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Recoverable *Cinchona* ammonium salts as organocatalysts in the enantioselective Michael addition of β-keto esters

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Dedicated to the memory of Professor Rafael Suan

ABSTRACT

Several dimeric *Cinchona*-alkaloid anthracenyldimethyl-derived ammonium salts, are used as organocatalysts in the enantioselective Michael addition reaction of cyclic β-keto esters to α,β-unsaturated carbonyl compounds, in the presence of diisopropylethylamine as a base (30 mol %), for the generation of enantiomerically enriched adducts bearing quaternary stereocenters. Quinine and quinidine-derived dimeric ammonium salts (1–10 mol %) afford the opposite and higher enantioselectivities of the corresponding adducts (up to 94% ee) in good yields (up to 98%). Substituted 2-alkoxycarbonyl-1-indanones are used as nucleophile precursors, as well as ethyl 2-oxocyclopentanecarboxylate and *tert*-butyl 2,5-dioxo-1-phenylpyrrolidine-3-carboxylate. These organocatalysts can be recovered at the end of the reaction by precipitation in ether and reused without any loss of activity.

1. Introduction

Enantioselective organocatalysis is one of the most fast growing topics in organic chemistry, with many organic reactions performed enantioselectively by the use of chiral organocatalysts.[1] For instance, the Michael addition reaction, one of the most basic organic transformations,[2] has been studied intensively in its enantioselective version when using organocatalysts.[3] However, these studies have been much less frequent with regards to its use in the enantioselective generation of a quaternary stereogenic center, probably one of the most challenging tasks for a synthetic organic chemist.[4]

Non-organocatalytic enantioselective Michael reactions using α-substituted β-keto esters leading to quaternary stereocenters have been performed using metal-derived chiral catalysts,[3a,5,6] although many of them suffer from typical drawbacks associated with metal complexes, such as air and moisture sensitivity, thus hampering large scale implementation. Thus, more convenient metal-free organocatalytic procedures for the enantioselective Michael addition of cyclic β-keto esters leading to quaternary stereocenters have been based mainly on the use of the very popular *Cinchona* alkaloids[7] as organocatalytic chiral tertiary bases.[3,8,9]

However, despite the fact that *Cinchona* alkaloid-derived ammonium salts are frequently used as chiral organocatalysts, especially when dealing with phase-transfer processes,[7,10] they have scarcely been used in this transformation. Quinine and cinchonidine-derived ammonium salts have been used as organocatalysts in the enantioselective Michael addition of cyclic β-keto esters, affording enantioselectivities only up to 28%.[8b,11]

In the few last years, we have been working on developing recoverable unsupported[12–14] and supported[15] *Cinchona* alkaloid-derived ammonium salts for their use in organocatalyzed enantioselective reactions. The recovery of the organocatalyst is very often a problem when scaling up a synthetic procedure and the use of an easily recyclable organocatalyst always adds an extra value to the methodology. Of particularly interest 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 transformations, such as asymmetric alkylation[12] and Michael addition[13] reactions of glycinate Schiff bases for the enantioselective synthesis of α-amino acids. Recently, they have also been employed in the enantioselective cyanoformylation of aldehydes.[14] Herein, we report the use of these dimeric ammonium salts as recoverable organocatalysts in the conjugate addition of cyclic β-keto esters and related substrates to Michael acceptors for the enantioselective generation of quaternary stereocenters.[16]

2. Results and discussion

For the first screening reactions, we used the dimeric cinchonidine-derived ammonium salt **1a**[12,13] as the organocatalyst (5 mol %), 2-*tert*-butoxycarbonyl-1-indanone **3a** as the model cyclic β-keto ester, and methyl vinyl ketone (3 equiv) as the Michael acceptor (Table 1). When diisopropylethylamine was used as the base (30 mol %) and dichloromethane as the solvent at room temperature, the corresponding Michael reaction took place in excellent

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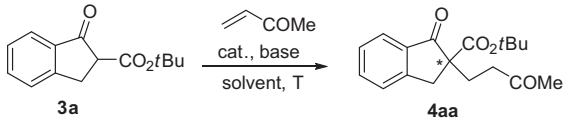
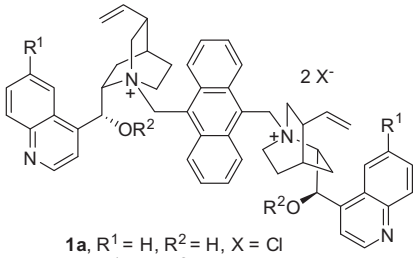
Table 1
Screening and optimization of the reaction conditions for the enantioselective Michael addition



Entry	Cat. (mol %)	Base	Solvent	T (°C)	t (h)	Yield[a] (%)	ee[b] (%)
1	**1a** (5)	iPr$_2$EtN	CH_2Cl_2	25	8	94	36 (*S*)
2	**1b** (5)	iPr$_2$EtN	CH_2Cl_2	25	9	85	5 (*S*)
3	**1c** (5)	iPr$_2$EtN	CH_2Cl_2	25	9	98	52 (*S*)
4	**1c** (5)	Et_3N	CH_2Cl_2	25	16	98	36 (*S*)
5	**1c** (5)	$PhCO_2K$	CH_2Cl_2	25	45	98	16 (*S*)
6	**1c** (5)	K_2CO_3	CH_2Cl_2	25	2	85	32 (*S*)
7	**1c** (5)	K_2CO_3	PhMe/$CHCl_3$	25	2	72	26 (*S*)
8	**1c** (5)	$PhCO_2K$	PhMe/$CHCl_3$	25	43	67	21 (*S*)
9	**1c** (5)	iPr$_2$EtN	CH_2Cl_2	0	16	70	50 (*S*)
10	**1c** (5)	iPr$_2$EtN	CH_2Cl_2	−20	16	59	64 (*S*)
11	**1c** (5)	iPr$_2$EtN	CH_2Cl_2	−40	20	98	68 (*S*)
12	**1d** (5)	iPr$_2$EtN	CH_2Cl_2	−40	4	75	33 (*S*)
13	**1e** (5)	iPr$_2$EtN	CH_2Cl_2	−40	2	98	2 (*S*)
14	**2** (5)	iPr$_2$EtN	CH_2Cl_2	−40	8	98	73 (*R*)
15	**2** (1)	iPr$_2$EtN	CH_2Cl_2	−40	14	87	73 (*R*)

[a] Determined by ^{1}H NMR (300 MHz) using diphenylmethane as the internal standard.
[b] The enantioselectivities and absolute stereochemistry were determined by chiral HPLC (see Section 4).

yield, but the corresponding adduct **4a** was obtained as the (*S*)-enantiomer in only 36% ee (Table 1, entry 1). The use of an O-allylated cinchonidine-derived ammonium salt **1b**[12,13] led to a considerable decrease in the enantioselectivity (Table 1, entry 2), but when the O-free quinine-derived dimeric ammonium salt **1c**[16] was employed, the enantioselectivity for (*S*)-**4a** increased up to 52% in excellent chemical yield in 9 h reaction time (Table 1, entry 3).



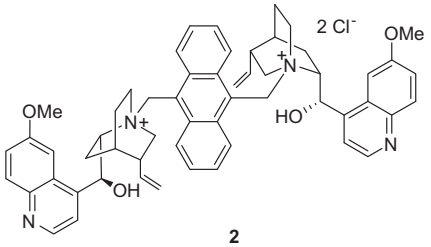
1a, R^1 = H, R^2 = H, X = Cl
1b, R^1 = H, R^2 = allyl, X = Br
1c, R^1 = OMe, R^2 = H, X = Cl
1d, R^1 = OMe, R^2 = H, X = BF_4
1e, R^1 = OMe, R^2 = H, X = PF_6

Attempts to improve the enantioselectivity by changing the base to triethylamine (Table 1, entry 4), potassium benzoate (Table 1, entry 5) or potassium carbonate (Table 1, entry 6) in dichloromethane as the solvent were unsuccessful, and lower enantioselectivities for (*S*)-**4aa** were observed. Changing the solvent from dichloromethane to a mixture of toluene/chloroform (7:3 v/v), which is usually effective in enantioselective phase-transfer reactions involving these dimeric ammonium salts,[12] was not effective when potassium benzoate or potassium carbonate was used as the base (Table 1, entries 7 and 8).

Lowering the reaction temperature was next explored. When the quinine-derived ammonium salt **1c** was used as the organocatalyst and diisopropylethylamine as the base in dichloromethane as the solvent, a reaction temperature of 0 °C did not produce any improvement in the enantioselectivity of the reaction compared to when working at 25 °C (Table 1, compare entries 3 and 9). However, when the reaction temperature was lowered to −20 °C, the Michael adduct (*S*)-**4aa** was obtained in 64% ee (Table 1, entry 10); when at −40 °C, 68% ee in excellent chemical yield was obtained (Table 1, entry 11). Decreasing the reaction temperature further, did not improve the enantioselectivity, only giving rise to much larger reaction times.

Changing the counteranion from a chloride **1c** to a tetrafluoroborate **1d** or hexafluorophosphate **1e**[16] in the quinine-derived organocatalyst, something that was usually beneficial for enantioinduction by strong ion-pair interactions using dimeric ammonium salts,[12b] decreased the enantioselectivity for (*S*)-**4aa** (Table 1, entries 12 and 13).

With the aim of obtaining an opposite enantioselection, we performed this enantioselective Michael reaction using the quinidine-derived dimeric ammonium salt **2**, which can be considered a pseudoenantiomer of the quinine-derived counterpart **1c**.[16] This was confirmed by the isolation of the corresponding opposite Michael adduct (*R*)-**4aa** in an excellent yield and with an even higher enantioselection (73% ee) (Table 1, entry 14). We also explored the possibility of lowering the catalyst loading and performed the reaction with only 1 mol % of **2**, obtaining (*R*)-**4aa** with the same enantioselectivity when using 5 mol %, although a longer reaction time was required (Table 1, entry 15).



2

With the most appropriate ammonium salt **2** and convenient reaction conditions (diisopropylethylamine as base, dichloromethane as solvent, −40 °C reaction temperature) established, we proceeded to extend the procedure to other β-keto esters and other Michael acceptors (Table 2). We decided to use the lowest amount of organocatalyst (1 mol %) possible unless we observed too slow reaction rates.

Changing the 2-*tert*-butyloxycarbonyl on 1-indanone **3** to a 2-methyloxycarbonyl group **3b** gave (*R*)-**4ba** in excellent yield in the reaction with methyl vinyl ketone, although with a lower

Table 2
Enantioselective Michael addition reaction organocatalyzed by quinidine-derived dimeric ammonium salt **2**[a]

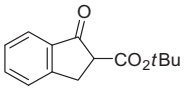
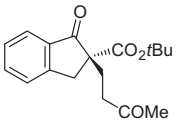
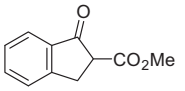
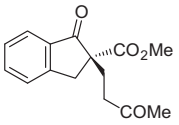
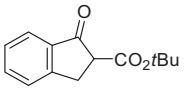
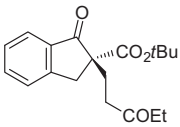
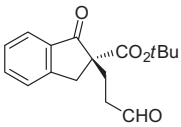
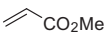
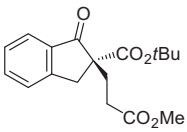
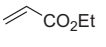
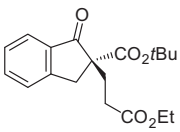
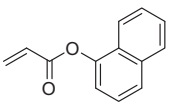
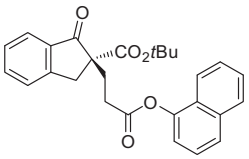
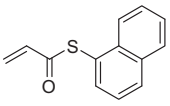
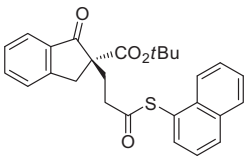
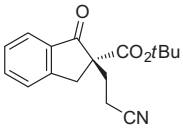
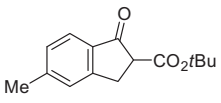
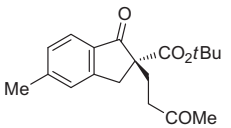
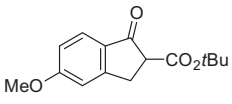
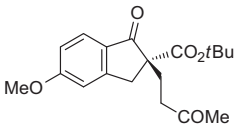
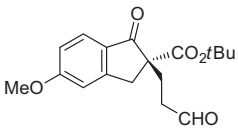
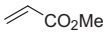
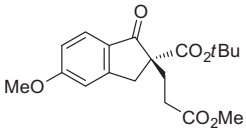
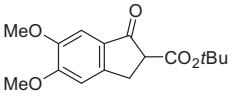
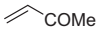
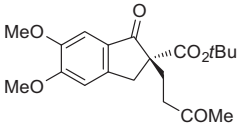
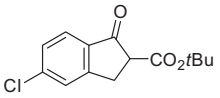
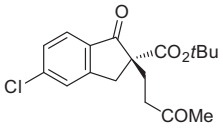
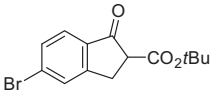
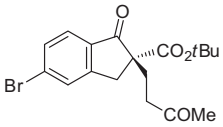
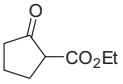
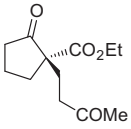
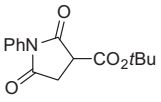
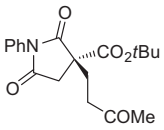
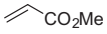
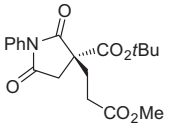
Entry	Keto ester	No.	Olefin	**2** (mol %)	*t* (d)	Product	No.	Yield[b] (%)	ee[c] (%)
1		**3a**		1	0.6		(*R*)-**4aa**	87	73
2		**3b**		1	1		(*R*)-**4ba**	98	51
3		**3a**		1	7		(*R*)-**4ab**	98	77
4				1	0.2		(*R*)-**4ac**	86	79
5				10	7		(*R*)-**4ad**	55	94
6[d]				5	7		(*R*)-**4ae**	40	83
7				5	3		(*R*)-**4af**	98	71
8				5	3		(*R*)-**4ag**	87	75
9[d]				10	6		(*R*)-**4ah**	98	51
10		**3c**		1	4		(*R*)-**4ca**	98	78
11		**3d**		5	3.5		(*R*)-**4da**	98	83
12				5	2		(*R*)-**4dc**	98	85
13[d]				10	7		(*R*)-**4dd**	68	82

Table 2 (*continued*)

Entry	Keto ester	No.	Olefin	**2** (mol %)	*t* (d)	Product	No.	Yield[b] (%)	ee[c] (%)
									
14		**3e**		5	7		(*R*)-**4ea**	92	81
15		**3f**		1	1		(*R*)-**4fa**	98	66
16		**3g**		1	0.7		(*R*)-**4ga**	98	68
17		**3h**		5	5		(*S*)-**4ha**	98	45
18		**3i**		5	0.3		(*R*)-**4ia**	98	70
19				10	7		(*R*)-**4id**	27	40

[a] Reaction conditions: catalyst **2** (5 mol %), *i*Pr$_2$EtN (30 mol %), CH_2Cl_2, −40 °C.
[b] Determined by ^{1}H NMR (300 MHz) using diphenylmethane as the internal standard.
[c] The enantioselectivities and absolute stereochemistry were determined by chiral HPLC (see Section 4).
[d] The reaction was performed at 25 °C.

enantioselection (51% ee) (Table 2, entry 2). Therefore, the *tert*-butyl group was the alkyl group of choice in the 2-alkyloxycarbonyl-1-indanones employed.

The reaction of 2-*tert*-butoxycarbonyl-1-indanone **3a** with other Michael acceptors gave higher enantioselectivities of the corresponding Michael adducts. Thus, the ethyl vinyl ketone gave the corresponding (*R*)-**4ab** in 77% ee (Table 2, entry 3), whereas the more reactive acrolein gave adduct (*R*)-**4ac** in 79% ee (Table 2, entry 4). The use of methyl acrylate as the Michael acceptor gave an excellent enantioselection for (*R*)-**4ad** (94%), although it was necessary to increase the amount of organocatalyst **2** to 10 mol % in order to achieve a reasonable reaction rate (Table 2, entry 5). Other acrylates employed, such as ethyl acrylate or naphthalen-1-yl acrylate, afforded lower enantioselectivities for the corresponding Michael adducts (*R*)-**4ae** and (*R*)-**4af** (83 and 71% ee, respectively) (Table 2, entries 6 and 7). A thioacrylate, such as (*S*)-naphthalen-1-yl prop-2-enethioate, was also used as a Michael acceptor, affording (*R*)-**4ag** in 75% ee (Table 2, entry 8). In the case of acrylonitrile, (*R*)-**4ah** was obtained in 98% yield but with a moderate 51% ee (Table 2, entry 9).

We also explored the use of substituted 2-*tert*-butoxycarbonyl-1-indanones as nucleophile precursors. Thus, the use of indanone **3c** bearing a 5-methyl group gave the corresponding adduct (*R*)-**4da** in 78% ee when reacting with methyl vinyl ketone (Table 2, entry 10), whereas the 5-methoxy group on **3d** with the same acceptor gave a slightly higher enantioinduction for the corresponding (*R*)-**4da** (83%). Other acceptors such as acrolein and methyl acrylate gave similar enantioselectivities for the final Michael adducts (*R*)-**4dc** and (*R*)-**4dc** when reacting with the β-keto ester **3d** (Table 2, entries 12 and 13). In addition, the use of 5,6-dimethoxy-substituted indanone carboxylate **3e** gave rise to an 81% ee of the corresponding adduct (*R*)-**4ea** when reacting with methyl vinyl ketone (Table 2, entry 14).

The influence of the presence of halogen atoms on the indanone carboxylate **3** was also explored. Thus, 5-chloro- or 5-bromo-substituted indanone carboxylates **3f** and **3g**, respectively, gave rise to lower enantioselections for the corresponding adducts (*R*)-**4fa** and (*R*)-**4ga** with methyl vinyl ketone than when electron-releasing groups were present (Table 2, entries 15 and 16).

The absence of an aryl group on the β-keto ester was shown to lower the enantioinduction. Thus, when ethyl 3-methyl-2-oxocyclopentanecarboxylate **3h** was used as a nucleophile precursor in the reaction with methyl vinyl ketone, the Michael adduct (*S*)-**4fa** (same enantioinduction, with just CIP rules in effect) was obtained in excellent 98% yield but in only 45% ee (Table 2, entry 17).

We also studied the performance of *tert*-butyl 2,5-dioxo-1-phenylpyrrolidine-3-carboxylate **3i** as a 'related' β-keto ester in this enantioselective reaction. Thus, the Michael reaction of **3i** with

Scheme 1.

methyl vinyl ketone gave the corresponding adduct (*R*)-**4ia** in almost quantitative yield and in 70% ee. When methyl acrylate was used as a Michael acceptor, (*R*)-**4id** was isolated in poor yield and in 40% ee even when using 10 mol % of organocatalyst **2** (Table 2, entries 18 and 19).

It is noteworthy that the ammonium salt **2** can be recovered in 95% yield once the reaction is complete after the evaporation of the dichloromethane, the addition of diethyl ether, and filtration of the precipitate. The recovered ammonium salt was reused up to three times in the model reaction (Table 2, entry 1), giving almost identical yields and enantioselectivities.

The Michael adducts obtained can be employed in further transformations. Thus, enantiomerically enriched Michael adduct (*R*)-**4aa** was employed in an intramolecular aldol condensation reaction promoted by DL-proline to obtain tetrahydro-1*H*-fluorene-9a-carboxylate **5** in 90% yield and without observing any loss of enantiointegrity being observed (Scheme 1). The use of inorganic bases for this cyclization reaction resulted in partial or total racemization.

3. Conclusions

It can be concluded that quaternary stereocenters can be created enantioselectively by a conjugate addition reaction between cyclic β-keto esters, or related systems and Michael acceptors, using *Cinchona*-derived dimeric ammonium species as chiral organocatalysts. The corresponding quinine-derived ammonium salt gave opposite enantioselectivity to that of its pseudoenantiomer from quinidine, which afforded the higher enantioselectivities. These organocatalysts can be easily separated from the reaction medium by precipitation from ether and filtration and reused without a loss in activity.

4. Experimental

4.1. 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 °C on a Bruker AC-300 at 300 MHz and 75 MHz, respectively, using $CDCl_3$ as solvent and TMS as the internal standard. MS (EI, 70 eV) were performed on a HP MS-GC-5973A. HRMS analyses were carried out on a Finnigan MAT 95S. Enantioselectivities were determined by chiral HPLC using Chiralcel columns and *n*-hexane/2-propanol mixtures as eluent. Reference racemic samples of adducts **4** were obtained by performing the enantioselective Michael reaction in the absence of organocatalysts.

Ammonium salts **1a**,[14b] **1b**,[12a] **1c**-**e**[16] and **2**[16] have been prepared following reported procedures. Compounds **3a**,[17] **3b**,[18] and **3c**–**i**,[17] as well as the Michael acceptors naphthalen-1-yl acrylate[19] and (*S*)-naphthalen-1-yl prop-2-enethioate[19] were prepared according to the literature. The absolute configurations for the adducts **4aa**, **ba**,**ad**,[6a] **4ac**[9b] and **4af**,**ag**[9c] were determined according to the described order of elution of their enantiomers in chiral HPLC, whereas in the case of compound **4ha**, it was assigned by the specific rotation according to its positive sign.[6b] The absolute configurations of the other adducts were assigned by analogy.

4.2. Typical procedure for the enantioselective Michael reaction

To a stirred solution of **3a** (232 mg, 1 mmol), methyl vinyl ketone (250 μL, 3 mmol) and **2** (9 mg, 0.01 mmol) in CH_2Cl_2 (6 mL) at −40 °C was added diisopropylethylamine (50 μL, 0.3 mmol). The mixture was stirred vigorously at the same temperature and after completion (TLC), the solvent was evaporated (15 Torr). The addition of diethyl ether (6 mL) allowed **2** to precipitate and was recovered by filtration. The filtrate was diluted with water (20 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organics were dried with $MgSO_4$, filtered, and evaporated in vacuo (15 Torr) to afford **4aa**.

Analytical and spectroscopic data for adducts **4aa**,**ba**,**ad**[6a] **4ab**,[9a] **4ac**,[9b] **4af**,**ag**,[9c] and **4ha**[6b] have been reported. Data for the other obtained adducts follow.

4.2.1. (*R*)-*tert*-Butyl 2-(3-ethoxy-3-oxopropyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate 4ae

Pale yellow oil; IR (film): *ν* 1739, 1702, 1254, 1154 cm^{-1}; ^{1}H NMR: δ_H 7.76 (d, $^3J_{H,H}$ = 7.7 Hz, 1H, C(7)-H), 7.62 (td, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.1 Hz, 1H, C(5)-H), 7.47 (d, $^3J_{H,H}$ = 7.7 Hz, 1H, C(4)-H), 7.39 (t, $^3J_{H,H}$ = 7.7 Hz, 1H, C(6)-H), 4.10 (q, $^3J_{H,H}$ = 7.1 Hz, 2H, $COOCH_2CH_3$), 3.64 (d, $^2J_{H,H}$ = 17.2 Hz, 1H, C(3)-H_A), 3.04 (d, $^2J_{H,H}$ = 17.4 Hz, 1H, C(3)-H_B), 2.50–2.14 (m, 4H, $CH_2CH_2COOCH_2CH_3$), 1.40 (s, 9H, $C(CH_3)_3$), 1.23 (t, $^3J_{H,H}$ = 7.2 Hz, 3H, $COOCH_2CH_3$); ^{13}C NMR: δ_C 202.3, 172.8, 169.8, 152.7, 135.2, 135.2, 127.7, 126.3, 124.7, 82.0, 60.4, 60.2, 37.2, 29.9, 29.6, 27.8, 14.1; MS (EI): *m*/*z* (%) 276 ($M^+-C_4H_8$, 14), 131 (100); HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}O_5$ ($M^+-C_4H_8$) 276.0998, found 276.1016; HPLC: Chiralcel AD, *λ* = 210 nm, *n*-hexane/2-propanol, 95:5, 1.0 mL/min, t_R (minor) = 11 .2 min, t_R (major) = 12.4 min.

4.2.2. (*R*)-*tert*-Butyl 2-(2-cyanoethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate 4ah

Greenish oil; IR (film): *ν* 2248, 1734, 1712, 1284, 1254, 1154 cm^{-1}; ^{1}H NMR: δ_H 7.78 (d, $^3J_{H,H}$ = 7.6 Hz, 1H, C(7)-H), 7.65 (td, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,H}$ = 1.1 Hz, 1H, C(5)-H), 7.50 (d, $^3J_{H,H}$ = 7.7 Hz, 1H, C(4)-H), 7.43 (t, $^3J_{H,H}$ = 7.2 Hz, 1H, C(6)-H), 3.65 (d, $^2J_{H,H}$ = 17.3 Hz, 1H, C(3)-H_A), 3.11 (d, $^2J_{H,H}$ = 17.4 Hz, 1H, C(3)-H_B), 2.60–2.54 (m, 2H, CH_2CH_2CN), 2.35–2.25 (m, 2H, CH_2CH_2CN), 1.38 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ_C 201.6, 169.2, 152.4, 135.7, 134.8, 128.1, 126.4, 124.9, 119.3, 82.8, 59.7, 37.6, 30.2, 27.7, 13.1; MS (EI): *m*/*z* (%) 229 ($M^+-C_4H_8$, 56), 184 (100); HRMS (EI): *m*/*z* calcd for $C_{13}H_{11}NO_3$ ($M^+-C_4H_8$) 229.0739, found 229.0740; HPLC: Chiralcel AD, *λ* = 210 nm, *n*-hexane/2-propanol, 98:2, 1.0 mL/min, t_R (minor) = 17.0 min, t_R (major) = 18.5 min.

4.2.3. (*R*)-*tert*-Butyl 5-methyl-1-oxo-2-(3-oxobutyl)-2,3-dihydro-1*H*-indene-2-carboxylate 4ca

Pale yellow oil; IR (film): *ν* 1733, 1712, 1155 cm^{-1}; ^{1}H NMR: δ_H 7.64 (d, $^3J_{H,H}$ = 7.8 Hz, 1H, C(7)-H), 7.26 (br s, 1H, C(4)-H), 7.20 (d, $^3J_{H,H}$ = 7.9 Hz, 1H, C(6)-H), 3.55 (d, $^2J_{H,H}$ = 17.3 Hz, 1H, C(3)-H_A), 2.94 (d, $^2J_{H,H}$ = 17.3 Hz, 1H, C(3)-H_B), 2.70–2.44 (m, 2H, $CH_2CH_2COCH_3$), 2.45 (s, 3H, C(5)-CH_3), 2.23–2.12 (m, 2H, $CH_2CH_2COCH_3$), 2.12 (s, 3H, $CH_2CH_2COCH_3$), 1.39 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ_C 207.8, 202.1, 170.2, 153.1, 146.5, 132.9, 129.0, 126.6, 124.4, 81.8, 60.0, 38.8, 37.6, 29.8, 28.3, 27.7, 22.0; MS (EI): *m*/*z* (%) 260 ($M^+-C_4H_8$, 27), 190 (100); HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}O_4$ ($M^+-C_4H_8$) 260.1049, found 260.1090; HPLC: Chiralcel AD-H, *λ* = 210 nm, *n*-hexane/2-propanol, 90:10, 1.0 mL/min, t_R (minor) = 10.7 min, t_R (major) = 16.0 min.

4.2.4. (*R*)-*tert*-Butyl 5-methoxy-1-oxo-2-(3-oxobutyl)-2,3-dihydro-1*H*-indene-2-carboxylate 4da

White solid; mp 93–95 °C; IR (KBr): ν 1731, 1717, 1697, 1267, 1155, 1107 cm^{-1}; ^1H NMR: δ_H 7.68 (d, $^3J_{H,H}$ = 8.4 Hz, 1H, C(7)-H), 6.92 (d, $^3J_{H,H}$ = 8.4 Hz, 1H, C(6)-H), 6.90 (br s, 1H, C(4)-H), 3.90 (s, 3H, C(5)-OCH_3), 3.56 (d, $^2J_{H,H}$ = 17.3 Hz, 1H, C(3)-H_A), 2.94 (d, $^2J_{H,H}$ = 17.3 Hz, 1H, C(3)-H_B), 2.69–2.43 (m, 2H, $CH_2CH_2COCH_3$), 2.26–2.10 (m, 2H, $CH_2CH_2COCH_3$), 2.13 (s, 3H, $CH_2CH_2COCH_3$), 1.40 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ_C 207.7, 200.6, 170.3, 165.7, 155.6, 128.4, 126.2, 115.8, 109.3, 81.8, 60.1, 55.6, 38.8, 37.6, 29.8, 28.4, 27.7; MS (EI): *m*/*z* (%) 276 ($M^+-C_4H_8$, 23), 56 (100); HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}O_5$ ($M^+-C_4H_8$) 276.0998, found 276.0744; HPLC: Chiralcel AD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, t_R (minor) = 7.9 min, t_R (major) = 12.0 min.

4.2.5. (*R*)-*tert*-Butyl 5-methoxy-1-oxo-2-(3-oxopropyl)-2,3-dihydro-1*H*-indene-2-carboxylate 4dc

Pale yellow oil; IR (film): ν 1725, 1699, 1256, 1148 cm^{-1}; ^1H NMR: δ_H 9.75 (s, 1H, CHO), 7.69 (d, $^3J_{H,H}$ = 8.4 Hz, 1H, C(7)-H), 6.93 (d, $^3J_{H,H}$ = 8.8 Hz, 1H, C(6)-H), 6.91 (br s, 1H, C(4)-H), 3.90 (s, 3H, C(5)-OCH_3), 3.58 (d, $^2J_{H,H}$ = 17.4 Hz, 1H, C(3)-H_A), 2.94 (d, $^2J_{H,H}$ = 17.2 Hz, 1H, C(3)-H_B), 2.65–2.46 (m, 2H, CH_2CH_2CHO), 2.33–2.14 (m, 2H, CH_2CH_2CHO), 1.40 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ_C 201.1, 200.4, 170.0, 165.7, 155.6, 128.2, 126.3, 115.8, 109.3, 81.9, 60.0, 55.6, 39.4, 37.4, 27.7, 26.6; MS (EI): *m*/*z* (%) 262 ($M^+-C_4H_8$, 16), 162 (100); HRMS (EI): *m*/*z* calcd for $C_{14}H_{14}O_5$ ($M^+-C_4H_8$) 262.0841, found 262.1174; HPLC: Chiralcel AD-H, λ = 210 nm, *n*-hexane/2-propanol, 90:10, 1.0 mL/min, t_R (minor) = 12.4 min, t_R (major) = 21.9 min.

4.2.6. (*R*)-*tert*-Butyl 5-methoxy-2-(3-methoxy-3-oxopropyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate 4dd

Pale yellow solid; mp 97–99 °C; IR (KBr): ν 1740, 1726, 1597, 1268, 1152 cm^{-1}; ^1H NMR: δ_H 7.68 (d, $^3J_{H,H}$ = 8.4 Hz, 1H, C(7)-H), 6.94–6.90 (m, 2H, C(4)-H, C(6)-H), 3.89 (s, 3H, C(5)-OCH_3), 3.65 (s, 3H, $COOCH_3$), 3.59 (d, $^2J_{H,H}$ = 17.3 Hz, 1H, C(3)-H_A), 2.96 (d, $^2J_{H,H}$ = 17.3 Hz, 1H, C(3)-H_B), 2.48–2.14 (m, 4H, $CH_2CH_2COOCH_3$), 1.40 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ_H 200.2, 173.3, 169.9, 165.7, 155.7, 128.3, 126.3, 115.8, 109.3, 81.8, 60.4, 55.6, 51.6, 37.1, 29.6, 29.5, 27.7; MS (EI): *m*/*z* (%) 292 ($M^+-C_4H_8$, 53), 175 (100); HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}O_6$ ($M^+-C_4H_8$) 292.0947, found 292.0945; HPLC: Chiralcel AD-H, λ = 210 nm, *n*-hexane/2-propanol, 90:10, 1.0 mL/min, t_R (minor) = 12.5 min, t_R (major) = 19.7 min.

4.2.7. (*R*)-*tert*-Butyl 5,6-dimethoxy-1-oxo-2-(3-oxobutyl)-2,3-dihydro-1*H*-indene-2-carboxylate 4ea

Pale brown solid; mp 160–161 °C; IR (KBr): ν 1721, 1700, 1503, 1320, 1274, 1157 cm^{-1}; ^1H NMR: δ_H 7.16 (s, 1H, C(7)-H), 6.89 (s, 1H, C(4)-H), 3.98 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.51 (d, $^2J_{H,H}$ = 17.0 Hz, 1H, C(3)-H_A), 2.90 (d, $^2J_{H,H}$ = 17.0 Hz, 1H, C(3)-H_B), 2.65–2.42 (m, 2H, $CH_2CH_2COCH_3$), 2.26–2.13 (m, 2H, $CH_2CH_2COCH_3$), 2.13 (s, 3H, $CH_2CH_2COCH_3$), 1.41 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ_C 207.7, 201.1, 170.3, 155.8, 149.6, 148.0, 127.8, 107.0, 104.7, 81.7, 60.1, 56.2, 55.9, 38.8, 37.4, 29.8, 28.3, 27.7; MS (EI): *m*/*z* (%) 262 ($M^+-CO_2C_4H_8$, 45), 205 (100); HRMS (EI): *m*/*z* calcd for $C_{15}H_{18}O_4$ ($M^+-CO_2C_4H_8$) 262.1205, found 262.1202; HPLC: Chiralcel AD-H, λ = 210 nm, *n*-hexane/2-propanol, 90:10, 1.0 mL/min, t_R (minor) = 14.3 min, t_R (major) = 25.6 min.

4.2.8. (*R*)-*tert*-Butyl 5-chloro-1-oxo-2-(3-oxobutyl)-2,3-dihydro-1*H*-indene-2-carboxylate 4fa

Dark green oil; IR (film): ν 1735, 1708, 1599, 1253, 1150 cm^{-1}; ^1H NMR: δ_H 7.69 (d, $^3J_{H,H}$ = 8.2 Hz, 1H, C(7)-H), 7.47 (br s, 1H, C(4)-H), 7.38 (d, $^3J_{H,H}$ = 8.5 Hz, 1H, C(6)-H), 3.59 (d, $^2J_{H,H}$ = 17.4 Hz, 1H, C(3)-H_A), 2.99 (d, $^2J_{H,H}$ = 17.5 Hz, 1H, C(3)-H_B), 2.73–2.44 (m, 2H, $CH_2CH_2COCH_3$), 2.26–2.10 (m, 2H, $CH_2CH_2COCH_3$), 2.14 (s, 3H, $CH_2CH_2COCH_3$), 1.39 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ_C = 207.4, 201.1, 169.6, 154.0, 141.7, 133.6, 128.5, 126.4, 125.6, 82.2, 60.0, 38.6, 37.4, 29.8, 28.2, 27.7; MS (EI): *m*/*z* (%) 280 ($M^+-C_4H_8$, 28), 210 (100); HRMS (EI): *m*/*z* calcd for $C_{14}H_{13}ClO_4$ ($M^+-C_4H_8$) 280.0502, found 280.0487; HPLC: Chiralcel AD-H, λ = 210 nm, *n*-hexane/2-propanol, 90:10, 1.0 mL/min, t_R (minor) = 9.0 min, t_R (major) = 12.2 min.

4.2.9. (*R*)-*tert*-Butyl 5-bromo-1-oxo-2-(3-oxobutyl)-2,3-dihydro-1*H*-indene-2-carboxylate 4ga

Greenish oil; IR (film): ν 1739, 1715, 1256, 1154 cm^{-1}; ^1H NMR: δ_H 7.65 (br s, 1H, C(4)-H), 7.61 (d, $^3J_{H,H}$ = 8.0 Hz, 1H, C(7)-H), 7.54 (d, $^3J_{H,H}$ = 8.0 Hz, 1H, C(6)-H), 3.59 (d, $^2J_{H,H}$ = 17.4 Hz, 1H, C(3)-H_A), 2.99 (d, $^2J_{H,H}$ = 17.6 Hz, 1H, C(3)-H_B), 2.70–2.45 (m, 2H, $CH_2CH_2COCH_3$), 2.29–2.11 (m, 2H, $CH_2CH_2COCH_3$), 2.13 (s, 3H, $CH_2CH_2COCH_3$), 1.39 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ_C 207.2, 201.3, 169.5, 154.0, 134.0, 131.3, 130.5, 129.5, 125.7, 82.1, 60.0, 38.6, 37.4, 29.7, 28.1, 27.6; MS (EI): *m*/*z* (%) 324 ($M^+-C_4H_8$, 26), 254 (100); HRMS (EI): *m*/*z* calcd for $C_{14}H_{13}BrO_4$ ($M^+-C_4H_8$) 323.9997, found 323.9978; HPLC: Chiralcel AD-H, λ = 210 nm, *n*-hexane/2-propanol, 90:10, 1.0 mL/min, t_R (minor) = 9.2 min, t_R (major) = 13.2 min.

4.2.10. (*R*)-*tert*-Butyl 2,5-dioxo-3-(3-oxobutyl)-1-phenylpyrrolidine-3-carboxylate 4ia

White solid; mp 128–129 °C; IR (KBr): ν 1735, 1714, 1389, 1372, 1197, 1151 cm^{-1}; ^1H NMR: δ_H 7.51–7.47 (m, 2H, ArH), 7.43–7.40 (m, 1H, ArH), 7.28–7.26 (m, 2H, ArH), 3.17 (d, $^2J_{H,H}$ = 18.3 Hz, 1H, C(4)-H_A), 2.89–2.81 (m, 1H, $CH_2CH_AH_BCOCH_3$), 2.76 (d, $^2J_{H,H}$ = 18.1 Hz, 1H, C(4)-H_B), 2.62–2.54 (m, 1H, $CH_2CH_AH_BCOCH_3$), 2.34–2.30 (m, 2H, $CH_2CH_2COCH_3$), 2.18 (s, 3H, $CH_2CH_2COCH_3$), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ_C 207.0, 174.8, 173.8, 168.2, 131.6, 129.3, 128.9, 126.3, 83.7, 54.3, 39.5, 38.6, 30.0, 27.8, 27.4; MS (EI): *m*/*z* (%) 245 ($M^+-CO_2C_4H_8$, 7), 193 (100); HRMS (EI): *m*/*z* calcd for $C_{14}H_{15}NO_3$ ($M^+-CO_2C_4H_8$) 245.1052, found 245.1059; HPLC: Chiralcel AS-H, λ = 210 nm, *n*-hexane/2-propanol, 95:5, 1.0 mL/min, t_R (major) = 38.4 min, t_R (minor) = 43.5 min.

4.2.11. (*R*)-*tert*-Butyl 3-(3-methoxy-3-oxopropyl)-2,5-dioxo-1-phenylpyrrolidine-3-carboxylate 4id

Colorless oil; IR (film): ν 1741, 1716, 1387, 1371, 1255, 1195, 1150 cm^{-1}; ^1H NMR: δ_H 7.51–7.39 (m, 3H, ArH), 7.28–7.26 (m, 2H, ArH), 3.69 (s, 3H, $COOCH_3$), 3.19 (d, $^2J_{H,H}$ = 18.2 Hz, 1H, C(4)-H_A), 2.79 (d, $^2J_{H,H}$ = 18.2 Hz, 1H, C(4)-H_B), 2.69–2.56 (m, 1H, $CH_2CH_AH_BCOOCH_3$), 2.50–2.36 (m, 3H, $CH_2CH_AH_BCOOCH_3$), 1.49 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ_C 174.5, 173.7, 172.7, 167.8, 131.6, 129.2, 128.8, 126.2, 83.8, 54.6, 51.9, 38.6, 29.3, 28.3, 27.7; MS (EI): *m*/*z* (%) 261 ($M^+-CO_2C_4H_8$, 60), 188 (100); HRMS (EI): *m*/*z* calcd for $C_{14}H_{15}NO_4$ ($M^+-CO_2C_4H_8$) 261.1001, found 261.0966; HPLC: Chiralcel AD-H, λ = 210 nm, *n*-hexane/2-propanol, 95:5, 1.0 mL/min, t_R (minor) = 22.3 min, t_R (major) = 24.9 min.

4.3. Experimental procedure for the intramolecular aldol condensation

To a stirred solution of (*R*)-*tert*-butyl 1-oxo-2-(3-oxobutyl)-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-**4aa**, (73% ee) (64 mg, 0.21 mmol) in a mixture of DMF/H_2O (1:1) (1 mL) was added DL-proline (24 mg, 0.21 mmol). The mixture was stirred vigorously at reflux (100 °C) until the total consumption of the substrate (TLC, 4 days) took place. The mixture was allowed to cool down at room temperature and water (20 mL) was added. The mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo (15 Torr) to afford the crude product, which was purified by crystallization from a mixture of hexane/EtOAc.

4.3.1. (*R*)-*tert*-Butyl 6-oxo-7,8,8a,9-tetrahydro-6*H*-fluorene-8a-carboxylate 5

White solid; mp 80–82 °C; IR (KBr): ν 1721, 1659, 1145, 766 cm^{-1}; ^1H NMR: δ_H 7.59 (d, $^3J_{H,H}$ = 7.3 Hz, 1H, C(4)-H), 7.39–7.37 (m, 1H, C(2)-H), 7.33–7.30 (m, 2H, C(1)-H, C(3)-H), 6.35 (s, 1H, C = CH), 3.49 (d, $^2J_{H,H}$ = 16.4 Hz, 1H, C(9)-H_A), 3.00 (d, $^2J_{H,H}$ = 16.4 Hz, 1H, C(9)-H_B), 2.77–2.70 (m, 1H, C(7)-H_A), 2.60–2.53 (m, 2H, C(7)-H_B, C(8)-H_A), 2.17–2.06 (m, 1H, C(8)-H_B), 1.31 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ_C 198.9, 172.2, 165.3, 145.9, 138.4, 131.7, 127.6, 125.2, 122.7, 118.5, 82.0, 55.2, 43.2, 35.2, 32.7, 27.7; MS (EI): m/z (%) 284 (M^+, 3), 57 (100); HRMS (EI): m/z calcd for $C_{18}H_{20}O_3$ (M^+) 284.1412, found 284.1431; HPLC: Chiralcel AD-H, λ = 210 nm, *n*-hexane/2-propanol, 97:3, 1 mL/min, t_R (major) = 12.8 min, t_R (minor) = 20.7 min.

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