810.

*2-Methyl-3-(trifluoroacetoxy)indan-1-ene (**1n**).* This compound was prepared according to procedure II from **2n** (219 mg, 1.5 mmol) as an orange oil (301 mg, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.03 (s, 3H), 3.40 (s, 2H), 7.09 (d, 1H, J = 7.2 Hz), 7.20−7.32 (m, 2H), 7.40 (d, 1H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.3, 39.4, 114.8 (q, J = 284 Hz), 117.0, 124.1, 125.5, 126.7, 130.0, 138.0, 139.9, 142.8, 155.0 (q, J = 43 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.31. IR (KBr, cm^{-1}): 714, 754, 1140, 1231, 1355, 1735, 1802, 2920. HRMS (CI^+, m/z): calcd for $C_{12}H_{10}F_3O_2$, $[M + H]^+$ 243.0633; found, 243.0630.

*2-Ethyl-3-(trifluoroacetoxy)indan-1-ene (**1o**).* This compound was prepared according to procedure II from **2o** (240 mg, 1.5 mmol) as a brown oil (327 mg, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, 3H, J = 7.5 Hz), 2.45 (q, 2H, J = 7.5 Hz), 3.42 (s, 2H), 7.11 (d, 1H, J = 7.2 Hz), 7.21−7.34 (m, 2H), 7.43 (d, 1H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.1, 20.1, 36.9, 114.8 (q, J = 284 Hz), 117.1, 124.3, 125.6, 126.8, 135.7, 138.0, 140.0, 141.9, 155.2 (q, J = 43 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.32. IR (KBr, cm^{-1}): 753, 1140, 1170, 1229, 1354, 1802, 2974. HRMS (CI^+, m/z): calcd for $C_{13}H_{12}F_3O_2$, $[M + H]^+$ 257.0789; found, 257.0793.

General Procedure for Catalytic Enantioselective Protonation of Enol Trifluoroacetates 1ac−o. Freshly distilled DMSO (1 mL) was added to $(DHQ)_2AQN$ (0.05 mmol, 43 mg) and dry potassium hydrogenocarbonate (0.6 mmol, 60 mg). After stabilization of the temperature to 18−20 °C and complete solubilization of $(DHQ)_2$-AQN, enol trifluoroacetates **1ac−o** (0.5 mmol) were added to the mixture. The reaction was stirred at 18−20 °C until complete disappearance of **1ac−o** (monitored by GC). The solution was diluted with AcOEt (10 mL), washed with brine (3 × 10 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (petroleum ether/AcOEt, 95/5, as eluent) to afford the pure ketones **2a−o**, which were analyzed by HPLC using a chiral column. A control experiment indicated that no racemization was observed when **2a** was stirred in DMSO for 1.5 h in the presence of potassium trifluoroacetate (1 equiv).

*2-Methyltetralone (**2a**).* Enantioenriched **2a** (68 mg, 85% yield) was prepared according to the general procedure from **1ac** (128 mg, 0.5 mmol) in 86% ee. HPLC: OD-H, heptane/2-propanol, 99.6/0.4, flow rate 0.5 mL/min, 20 °C, retention time of both enantiomers, 7.52 min (minor), 8.29 min (major, *S* enantiomer). The absolute configuration was assigned by comparison with literature data.[27]

*2-Ethyltetralone (**2b**).* Enantioenriched **2b** (83 mg, 95% yield) was prepared according to the general procedure from **1b** (135 mg, 0.5 mmol) in 81% ee. HPLC: AD-H, heptane/2-propanol, 99.96/0.04, flow rate 1.2 mL/min, 20 °C, retention time of both enantiomers, 14.41 min (major, *S* enantiomer), 16.54 min (minor). The absolute configuration was assigned by comparison with literature data.[11]

*2-Benzyltetralone (**2c**).* Enantioenriched **2c** (117 mg, 99% yield) was prepared according to the general procedure from **1c** (166 mg, 0.5 mmol) in 86% ee. HPLC: OJ-H, heptane/2-propanol, 90/10, flow rate 1 mL/min, 20 °C, retention time of both enantiomers, 9.48 min (major, *R* enantiomer), 11.65 min (minor). The absolute configuration was assigned by comparison with literature data.[37]

*2-Fluorotetralone (**2d**).* Enantioenriched **2d** (66 mg, 80% yield) was prepared according to the general procedure from **1d** (130 mg, 0.5 mmol) in 85% ee. HPLC: Daicel Chiralcel OJ-H, heptane/2-propanol, 95/5, flow rate 1 mL/min, 20 °C, retention time of both enantiomers, 13.65 min (major, *S* enantiomer), 15.04 min (minor). The absolute configuration was assigned by comparison with literature data.[15]

*5-Methoxy-2-methyltetralone (**2e**).* Enantioenriched **2e** (94 mg, 99% yield) was prepared according to the general procedure from **1e** (143 mg, 0.5 mmol) in 89% ee. HPLC: AD-H, heptane/2-propanol, 99.8/0.2, flow rate 1 mL/min, 20 °C, retention time of both enantiomers, 13.57 min (major), 17.66 min (minor).

*2-Benzyl-5-methoxytetralone (**2f**).* Enantioenriched **2f** (130 mg, 98% yield) was prepared according to the general procedure from **1f** (181 mg, 0.5 mmol) in 93% ee. HPLC: OB, heptane/2-propanol, 99/1, flow rate 1 mL/min, 20 °C, retention time of both enantiomers, 15.80 min (major), 28.34 min (minor).

*5-Methoxy-2-(2-methylbenzyl)tetralone (**2g**).* Enantioenriched **2g** (123 mg, 88% yield) was prepared according to the general procedure from **1g** (188 mg, 0.5 mmol) as a pale yellow solid in 83% ee. Mp: 69−70 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76−1.85 (m, 1H), 2.09−2.18 (m, 1H), 2.34 (s, 3H), 2.5−2.74 (m, 3H), 3.08 (dt, 1H, J = 18.0 Hz, J = 4.5 Hz), 3.58 (dd, 1H, J = 3.9 Hz, J = 14.1 Hz), 3.86 (s, 3H), 7.02 (d, J = 8.1 Hz), 7.15 (s, 4H), 7.29 (t, 1H, J = 8.1 Hz), 6.9 (d, 1H, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9, 22.5, 27.4, 33.2, 48.0, 56.0, 114.4, 119.4, 125.1, 126.6, 127.2, 130.4, 130.8, 133.3, 133.9, 135.8, 138.67, 157.1, 200.2. IR (KBr, cm^{-1}): 750, 764, 795, 1195, 1224, 1260, 1539, 1599, 2833, 2851, 2915, 2950, 3004, 3064. HRMS (CI^+, m/z): calcd for $C_{19}H_{21}O_2$ $(M + H)^+$, 281.1541; found, 281.1547. HPLC: OD-H, heptane/2-propanol, 99/1, flow rate 0.8 mL/min, 20 °C, retention time of both enantiomers, 14.11 min (minor), 14.99 min (major).

*6-Methoxy-2-methyltetralone (**2h**).* Enantioenriched **2h** (74 mg, 78% yield) was prepared according to the general procedure from **1h** (143 mg, 0.5 mmol) in 72% ee. HPLC: OB, heptane/2-propanol, 99.8/0.2, flow rate 0.8 mL/min, 20 °C, retention time of both enantiomers, 41.99 min (major), 55.19 min (minor).

*2-Benzyl-6-methoxytetralone (**2i**).* Enantioenriched **2i** (119 mg, 89% yield) was prepared according to the general procedure from **1i** (181 mg, 0.5 mmol) in 82% ee. HPLC: OJ-H, heptane/2-propanol, 90/10, flow rate 1 mL/min, 20 °C, retention time of both enantiomers, 14.95 min (major), 19.22 min (minor).

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*2-Allyl-6-methoxytetralone (**2j**).* Enantioenriched **2j** (103 mg, 95% yield) was prepared according to the general procedure from **1j** (156 mg, 0.5 mmol) in 76% ee. HPLC: AD-H, heptane/2-propanol, 99.8/0.2, flow rate 1 mL/min, 20 °C, retention time of both enantiomers, 42.68 min (major), 54.56 min (minor).

*2-Benzyl-7-methoxytetralone (**2k**).* Enantioenriched **2k** (132 mg, 99% yield) was prepared according to the general procedure from **1k** (181 mg, 0.5 mmol) in 55% ee. HPLC: OJ-H, heptane/2-propanol, 90/10, flow rate 1 mL/min, 20 °C, retention time of both enantiomers, 14.21 min (major), 16.32 min (minor).

*2-Methylchromanone (**2l**).* Enantioenriched **2l** (67 mg, 83% yield) was prepared according to the general procedure from **1l** (123 mg, 0.5 mmol) as a pale yellow oil in 73% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, 2H, J = 7.2 Hz), 2.78−2.91 (m, 1H), 4.13 (t, 1H, J = 11.1), 4.46−4.51 (m, 1H), 6.92−7.02 (m, 2H), 7.41−7.47 (m, 1H), 7.89 (d, 1H, J = 1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.8, 40.8, 72.3, 117.8, 120.6, 121.4, 127.4, 135.8, 161.8, 194.9. IR (KBr, cm^{-1}): 756, 1297, 1694, 2876, 2973. HRMS (EI, m/z): calcd for $C_{10}H_{10}O_2$, 162.0681; found, 162.0681. HPLC: OJ-H, heptane/2-propanol, 99.6/0.4, flow rate 1 mL/min, 20 °C, retention time of both enantiomers, 14.90 min (minor), 16.72 min (major).

*2-Benzylchromanone (**2m**).* Enantioenriched **2m** (95 mg, 80% yield) was prepared according to the general procedure from **1m** (167 mg, 0.5 mmol) in 75% ee. HPLC: OD-H, heptane/2-propanol, 99.2/0.8, flow rate 1 mL/min, 20 °C, retention time of both enantiomers, 18.38 min (minor), 20.48 min (major).

*2-Methylindanone (**2n**).* Enantioenriched **2n** (61 mg, 84% yield) was prepared according to the general procedure from **1n** (121 mg, 0.5 mmol) in 69% ee. HPLC: OJ-H, heptane/2-propanol, 99.6/0.4, flow rate 1 mL/min, 20 °C, retention time of both enantiomers, 15.58 min (major, *S* enantiomer), 18.62 min (minor). The absolute configuration was assigned by comparison with literature data.[27]

*2-Ethylindanone (**2o**).* Enantioenriched **2o** (73 mg, 91% yield) was prepared according to the general procedure from **1o** (128 mg, 0.5 mmol) in 73% ee. HPLC: OJ-H, heptane/2-propanol, 99.6/0.4, flow rate 1 mL/min, 20 °C, retention time of enantiomers, 10.51 min (major, *S* enantiomer), 12.80 min (minor). The absolute configuration was determined by analogy with that of **2n**.

Protonation of the Potassium Enolate of 2-Methyltetralone by $(DHQ)_2AQN\cdot CF_3COOH$ or $(DHQ)_2AQN\cdot 2CF_3COOH$. A solution of $(DHQ)_2AQN\cdot CF_3COOH$ or $(DHQ)_2AQN\cdot 2CF_3COOH$ was previously prepared by addition of 0.5 mmol of CF_3COOH (37 μL) or 1 mmol of CF_3COOH (74 μL), respectively, to a solution of $(DHQ)_2AQN$ (0.5 mmol, 429 mg) in DMSO (1.2 mL) under an inert atmosphere and was stirred for 3 h.

A solution of **1aa** (0.5 mmol, 100 mg) in DMSO at room temperature (0.6 mL) was added to a mixture of *t*-BuOK (56 mg, 0.5 mmol) in DMSO (0.2 mL). After 30 min (red solution) and control of the disappearance of the starting material (monitored by GC), the solution of $(DHQ)_2AQN\cdot CF_3COOH$ or $(DHQ)_2AQN\cdot 2CF_3COOH$ (0.5 mmol) in DMSO at room temperature (1.2 mL) was added to the previous stirred solution. After 1 h, the solution was diluted with AcOEt (20 mL) and washed with water (20 mL), and the aqueous layer was extracted with AcOEt (2 × 20 mL). The combined organic layers were washed with brine (3 × 50 mL) and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by flash chromatography (petroleum ether/AcOEt, 95/5), affording the pure 2-methyltetralone (63 mg, 79%) as a racemic mixture according to chiral HPLC analysis.

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra for all new compounds and control experiments and HPLC chromatograms for enantioenriched ketones **2a**−**o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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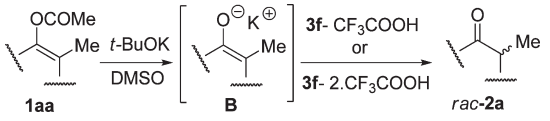

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