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Enantioselective α-Benzoyloxylation of Ketones Promoted by Primary Amine Catalyst

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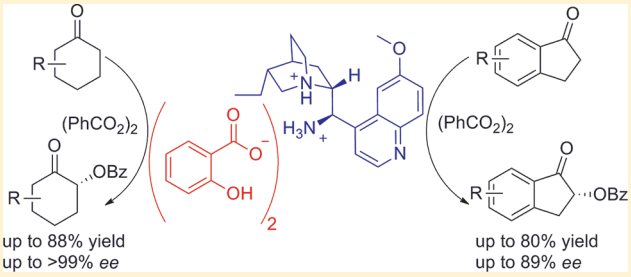
Supporting Information

ABSTRACT: A mixture of 9-amino-(9-deoxy)*epi*-dihydroquinidine and salicylic acid was able to promote the direct reaction of various cyclohexanones with dibenzoyl peroxide, thus affording the corresponding protected α-hydroxy carbonyl compounds in high yield and enantioselectivity. Interestingly the same catalytic salt was found to be active when 1-indanones derivatives were directly employed in the reaction with dibenzoyl peroxide furnishing chiral 1-oxo-2,3-dihydro-1*H*-inden-2-yl benzoates in high yields and enantioselectivity. Furthermore their treatment with $NaBH_4$ gives easy access to the corresponding enantioenriched 1,2-diols in high yields and without any loss of stereoselectivity.



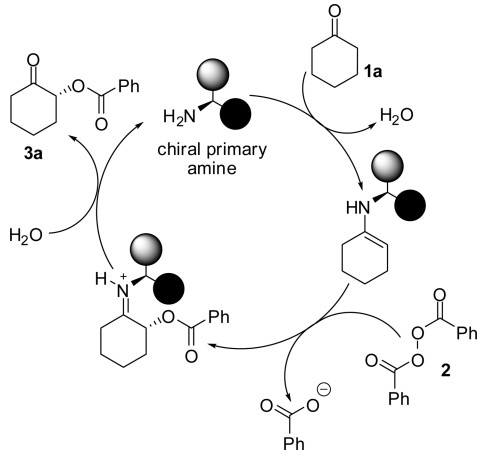
INTRODUCTION

The development of catalytic methods that furnish enantioenriched α-functionalized ketones starting from the commercially available precursors, thus avoiding the preparation of reactive metal enolates, are highly required.[1] In this field the construction of enantiomerically active α-hydroxy or protected α-hydroxy carbonyl compounds represents an important goal for asymmetric organocatalysis principally because of the important role that this class of substrates play as natural products or fundamental building blocks for the construction of more elaborated structures.[2]

During the past years chiral primary amines derived from commercially available cinchona alkaloids[3] were revealed to be among the most powerful catalysts able to promote the functionalization of sterically demanding carbonyl compounds such as ketones and branched aldehydes via iminium ion,[4] enamine,[5] and dienamine[6] activation modes. Because of the great ability to impart a unique reaction pathway and elevated enantioselectivity,[7] we believed that this class of catalysts could efficiently promote the reaction between diverse cyclic saturated ketones and dibenzoyl peroxide in order to furnish enantioenriched α-benzoyloxylated carbonyl compounds. Our idea is to exploit the capability of primary amine to condense with the cyclic ketone and furnish a sufficiently stable and reactive enamine with the required nucleophilicity[8] to react with the electrophilic dibenzoyl peroxide (Scheme 1).

In this report we would like to present our results for the reaction of α-benzoyloxylation of cyclic ketones under enamine catalysis using 9-amino(9-deoxy)*epi*-hydroquinidine as catalyst and dibenzoyl peroxide as oxidizing agent.[9]

Scheme 1. Proposed Catalytic Cycle for the α-Benzoyloxylation of Cyclohexanone



RESULTS AND DISCUSSION

Our screening started by comparing the reactivity of different primary amine-based organocatalysts (Figure 1) for the reaction of cyclohexanone and dibenzoyl peroxyde.

As outlined in Table 1, among the various chiral primary amines tested, those based on the scaffold of cinchona alkaloid, in combination with salicylic acid as co-catalyst were revealed to be the most active for the enantioselective α-functionalization of cyclohexanone albeit with low amount of isolated product (Table 1, entry 1−5). We screened other acids, but no

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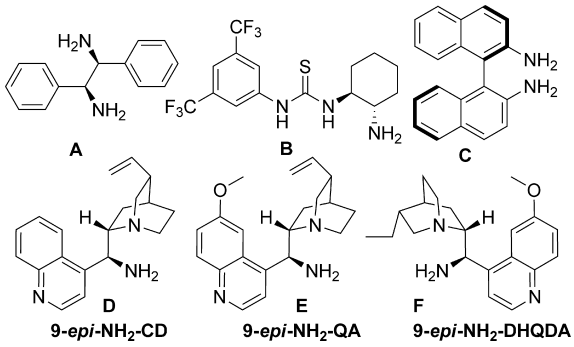


Figure 1. Primary amine tested for the α-functionalization of cyclic ketone.

improvements, especially of yields, were observed (Table 1, entry 6–13).

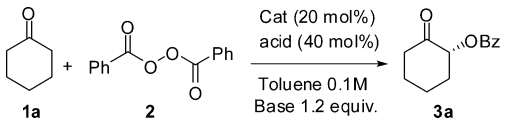
Interestingly salicylic acid was revealed to be the best choice probably because of a fruitful hydrogen bond interaction between the hydroxyl group of the acid and the carbonyl groups of the benzoyl peroxide. We then decided to study the effect of an inorganic base[5a] that might increase the reaction rate and maintain the good level of enantioselectivity by quenching the benzoic acid generated during the course of the reaction (Scheme 1). The addition of 1.2 equiv of solid Na_2CO_3 had a negative effect on the yield of the process when catalyst **D** and salicylic acid were used (Table 1, entry 14) but gave a better yield after 24 h of reaction time and furnished high enantiocontrol when catalyst **F** was used (Table 1, entry 15). Indeed as outlined in Table 2 the use of weaker or stronger inorganic bases did not furnish significant improvements if compared to those obtained using Na_2CO_3.

The effects of different solvents were then considered. Interestingly, as shown in Table 3 (entries 1 and 2), the reaction can be performed in water as well as in absence of solvent with relevant results. However, under these conditions, the presence of various undefined byproducts was observed in the crude mixture of the reaction. Also the use of more polar solvents such as methanol (MeOH), ethyl acetate (EtOAc), and tetrahydrofuran (THF) did not furnish satisfying results so that toluene was revealed to be the best compromise in term of yield and enantioselectivity (Table 3, entries 3–6).

We next carried out the reaction with different molar amounts of ketone and at different concentrations of benzoyl peroxide because as already observed in Table 1, an excess of cyclohexanone could increase the yield of the reaction (entry 13). For this reason we believed that a further study on the effect of the different ratio between ketone and peroxide was necessary once the screening of solvents and bases was completed. We found that a good compromise between yield (80%) and enantioselectivity (96.5% ee) could be achieved in a 0.4 M solution of toluene at 0 °C (Table 4, entry 5). The α-benzoyloxylation was performed using a 10 mol % of catalyst loading thus highlighting the efficiency of the process.

With the optimized condition in hand we explored the scope of the benzoyloxylation of cyclic ketones with different substituents and heteroatoms (Table 5). As outlined in Table 5 the reaction furnished the desired 2-oxocyclohexyl benzoates **3a–i** in high yields and excellent enantioselectivities. In any case the presence of the ketone functionalized at both α-positions has never been observed. Interestingly when 9-amino(9-deoxy)*epi*-hydroquinine (*ent*-**F**), the pseudoenantiomer of catalyst **F**, was employed, the opposite enantiomers of the α-functionalized ketones were obtained with good level of yields and enantioselectivities for almost all entries (Table 5, entries 3, 5, 8, and 10). The absolute configuration of compounds **3a** was assigned to be *R* by comparison with the previously reported literature data,[10] and by analogy it was assigned to be the same for compounds **3b–i**.[11] When racemic ketone **1b** was used, the reaction resulted to be highly enantioselective and regioselective; however, poor diastereoselectivity was observed for the corresponding product **3b** (Table

Table 1. Catalyst and Acid Screening for the α-Benzoyloxylation of Cyclohexanone[a]



entry	cat.	acid	base	yield (%)[c]	ee (%)[d]
1	A	2-OH-PhCOOH	none	none	nd
2	B	2-OH-PhCOOH	none	none	nd
3	C	2-OH-PhCOOH	none	<5	nd
4	D	2-OH-PhCOOH	none	35	86
5	E	2-OH-PhCOOH	none	17	84
6	D	TFA	none	none	nd
7	D	DCA	none	5	88
8	D	PTSA	none	<5	nd
9	D	PhCOOH	none	<5	nd
10	D	$(PhO)_2PO_2H$	none	none	nd
11	D	D-NBocPhGlyOH	none	20	90
12	D	2-F-PhCOOH	none	9	95
13[b]	D	2-F-PhCOOH	none	16	95
14	D	2-OH-PhCOOH	Na_2CO_3	15	95
15	F	2-OH-PhCOOH	Na_2CO_3	30	96

[a]Unless otherwise noted, the reactions were performed with 0.1 mmol of **1a** and 0.12 mmol of **2** at room temperature for 24 h. [b]Reaction performed using 0.2 mmol of **1a**. [c]Isolated yield. [d]Determined by HPLC analysis on a chiral stationary phase.

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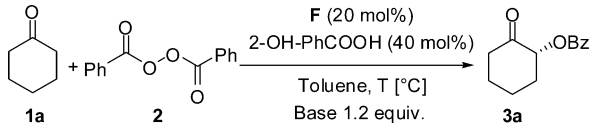
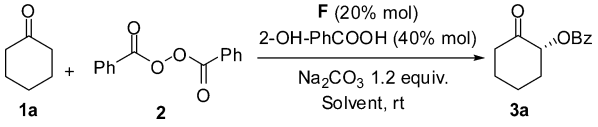
Table 2. Base Screening for the α-Benzoyloxylation of Cyclohexanone[a]



entry	cat.	acid	base	yield (%)[b]	ee (%)[d]
1	**F**	2-OH-PhCOOH	Na_2CO_3	30	96
2	**F**	2-OH-PhCOOH	$NaHCO_3$	35	93
3	**F**	2-OH-PhCOOH	K_2CO_3	48	90

[a]Unless otherwise noted, the reactions were performed with 0.1 mmol of **1a** and 0.12 mmol of **2** at room temperature for 24 h. [b]Isolated yield. [d]Determined by HPLC analysis on a chiral stationary phase.

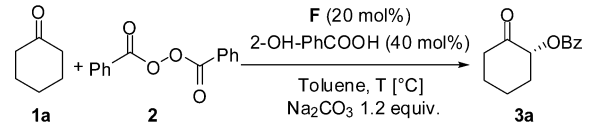
Table 3. Solvent Screening for the α-Benzoyloxylation of Cyclohexanone[a]



entry	solvent	yield (%)[b]	ee (%)[d]
1	H_2O	29	77
2	neat	65	90
3	MeOH	none	nd
4	AcOEt	<5	nd
5	THF	25	88
6	toluene	30	96

[a]Unless otherwise noted, the reactions were performed with 0.1 mmol of **1a** and 0.12 mmol of **2** at room temperature for 24 h. [b]Isolated yield. [d]Determined by HPLC analysis on a chiral stationary phase.

Table 4. Optimization Study for the α-Benzoyloxylation of Cyclohexanone[a]



entry	**1a**:**2**	*T* [°C]/time [h]	concn [M]	yield (%)[c]	ee (%)[d]
1	10:1	25/24	1	85	83
2	10:1	25/24	0.1	83	96
3	5:1	25/24	0.1	60	95.5
4	2:1	25/24	0.1	82	90
5[b]	2.5:1	0/80	0.4	80	96.5

[a]Unless otherwise noted, the reactions were performed on a 0.1 mmol scale at room temperature for 24 h. [b]Reaction performed using 10 mol % of catalyst **F** and 20 mol % of salicylic acid. [c]Isolated yields. [d]Determined by HPLC analysis on a chiral stationary phase.

5, entry 2). Using 4-phenylcyclohexanone **1c**, the desymmetrization pathway resulted to be efficient especially for the diastereoisomer *cis*-**3c**, which was obtained with ee of 99% (Table 5, entries 4 and 5). The same asymmetric desymmetrization pathway has been observed for the α-aminoxylation of 4-substituted ketone catalyzed by proline.[2f]

The presence of two methyl groups in the 4 position of the cyclohexanone was well tolerated in the reaction and furnished the corresponding α-benzoyloxylated carbocycle in high yield and excellent enantioselectivity (Table 5, entry 6). Heteroatoms such as oxygen and sulfur as part of the cyclic framework of the ketone could be employed maintaining the same level of enantioselection observed so far (Table 5, entries 7−10). However in the case of sulfur yields are not good using both catalyst **F** and its pseudoenantiomer *ent*-**F**. This negative result could be ascribed to parasitic reactions that totally consumed the peroxide and a large amount of the cyclic ketone. In this case the desired products **3f** and *ent*-**3f** were obtained as a part of a highly complex reaction mixture, where unidentified tars and plausible polymeric materials were the main products. The good results observed in term of yields and enantioselectivity using cycloheptanone **1g** and cyclooctanone **1h** extend the applicability of our methodology to medium ring-sized ketones, which generally are challenging substrates for enamine-activation catalysis (Table 5, entries 11 and 12).[9] Also in the presence of a carbamate as substituent the reaction can be performed with good efficiency and stereoselection (Table 5, entry 13). In this last case the low value recorded of both enantioselectivity and yields were probably due to the presence of Boc moiety that could obstruct the catalyst salt during the enamine formation thus reducing the reaction rate and at the same time the stereocontrol.

In order to expand the scope of the α-benzoyloxylation reaction, we tried to focus our attention on 1-indanones as plausible precursors of new protected α-oxygenated compounds. Although, to the best of our knowledge 1-indanones

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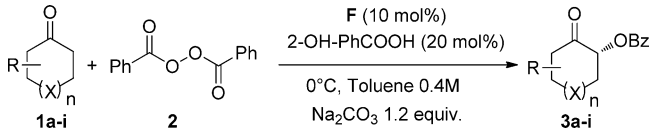
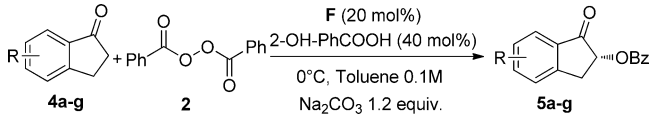
Table 5. Direct α-Benzoyloxylation of Various Cyclic Ketones[a]



		cyclic ketones **1**		oxocyclic benzoates **3**				
entry	X/*n*	compound	R	product	R	yield (%)[b]	d.r[c]	ee (%)[d] *cis/trans*
1	CH_2/1	**1a**	H	**3a**	H	80		96.5
2	CH_2/1	**1b**	3-Me	**3b**	4-Me	88	1:1	>99/96.5
3[e]	CH_2/1	**1b**	3-Me	*ent*-**3b**	4-Me	87	1:1	>99/82
4	CH_2/1	**1c**	4-Ph	**3c**	5-Ph	70	1:1	>99/37
5[e]	CH_2/1	**1c**	4-Ph	*ent*-**3c**	5-Ph	65	1:1	>99/60
6	C/1	**1d**	4,4-Me	**3d**	5,5-Me	80	none	96.4
7	O/1	**1e**	H	**3e**	H	71	none	91
8[e]	O/1	**1e**	H	*ent*-**3e**	H	70	none	90
9	S/1	**1f**	H	**3f**	H	22	none	94.5
10[e]	S/1	**1f**	H	*ent*-**3f**	H	21	none	90
11	CH_2/2	**1g**	H	**3g**	H	60	none	>99
12	CH_2/3	**1h**	H	**3h**	H	96	none	93
13	N/1	**1i**	4-Boc	**3i**	5-Boc	49	none	80

[a]Unless otherwise noted, the reactions were performed for 80 h at 0 °C using 0.2 mmol of **2** and 0.5 mmol of **1a**−**f**, 0.02 mmol of catalyst **F**, and 0.04 mmol salicylic acid in a 0.4 M toluene solution. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis on a chiral stationary phase. [e]Reaction performed using the pseudoenantiomeric form of catalyst **F**.

Table 6. Direct α-Benzoyloxylation of 1-Indanones[a]



entry	R	product	yield (%)[b]	ee (%)[c]
1	H	**5a**	80	84
2	5-Br	**5b**	66	80
3	5-F	**5c**	55	79
4	5-OMe	**5d**	30	77
5	6-Me	**5e**	82	60
6	5-Cl	**5f**	68	76
7	4-CF_3	**5g**	37	40
8[d]	H	**5a**	40	89
9[e]	H	**5a**	77	84

[a]Unless otherwise noted, the reactions were performed for 80 h at 0 °C using 0.2 mmol of **2** and 0.5 mmol of **4a**−**e**, 0.04 mmol of catalyst **F**, and 0.08 mmol salicylic acid in a 0.1 M toluene solution. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Reaction performed for 7 days at 0 °C using 2 equiv of **4a**. [e]Reaction performed using 10 mol % of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as radical scavenger.

have never been used for the enantioselective α-oxygenation performed by means of organocatalytic strategies, we envisaged that 9-amino(9-deoxy)*epi*-hydroquinidine **F** could be efficiently applied for our purpose. In fact although 1-indanone derivatives represent a class of bulky aromatic ketones, the almost complete coplanarity of the five-membered cyclopentanone with respect to the fused aromatic ring represents an advantage for the approach of the primary amine catalyst thus promoting the enamine formation and the subsequent addition to the dibenzoyl peroxide. As outlined in Table 6 the reaction, performed under the optimized condition but using 20 mol % of catalyst loading, proceeded smoothly at 0 °C, furnishing the desired α-benzoylindanones from moderate to good yields and good enantioselectivity (Table 6, entries 1−7). Various substituents that differentiate the stereoelectronic nature of the starting 1-indanones could be applied with a general good efficiency of the process. Yields and enantioselectivity are generally quite good apart from 5-methoxy-1-indanone **4d** that furnished the desired product **5d** in 30% isolated yield (Table 6, entry 4) and 4-trifluoromethyl-1-indanone **4g** that allowed us to isolate the desired α-benzoylindanone **5g** in 37% isolated yield and only 40% enantiomeric excess (Table 6, entry 7).

Interestingly the enantioselectivity could be increased to 89% ee by performing the reaction with 2 equiv of ketone **4a**; however, the corresponding product **5a** was isolated after 7 days of reaction in a lower yield if compared with the reaction conducted with 2.5 equiv of **4a** (Table 6, entry 8). In order to exclude the presence of a possible radical side pathway that might affect the stereocontrol of the α-benzoyloxylation, we performed a test reaction using 10 mol % 2,6-di-*tert*-butyl-4-methylphenol (BHT), and compound **5a** was isolated without any decrease of yield and enantiocontrol (Table 6, entry 9).

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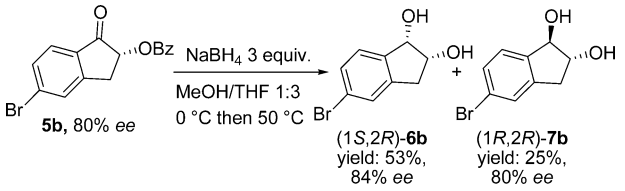
To enhance the synthetic utility of this methodology, we developed a one-pot procedure for the synthesis of 1,2-diols[2g] starting from enantioenriched (*R*)-5-bromo-1-oxo-2,3-dihydro-1*H*-inden-2-yl benzoate **5b**. The reaction was conducted with 3 equiv of $NaBH_4$ as reducing agent in a 1:3 mixture of MeOH and THF at 0 °C for 15 min then the solution was placed at 50 °C for 18 h. The crude mixture gave a 4:1 mixture of the corresponding 1,2-diols in favor of *cis*-isomer. After purification *cis*-(1*S*,2*R*)-**6b** was isolated in a 53% yield and 84% ee and *trans*-(1*R*,2*R*)-**7b** in 25% yield and 80% ee[12] (Scheme 2).

Scheme 2. Synthesis of 5-Bromo-2,3-dihydro-1*H*-indene-1,2-diol



CONCLUSION

In conclusion we have explored the reactivity of cyclic ketones for the enantioselective synthesis of their protected α-hydroxy derivatives using 9-amino(9-deoxy)*epi*-hydroquinidine (**F**) in combination with salicylic acid as catalyst. The reaction demonstrated to be extremely efficient and highly enantioselective thus furnishing a new and alternative procedure[11] for the synthesis of protected α-hydroxy ketones. The new methodology was also effectively applied to the direct enantioselective synthesis of α-oxygenated 1-indanones derivatives that might be easily converted into 1,2-diols thus furnishing a new way of synthesis of this important class of compounds.

EXPERIMENTAL SECTION

General. The ^{1}H and ^{13}C NMR spectra were recorded on 400 and 600 MHz spectrometers. NOE spectra were recorded using the DPFGSE-NOE sequence,[13] using a mixing time of 2.00 s and "rsnob" 20 ÷ 50 Hz wide selective pulses, depending on the crowding of the spectra region. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CDCl_3$ and CD_3CN). Coupling constants are given in Hz. Carbon types were determined from DEPT ^{13}C NMR[14] experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet, m, multiplet; bs, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230−400 mesh) according to the method of Still.[15] Melting points of solid new samples were determined by melting point apparatus or by differential scanning calorimetry (DSC) on a DSC apparatus, adopting a temperature program consisting of two heating and one cooling ramps starting from room temperature (heating/cooling rate 2 °C/min under a nitrogen atmosphere). Each sample (3−5 mg) was heated up to only 150 °C in order to avoid thermal decomposition. Organic solutions were concentrated under reduced pressure on a rotary evaporator. Optical rotations are reported as follows: $[\alpha]^{rt}_D$ (*c* in g per 100 mL, solvent, % ee). All reactions were set up in the air and using undistilled solvent, without any precautions to exclude moisture. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[16] Commercially available chiral primary amine catalysts **A** ((1*S*,2*S*)-1,2-diphenylethane-1,2-diamine) and **C** ((*R*)-1,1′-binaphthyl-2,2′-diamine) were used as received. Catalyst **B**,[17] **D**, **E**, **F**,[18] and *ent*-**F** were prepared from literature procedure. All cyclohexanone and 1-indanone derivatives were commercially available and used as received. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture and confirmed by HPLC analysis on chiral stationary phase columns. HPLC analysis on chiral stationary phase were performed using Chiralpak AD-H column, Chiralcel OD-H column, Chiralcel OJ-H, and Lux Amylose-2 columns and *i*-PrOH/hexane as the eluent. HPLC traces for compounds **3a**−**i**, **5a**−**g**, *cis*-(1*S*,2*R*)-**6b**, and *trans*-(1*R*,2*R*)-**7b** were compared to racemic samples prepared by mixing the two product antipodes obtained performing the reaction with catalyst 9-amino(9-deoxy)*epi*-hydroquinidine (**F**) and the pseudoenantiomer 9-amino(9-deoxy)*epi*-hydroquinine (*ent*-**F**) separately.

General Procedure for the Benzoyloxylation of Cyclohexanone. All reactions were carried out in undistilled toluene. In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **F** (0.02 mmol, 10 mol %) was dissolved in 500 μL of toluene, and 2 hydroxybenzoic acid (0.04 mmol, 20 mol %) was added. The resulting solution was stirred at 0 °C for 10 min. Cyclohexanone derivative (0.5 mmol, 2.5 equiv) was added, followed by the addition of the dibenzoyl peroxide (0.2 mmol) and Na_2CO_3 (1.2 equiv) at 0 °C. Stirring was continued for 80−84 h. The crude mixture was diluted with CH_2Cl_2 and flushed through a short plug of silica, using dichloromethane/ethyl acetate 1:1 as the eluent (20 mL). Solvent was removed *in vacuo*. Crude product was purified by flash column chromatography using hexane/diethyl ether as the eluent mixture.

(1*R*)-2-Oxocyclohexyl Benzoate[10] (3a) (Table 5, entry 1). The reaction was carried out following the general procedure. The title compound was isolated as a white solid by column chromatography (hexane/Et_2O = 80/20) in 80% yield and 96.5% ee. HPLC analysis on a Chiralcel OD-H column: 90/10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 214 nm: τ_{major} = 7.186 min, τ_{minor} = 10.328 min; ESI-MS: 219 $(M + 1)^+$, 241 $(M + Na)^+$. $[\alpha]^{20}_D$ = +15.6 (*c* 0.77, $CHCl_3$, 96.5% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62−1.77(m, 1H), 1.78−1.91 (m, 1H), 1.92−1.99 (m, 1H), 1.99−2.08 (m, 1H), 2.09−2.19 (m, 1H), 2.38−2.52 (m, 2H), 2.54−2.62 (m, 1H), 5.41 (ddd, 1H, *J* = 12.1 Hz, *J* = 7.3 Hz, *J* = 1.1 Hz), 7.44 (m, 2H), 7.57 (m, 1H), 8.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8 (CH_2), 27.2 (CH_2), 33.2 (CH_2), 40.7 (CH_2), 76.9 (CH), 128.3 (CH), 129.7 (C), 129.9 (CH), 133.1 (CH), 165.6 (C), 204.3 (C).

(1*R*,4*S*)-4-Methyl-2-oxocyclohexyl Benzoate[9] (*cis*-3b) and (1*R*,4*R*)-4-Methyl-2-oxocyclohexyl Benzoate[9] (*trans*-3b) (Table 5, entry 2). The reaction was carried out following the general procedure to furnish the crude product **3b** as 1:1 mixture of *cis*-isomer (1*R*,4*S*)-**3b** and *trans*-isomer (1*R*,4*R*)-**3b**. A white solid was isolated by column chromatography (hexane/Et_2O = 85/15) in 88% yield as a mixture of *cis*- and *trans*- isomers and >99% ee for *cis*-**3b** isomer HPLC analysis on a Chiralcel OD-H column: 99/1 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 13.07 min, τ_{minor} = 20.64 min; and 96.5% ee for *trans*-**3b** isomer HPLC analysis on a Chiralcel OD-H column: 90/10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 214 nm: τ_{major} = 6.412 min, τ_{minor} = 9.837 min; ESI-MS: 233 $(M + 1)^+$, 255 $(M + Na)^+$, 271 $(M + K)^+$. $[\alpha]^{20}_D$ *cis*-**3b** = +14.5 (*c* 0.33, $CHCl_3$, >99% ee); $[\alpha]^{20}_D$ *trans*-**3b** = +13.2 (*c* 0.11, $CHCl_3$, 96.5% ee). ^{1}H NMR (400 MHz, $CDCl_3$) *trans*-**3b** δ 1.09 (d, 3H, *J* = 6.3 Hz), 1.60 (m, 1H), 1.87−2.05 (m, 3H), 2.21 (td, 1H, *J* = 12.9 Hz, *J* = 0.9 Hz), 2.36−2.43 (m, 1H), 2.50−2.56 (m, 1H), 5.40 (ddd, 1H, *J* = 12.5 Hz, *J* = 7.1 Hz, *J* = 0.9 Hz), 7.44 (m, 2H), 7.57 (m, 1H), 8.1 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 31.7, 32.3, 35.0, 48.7, 77.2, 128.3, 129.7 129.9 133.1, 165.7, 203.7.

(1*R*,5*R*)-2-Oxo-5-phenylcyclohexyl Benzoate (*cis*-3c) and (1*R*,5*S*)-2-Oxo-5-phenylcyclohexyl Benzoate (*trans*-3c) (Table 5, entry 4). The reaction was carried out following the general procedure to furnish the crude product **3c** as a 1:1 mixture of *cis*-(1*R*,5*S*)-**3c** and *trans*-(1*R*,5*R*)-**3c**. The title compound was isolated as a colorless oil by column chromatography (hexane/Et_2O = 80/20) in 70% yield as a mixture of *cis*- and *trans*-isomers and >99% ee for *cis*-**3c** isomer HPLC analysis on a Chiralcel AD-H column: 99/1 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 24.23 min, τ_{minor} = 27.99 min; and 37% ee for *trans*-**3c** isomer HPLC analysis on a Chiralpak AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.750 mL/

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min, λ = 214 nm: τ_{major} = 15.40 min, τ_{minor} = 24.51 min; HRMS (ESI$^+$) calcd for $C_{19}H_{19}O_3$ 295.1329, found 295.1326; *cis*-**3c**: $[\alpha]^{20}_D$ = +30.6 (*c* 0.51, $CHCl_3$, 99% ee). *trans*-**3c**: $[\alpha]^{20}_D$ = −10.7 (*c* 1.04, $CHCl_3$, 37% ee). ^{1}H NMR (400 MHz, $CDCl_3$) *cis*-**3c** (9:1 mixture of *cis*:*trans* isomers) δ 2.21−2.33 (m, 2H), 2.47−2.58 (m, 3H), 2.75−2.85 (m, 1H), 3.48 (quint, 1H, *J* = 6.7 Hz), 5.37 (m, 1H), 7.22−7.30 (m, 1H), 7.33−7.40 (m, 4H), 7.44−7.53 (m, 2H), 7.57−7.65 (m, 1H), 8.08−8.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.3 (CH_2), 37.2 (CH), 37.8 (CH_2), 38.3 (CH_2), 75.7 (CH), 126.7 (CH), 126.8 (CH), 128.5 (CH), 128.8 (CH), 129.8 (CH), 133.4 (CH), 142.4 (C), 165.4 (C), 206.0 (C). ^{1}H NMR (400 MHz, $CDCl_3$) *trans*-**3c** δ 1.91−2.05 (m, 1H), 2.19−2.36 (m, 2H), 2.56−2.76 (m, 3H), 3.31 (tt, 1H, *J* = 12.6 Hz, *J* = 3.4 Hz), 5.64 (ddd, 1H, *J* = 12.7 Hz, *J* = 6.3 Hz, *J* = 0.7 Hz), 7.22−7.30 (m, 3H), 7.32−7.38 (m, 2H), 7.45 (M, 2H), 7.58 (m, 1H), 8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.4 (CH_2), 39.8 (CH_2), 39.9 (CH_2), 41.9 (CH), 76.0 (CH), 126.6 (CH), 127.0 (CH), 128.4 (CH), 128.8 (CH), 129.6 (C), 129.9 (CH), 133.2 (CH), 143.1 (C), 165.5 (C), 203.7 (C).

(*R*)-5,5-Dimethyl-2-oxocyclohexyl Benzoate[10] (3d) (Table 5, entry 6). The reaction was carried out following the general procedure. The title compound was isolated as a colorless oil by column chromatography (pentane/Et_2O = 80/20) in 80% yield and 96.4% ee. HPLC analysis on a Chiralpak AD-H column: 80/20 hexane/*i*-PrOH, flow rate 0.700 mL/min, λ = 214 nm: τ_{major} = 8.25 min, τ_{minor} = 9.56 min; ESI-MS: 247 (M + 1)$^+$, 269 (M + Na)$^+$. $[\alpha]^{20}_D$ = +19.2 (*c* 0.94, $CHCl_3$, 96.4% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.32 (s, 3H), 1.66−1.83 (m, 2H), 1.90 (t, *J* = 16.0 Hz, 1H), 2.12 (ddd, *J* = 12.6 Hz, *J* = 6.4 Hz, *J* = 3.3 Hz, 1H,), 2.42 (ddd, *J* = 14.3 Hz, *J* = 4.6 Hz, 2.7 Hz, 1H), 2.64 (td, *J* = 14.0 Hz, *J* = 6.4 Hz, 1H), 5.55 (dd, *J* = 13.0 Hz, *J* = 6.4 Hz, 1H), 7.39−7.47 (m, 2H), 7.53−7.59 (m, 1H), 8.04−8.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 31.6, 32.3, 37.2, 39.8, 45.5, 74.4, 128.5, 129.9, 130.1, 133.3, 165.9, 205.1.

(*R*)-4-Oxotetrahydro-2*H*-pyran-3-yl Benzoate[19] (3e) (Table 5, entry 7). The reaction was carried out following the general procedure. The title compound was isolated as a white solid by column chromatography (pentane/Et_2O = 75/25) in 71% yield and 91% ee. HPLC analysis on a Chiralcel OD-H column: 9/1 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 10.15 min, τ_{minor} = 13.91 min; ESI-MS: 221 (M + 1)$^+$, 243 (M + Na)$^+$. Mp (DSC, 2 °C/min): 79 °C. $[\alpha]^{20}_D$ = +11.9 (*c* 1.02, $CHCl_3$, 91% ee). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.60 (m, 1H), 2.84 (m, 1H), 3.73 (m, 2H), 4.31 (m, 1H), 4.46 (m, 1H), 5.52 (m, 1H), 7.45 (m, 2H), 7.58 (m, 1H), 8.07 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 42.2 (CH_2), 68.2 (CH_2), 70.5 (CH_2), 74.0 (CH), 128.4 (CH), 129.0 (C), 129.9 (CH), 133.4 (CH), 165.0 (C), 200.3 (C).

(*S*)-4-Oxotetrahydro-2*H*-thiopyran-3-yl Benzoate[20] (3f) (Table 5, entry 9). The reaction was carried out following the general procedure. The title compound was isolated as a white solid by column chromatography (pentane/Et_2O = 80/20) in 22% yield and 94.5% ee. HPLC analysis on a Chiralcel OD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.750 mL/min, λ = 254 nm: τ_{major} = 10.41 min, τ_{minor} = 12.08 min; ESI-MS: 259 (M + Na)$^+$, 275 (M + K)$^+$. $[\alpha]^{20}_D$ = +17.1 (*c* 0.23, $CHCl_3$, 94.5% ee). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.90−3.02 (m, 4H), 3.14−3.23 (m, 2H), 5.61 (dd, 1H, *J* = 11.2 Hz, *J* = 5.8 Hz), 7.45 (m, 2H), 7.59 (m, 1H), 8.09 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 30.04 (CH_2), 34.7 (CH_2), 44.8 (CH_2), 77.1 (CH), 128.4 (CH), 129.3 (CH), 129.9 (CH), 133.4 (CH), 165.1 (C), 201.5 (C).

(*R*)-2-Oxocycloheptyl Benzoate[10] (3g) (Table 5, entry 11). The reaction was carried out following the general procedure. The title compound was isolated as a white solid by column chromatography (hexane/EtOAc = 85/15) in 60% yield and >99% ee. HPLC analysis on a Chiralcel OD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.800 mL/min, λ = 254 nm: τ_{major} = 10.15 min, τ_{minor} = 12.96 min; ESI-MS: 233 (M + 1)$^+$, 255 (M + Na)$^+$. $[\alpha]^{20}_D$ = −33.7 (*c* 0.97, $CHCl_3$, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38−1.51 (m, 1H), 1.65−1.99 (m, 6H), 2.13 (m, 1H), 2.51 (m, 1H), 2.70 (m, 1H), 5.46 (dd, 1H, *J* = 9.7 Hz, *J* = 3.5 Hz), 7.45 (m, 2H), 7.57 (m, 1H), 8.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0 (CH_2), 26.4 (CH_2), 28.4 (CH2), 30.4 (CH_2), 40.7 (CH_2), 79.0 (CH), 128.4 (CH), 129.7 (C), 129.8 (CH), 133.1 (CH), 165.9 (C), 207.3 (C).

(*R*)-2-Oxocyclooctyl Benzoate[10] (3h) (Table 5, entry 12). The reaction was carried out following the general procedure. The title compound was isolated as a white solid by column chromatography (pentane/Et_2O = 90/10) in 96% yield and 93% ee. HPLC analysis on a Chiralcel OD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.750 mL/min, λ = 214 nm: τ_{major} = 8.15 min, τ_{minor} = 9.89 min; ESI-MS: 247 (M + 1)$^+$, 269 (M + Na)$^+$. $[\alpha]^{20}_D$ = −30.7 (*c* 0.95, $CHCl_3$, 93% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18−1.33 (m, 2H), 1.49−1.75 (m, 4H), 1.80−2.13 (m, 4H), 2.27−2.37 (m, 1H), 2.42 (ddd, *J* = 14.1 Hz, *J* = 9.0 Hz, *J* = 3.5 Hz, 1H), 2.74 (ddd, *J* = 14.1 Hz, *J* = 9.4 Hz, *J* = 3.5 Hz, 1H), 5.42 (dd, *J* = 8.6 Hz, *J* = 3.7 Hz, 1H), 7.39−7.48 (m, 2H), 7.53−7.60 (m, 1H), 8.03−8.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 24.7, 24.8, 27.7, 31.5, 40.7, 77.6, 128.6, 129.8, 130.0, 133.5, 166.2, 211.8.

(*R*)-*tert*-Butyl 3-(Benzoyloxy)-4-oxopiperidine-1-carboxylate[9] (3i) (Table 5, entry 13). The reaction was carried out following the general procedure. The title compound was isolated as a pale yellow oil by column chromatography (hexane/acetone = gradient 5%−15% acetone) in 49% yield and 80% ee. HPLC analysis on a Chiralcel AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.700 mL/min, λ = 254 nm: τ_{major} = 12.65 min, τ_{minor} = 14.47 min; ESI-MS: 320 (M + 1)$^+$, 343 (M + Na)$^+$. $[\alpha]^{20}_D$ = +22.1 (*c* 0.83, $CHCl_3$, 80% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.49−2.80 (m, 2H), 3.04−3.58 (m, 2H), 4.11−4.79 (m, 2H), 5.36 (dd, *J* = 10.5 Hz, *J* = 6.5 Hz, 1H), 7.38−7.50 (m, 2H), 7.53−7.64 (m, 1H), 8.0−8.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 40.7, 43.9 (broad signal), 48.1 (broad signal), 74.1, 81.4, 128.7, 129.3, 130.2, 133.7, 154.4, 165.3, 201.7.

General Procedure for the Benzoyloxylation of 1-Indanones. All reactions were carried out in undistilled toluene. In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **F** (0.04 mmol, 20 mol %) was dissolved in 1.0 mL of toluene, and 2 hydroxybenzoic acid (0.08 mmol, 40 mol %) was added. The resulting solution was stirred at 0 °C for 10 min. 1-Indanone derivative (2.5 equiv) was added, followed by the addition of the dibenzoyl peroxide (0.2 mmol) and Na_2CO_3 (1.2 equiv) at 0 °C. Stirring was continued for 80 h. The crude mixture was diluted with CH_2Cl_2 and flushed through a short plug of silica, using dichloromethane/ethyl acetate 1:1 as the eluent (20 mL). Solvent was removed in vacuo. Crude product was purified by flash column chromatography using dichloromethane/diethyl ether 99:1 as the eluent mixture.

(*R*)-1-Oxo-2,3-dihydro-1*H*-inden-2-yl Benzoate (5a) (Table 6, entry 1). The reaction was carried out following the general procedure. The title compound was isolated as a white solid by column chromatography (dichloromethane/diethyl ether = 99/1) in 80% yield and 84% ee. HPLC analysis on a Chiralcel OD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214 nm: τ_{major} = 13.48 min, τ_{minor} = 14.72 min; HRMS (ESI$^+$) calcd for $C_{16}H_{13}O_3$ 253.0859, found 253.0857. Mp (DSC, 2 °C/min): 70 °C. $[\alpha]^{20}_D$ = −56.1 (*c* 0.82, $CHCl_3$, 84% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (dd, 1H, *J* = 17.1 Hz, *J* = 4.7 Hz), 3.77 (dd, 1H, *J* = 16.9 Hz, *J* = 8.0 Hz), 5.65 (dd, 1H, *J* = 8.0 Hz, *J* = 4.8 Hz), 7.40−7.51 (m, 4H), 7.58 (m, 1H), 7.67 (td, 1H, *J* = 7.5 Hz, *J* = 1.2 Hz), 7.84 (bd, 1H, *J* = 7.7 Hz), 8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.6 (CH_2), 74.4 (CH), 124.5 (CH), 126.7 (CH), 128.1 (CH), 128.4 (CH), 129.3 (C), 133.4 (CH), 134.6 (C), 135.9 (CH), 150.4 (C), 166.0 (C), 200.4 (C).

(*R*)-5-Bromo-1-oxo-2,3-dihydro-1*H*-inden-2-yl Benzoate (5b) (Table 6, entry 2). The reaction was carried out following the general procedure. The title compound was isolated as a white solid by column chromatography (dichloromethane/diethyl ether = 99/1) in 66% yield and 80% ee. HPLC analysis on a Chiralcel OD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.850 mL/min, λ = 254 nm: τ_{major} = 37.63 min, τ_{minor} = 33.61 min; HRMS (ESI$^-$) calcd for $C_{16}H_{10}BrO_3$ 328.9892, 330.9871, found 328.9890, 330.9869. $[\alpha]^{20}_D$ = −3.7 (*c* 1.0, $CHCl_3$, 80% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (m, 1H), 3.75 (m, 1H), 5.60 (dd, 1H, *J* = 8.0 Hz, *J* = 4.8 Hz), 7.45 (m, 2H), 7.56−7.62 (m, 2H), 7.66−7.72 (m, 2H), 8.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.2 (CH_2), 74.2 (CH), 125.7 (CH), 128.5

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(CH), 129.1 (C), 130.0 (CH), 131.3 (C), 131.9 (CH), 133.4 (C), 133.5 (CH), 151.9 (C), 166.0 (C), 199.2 (C).

(*R*)-5-Fluoro-1-oxo-2,3-dihydro-1*H*-inden-2-yl Benzoate (5c) (Table 6, entry 3). The reaction was carried out following the general procedure. The title compound was isolated as a white solid by column chromatography (dichloromethane/diethyl ether = 99/1) in 55% yield and 79% ee. HPLC analysis on a Chiralpak AD-H column: 90:10 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 254 nm: τ_{major} = 20.37 min, τ_{minor} = 22.98 min; HRMS (ESI$^+$) calcd for $C_{16}H_{12}FO_3$ 271.0765, found 271.0763. Mp (DSC, 2 °C/min): 119 °C. $[\alpha]^{20}_D$ = −40.5 (*c* 0.89, $CHCl_3$, 79% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (m, 1H), 3.76 (m, 1H), 5.62 (dd, 1H, *J* = 8.0 Hz, *J* = 4.7 Hz), 7.11−7.19 (m, 2H), 7.45 (m, 2H), 7.59 (m, 1H), 7.86 (m, 1H), 8.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5 (d, CH_2, *J* = 1.7 Hz), 74.3 (CH), 113.5 (d, CH, J_{C-F} = 22.7 Hz), 116.6 (d, CH, J_{C-F} = 23.7 Hz), 127.0 (d, CH, J_{C-F} = 10.6 Hz), 128.4 (CH), 129.2 (C), 130.0 (CH), 131.1 (d, C, J_{C-F} = 1.6 Hz), 133.5 (CH), 153.3 (d, C, J_{C-F} = 10.5 Hz), 166.0 (C), 166.5 (C), 169.1 (C), 198.6 (C).

(*R*)-5-Methoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl Benzoate (5d) (Table 6, entry 4). The reaction was carried out following the general procedure. The title compound was isolated as a white solid by column chromatography (dichloromethane/diethyl ether = 99/1) in 30% yield and 77% ee. HPLC analysis on a Chiralpak AD-H column: 80/20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 14.88 min, τ_{minor} = 22.27 min; HRMS (ESI$^+$) calcd for $C_{17}H_{15}O_4$ 283.0965, found 283.0963. Mp (DSC, 2 °C/min): 140 °C. $[\alpha]^{20}_D$ = −6.4 (*c* 0.45, $CHCl_3$, 77% ee).^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (dd, 1H, *J* = 17.0 Hz, *J* = 4.5 Hz), 3.73 (dd, 1H, *J* = 16.9 Hz, *J* = 7.7 Hz), 3.91 (s, 3H), 5.63 (dd, 1H, *J* = 7.8 Hz, *J* = 4.5 Hz), 6.90 (bs, 1H), 6.97 (m, 1H), 7.45 (m, 2H), 7.58 (m, 1H), 7.78 (d, 1H, *J* = 8.5 Hz), 8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.9 (CH_2), 55.8 (CH_3), 74.5 (CH), 109.8 (CH), 116.2 (CH), 126.6 (CH), 127.9 (C), 128.4 (CH), 129.4 (CH), 130.0 (CH), 133.4 (CH), 153.6 (C), 166.1 (C), 166.2 (C), 198.5 (C).

(*R*)-6-Methyl-1-oxo-2,3-dihydro-1*H*-inden-2-yl Benzoate (5e) (Table 6, entry 5). The reaction was carried out following the general procedure. The title compound was isolated as a white solid by column chromatography (dichloromethane/diethyl ether = 99/1) in 82% yield and 60% ee. HPLC analysis on a Chiralcel OD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 254 nm: τ_{major} = 12.19 min, τ_{minor} = 14.38 min; HRMS (ESI$^+$) calcd for $C_{17}H_{15}O_3$ 267.1016, found 267.1014. Mp (DSC, 2 °C/min): 85 °C. $[\alpha]^{20}_D$ = −53.3 (*c* 0.97, $CHCl_3$, 60% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.14 (dd, 1H, *J* = 16.9 Hz, *J* = 4.8 Hz), 3.72 (dd, 1H, *J* = 17.0 Hz, *J* = 8.2 Hz), 5.64 (dd, 1H, *J* = 8.0 Hz, *J* = 4.8 Hz), 7.34−7.39 (m, 1H), 7.41−7.51 (m, 3H), 7.58 (m, 1H), 7.64 (bs, 1H), 8.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 33.2 (CH_2), 74.7 (CH), 124.4 (CH), 126.3 (CH), 128.4 (CH), 129.4 (C), 130.0 (CH), 133.3 (CH), 134.7 (C), 137.1 (CH), 138.2 (C), 147.7 (C), 166.0 (C), 200.5 (C).

(*R*)-5-Chloro-1-oxo-2,3-dihydro-1*H*-inden-2-yl Benzoate (5f) (Table 6, entry 6). The reaction was carried out following the general procedure. The title compound was isolated as a white solid by column chromatography using dichloromethane as the eluent in 68% yield and 76% ee. HPLC analysis on a Chiralcel AD-H column: 80/20 hexane/*i*-PrOH, flow rate 0.750 mL/min, λ = 254 nm: τ_{major} = 15.99 min, τ_{minor} = 20.12 min; HRMS (ESI$^+$) calcd for $C_{16}H_{12}ClO_3$ 287.0397, found 287.0395. Mp: 162.1−163.2 °C. $[\alpha]^{20}_D$ = −10.5 (*c* 0.78, $CHCl_3$, 76% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (dd, *J* = 17.4 Hz, *J* = 4.9 Hz, 1H), 3.74 (dd, *J* = 17.4 Hz, *J* = 8.2 Hz, 1H), 5.6 (dd, *J* = 8.1 Hz, *J* = 4.8 Hz, 1H), 7.39−7.51 (m, 1H), 7.56−7.63 (m, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 8.07−8.11 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 74.5, 125.9, 127.9, 127.1, 128.7, 129.3, 129.4, 130.2, 133.3, 133.7, 142.7, 152.0, 166.1, 199.2.

(*R*)-1-Oxo-4-(trifluoromethyl)-2,3-dihydro-1*H*-inden-2-yl Benzoate (5g) (Table 6, entry 7). The reaction was carried out following the general procedure. The title compound was isolated as a pale yellow solid by column chromatography (hexane/Et_2O = 9:1) in 37% yield and 40% ee. HPLC analysis on a Chiralcel AD-H column: 92/8 hexane/*i*-PrOH, flow rate 0.700 mL/min, λ = 254 nm: τ_{major} = 13.03 min, τ_{minor} = 14.29 min; HRMS (ESI$^+$) calcd for $C_{17}H_{12}F_3O_3$ 321.0660, found 321.0662. Mp: 92.6−94.0 °C. $[\alpha]^{20}_D$ = −13.5 (*c* 0.66, $CHCl_3$, 40% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 (dd, *J* = 17.8 Hz, *J* = 4.8 Hz, 1H), 3.99 (m, 1H), 5.64 (dd, *J* = 8.1 Hz, *J* = 4.8 Hz, 1H), 7.46 (m, 2H), 7.60 (m, 2H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 8.07−8.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.3 (CH_2), 73.8 (CH), 123.5 (q, J_{C-F} = 273.5 Hz, C), 127.9 (CH), 128.5 (CH), 128.6 (CH), 128.6 (q, J_{C-F} = 32.7 Hz, C), 129.0 (C), 130.1 (CH), 132.3 (q, J_{C-F} = 5.0 Hz, CH), 133.6 (CH), 133.6 (CH), 136.0 (C), 147.7 (C), 165.9 (C), 199.17 (C).

Synthesis of *cis*-(1*S*,2*R*)-6b and *trans*-(1*R*,2*R*)-7b. Compound **5b** (40 mg, 0.12 mmol, 80% ee) was dissolved in 2 mL of a 1:3 solution of MeOH/THF and stirred at room temperature for several minutes. Then 3 equiv (13.7 mg, 0.36 mmol) of solid $NaBH_4$ was added at 0 °C, and stirring was continued until the disappearance of **5b** was observed (15 min, checked by TLC). The reaction was then placed in an oil bath at 50 °C in a sealed tube for 18 h. The crude mixture was diluted with dichloromethane and treated with a saturated aqueous solution of Na_2CO_3. The organic phase was separated, and the aqueous phase was extracted two times with dichloromethane. Organic phases were collected and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude mixture was analyzed by NMR (dr = 4:1 in favor of *cis*-**6b**) and purified by column chromatography using hexane/acetone 75/25 as the eluent mixture to give *cis*-(1*S*,2*R*)-**6b** in 53% yield and 84% ee. HPLC analysis on a Chiralcel OJ-H column: 90/10 hexane/*i*-PrOH, flow rate 0.600 mL/min, λ = 214 nm: τ_{minor} = 17.17 min, τ_{major} = 18.96 min; and *trans*-(1*R*,2*R*)-**7b** in a 25% yield and 80% ee HPLC analysis on a Lux Amylose-2 column: 95/5 hexane/*i*-PrOH, flow rate 0.700 mL/min, λ = 230.16 nm: τ_{major} = 34.66 min, τ_{minor} = 32.42 min. $[\alpha]^{20}_D$ *cis*-(1*S*,2*R*)-**6b** = −5.3 (*c* 0.57, acetone, 84% ee). HRMS (ESI$^-$) calcd for $C_9H_8BrO_2$ 226.9713, 228.9693, found 226.9711, 228.9690. Mp *cis*-(1*S*,2*R*)-**6b**: 123.0−124.5 °C. Mp *trans*-(1*S*,2*R*)-**7b**: 187.0−189.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *cis*-(1*S*,2*R*)-**6b** δ 2.84 (dd, 1H, *J* = 16.5 Hz, *J* = 3.1 Hz), 3.03 (dd, 1H, *J* = 16.5 Hz, *J* = 5.6 Hz), 3022 (d, 1H, *J* = 4.6 Hz), 3.55 (d, 1H, *J* = 7.0 Hz), 4.38 (m, 1H), 4.87 (m, 1H), 7.26−7.31 (m, 2H), 7.37−7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *cis*-(1*S*,2*R*)-**6b** δ 38.9 (CH_2), 74.0 (CH), 75.9 (CH), 118.3 (C), 122.1 (C), 127.5 (CH), 129.0 (CH), 130.5 (CH), 143.7 (C), 144.5 (C). ^{1}H NMR (400 MHz, CD_3CN, poor solubility) *trans*-(1*R*,2*R*)-**7b** δ 2.69 (dd, 1H, *J* = 16.0 Hz, *J* = 6.8 Hz), 3.17 (m, 1H), 3.39 (d, 1H, *J* = 5.0 Hz), 3.60 (d, 1H, *J* = 6.0 Hz), 4.19 (m, 1H), 4.76 (m, 1H), 7.24 (m, 2H), 7.37−7.43 (m, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 38.5 (CH_2), 81.2 (CH), 82.5 (CH), 118.3 (C), 122.0 (C), 127.1 (CH), 128.7 (CH), 130.6 (CH), 143.4 (C), 143.6 (C).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedures, ^{1}H and ^{13}C NMR spectra, characterization data, and HPLC traces for compounds **3a−i**, **5a−g**, **6b**, and **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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NOTE ADDED AFTER ASAP PUBLICATION

The toc/abstract graphic and Figure 1 contained errors in the version published ASAP February 29, 2012. The correct version reposted March 2, 2012.