Enantioselective alkylation of β-keto esters promoted by dimeric *Cinchona*-derived ammonium salts as recoverable organocatalysts

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Dedicated to Professors Rita H. Rossi, Julio C. Podestá, Manuel González Sierra and Oscar S. Giordano

Abstract
Dimeric anthracenyldimethyl-derived Cinchona ammonium salts are used as chiral organocatalysts in 5 mol% for the phase-transfer enantioselective alkylation reaction of 2-alkoxycarbonyl-1-indanones with activated bromides. The corresponding adducts bearing a new all-carbon quaternary center are obtained usually in high yield and with moderate and opposite enantioselectivity (up to 55%) when using ammonium salts derived from quinidine and its pseudoenantiomer quinine as organocatalysts. These catalysts can be almost quantitatively recovered by precipitation in ether and reused.

Keywords: asymmetric synthesis; ammonium salts; phase-transfer catalysis; alkylation; β-keto esters

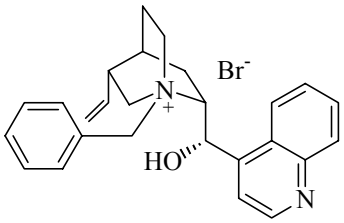
Introduction

The enantioselective generation of a quaternary stereogenic center is probably one of the most challenging tasks for a synthetic organic chemist,[1] and results particularly interesting when is carried out on substrates such as β-keto esters which offer ample opportunity for further structural elaboration.[2] Among the transformations suitable for this purpose, the enantioselective alkylation of α-substituted β-keto esters has been performed under palladium catalysis,[3] although the development of metal-free alkylation procedures based on the fast forwarding topic of enantioselective organocatalysis[4] is nowadays desirable.

Among the organocatalytic methodologies, phase transfer catalysis (PTC) is one of the most simple and convenient, its use in many enantioselective transformations being profuse and successful.[5] The most frequently employed chiral catalysts in enantioselective PTC

transformations are ammonium salts derived from *Cinchona* alkaloids,[6] due to its availability and low price.

Surprisingly, the use of the PTC methodology for the enantioselective alkylation of α-substituted β-keto esters leading to quaternary stereocenters has been rather limited. Thus, a dimeric mandelamide-derived phosphonium salt was pioneeringly used in the liquid-liquid phase transfer catalyzed alkylation of *tert*-butyl 2-oxocyclopentanecarboxylate, giving enantioselectivities up to 50%.[7] More recently a binaphthyl-derived with C_2-symmetry ammonium salt has afforded high *ee*'s in the alkylation of several cyclic β-keto esters.[8] However, the use of the popular *Cinchona* alkaloid-derived ammonium salts as phase-transfer organocatalysts has been limited to the use of cinchonine-, cinchonidine- and quinine-derived ammonium salts in the solid-liquid phase transfer benzylation of *tert*-butyl 2-oxocyclopentanecarboxylate achieving enantioselections in the range 7-46%, the highest value being obtained using the cinchonine-derived salt **1**.[9] In addition, very high *ee*'s have been obtained with some electrophiles using the cinchonine-derived salt **2** in the alkylation reaction of different cyclic β-keto esters under solid-liquid phase transfer conditions.[10]



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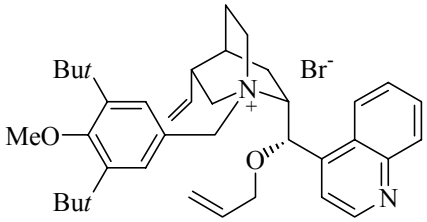
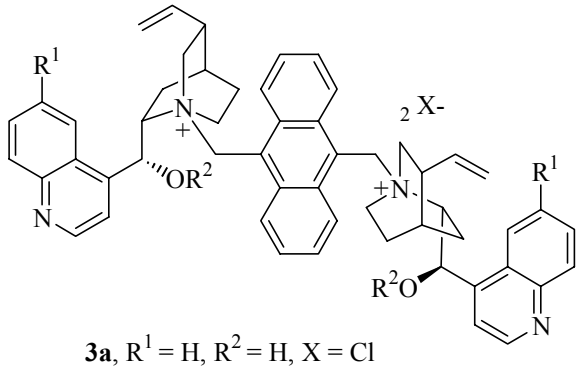


2

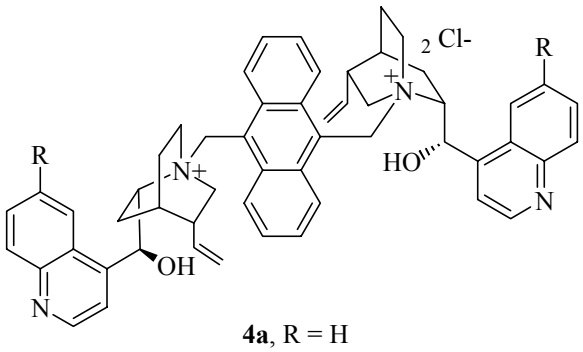
Our group has been working in the last years on developing recoverable unsupported[11-13] and supported[14] *Cinchona* alkaloid-derived ammonium salts for their use as chiral organocatalysts in enantioselective transformations. The recovery of the organocatalyst is an important problem when scaling up a synthetic procedure, the development of recyclable organocatalyst being therefore attractive for industrial purposes. Particularly interesting has been the preparation of a series of dimeric anthracenyldimethyl-derived ammonium salts from *Cinchona* alkaloids, which have been employed as recoverable organocatalysts in enantioselective reactions such as asymmetric alkylation[11] and Michael addition[12] reactions of glycinate Schiff bases for the enantioselective synthesis of α-amino acids, being also used in enantioselective cyanoformylations.[13] Recently, these dimeric ammonium salts have been employed in the conjugate addition of cyclic β-keto esters and related substrates achieving enantioselectivities up to 94% *ee*.[15] Now we report the use of these dimeric ammonium salts in the alkylation of cyclic β-keto esters leading to the enantioselective generation of quaternary stereocenters.

Results and Discussion

The benzylation of 2-*tert*-butoxycarbonyl-1-indanone **5a** using different dimeric *Cinchona*-derived ammonium salts was used as a model reaction in order to optimize the reaction conditions (Table 1). Thus, 2-*tert*-butoxycarbonyl-1-indanone **5a** reacted with benzyl bromide in the presence of dimeric cinchonidine-derived ammonium salt **3a** (5 mol%) as a phase transfer catalyst using solid potassium carbonate (5 eq) as base and a mixture of toluene/chloroform 7/3 v/v as solvent at room temperature. This solvent mixture has afforded good results when working with this type of dimeric ammonium salts.[11] Under this conditions, the corresponding adduct (*S*)-**6aa**, bearing a new quaternary stereocenter, was obtained in 30% *ee* (Table 1, entry 1), its absolute configuration being assigned according to the HPLC retention time of the corresponding enantiomers in the literature.[8] However, when the *O*-allylated cinchonidine-derived ammonium salt **3b** was used as catalyst under these reaction conditions, the enantioselectivity for (*S*)-**6aa** dropped dramatically (Table 1, entry 2). When the quinine-derived dimeric ammonium salt **3c** was employed as phase-transfer catalyst, the enantioselectivity for (*S*)-**6aa** raised up to 31% (Table 1, entry 3), whereas exchanging the chloride counteranion in **3c** by a tetrafluoroborate **3d** or a hexafluorophosphate **3e**, an anion exchange that increases in some cases the efficiency of these type of dimeric catalysts,[11b] gave rise to lower enantioselections (Table 2, entries 4 and 5).

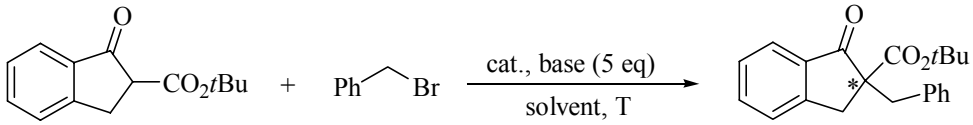


3a, R^1 = H, R^2 = H, X = Cl
3b, R^1 = H, R^2 = allyl, X = Br
3c, R^1 = OMe, R^2 = H, X = Cl
3d, R^1 = OMe, R^2 = H, X = BF_4
3e, R^1 = OMe, R^2 = H, X = PF_6



4a, R = H
4b, R = OMe

Table 1. Enantioselective benzylation of β-keto ester **5a**. Optimization reactions



5a **6aa**

Entry	Catalyst (mol%)	Base	Solvent	*T* (ºC)	*t* (h)	Yield (%)[a]	*ee* (%)[b]
1	**3a** (5)	K_2CO_3 (s)	PhMe/$CHCl_3$	25	5	66	30 (*S*)
2	**3b** (5)	K_2CO_3 (s)	PhMe/$CHCl_3$	25	5	72	5 (*S*)
3	**3c** (5)	K_2CO_3 (s)	PhMe/$CHCl_3$	25	5	61	31 (*S*)
4	**3d** (5)	K_2CO_3 (s)	PhMe/$CHCl_3$	25	5	39	20 (*S*)
5	**3e** (5)	K_2CO_3 (s)	PhMe/$CHCl_3$	25	5	98	24 (*S*)
6	**4a** (5)	K_2CO_3 (s)	PhMe/$CHCl_3$	25	42	98	27 (*R*)
7	**4b** (5)	K_2CO_3 (s)	PhMe/$CHCl_3$	25	43	98	42 (*R*)
8	**4b** (5)	Cs_2CO_3 (s)	PhMe/$CHCl_3$	25	16	98	36 (*R*)
9	**4b** (5)	LiOH (s)	PhMe/$CHCl_3$	25	19	27	0
10	**4b** (5)	NaOH (s)	PhMe/$CHCl_3$	25	16	67	22 (*R*)
11	**4b** (5)	KOH (s)	PhMe/$CHCl_3$	25	1	98	55 (*R*)
12	**4b** (5)	$CsOH{\cdot}H_2O$ (s)	PhMe/$CHCl_3$	25	1	98	48 (*R*)
13	**4b** (5)	$K_3PO_4{\cdot}H_2O$ (s)	PhMe/$CHCl_3$	25	8	98	42 (*R*)
14	**4b** (5)	50% aq KOH	PhMe/$CHCl_3$	25	1	98	30 (*R*)
15	**4b** (5)	KOH (s)	PhMe	25	2	98	50 (*R*)
16	**4b** (5)	KOH (s)	CH_2Cl_2	25	2	98	53 (*R*)
17	**4b** (5)	KOH (s)	PhMe/$CHCl_3$	0	6	98	53 (*R*)
18	**4b** (5)	KOH (s)	PhMe/$CHCl_3$	-40	7	30	16 (*R*)
19	**4b** (5)	iPr_2EtN	CH_2Cl_2	25	3	32	11 (*R*)
20	**4b** (10)	KOH (s)	PhMe/$CHCl_3$	25	2	98	51 (*R*)
21	**3c** (5)	KOH (s)	PhMe/$CHCl_3$	25	1	85	9 (*S*)

[a]Determined by ^{1}H NMR (300 MHz) using diphenylmethane as internal standard. [b]Enantioselectivities and absolute stereochemistry determined by chiral HPLC (see Experimental Section).

When the pseudoenantiomer of **3a**, the cinchonine-derived ammonium salt **4a** was used as phase-transfer catalyst, the expected opposite enantioinduction was observed and the benzylation adduct (*R*)-**6aa** was obtained in 27% *ee* (Table 1, entry 6). However, the use of the pseudoenantiomeric salt of **3c** as catalyst, the quinidine-derived salt **4b**, afforded the corresponding adduct (*R*)-**6aa** in a higher 42% *ee* (Table 1, entry 7). The change of the potassium carbonate as base by cesium carbonate diminished the obtained enantioselectivity for (*R*)-**6aa**.

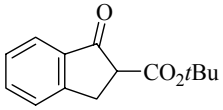
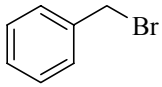
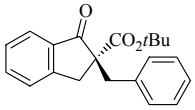
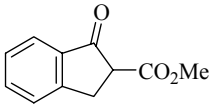
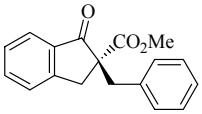
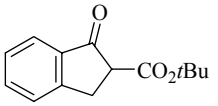
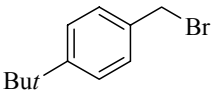
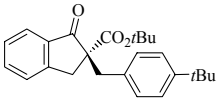
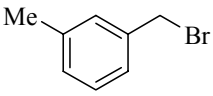
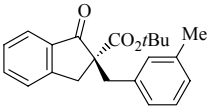
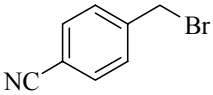
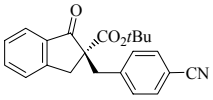
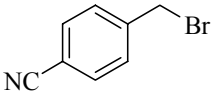
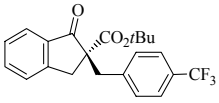
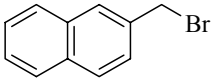
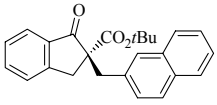
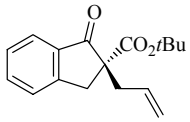
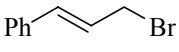
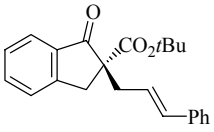
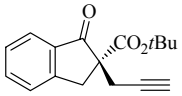
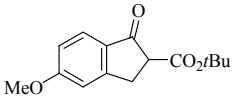
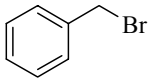
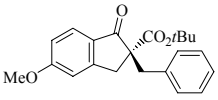
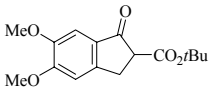
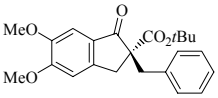
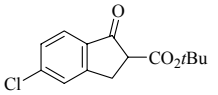
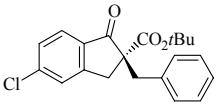
The use of solid hydroxide-based bases was then explored, observing that lithium hydroxide gave no stereoinduction at all (Table 1, entry 9), whereas the use of solid sodium hydroxide afforded 22% *ee* for (*R*)-**6aa** (Table 1, entry 10). When solid potassium carbonate was used as base, the reaction rate increased notably and the benzylated adduct (*R*)-**6aa** was obtained in 55% *ee* (Table 1, entry 11), lower enantioselectivities being obtained when using monohydrated cesium hydroxide or potassium phosphate as solid bases (Table 1, entries 12 and 13). In addition, liquid-liquid phase-transfer catalyzed conditions were attempted using 50% aqueous potassium hydroxide and the mixture toluene/chloroform as solvent at room temperature, but the enantioselectivity for (*R*)-**6aa** resulted in only 30% (Table 1, entry 14).

The use of other solvents such as toluene or dichloromethane under the above mentioned solid-liquid phase-transfer conditions using potassium hydroxide as base, gave slightly lower enantioselectivities for (*R*)-**6aa** than when using the mixture toluene/chloroform 7/3 (Table 1, entries 15 and 16). In addition, lowering the reaction temperature to 0 ºC proved ineffective (Table 1, entry 17), whereas an even lower reaction temperature (-40 ºC) showed clearly detrimental (Table 1, entry 18). Moreover, the use of homogeneous reaction conditions achieved using diisopropylethylamine as base and dichloromethane as solvent, a method that has shown effective in the enantioselective Michael addition reaction of cyclic β-keto esters catalyzed by these dimeric ammonium salts,[15] gave rise to much lower enantioinduction for (*R*)-**6aa** (Table 1, entry 19). Furthermore, using twice the loading of catalyst **4b** (10 eq) did not improve the observed *ee* for (*R*)-**6aa** (Table 1, entry 20). Finally, when the quinine-derived pseudoenantiomeric ammonium salt **3c** was employed as catalyst, instead of **4b**, under the most appropriate reaction conditions conditions, the corresponding (*S*)-**6aa** was obtained in only 9% *ee* (Table 1, entry 21).

Once the most effective catalyst and reaction conditions were established [**4b** (5 mol%), KOH(s), PhMe/$CHCl_3$, 25 ºC], we explored the scope of this enantioselective alkylation reaction by changing the β-keto ester pro-nucleophile and the electrophile, the obtained results using **4b** as phase-transfer organocatalyst being shown in Table 2. Thus, when the *tert*-butyl group present in the starting pro-nucleophile **5a** was changed by the methyl group present in **5b**, the corresponding adduct (*R*)-**6ba** was obtained, after reaction with benzyl bromide, in a much lower enantioselectivity (24% *ee*) (Table 2, compare entries 1 and 2). Therefore, a *tert*-butyl was set as the group of choice.

Then we proceed to check the influence of different substituents on the aromatic ring of the electrophile. Thus, the presence of a *tert*-butyl or a methyl group gave rise to lower and similar enantioselectivities for the corresponding adducts (*R*)-**6ab** and (*R*)-**6ac**, respectively (Table 2, entries 3 and 4), whereas the presence of electron-withdrawing substituents such as cyano or trifluoromethyl groups raised up again slightly the enantioselectivity for the corresponding adducts (*R*)-**6ad** and (*R*)-**6ae** (Table 2, entries 5 and 6). Moreover, using 2-(bromomethyl)naphthalene as electrophile in the alkylation of **5a**, the alkylated adduct (*R*)-**6af** was obtained in 50% *ee* (Table 2, entry 7).

Table 2. Enantioselective alkylation organocatalyzed by ammonium salt **4b**[a]

Entry	Keto ester	No.	Electrophile	t (h)	Product	No.	Yield (%)b	ee (%)c
1		**5a**		1		**6aa**	98	55
2		**5b**		1		**6ba**	87	24
3		**5a**		2		**6ab**	98	48
4		**5a**		5		**6ac**	86	47
5		**5a**		3		**6ad**	89	50
6		**5a**		1		**6ae**	97	52
7		**5a**		1		**6af**	98	50
8		**5a**		2		**6ag**	59	41
9		**5a**		2		**6ah**	98	48
10		**5a**		8		**6ai**	92	40
11		**5c**		2		**6ca**	98	40
12		**5d**		2		**6da**	86	33
13		**5e**		2		**6ea**	98	38

[a] Reaction conditions: Catalyst **4b** (5 mol%), KOH (s) (5 eq), PhMe/$CHCl_3$ (7/3 v/v), 25 ºC. [b] Determined by ^1H NMR (300 MHz) using diphenylmethane as internal standard. [c] Enantioselectivities and absolute stereochemistry determined by chiral HPLC (see Experimental Section).

In addition, the use of allylic bromides as electrophiles was also attempted, giving rise to the products (*R*)-**6ag** and (*R*)-**6ah** in 41 and 48% *ee* when using allyl bromide and (*E*)-(3-bromoprop-1-en-1-yl)benzene, respectively, as allylating reagents (Table 2, entries 8 and 9). Furthermore, the use of propargyl bromide as electrophile afforded the corresponding adduct (*R*)-**6ai** in 40% *ee* (Table 2, entry 10).

We also explored the influence of substituents on the β-keto ester pro-nucleophile on the enantioselectivity of the benzylation reaction. Thus the use of indanone **5c** bearing a 5-methoxy group was not beneficial and the adduct (*R*)-**6ca** was obtained in 40% *ee*, a value that was lower when using as pro-nucleophile the 5,6-dimethoxy-containing indanone **5d** (Table 2, entries 11 and 12). In addition, the use of 5-chloro-containing indanone **5e** gave rise to the corresponding adduct (*R*)-**6ea** in 38% *ee* (Table 2, entry 13).

It is interesting to remark that the ammonium salt **4b** can be recovered by filtration in a 95% yield, once the reaction was completed, after separation of the base by filtration, evaporation of the solvent and addition of ethyl ether. The recovered ammonium salt has been reused up to three times in the model reaction (Table 2, entry 1) giving rise to almost identical yields and enantioselectivities.

We conclude that quaternary stereocenters can be created in moderate enantioselectivity and usually high yields by an alkylation reaction between cyclic β-keto esters using *Cinchona*-derived dimeric ammonium as chiral organocatalysts under solid-liquid phase-transfer conditions. The corresponding quinine-derived ammonium salt gave opposite enantioselectivity that its pseudoenantiomer from quinidine, which afforded higher enantioselection values. These organocatalysts can be separated from the reaction medium by precipitation in ether, and reused without loss of activity.

Experimental Section

General. All the reagents and solvents employed were of the best grade available and were used without further purification. Melting points are uncorrected. IR data were collected on a Nicolet Impact 400D-FT spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded at 25 ºC on a Bruker AC-300 or a Bruker Advance 400 at 300 MHz and 75 MHz, and 400 MHz and 100 MHz, respectively, using $CDCl_3$ as solvent and TMS as internal standard. MS (EI, 70 eV) were performed on a HP MS-GC-5973A. HRMS analyses were carried out on a Finnigan MAT 95S. Elemental analysis were performed on a Carlo Erba CHNS-O EA1108 analyzer. Enantioselectivities were determined by chiral HPLC using Chiralcel columns and *n*-hexane/2-propanol mixtures as eluent. Reference racemic samples of adducts **6** were obtained by performing the enantioselective alkylation reaction using *n*-tetrabutylammonium bromide as catalyst.

Ammonium salts **3a**,[13b] **3b**,[11a] **3c-e**,[15] **4a**[13b] and **4b**[15] have been prepared following reported procedures. Compounds **5** were prepared following a literature procedure.[16] Absolute

configuration for adducts **6aa**,**ag**,**ah**[8] and **6ba**[10] was determined according to the described order of elution of their enantiomers in chiral HPLC. The absolute configuration of other adducts was assigned by analogy.

Alkylation reactions under PTC conditions. Typical procedure. To a mixture of **5a** (232 mg, 1 mmol) and **4b** (46 mg, 0.05 mmol) in toluene/chloroform (7/3) (6 mL) was added benzyl bromide (143 μL, 1.2 mmol) and KOH (281 mg, 5 mmol) at room temperature. The mixture was stirred during 1h until reaction completion (TLC) and filtered to remove the solid base. The solvent was evaporated (15 Torr) and diethyl ether (6 mL) was added to precipitate **4b** which was recovered by filtration. The filtrate was diluted with water (20 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with water and brine, dried ($MgSO_4$), filtered and evaporated in vacuo (15 Torr) to afford (*R*)-**4aa**.
Analytical and spectroscopical data for compounds **6aa**,**ag**,**ah**[8] and **6ba**[10] have been reported. Data for the other obtained compounds **6** follow.
(*R*)-*tert*-Butyl 2-(4-(*tert*-butyl)benzyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (6ab). Colorless oil, IR (film) (ν_{max}, cm^{-1}): 738, 844, 921, 1020, 1150, 1215, 1252, 1367, 1464, 1608, 1709, 1738 and 2963. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 1.24 (9H, s, $C_6H_4C(CH_3)_3$), 1.38 (9H, s, $CO_2C(CH_3)_3$), 3.12 (1H, d, $^2J_{HH}$ = 17.3 Hz, C(3)-H_A indanone), 3.16 (1H, d, $^2J_{HH}$ = 13.9 Hz, $CH_AH_BC_6H_4C(CH_3)_3$), 3.45 (1H, d, $^2J_{HH}$ = 14.2 Hz, $CH_AH_BC_6H_4C(CH_3)_3$), 3.57 (1H, d, $^2J_{HH}$ = 17.2 Hz, C(3)-H_B indanone), 7.08 (2H, d, $^3J_{HH}$ = 8.3 Hz, $C_6H_4C(CH_3)_3$), 7.19 (2H, d, $^3J_{HH}$ = 8.4 Hz, $C_6H_4C(CH_3)_3$), 7.30-7.36 (2H, m, C(4)-H, C(6)-H indanone), 7.51 (1H, td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.2 Hz, C(5)-H indanone), 7.73 (1H, d, $^3J_{HH}$ = 7.7 Hz, C(7)-H indanone). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 27.8 ($CO_2C(CH_3)_3$), 31.2 ($C_6H_4C(CH_3)_3$), 34.3 ($C_6H_4C(CH_3)_3$), 35.7 and 38.9 (2C, $CH_2C_6H_4C(CH_3)_3$ and C(3) indanone), 62.7 (C(2) indanone), 82.0 ($CO_2C(CH_3)_3$), 124.5, 125.0, 126.1, 127.3, 129.6, 133.8, 134.9, 135.3, 149.4 and 153.4 (10C, ArC), 169.7 ($CO_2C(CH_3)_3$), 202.6 (C=O indanone). MS, m/z (%) = 322 (M-C_4H_8, 67), 277 (100). HRMS (EI), m/z calcd for $C_{21}H_{22}O_3$ (M-C_4H_8) 322.1569, found 322.1891. HPLC: Daicel Chiralpak AD-H, λ = 210 nm, *n*-hexane/2-propanol, 99:1, 1.0 mL/min, t_r = 6.9, 7.9 min (26:74).
(*R*)-*tert*-Butyl 2-(3-methylbenzyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (6ac). Colorless oil, IR (film) (ν_{max}, cm^{-1}): 702, 748, 781, 846, 936, 1027, 1152, 1215, 1255, 1368, 1464, 1607, 1711, 1737, 2927 and 2977. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 1.38 (9H, s, $C(CH_3)_3$), 2.24 (3H, s, CH_3), 3.11 (1H, d, $^2J_{HH}$ = 17.2 Hz, C(3)-H_A indanone), 3.18 (1H, d, $^2J_{HH}$ = 14.0 Hz, $CH_AH_BC_6H_4CH_3$), 3.43 (1H, d, $^2J_{HH}$ = 14.1 Hz, $CH_AH_BC_6H_4CH_3$), 3.56 (1H, d, $^2J_{HH}$ = 17.2 Hz, C(3)-H_B indanone), 6.97-6.93 (3H, m, Ar-H), 7.08-7.04 (1H, m, Ar-H), 7.35-7.29 (2H, m, Ar-H), 7.51 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, C(5)-H indanone), 7.73 (1H, d, $^3J_{HH}$ = 7.7 Hz, C(7)-H indanone). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 21.3 ($C_6H_4CH_3$), 27.7 ($CO_2C(CH_3)_3$), 35.6 and 39.3 (2C, $CH_2C_6H_4CH_3$ and C(3) indanone), 62.5 (C(2) indanone), 82.0 ($CO_2C(CH_3)_3$), 124.4, 126.1, 126.9, 127.3, 127.4, 128.0, 130.7, 135.0, 135.4, 136.8, 137.7 and 153.4 (12C, ArC), 169.7 ($CO_2C(CH_3)_3$), 202.6 (C=O indanone). MS, m/z (%) = 280 (M-C_4H_8, 75), 235 (100). HRMS

(EI), m/z calcd for $C_{18}H_{16}O_3$ (M-C_4H_8) 280.1099, found 280.1082. HPLC: Daicel Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 99:1, 0.5 mL/min, t_r = 13.4, 15.4 min (26:74).

(*R*)-*tert*-Butyl 2-(4-cyanobenzyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (6ad). White solid, mp 118-120 ºC, IR (KBr) (ν_{max}, cm^{-1}): 574, 737, 762, 848, 857, 1142, 1243, 1289, 1369, 1608, 1705, 1739, 2231, 2932 and 2972. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.36 (9H, s, $C(CH_3)_3$), 3.04 (1H, d, $^2J_{HH}$ = 17.2 Hz, C(3)-H_A indanone), 3.33 (1H, d, $^2J_{HH}$ = 14.1 Hz, CH_AH$_B$C$_6$H$_4$CN), 3.45 (1H, d, $^2J_{HH}$ = 14.1 Hz, CH$_A$$H_BC_6H_4$CN), 3.58 (1H, d, $^2J_{HH}$ = 17.2 Hz, C(3)-H_B indanone), 7.28 (2H, d, $^3J_{H,H}$ = 8.2 Hz, C$_6$$H_4$CN), 7.32-7.37 (2H, m, C(4)-H, C(6)-H indanone), 7.47 (2H, d, $^3J_{HH}$ = 8.2 Hz, C$_6$$H_4$CN), 7.55 (1H, td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.0 Hz, C(5)-H indanone), 7.73 (1H, d, $^3J_{HH}$ = 7.3 Hz, C(7)-H indanone). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 27.7 ($CO_2C(CH_3)_3$), 35.7 and 39.2 (2C, $CH_2C_6H_4CN$ and C(3) indanone), 61.8 (C(2) indanone), 82.5 ($CO_2C(CH_3)_3$), 110.6 (ArC), 118.7 (CN), 124.6, 126.1, 127.7, 130.7, 131.9, 135.1, 135.4, 142.5 and 152.8 (9C, ArC), 169.3 ($CO_2C(CH_3)_3$), 202.0 (C=O indanone). MS, m/z (%) = 247 (M-$CO_2C_4H_8$, 41), 131 (100). HRMS (EI), m/z calcd for $C_{17}H_{13}NO$ (M-$CO_2C_4H_8$) 247.0997, found 247.0983. Anal. Calcd for $C_{22}H_{21}NO_3$ (347.15): C, 76.06; H, 6.09; N, 4.03%, Found: C, 76.05; H, 6.10; N, 3.99%. HPLC: DAICEL Chiralcel OD-H, λ = 210 nm, *n*-hexane/2-propanol, 95:5, 1.0 mL/min, t_r = 9.7, 11.5 min (75:25).

(*R*)-*tert*-Butyl 1-oxo-2-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1*H*-indene-2-carboxylate (6ae). White solid, mp 87-89 ºC, IR (KBr) (ν_{max}, cm^{-1}): 764, 821, 847, 908, 1015, 1068, 1125, 1158, 1235, 1324, 1607, 1617, 1700, 1717, 2919, 2969 and 2990. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.37 (9H, s, $C(CH_3)_3$), 3.06 (1H, d, $^2J_{HH}$ = 17.2 Hz, C(3)-H_A indanone), 3.31 (1H, d, $^2J_{HH}$ = 14.1 Hz, CH_AH$_B$C$_6$H$_4$CF$_3$), 3.49 (1H, d, $^2J_{HH}$ = 14.1 Hz, CH$_A$$H_BC_6H_4CF_3$), 3.58 (1H, d, $^2J_{HH}$ = 17.2 Hz, C(3)-H_B indanone), 7.32-7.27 (2H, m, C(4)-H, C(6)-H indanone), 7.35 (2H, d, $^3J_{HH}$ = 7.5 Hz, C$_6$$H_4CF_3$), 7.44 (2H, d, $^3J_{HH}$ = 8.1 Hz, C$_6$$H_4CF_3$), 7.54 (1H, td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 0.9 Hz, C(5)-H indanone), 7.74 (1H, d, $^3J_{HH}$ = 7.6 Hz, C(7)-H indanone). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 27.7 ($CO_2C(CH_3)_3$), 35.7 and 38.9 (2C, $CH_2C_6H_4CF_3$ and C(3) indanone), 62.1 (C(2) indanone), 82.4 ($CO_2C(CH_3)_3$), 124.6, 125.1, 125.1, 125.2, 126.1, 127.6, 130.3, 135.2, 135.3, 141.1 and 153.0 (11C, 10 x ArC and CF_3), 169.4 ($CO_2C(CH_3)_3$), 202.2 (C=O indanone). MS, m/z (%) = 334 (M-C_4H_8, 45), 157 (100). HRMS (EI), m/z calcd for $C_{18}H_{13}F_3O_3$ (M-C_4H_8) 334.0817, found 334.0844. Anal. Calcd for $C_{22}H_{21}F_3O_3$ (390.14): C, 67.68; H, 5.42%, Found: C, 67.80; H, 5.35%. HPLC: Daicel Chiralcel OD-H, λ = 210 nm, *n*-hexane/2-propanol, 99:1, 1.0 mL/min, t_r = 6.3, 7.3 min (76:24).

(*R*)-*tert*-Butyl 2-(naphthalen-2-ylmethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (6af). White solid, mp 77-79 ºC, IR (KBr) (ν_{max}, cm^{-1}): 729, 747, 811, 845, 1152, 1282, 1368, 1437, 1464, 1604, 1709, 1726, 2924 and 2978. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.39 (9H, s, $C(CH_3)_3$), 3.17 (1H, d, $^2J_{HH}$ = 17.2 Hz, C(3)-H_A indanone), 3.42 (1H, d, $^2J_{HH}$ = 14.1 Hz, CH_AH$_B$Naph), 3.58 (1H, d, $^2J_{HH}$ = 17.2 Hz, C(3)-H_B indanone), 3.62 (1H, d, $^2J_{HH}$ = 14.1 Hz, CH$_A$$H_B$Naph), 7.32-7.27 (3H, m, Ar-H), 7.42-7.38 (2H, m, Ar-H), 7.48 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.1 Hz, Ar-H), 7.66-7.62 (2H, m, Ar-H), 7.75-7.71 (3H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 27.8 ($CO_2C(CH_3)_3$), 35.6 and 39.4 (2C, CH_2Np and C(3) indanone), 62.5 (C(2) indanone), 82.1

($CO_2C(CH_3)_3$), 124.5, 125.5, 125.9, 126.1, 127.4, 127.5, 127.5, 127.8, 128.2, 128.7, 132.2, 133.2, 134.5, 135.0, 135.3 and 153.3 (16C, ArC), 169.7 ($CO_2C(CH_3)_3$), 202.6 (C=O indanone). MS, m/z (%) = 272 (M-$CO_2C_4H_8$, 52), 141 (100). HRMS (EI), m/z calcd for $C_{20}H_{16}O$ (M-$CO_2C_4H_8$) 272.1201, found 272.1201. Anal. Calcd for $C_{25}H_{24}O_3$ (372.17): C, 80.62; H, 6.49%, Found: 80.31; H, 6.42%. HPLC: Daicel Chiralpak AD-H, λ = 210 nm, *n*-hexane/2-propanol, 97:3, 1.0 mL/min, t_r = 10.9, 12.3 min (25:75).

(*R*)-*tert*-Butyl 1-oxo-2-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-indene-2-carboxylate (6ai). White solid, mp 93-95 ºC, IR (KBr) (ν_{max}, cm^{-1}): 646, 664, 771, 844, 935, 1034, 1147, 1158, 1255, 1292, 1333, 1370, 1429, 1466, 1606, 1701, 1729, 2935, 2983 and 3287. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.37 (9H, s, $C(CH_3)_3$), 1.81 (1H, t, $^4J_{HH}$ = 2.6 Hz, $CH_AH_BC{\equiv}C\mathit{H}$), 2.79 (1H, dd, $^2J_{HH}$ = 16.8 Hz, $^4J_{HH}$ = 2.6 Hz, $C\mathit{H}_AH_BC{\equiv}CH$), 2.96 (1H, dd, $^2J_{HH}$ = 16.8 Hz, $^4J_{HH}$ = 2.6 Hz, $CH_A\mathit{H}_BC{\equiv}CH$), 3.35 (1H, d, $^2J_{HH}$ = 17.2 Hz, C(3)-H_A indanone), 3.65 (1H, d, $^2J_{HH}$ = 17.3 Hz, C(3)-H_B indanone), 7.39 (1H, t, $^3J_{HH}$ = 7.7 Hz, C(6)-H indanone), 7.51 (1H, d, $^3J_{HH}$ = 7.7 Hz, C(4)-H indanone), 7.63 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.1 Hz, C(5)-H indanone), 7.77 (1H, d, $^3J_{HH}$ = 7.7 Hz, C(7)-H indanone). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 23.6 ($\mathit{C}H_2C{\equiv}CH$), 27.6 ($CO_2C(\mathit{C}H_3)_3$), 36.7 (C(3) indanone), 59.7 (C(2) indanone), 70.2 (C≡*C*H), 79.6 and 82.3 (2C, $CO_2\mathit{C}(CH_3)_3$ and *C*≡CH), 124.6, 126.2, 127.6, 135.2, 135.3 and 153.4 (6C, ArC), 168.9 ($\mathit{C}O_2C(CH_3)_3$), 201.4 (C=O indanone). MS, m/z (%) = 214 (M-C_4H_8, 77), 157 (100). HRMS (EI), m/z calcd for $C_{13}H_{10}O_3$ (M-C_4H_8) 214.0630, found 214.0518. Anal. Calcd for $C_{17}H_{18}O_3$ (270.13): C, 75.53; H, 6.71%, Found: C, 74.97; H, 6.68%. HPLC: Daicel Chiralpak AD-H, λ = 210 nm, *n*-hexane/2-propanol, 99:1, 0.5 mL/min, t_r = 19.4, 21.8 min (30:70).

(*R*)-*tert*-Butyl 2-benzyl-5-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (6ca). Colorless oil, IR (film) (ν_{max}, cm^{-1}): 702, 844, 1027, 1090, 1153, 1262, 1368, 1454, 1493, 1600, 1705, 1735, 2931 and 2977. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.39 (9H, s, $C(CH_3)_3$), 3.05 (1H, d, $^2J_{HH}$ = 17.2 Hz, C(3)-H_A indanone), 3.24 (1H, d, $^2J_{HH}$ = 14.1 Hz, $C\mathit{H}_AH_BPh$), 3.42 (1H, d, $^2J_{HH}$ = 14.1 Hz, $CH_A\mathit{H}_BPh$), 3.52 (1H, d, $^2J_{HH}$ = 17.2 Hz, C(3)-H_B indanone), 3.83 (3H, s, C(5)-OCH_3), 6.76 (1H, d, $^2J_{HH}$ = 1.9 Hz, C(4)-H indanone), 6.84 (1H, dd, $^3J_{HH}$ = 8.5 Hz, $^2J_{HH}$ = 2.2 Hz, C(6)-H indanone), 7.18-7.10 (5H, m, Ph), 7.65 (1H, d, $^3J_{HH}$ = 8.5 Hz, C(7)-H indanone). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 27.7 ($CO_2C(\mathit{C}H_3)_3$), 35.5 and 39.3 (2C, $\mathit{C}H_2Ph$ and C(3) indanone), 55.5 (OCH_3), 62.6 (C(2) indanone), 81.9 ($CO_2\mathit{C}(CH_3)_3$), 109.1, 115.5, 126.2, 126.5, 128.1, 128.5, 129.9, 137.0, 156.4 and 165.5 (10C, ArC), 169.9 ($\mathit{C}O_2C(CH_3)_3$), 200.6 (C=O indanone). MS, m/z (%) = 296 (M-C_4H_8, 44), 161 (100). HRMS (EI), m/z calcd for $C_{18}H_{16}O_4$ (M-C_4H_8) 296.1049, found 296.1057. HPLC: Daicel Chiralcel OD-H, λ = 210 nm, *n*-hexane/2-propanol, 97:3, 1.0 mL/min, t_r = 8.8, 10.3 min (70:30).

(*R*)-*tert*-Butyl 2-benzyl-5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (6da). Pale brown solid, mp 158-160 ºC, IR (KBr) (ν_{max}, cm^{-1}): 706, 864, 1029, 1109, 1151, 1223, 1276, 1315, 1368, 1455, 1471, 1501, 1592, 1703, 2937 and 2981. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.39 (9H, s, $C(CH_3)_3$), 3.01 (1H, d, $^2J_{HH}$ = 17.0 Hz, C(3)-H_A indanone), 3.27 (1H, d, $^2J_{HH}$ = 14.1 Hz, $C\mathit{H}_AH_BPh$), 3.41 (1H, d, $^2J_{HH}$ = 14.3 Hz, $CH_A\mathit{H}_BPh$), 3.46 (1H, d, $^2J_{HH}$ = 16.9 Hz, C(3)-H_B indanone), 3.91, 3.89 (6H, 2 x s, C(5)-OCH_3, C(6)-OCH_3), 6.75 (1H, s, C(4)-H indanone),

7.16-7.13 (6 H, m, C(7)-H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 27.8 ($CO_2C(CH_3)_3$), 35.3 and 39.3 (2C, CH_2Ph and C(3) indanone), 56.0 and 56.1 (2C, C(5)-OCH_3 and C(6)-OCH_3), 62.6 (C(2) indanone), 81.9 ($CO_2C(CH_3)_3$), 104.7, 106.9, 126.5, 128.1, 128.1, 129.9, 137.0, 148.9, 149.4 and 155.7 (10C, ArC), 170.1 ($CO_2C(CH_3)_3$), 201.1 (C=O indanone). MS, m/z (%) = 282 (M-$CO_2C_4H_8$, 81), 191 (100). HRMS (EI), m/z calcd for $C_{18}H_{18}O_3$ (M-$CO_2C_4H_8$) 282.1256, found 282.1260. Anal. Calcd for $C_{23}H_{26}O_5$ (382.18): C, 72.23; H, 6.85%, Found: C, 71.63; H, 6.85%. HPLC: Daicel Chiralcel OD-H, λ = 210 nm, *n*-hexane/2-propanol, 92:8, 1.0 mL/min, t_r = 8.3, 9.9 min (67:33).

(*R*)-*tert*-Butyl 2-benzyl-5-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (6ea). White solid, mp 95-96 ºC, IR (KBr) (ν_{max}, cm^{-1}): 701, 841, 935, 1148, 1250, 1368, 1423, 1578, 1601, 1706, 1733, 2931 and 2977. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.38 (9 H, s, $C(CH_3)_3$), 3.09 (1 H, d, $^2J_{HH}$ = 17.4 Hz, C(3)-H_A), 3.29 (1 H, d, $^2J_{HH}$ = 14.1 Hz, C$H_A$$H_B$Ph), 3.39 (1 H, d, $^2J_{HH}$ = 14.0 Hz, CH_AH_BPh), 3.53 (1 H, d, $^2J_{HH}$ = 17.5 Hz, C(3)-H_B), 7.12-7.21 (5 H, m, Ph), 7.28-7.32 (2 H, m, C(4)-H, C(6)-H), 7.64 (1 H, d, $^3J_{HH}$ = 8.1 Hz, C(7)-H). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 27.7 ($CO_2C(CH_3)_3$), 35.2 and 39.2 (2C, CH_2Ph and C(3) indanone), 62.5 (C(2) indanone), 82.3 ($CO_2C(CH_3)_3$), 125.5, 126.3, 126.8, 128.3, 128.3, 129.9, 133.9, 136.4, 141.5 and 154.7, (10C, ArC), 169.4 ($CO_2C(CH_3)_3$), 201.3 (C=O indanone). MS, m/z (%) = 300 (M-C_4H_8, 63), 91 (100). HRMS (EI), m/z calcd for $C_{17}H_{13}ClO_3$ (M-C_4H_8) 300.0553, found 300.0539. Anal. Calcd for $C_{21}H_{21}ClO_3$ (356.12): C, 70.68; H, 5.93%, Found: C, 71.18; H, 5.88%. HPLC: Daicel Chiralcel OD-H, λ = 210 nm, *n*-hexane/2-propanol, 99:1, 0.5 mL/min, t_r = 15.9, 18.7 min (69:31).

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