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Organocatalytic asymmetric decarboxylative addition of β-ketoacids to methyleneindolinones derivatives

Anita Kumari[a], Jasneet Kaur[a], Vimal K. Bhardwaj[b] and Swapandeep Singh Chimni[a]*

Abstract: The quinine squaramide-catalyzed enantioselective decarboxylative addition reaction of various β-keto acids with methyleneindolinones has been developed. Through this methodology, various oxindole derivatives were synthesized in good yields (up to 93%) and excellent enantiomeric excess (up to 99% ee) and moderate diastereoselectivity (up to 66:34).

Introduction

Decarboxylative carbon-carbon bond formation is an important reaction in Nature catalyzed by polyketides synthases for the synthesis of polyketides.[1] The synthesis of polyketides involves a series of reactions *viz*. decarboxylation, condensation, cyclization, and aromatization reactions which occurs in the active site of polyketide synthase.[2] The decarboxylation of CoA-Malonic acid half thioester initiates the reaction by generation of CoA-enolate which adds on to the acyl group carried by the cysteine residue in the catalytic site of PKS. The formation of enolate is made possible through the involvement of the amino acids asparagine and protonated histidine that activates the CoA bound malonic acid half thioester for decarboxylation through hydrogen bonding.[3]

Inspired by nature, organic chemists have used malonic acid half thioesters (MAHTs) as thioester enolate equivalents in various decarboxylative addition reactions.[4] Several metal based approaches towards the decarboxylative addition of MAHTs to different electrophiles have been developed. In 1978, Kobuke and Yoshida reported the first example of decarboxylative addition reaction of MAHTs with thioacetate in presence of a magnesium salt and imidazole to afford product in up to 60% yield.[5] The first asymmetric decarboxylative addition reaction of MAHTs to aldehydes was disclosed by Shair and co-workers in 2005 using Cu (II) as a catalyst and chiral *bis*(oxazoline) ligands to provide the product in up to 96% *ee*.[6] The first asymmetric organocatalytic decarboxylative carbon-carbon bond formations with imines or nitroolefins were independently reported in 2007 by Ricci and Wennemers research groups.[7] These reports attracted many organic chemists to develop new decarboxylative addition reactions catalyzed by small organic molecules as well as metal catalysts.

The organocatalytic activation of malonic acid half thioester involving bifunctional organocatalyst is inspired from the catalytic function of PKS (**Figure 1**).[8] The same mode of activation can be extended to decarboxylation of β-ketoacid to obtain enolate intermediate. In this context, we have planned the decarboxylative addition reaction of methyleneindolinones with β-ketoacids.[9]

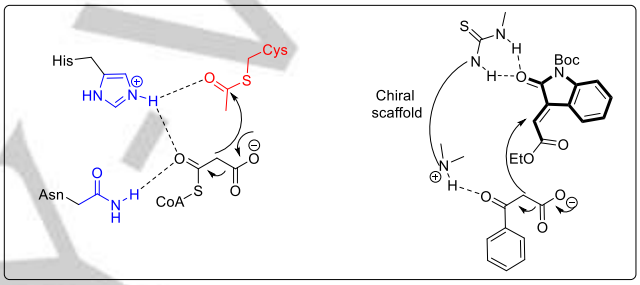

Figure 1: Design of organocatalyst mimicking the active site of enzyme PKS

Herein, we report our evaluation of the catalytic potential of *Cinchona*-derived organocatalyst (**Figure 2**) for enantioselective addition of β-ketoacids with methyleneindolinones to construct chiral oxindole motifs.

Results and Discussion

Initially, the catalytic ability of Cinchonidine thiourea (**CDT**) **III** was investigated for decarboxylative addition of 3-oxo-3-phenylpropanoic acid (**1a**) to methyleneindolinones (**2a**) in dichloromethane at room temperature. The reaction completed in 12h to afford the adduct **3a** in 92% yield, 84% *ee* with 57:43 *dr* (**Table 1**, **entry 1**).

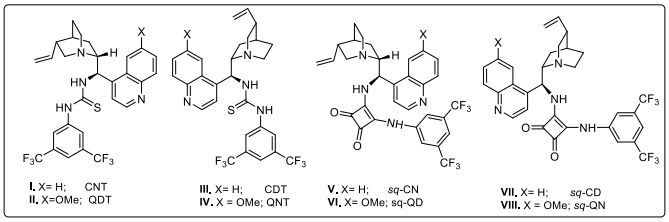

Figure 2. *Cinchona*-derived organocatalysts used in decarboxylative addition reaction of β-ketoacids with methyleneindolinones.

Encouraged by this result, we studied the catalytic performance of other *Cinchona* derived thiourea on the same reaction. The Cinchonine thiourea (**CNT**) **I** provided the product in 89% yield, 80% *ee* with 58:42 *dr* (**Table 1**, **entry 2**). The reaction catalyzed by quinine thiourea (**QNT**) **IV** afforded **3a** in 88% yield, 82% *ee* with 59:41 *dr* while its

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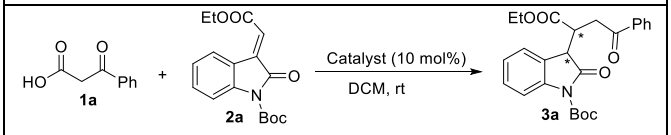
pseudoenantiomeric partner quinidine thiourea (**QDT**) **II** yielded **3a** in 74% *ee* with 61:39 *dr* (**Table 1**, **entry 3-4**). Further, we examined the catalytic ability of squaramide derivatives of *Cinchona* alkaloids for decarboxylative addition reaction of 3-oxo-3-phenylpropanoic acid (**1a**) with methyleneindolinones (**2a**). The Cinchonine squaramide **V** gave the desired product in 89% yield with 92% *ee* and 60:40 *dr* while its pseudoenantiomeric partner cinchonidine squaramide **VII** afforded the product in 93% yield with 53% *ee* and 57:43 *dr* (**Table 1**, **entry 5-6**). Next, we examined the catalytic ability of quinidine **VI** and quinine squaramide **VIII** for the model reaction.

Table 1: Screening of organocatalysts for the reaction of 1a with 2a [a]

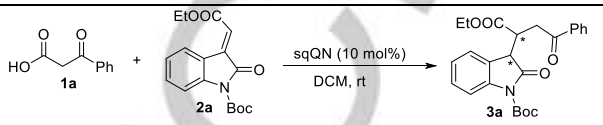


Entry	Catalyst	Time (h)	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	**CDT (III)**	12	92	(-)-84 (87)	57:43
2	**CNT (I)**	12	89	(+)-80 (55)	58:42
3	**QNT (IV)**	12	88	(-)-82 (84)	59:41
4	**QDT (II)**	12	91	(+)-74 (62)	61:39
5	**sqCN (V)**	9	89	(+)-92 (96)	60:40
6	**sqCD (VII)**	9	93	(-)-53 (58)	57:43
7	**sqQD (VI)**	9	93	(+)-93 (86)	62:38
8	**sqQN (VIII)**	9	92	(-)-96 (96)	63:37

[a]Reaction conditions: 0.1mmol methyleneindolinones **2a**, 0.12 mmol of *β*-ketoacid **1a**, and catalyst (10 mol %) in dry solvent (0.5 mL). [b]Yield refers to isolated yield after column chromatography. [c]Enantiomeric excess (*ee*) determined by chiral HPLC and values in parentheses are for the minor diastereomer. [d]Determined by ^{1}H NMR analysis of crude reaction mixture.

The product was obtained in 92-93% yield, 93-96% *ee* and 62:38-63:37 *dr* (**Table 1**, **entry 7-8**). Based on this screening, quinine squaramide **VIII** was selected as optimized catalyst for further optimization studies. Further optimization of reaction condition was done by performing the model reaction in various solvents. The model reaction was performed in chloroform to provide the product **3a** in 90% yield, 97% *ee* and 63:37 *dr* (**Table 2**, **entry 2**). Non-polar solvents *i.e*. toluene afforded 3a in 88% yield with 97% *ee* and 63:37 *dr* (**Table 2**, **entry 3**). Then, various ethereal solvents were screened for this reaction (**Table 2**, **entry 4-7**). Among different ethereal solvents, cyclopentylmethylether (CPME) emerged as best solvent that provides the product in 93% yield with 99% *ee* and 64:36 *dr* (**Table 2**, **entry 4**).

Table 2: Screening of solvent for the reaction of 1a with 2a using sqQN as an organocatalyst [a]

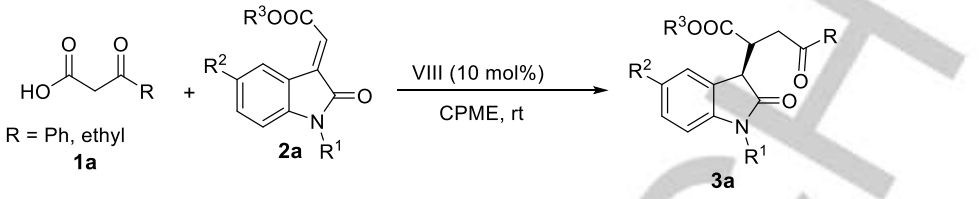


Entry	Solvent	Time (h)	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	DCM	9	92	96(96)	63:37
2	Chloroform	9	90	97(96)	63:37
3	Toluene	5	88	97(98)	63:37
4	CPME	4	93	99(98)	64:36
5	MTBE	4	90	97(97)	62:38
6	1,4-dioxane	4	92	96(98)	60:40
7	THF	4	89	96(96)	62:38
8[e]	CPME	8	89	95(96)	61:39
9[f]	CPME	2	91	96(98)	62:38

[a]Reaction conditions: 0.1 mmol methyleneindolinones **2a**, 0.12 mmol of *β*-ketoacid **1a**, and catalyst (10 mol%) in dry solvent (0.5 mL). [b]Yield refers to isolated yield after column chromatography. [c]Enantiomeric excess (*ee*) determined by chiral HPLC and values in parentheses are for the minor diastereomer. [d]Determined by ^{1}H NMR analysis of crude reaction mixture. [e]catalyst loading (5 mol%). [f]catalyst loading (20 mol%); CPME = cyclopentylmethylether, MTBE = methyl *tert*-butyl ether

On varying the amount of catalyst from 10 mol% to 20 mol%, no significant effect on enantiomeric excess and diastereoselectivity was observed but lowering the catalyst amount from 10 mol% to 5 mol% results in prolong reaction time without much effect on yield and enantiomeric excess. Thus, the optimized conditions consist of 10 mol% of quinine squaramide, 0.5 mL of CPME as a solvent at 25 °C. These optimized conditions were used to study the substrate scope of this reaction.

Table 3: Substrate Scope for the addition reaction of different *β*-ketoacid derivatives with methyleneindolinones[a]

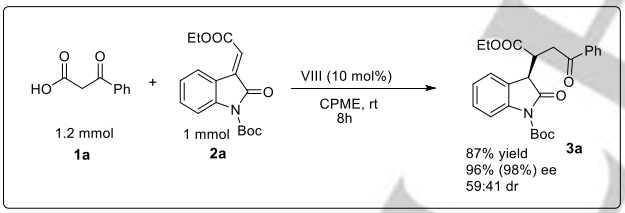


Entry	1(R)	2 (R^1, R^2, R^3)	3	Yield[b] (%)	ee[c] (%)	dr[d]
1	**1a** (Ph)	**2a** (R^1= Boc, R^2=H, R^3= Et)	**3a**	93	99(98)	64:36
2	**1a** (Ph)	**2b** (R^1= Boc, R^2=F, R^3= Et)	**3b**	89	95(92)	61:39
3	**1a** (Ph)	**2c** (R^1= Boc, R^2=Cl, R^3= Et)	**3c**	91	97(95)	61:39
4	**1a** (Ph)	**2d** (R^1= Boc,R^2=Br, R^3= Et)	**3d**	88	95(96)	62:38
5	**1a** (Ph)	**2e** (R^1= Boc, R^2=I, R^3= Et)	**3e**	89	96(97)	57:43
6	**1a** (Ph)	**2f**(R^1= Boc, R^2=OMe, R^3= Et)	**3f**	92	96(94)	58:42
7	**1a** (Ph)	**2g**(R^1= Boc, R^2=Me, R^3= Et)	**3g**	90	96(96)	60:40
8	**1a** (Ph)	**2h** (R^1=Cbz, R^2=H, R^3= Et)	**3h**	87	95(96)	64:36
9	**1a** (Ph)	**2i** (R^1=Boc, R^2=H, R^3= *t*-butyl)	**3i**	86	95(97)	59:41
10	**1b** (Et)	**2i** (R^1= Boc, R^2=H, R^3= *t*-butyl)	**3j**	85	93(96)	55:45
11	**1c (**thiophene**)**	**2a** (R^1= Boc, R^2=H, R^3= Et)	**3k**	90	98(99)	61:39
12	**1d** (4-ClPh)	**2a** (R^1= Boc, R^2=H, R^3= Et)	**3l**	92	90(93)	60:40
13	**1e** (4-BrPh)	**2a** (R^1= Boc, R^2=H, R^3= Et)	**3m**	89	92(88)	63:37
14	**1f** (4-FPh)	**2a** (R^1= Boc, R^2=H, R^3= Et)	**3n**	91	97(98)	62:38
15	**1g** (4-OMePh)	**2a** (R^1= Boc, R^2=H, R^3= Et)	**3o**	90	97(97)	64:36
16	**1h** (2-OMePh)	**2a** (R^1= Boc, R^2=H, R^3= Et)	**3p**	89	89(83)	59:41
17	**1i** (4-MePh)	**2a** (R^1= Boc, R^2=H, R^3= Et)	**3q**	90	96(97)	60:40
18	**1j** (2-naphthylPh)	**2a** (R^1= Boc, R^2=H, R^3= Et)	**3r**	88	95(95)	66:34

[a]Reaction conditions: 0.1 mmol methyleneindolinones **2a**, 0.12 mmol of *β*-ketoacid **1a**, and **VIII** (10 mol%) in CPME (0.5 mL) at rt in 4h. [b]Yield refers to isolated yield after column chromatography. [c]Enantiomeric excess (*ee*) determined by chiral HPLC and values in parentheses are for the minor diastereomer. [d]Determined by ^{1}H NMR analysis of crude reaction mixture, the low *dr* may arise due to enolizable 3-substituted oxindole.

The reaction of 3-oxo-3-phenylpropanoic acid (**1a**) with methyleneindolinones derivative (**2b**-**2e**) provided **3b**-**3e** in 88-91% yield, 95-97% *ee* and 57:43-62:38 *dr* (**Table 3**, **entry 2**-**5**). The 5-methoxy-*N*-Boc-methyleneindolinone (**2f**) and 5-methyl-*N*-Boc-methyleneindolinone (**2g**) reacted with (**1a**) yielding desired adduct **3f**-**3g** in 90-92% yield, 96% enantiomeric excess in both and 58:42-60:40 *dr* (**Table 3**, **entry 6**-**7**). The reaction of **2h** and **2i** with 3-oxo-3-phenylpropanoic acid (**1a**) provided **3h** and **3i** in 86-87% yield, up to 95% enantiomeric excess and 59:41-64:36 *dr* (**Table 3**, **entry 8**-**9**). The 3-oxopentanoic acid (**1b**) reacted with (**2i**) to provide the adduct **3j** in 85% yield, 93% *ee* and 55:45 *dr* (**Table 3**, **entry 10**).The (**1c**) reacted with (**2a**) to afford **3k** in 98% *ee* with 61:39 *dr* (**Table 3**, **entry 11**). The 3-(4-chlorophenyl)-3-oxopropanoic acid (**1d**), 3-(4-bromophenyl)-3-oxopropanoic acid (**1e**) and 3-(4-fluorophenyl)-3-oxopropanoic acid (**1f**) reacted well with (**2a**) to afford **3l**-**3n** in 89-92% yield, 90-97% enantiomeric excess with 60:40-63:37 *dr* (**Table 3**, **entry 12**-**14**). The reaction of **1g** and **1h** with **2a** provided **3o**-**3p** in 89-90% *ee* with 59:41-64:36 *dr* (**Table 3**, **entry 15**-**16**). The reaction of **2a** with **1i** afforded **3q** in 90% yield with 96% *ee* and 60:40 *dr* (**Table 3**, **entry 17**). The **1j** reacted with (**2a**) to provide **3r** in 88% yield, 95% enantiomeric excess and 66:34 *dr* (**Table 3**, **entry 18**).

A scale-up reaction was performed to demonstrate the practical utility of this process. The reaction of 3-oxo-3-phenylpropanoic acid (**1a**) with methyleneindolinones derivative (**2a**) on a 1.0 mmol scale with 10 mol% of **VIII** resulted in the formation of **3a** in 87% yield with 96% (98%) *ee* and 59:41 *dr* (**Scheme 1**). The applicability of acetophenone as donor to obtain the product **3a** was also explored. The reaction was very slow, only traces of **3a** could be detected on TLC after running the reaction for 4 days.



Scheme 1: Scale-up of the reaction

The (*R*, *R*) absolute configuration of adducts was assigned on the basis of single-crystal X-ray diffraction analysis[10] of compound **3i** (**Figure 3**). Based on the absolute configuration, the transition state was proposed to rationalize the stereochemistry of the product. The NH of the quinine-squaramide catalyst activates and orients methyleneindolinones *via* double hydrogen bonding. Simultaneously, the *β*-ketoacid gets activated by the tertiary amine of the catalyst which undergoes *Si* face addition to the activated methyleneindolinones which is succeeded by decarboxylation to afford (*R*, *R*)-configured product.

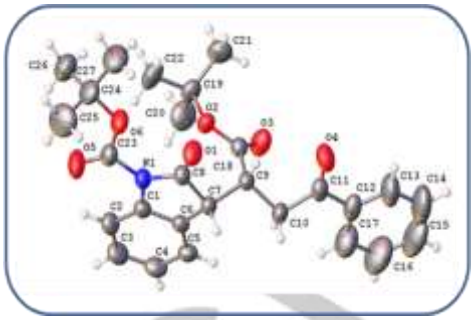


Figure 3. X-ray structure of **3i**. Thermal ellipsoids are set at 50% probability.

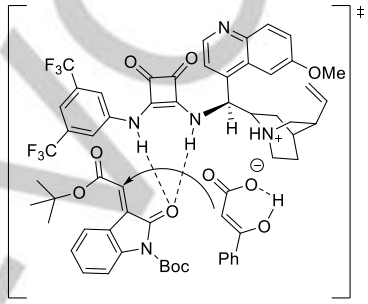


Figure 4: Proposed transition state

To gain insight into the reaction mechanism of enantioselective decarboxylative addition reaction, high resolution mass spectroscopy (HRMS) analysis of the reaction mixture was performed. After running the reaction of 3-oxo-3-phenylpropanoic acid (**1a**) with **2a** catalyzed by **VIII** for 30 minutes, an aliquot of the reaction mixture was analyzed with HRMS. The signals observed at *m/z* 631.2073, correspond to the protonated catalyst **VIII**+**H**$^+$ (**A**) while signal at *m/z* 1112.3768 correspond to the complex **E** formed as result of the Michael addition of 3-oxo-3-phenylpropanoic acid (**1a**) to the methyleneindolinones derivative (**2a**). The complex **E** undergoes decarboxylation to provide complex **C** which is observed at *m/z* 1068.3857 (**VIII**+ **3a**). The presence of Complex **E** in the HRMS of the reaction mixture is indicative of the initial Michael addition of 3-oxo-3-phenylpropanoic acid (**1a**) to methyleneindolinones derivative (**2a**) which is succeeded by decarboxylation giving complex **C**. (**Figure 5**).

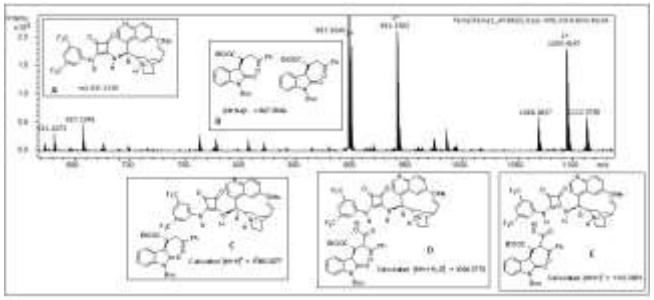


Figure 5: HRMS analysis of the reaction between **1a** and **2a**.

Conclusion

We have developed a quinine squaramide-catalyzed enantioselective decarboxylative addition reaction of various *β*-keto acids with methyleneindolinones. Through this methodology, various oxindole derivatives were synthesized in good yields (up to 93%) and excellent enantiomeric excess (up to 99% *ee*) and moderate diastereoselectivity (up to 64:36). A wide range of substituted methyleneindolinones and *β*-keto acids reacted well under the optimized reaction conditions.

Experimental Section

All reactions were performed in oven-dried glassware. All solvents and commercially available chemical were used without further purification. ^{1}H NMR spectra were recorded in $CDCl_3$ on a BRUKER AVANCE III (500 MHz) spectrometer and JEOL (400 MHz). ^{13}C NMR spectra were recorded in $CDCl_3$ on BRUKER AVANCE III (125 MHz) and JEOL (100 MHz). Chemical shifts (*δ*) are expressed in ppm downfield from internal TMS. MS were recorded on micrOTOF-Q II 10356 Mass Spectrometer. Optical rotations were determined with an AUTOPOL IV polarimeter at 25 °C using sodium D light. Enantiomeric excess was determined by using Shimadzu LC-20AD using Daicel Chiralpak IA, AS-H and AD-H column.

Material

Isatins and their derivatives were purchased from Spectrochem, India, Alfa Aesar and Sigma, Aldrich. *N*-boc protected isatins and methyleneindolinones were prepared according to the literature method.[11] The *β*-ketoacid were synthesized from *β*-ketoester (ethyl benzoyl acetate and ethyl acetoacetate) purchased from Spectrochem, India and Sigma, Aldrich. The *β*-ketoester were prepared from procedures already reported in the literature.[12]

Procedure for preparation of *β*-ketoacid

In a round-bottomed flask, 1N-NaOH (20 mL) was added to ethyl benzoylacetate (or other *β*-ketoester) (20 mmol). After stirring for overnight at room temperature, the reaction mixture was washed with diethyl ether (50 mL×4). The obtained aqueous layer was acidified with 3N-HCl to pH 1, and a precipitated white solid was filtered and dried under reduced pressure to give benzoylacetic acid in 80% yield in a pure form and is used as such for a reaction.

The catalysts **I**, **II**, **III** and **IV**, were synthesized by the procedures reported in literature.[13] The catalysts **V**, **VI**, **VII** and **VIII** were also prepared based on previous procedures.[14]

General Procedure

To the solution of methyleneindolinones **2a** (0.1 mmol), *β*-ketoacids **1a** (0.12 mmol), in 0.5 mL of CPME, organocatalyst (10 mol %) was added at 25 °C. The reaction mixture was stirred for 4 h and the progress of the reaction was monitored at regular intervals by thin layer chromatography (TLC). After the completion of reaction, the crude reaction mixture was purified by column chromatography on silica gel (mesh 60-120) using hexane-ethyl acetate (85:15) as eluent. The enantiomeric excess of the purified **3** were determined using Diacel Chiralpak columns. The racemic standards were prepared using DABCO (10 mol %) as a catalyst.

Characterization Data

***tert*-Butyl-(*R*)-3-((*R*)-1-ethoxy-1,4-dioxo-4-phenylbutan-2-yl)-2-oxoindoline-1-carboxylate (3a):** White solid; 93% yield; $[\alpha]_D^{25}$= -15.1 (*c* 0.10, $CHCl_3$); 99% (98%) *ee*; 63:37 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 70:30, 1 mL/min, 254 nm, (Isomer A) t_R = 5.51 min (major), t_R = 8.76 min (minor) and (Isomer B) t_R = 6.58 min (minor) and t_R = 7.44 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.93-7.95 (m, 2H), 7.83-7.85 (m, 1H), 7.53-7.58 (m, 1H), 7.42-7.46 (m, 2H), 7.29-7.35 (m, 2H), 7.13-7.19 (m,1H), 4.16 (d, *J* = 3.84 Hz, 1H), 4.01-4.13 (m, 3H), 3.94 (d, *J* = 3.94 Hz, 1H), 3.55-3.81 (m, 1H) 3.48 (dd, *J*= 6.64 Hz, *J* = 18.0 Hz, 1H), 2.71 (dd, *J* = 3.96 Hz, *J* = 17.2 Hz, 1H) 1.64-1.66 (m, 9H), 1.09-1.13 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 13.80, 28.10, 36.08, 36.96, 41.50, 41.98, 45.87, 47.30, 61.36, 61.40, 84.38, 84.60, 114.9, 115.1, 123.6, 123.7, 124.4, 124.5, 125.0, 125.8, 128.1, 128.5, 128.5, 128.6, 128.8, 133.3, 133.4, 136.4, 136.5, 140.3, 140.6, 149.1, 149.2, 171.5, 172.3, 173.9, 174.8, 197.4, 197.5; HRMS (ESI-TOF) *m/z*: calcd for $C_{25}H_{27}NO_6$ $[M+Na]^+$ 460.1736; found 460.1702.

***tert*-Butyl-(*R*)-3-((*R*)-1-ethoxy-1,4-dioxo-4-phenylbutan-2-yl)-5-fluoro-2-oxoindoline-1-carboxylate (3b):** White solid; 89% yield; $[\alpha]_D^{25}$= -16.9 (*c* 0.10, $CHCl_3$); 95% (92%) *ee*; 61:39 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 92:8, 1 mL/min, 254 nm, (Isomer A) t_R = 8.28 min (major), t_R = 18.0 min (minor) and (Isomer B) t_R = 10.8 min (minor) and t_R = 14.9 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.94-7.96 (m, 2H), 7.82-7.85 (m, 1H), 7.55-7.59 (m, 1H), 7.45-7.48 (m, 2H), 7.00-7.09 (m, 2H), 4.14 (d, *J* = 3.80 Hz, 1H), 3.95-4.12 (m, 3H), 3.90 (d, *J* = 2.30 Hz, 1H), 3.66-3.80 (m, 1H), 3.51 (dd, *J* = 5.95 Hz, *J* = 18.1 Hz, 1H), 2.76 (dd, *J* = 4.25 Hz, *J* = 17.3 Hz, 1H), 1.63-1.65 (m, 9H), 1.11-1.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.78, 28.09, 36.22, 37.11, 41.55, 42.06, 45.92, 47.31, 61.47, 61.49, 84.49, 84.73, 111.1, 111.3; 114.8, 115.0, 115.2, 115.4, 116.2, 116.3, 116.4, 116.5, 128.1, 128.6, 128.7, 133.4, 133.5, 136.3, 136.4, 136.5, 136.6, 149.0, 149.1, 158.9, 171.2, 172.0, 173.3, 174.4, 197.1, 197.3; HRMS (ESI-TOF) *m/z*: calcd for $C_{25}H_{26}FNO_6$ $[M+Na]^+$ 478.1642; found 478.1654.

***tert*-Butyl-(*R*)-5-chloro-3-((*R*)-1-ethoxy-1,4-dioxo-4-phenylbutan-2-yl)-2-oxoindoline-1-carboxylate (3c):** White solid; 91% yield; $[\alpha]_D^{25}$= -24.0 (*c* 0.10, $CHCl_3$); 97% (95%) *ee*; 61:39 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 97.5:2.5, 1 mL/min, 254 nm, (Isomer A) t_R = 18.1 min (major), t_R = 35.4 min (minor) and (Isomer B) t_R = 24.4 min (minor) and t_R = 38.3 min (major)]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.94-7.97 (m, 2H), 7.78-7.81 (m, 1H), 7.55-7.59 (m, 1H), 7.45-7.48 (m, 2H), 7.33 (s, 1H), 7.28-7.30 (m, 1H), 4.06-4.13 (m, 2H), 3.95-4.01 (m, 1H), 3.87 (d, *J* = 2.95 Hz, 1H), 3.72-3.79 (m, 1H), 3.53 (dd, *J* = 18.2 Hz, *J* = 5.65 Hz, 1H), 2.79 (dd, *J* = 17.3 Hz, *J* = 4.30 Hz, 1H), 1.63-1.64 (m, 9H), 1.11-1.13 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 13.79, 13.81, 28.09, 36.26, 37.26, 41.54, 42.11, 45.64, 47.09, 61.52, 84.65, 84.93, 116.2, 116.3, 123.8, 124.0, 128.0, 128.1, 128.4, 128.6, 128.7, 128.9, 129.8, 129.9, 133.4, 133.5, 136.4, 136.4, 138.8, 139.1, 148.9, 149.0, 171.2, 172.0, 173.1, 174.2, 197.1, 197.3; HRMS (ESI-TOF) *m/z*: calcd for $C_{25}H_{26}ClNO_6$ $[M+Na]^+$ 494.1346; found 494.1339.

***tert*-Butyl-(*R*)-5-bromo-3-((*R*)-1-ethoxy-1,4-dioxo-4-phenylbutan-2-yl)-2-oxoindoline-1-carboxylate (3d):** White solid; 88% yield; $[\alpha]_D^{25}$= -24.9 (*c* 0.10, $CHCl_3$); 95% (96%) *ee*; 62:38 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 92:8, 1 mL/min, 254 nm, (Isomer A) t_R = 9.80 min (major), t_R = 14.4 min (minor) and (Isomer B) t_R = 11.6 min (minor) and t_R = 16.2 min (major)]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.94-7.97 (m, 2H), 7.73-7.76 (m, 1H), 7.56-7.58 (m, 1H), 7.43-7.48 (m, 4H), 4.06-4.13 (m, 2H), 3.94-3.99 (m, 1H), 3.87 (d, *J*= 2.95 Hz, 1H), 3.76 (dd, *J* = 18.4 Hz, *J* = 8.50 Hz, 1H), 3.54 (dd, *J* = 18.2 Hz, *J* = 5.55 Hz, 1H), 2.80 (dd, *J* = 17.3 Hz, *J* = 4.35 Hz, 1H), 1.62-1.64 (m, 9H), 1.11-1.13 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 13.74, 13.82, 28.10, 36.27,37.31, 41.58, 42.17, 45.6, 47.02, 61.53, 84.67, 84.96, 116.6, 116.7, 126.6, 126.8, 128.2, 128.4, 128.6, 128.7, 131.4, 131.8, 133.4, 133.5, 136.4, 136.5, 139.4, 148.9, 149.0, 171.2, 171.9, 173.0, 174.1, 197.1, 197.3; HRMS (ESI-TOF) *m/z*: calcd for $C_{25}H_{26}BrNO_6$ $[M+Na]^+$ 538.0841; found 538.0834.

***tert*-Butyl-(*R*)-3-((*R*)-1-ethoxy-1,4-dioxo-4-phenylbutan-2-yl)-5-iodo-2-oxoindoline-1-carboxylate (3e):** White solid; 89% yield; $[\alpha]_D^{25}$= -21.0 (*c* 0.10, $CHCl_3$); 96% (97%) *ee*; 57:43 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 92:8, 1 mL/min, 254 nm, (Isomer A) t_R = 7.23 min (major), t_R = 9.44 min (minor) and (Isomer B) t_R = 8.19 min (minor) and t_R = 11.0 min (major)]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.94-7.98 (m, 2H), 7.56-7.65 (m, 4H), 7.45-7.49 (m, 2H), 4.03-4.13 (m, 2H), 3.93-3.98 (m, 1H), 3.85 (d, *J* = 3.0 Hz, 1H), 3.72-3.81 (m, 1H), 3.54 (dd, *J* = 5.45 Hz, *J*= 18.2 Hz), 2.79 (dd, *J* = 4.30 Hz, *J* =17.3 Hz, 1H), 1.62-1.64 (m, 9H), 1.10-1.14 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 13.79, 13.84, 28.09, 36.22, 37.35, 41.56, 42.18, 45.34, 46.83, 61.52, 84.66, 84.97, 87.71, 87.77, 116.9, 117.1, 128.2, 128.6, 128.7, 128.8, 136.4, 136.5, 137.4, 137.8, 140.1, 140.4, 148.9, 149.0, 171.2, 171.9, 172.9, 173.9, 197.1, 197.4; HRMS (ESI-TOF) *m/z*: calcd for $C_{25}H_{26}INO_6$ $[M+Na]^+$ 586.0703; found 586.0717.

***tert*-Butyl-(*R*)-3-((*R*)-1-ethoxy-1,4-dioxo-4-phenylbutan-2-yl)-5-methoxy-2-oxoindoline-1-carboxylate (3f):** White solid; 92% yield; $[\alpha]_D^{25}$= -27.9 (*c* 0.10, $CHCl_3$); 96% (94%) *ee*; 58:42 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 92:8, 1 mL/min, 254 nm, (Isomer A) t_R = 8.87 min (major), t_R = 14.1 min (minor) and (Isomer B) t_R = 11.0 min (minor) and t_R = 13.3 min (major)]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.92-7.95 (m, 2H), 7.75 (d, *J* = 8.85 Hz, 1H), 7.53-7.56 (m, 1H), 7.42-7.46 (m, 2H), 6.82-6.89 (m, 2H), 4.06-4.16 (m, 2H), 3.97-4.01 (m, 1H), 3.90 (d, *J* = 3.10 Hz, 1H), 3.71-3.78 (m, 3H), 3.57-3.62 (m, 1H), 3.48 (dd, *J* = 18.1 Hz, *J* = 6.50 Hz, 1H), 2.66 (dd, *J* = 17.3 Hz, *J* = 3.80 Hz, 1H), 1.62-1.65 (m, 9H), 1.11-1.15 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 13.80, 13.82, 28.12, 35.87, 37.01, 41.50, 42.02, 46.18, 47.57, 55.65, 61.34, 61.40, 84.13, 84.36, 109.8, 110.2, 113.4, 113.5, 115.8, 116.0, 127.2, 128.1, 128.5, 128.6, 133.2, 133.3, 133.6, 133.9, 136.5, 136.7, 149.2, 149.3, 156.8, 156.9, 171.4, 172.2, 173.0, 174.7, 197.3, 197.4; HRMS (ESI-TOF) *m/z*: calcd for $C_{26}H_{29}NO_7$ $[M+Na]^+$ 490.1842; found 490.2223.

***tert*-Butyl-(*R*)-3-((*R*)-1-ethoxy-1,4-dioxo-4-phenylbutan-2-yl)-5-methyl-2-oxoindoline-1-carboxylate (3g):** White solid; 90% yield; $[\alpha]_D^{25}$= -27.9 (*c* 0.10, $CHCl_3$); 96% (96%) *ee*; 60:40 *dr*; HPLC [Chiralpak IA, hexane/*i*-PrOH, 97:3, 1 mL/min, 254 nm, (Isomer A) t_R = 18.6 min (major), t_R = 30.6 min (minor) and (Isomer B) t_R = 25.7 min (minor) and t_R = 33.2 min (major)]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.93-7.95 (m, 2H), 7.70 (d, *J*= 8.65 Hz, 1H), 7.43-7.57 (m, 2H), 7.09-7.12 (m, 2H), 4.07-4.15 (m, 2H), 3.97-4.01 (m, 1H), 3.88 (d, *J* = 2.95 Hz, 1H), 3.56-3.77 (m, 1H), 3.48 (dd, *J* = 18.1 Hz, *J* = 6.55 Hz, 1H), 2.65 (dd, *J* = 17.3 Hz, *J* = 3.70 Hz, 1H), 2.32-2.35 (m, 3H), 1.62-1.65 (m, 9H), 1.11-1.14 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 13.81, 13.83, 21.06, 21.09, 28.14, 35.97, 37.10, 41.54, 42.03, 45.99, 47.38, 61.32, 61.37, 84.17, 84.41, 114.8, 114.9, 124.2, 124.3, 125.0, 125.8, 128.1, 128.5, 128.6, 128.9, 129.3, 133.3, 133.4, 134.0, 134.2, 136.5, 136.6, 137.9, 138.2, 149.2, 171.5, 172.3, 174.0, 174.9, 197.5, 197.6; HRMS (ESI-TOF) *m/z*: calcd for $C_{26}H_{29}NO_6$ $[M+Na]^+$ 474.1893; found 474.1857.

Benzyl-(*R*)-3-((*R*)-1-ethoxy-1,4-dioxo-4-phenylbutan-2-yl)-2-oxoindoline-1-carboxylate (3h): Brown solid; 87% yield; $[\alpha]_D^{25}$= -12.9 (*c* 0.10, $CHCl_3$); 95% (96%) *ee*; 64:36 *dr*; HPLC [Chiralpak AS-H, hexane/*i*-PrOH, 80:20, 1 mL/min, 254 nm, (Isomer A) t_R = 12.8 min (minor), t_R = 17.4 min (major) and (Isomer B) t_R = 20.4 min (major) and t_R = 29.2 min (minor)]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.89-7.95 (m, 3H), 7.49-7.57 (m, 3H), 7.41-7.46 (m, 2H), 7.36-7.40 (m, 2H), 7.29-7.35 (m, 3H), 7.14-7.20 (m, 1H), 5.40-5.50 (m, 2H), 4.19 (d, *J* = 3.75 Hz, 1H), 3.99-4.11 (m, 3H) , 3.95 (d, *J* = 3.15 Hz, 1H), 3.64-3.79 (m, 1H) , 3.49 (dd, *J* = 6.15 Hz, *J* =18.0 Hz, 1H), 2.72 (dd, *J* = 4.10 Hz, *J* = 17.2 Hz, 1H), 1.04-1.08 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 13.78, 36.12, 37.05, 41.69, 42.33, 45.77, 47.28, 61.41, 61.44, 68.62, 68.73, 115.1, 115.3, 123.6, 123.7, 124.7, 124.8, 125.2, 126.0, 128.1, 128.2, 128.5, 128.6, 128.7, 128.8, 129.0, 133.3, 133.4, 134.9, 135.0, 136.5, 139.9, 140.2, 150.8, 150.9, 171.3, 172.2, 173.7, 174.5, 197.2, 197.4;

HRMS (ESI-TOF) *m/z*: calcd for $C_{28}H_{25}NO_6$ $[M+Na]^+$ 494.1580; found 494.1561.

***tert*-Butyl-(*R*)-3-((*R*)-1-(*tert*-butoxy)-1,4-dioxo-4-phenylbutan-2-yl)-2-oxoindoline-1-carboxylate (3i):** White solid; 86% yield; $[\alpha]_D^{25}$= -90.0 (*c* 0.20, $CHCl_3$); 95% (97%) *ee*; 59:41 *dr*; HPLC [Chiralpak IA, hexane/*i*-PrOH, 97:3, 0.5 mL/min, 254 nm, (Isomer A) t_R = 25.6 min (major), t_R = 50.0 min (minor) and (Isomer B) t_R = 45.4 min (minor) and t_R = 55.2 min (major)]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.96-7.99 (m, 1H), 7.82-7.87 (m, 1H), 7.55-7.58 (m, 1H), 7.43-7.48 (m, 2H), 7.31-7.37 (m, 2H), 7.12-7.20 (m, 1H), 3.95-4.10 (m, 1H), 3.90 (s, 1H), 3.63-3.89 (m, 1H), 3.50 (dd, *J* = 5.60 Hz, *J* = 18.3 Hz, 1H) , 2.85 (dd, *J* =4.8, *J* =17.2 Hz, 1H), 1.63-1.65 (m, 9H), 1.66 (s, 4H), 1.18-1.24 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 27.50, 27.60, 28.12, 37.22, 37.33, 42.36, 43.01, 45.84, 47.56, 81.94, 84.26, 84.42, 114.8, 115.0, 123.6, 123.7, 124.3, 124.4, 125.5, 126.5, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 133.2, 133.3, 136.6, 136.7, 140.3, 140.7, 149.2, 149.3, 170.1, 170.2, 174.2, 174.7, 197.3,197.8; HRMS (ESI-TOF) *m/z*: calcd for $C_{27}H_{31}NO_6$ $[M+Na]^+$ 488.2049; found 488.2177.

***tert*-Butyl-(*R*)-3-((*R*)-1-(*tert*-butoxy)-1,4-dioxohexan-2-yl)-2-oxoindoline-1-carboxylate (3j):** White solid; 85% yield; $[\alpha]_D^{25}$= -54.0 (*c* 0.50, $CHCl_3$); 55:45 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 95:5, 1 mL/min, 254 nm, (Isomer A) t_R = 8.89 min (major), t_R = 11.9 min (minor) and (Isomer B) t_R = 13.1 min (minor) and t_R = 15.2 min (major)]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.80-7.85 (m, 1H), 7.29-7.33 (m, 1H), 7.24-7.26 (m, 1H), 7.12-7.17 (m, 1H), 3.68-3.89 (m, 2H), 2.83-3.21 (m, 1H) , 2.25-2.59 (m, 3H), 1.63-1.64 (m, 9H), 1.20-1.24 (m, 9H), 1.04-1.04 (m, 3H); ^{13}C (125 MHz, $CDCl_3$) 7.64, 27.50, 27.57, 28.10, 36.06, 36.22, 40.25, 40.80, 42.20, 42.71, 45.52, 47.55, 81.84, 81.56, 84.30, 84.42, 114.8, 115.0, 123.5, 123.6, 124.4, 125.5, 126.2, 128.3, 128.6, 140.2, 140.6, 149.1, 149.2, 170.2, 171.1, 174.0, 174.6, 208.2, 208.2; HRMS (ESI-TOF) *m/z*: calcd for $C_{23}H_{31}NO_6$ $[M+Na]^+$ 440.2049; found 440.1971.

***tert*-Butyl-(*R*)-3-((*R*)-1-ethoxy-1,4-dioxo-4-(thiophen-2-yl)butan-2-yl)-2-oxoindoline-1-carboxylate (3k):** Brown semi-solid; 90% yield; $[\alpha]_D^{25}$= -59.9 (*c* 0.10, $CHCl_3$); 98% (99%) *ee*; 61:39 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 90:10, 1 mL/min, 254 nm, (Isomer A) t_R = 9.89 min (major), t_R = 18.5 min (minor) and (Isomer B) t_R = 14.4 min (minor) and t_R = 16.9 min (major)]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.82 (d, *J* = 8.60, 1H), 7.73-7.74 (m, 1H), 7.62-7.65 (m, 1H), 7.29-7.33 (m, 2H), 7.09-7.18 (m, 2H), 4.18 (d, *J* = 3.80 Hz, 1H), 3.97-4.14 (m, 3H), 3.90 (d, *J* = 3.40 Hz, 1H), 3.55-3.70 (m, 1H), 3.43 (dd, *J* = 6.48 Hz, *J* = 17.5 Hz, 1H), 2.67 (dd, *J* =1.12 Hz, *J* = 16.7 Hz, 1H), 1.64-1.66 (m, 9H), 1.08-1.13 (m, 3H),^{13}C NMR (125 MHz, $CDCl_3$) *δ* 13.77, 28.11, 36.61, 37.52, 41.45, 42.12, 45.79, 47.23, 61.41, 61.47, 84.38, 84.62, 114.9, 115.1, 123.5, 123.8, 124.4, 124.6, 124.9, 125.8, 128.1, 128.2, 128.5, 128.9, 132.2, 132.6, 133.9, 134.1, 140.3, 140.6, 143.6, 149.1, 149.2, 171.3, 172.0, 173.9, 174.8, 190.1, 190.3; HRMS (ESI-TOF) *m/z*: calcd for $C_{23}H_{25}NO_6S$ $[M+Na]^+$ 466.1300; found 466.1537.

***tert*-Butyl 3-(4-(4-chlorophenyl)-1-ethoxy-1,4-dioxobutan-2-yl)-2-oxoindoline-1-carboxylate (3l):** Brown semi-solid; 92% yield; $[\alpha]_D^{25}$= -25.8 (*c* 0.10, $CHCl_3$); 90% (93%) *ee*; 60:40 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 90:10, 1 mL/min, 254 nm, (Isomer A) t_R = 9.90 min (major), t_R = 18.1 min (minor) and (Isomer B) t_R = 12.8 min (minor) and t_R = 14.3 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.83-7.88 (m, 3H), 7.41-7.43 (m, 2H), 7.28-7.34 (m, 2H), 7.13-7.19 (m, 1H), 3.93-4.17 (m, 4H), 3.48-3.74 (m, 1H), 3.43 (dd, *J* = 6.75 Hz, *J* = 17.9 Hz, 1H), 2.64 (dd, *J* = 3.80 Hz, *J* = 17.2 Hz, 1H), 1.64-1.65 (m, 9H), 1.10-1.13 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ13.81, 28.13, 36.00, 36.87, 41.97, 45.90, 47.28, 61.41, 84.44, 84.66, 115.0, 115.2, 123.6, 123.7, 124.4, 124.5, 124.9, 125.7, 139.8, 139.9, 140.3, 140.6, 149.1, 149.2, 196.2, 196.3; HRMS (ESI-TOF) *m/z*: calcd for $C_{25}H_{26}ClNO_6$ $[M+Na]^+$ 494.1346; found 494.1324.

***tert*-Butyl-(*R*)-3-((*R*)-4-(4-bromophenyl)-1-ethoxy-1,4-dioxobutan-2-yl)-2-oxoindoline-1-carboxylate (3m):** Semi-solid; 89% yield; $[\alpha]_D^{25}$= -10.0 (*c* 0.20, $CHCl_3$); 92% (88%) *ee*; 63:37 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 92:8, 1 mL/min, 254 nm, (Isomer A) t_R = 12.6 min (major), t_R = 24.3 min (minor) and (Isomer B) t_R = 17.3 min (minor) and t_R = 18.8 min (major)]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.79-7.84 (m, 3H), 7.59 (d, *J* = 8.45 Hz, 2H), 7.28-7.34 (m, 2H), 7.14-7.19 (m, 1H), 4.17 (d, *J* = 3.70 Hz, 1H) 3.99-4.11 (m, 3H), 3.93 (d, *J* = 3.00 Hz, 1H), 3.47-3,72 (m, 1H), 3.42 (dd, *J* = 6.8 Hz, *J* =18.0 Hz, 1H) , 2.63 (dd, *J* =3.80 Hz, *J* =17.2 Hz, 1H), 1.64- 1.65 (m, 9H), 1.10-1.13 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 13.82, 28.13, 35.99, 36.86, 41.95, 45.89, 47.28, 61.42, 61.48, 84.45, 84.67, 115.0, 115.2, 123.6, 123.7, 124.4, 124.6, 124.9, 125.7, 128.5, 128.6, 128.9, 129.7, 129.9, 131.9, 132.0, 135.2, 135.3, 140.3, 140.6, 149.1, 149.2, 171.4, 172.2, 173.8,174.6,196.4, 196.5; HRMS (ESI-TOF) *m/z*: calcd for $C_{25}H_{26}BrNO_6$ $[M+Na]^+$ 538.0841; found 538.0850.

***tert*-Butyl-(*R*)-3-((*R*)-1-ethoxy-4-(4-fluorophenyl)-1,4-dioxobutan-2-yl)-2-oxoindoline-1-carboxylate (3n):** Semi-solid; 91% yield; $[\alpha]_D^{25}$= -15.9 (*c* 0.10, $CHCl_3$); 97% (98%) *ee*; 62:38 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 90:10, 1 mL/min, 254 nm, (Isomer A) t_R = 8.85 min (major), t_R = 16.4 min (minor) and (Isomer B) t_R = 11.6 min (minor) and t_R = 13.0 min (major)]; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.95-7.98, (m, 2H), 7.84 (d, *J* = 8.15 Hz, 1H), 7.28-7.33 (m, 2H), 7.10-7.19 (m, 3H), 4.17(d, *J* = 3.70 Hz, 1H), 3.90-4.10 (m, 3H), 3.93 (d, *J* = 3.15, 1H),3.50-3.75 (m, 2H), 3.44 (dd, *J* = 6.75 Hz , *J* =17.9 Hz, 1H) , 2.65 (dd, *J* = 3.80 Hz, *J* =17.1, Hz, 1H), 1.64-1.66 (s, 9H), 1.10-1.13 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 13.81, 28.12, 35.96, 41.60, 42.02, 45.90, 47.30, 61.39, 61.45, 84.42, 84.64, 115.0, 115.1, 115.6, 115.7, 115.8, 115.9, 123.6, 123.7, 124.4, 124.5, 125.0, 125.7, 128.5, 128.8, 130.8, 130.9, 132.9, 140.3, 140.6, 149.1, 149.2, 171.4, 172.2, 173.8, 174.6, 195.8, 195.9;

HRMS (ESI-TOF) *m/z*: calcd for $C_{25}H_{26}FNO_6$ $[M+Na]^+$ 478.1642; found 478.1601.

***tert*-Butyl-(*R*)-3-((*R*)-1-ethoxy-4-(4-methoxyphenyl)-1,4-dioxobutan-2-yl)-2-oxoindoline-1-carboxylate (3o):** Semi-solid; 90% yield; $[\alpha]_D^{25}$= -26.9 (*c* 0.10, $CHCl_3$); 97% (97%) *ee*; 64:36 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 90:10, 1 mL/min, 254 nm, (Isomer A) t_R = 13.8 min (major), t_R = 30.2 min (minor) and (Isomer B) t_R = 19.7 min (minor) and t_R = 21.6 min (major)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91-7.94 (m, 2H), 7.83 (d, *J* = 8.20 Hz, 1H), 7.29-7.33 (m, 2H), 7.12-7.18 (m, 1H), 6.91 (d, *J* = 8.90 Hz, 2H), , 4.15 (d, *J* = 3.80 Hz, 1H), 3.99-4.15 (m, 3H), 3.91 (d, *J* = 3.10 Hz, 1H), 3.85-3.86 (m, 3H) , 3.56-3.3.75 (m, 1H), 3.43 (dd, *J* = 6.40 Hz, *J* =17.8 Hz, 1H), 2.67 (dd, *J* = 4.15 Hz, *J* = 17.0 Hz, 1H), 1.64-1.66 (m, 9H), 1.09-1.12 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.80, 28.13, 35.75, 36.66, 41.63, 42.21, 45.91, 47.34, 55.48, 61.27, 61.32, 84.30, 84.53, 113.7, 113.8, 114.9, 115.1, 123.6, 123.7, 124.3, 124.4, 125.2, 126.0, 128.4, 128.8, 129.7, 130.5, 140.3, 140.6, 149.1, 149.2, 163.6, 163.7, 171.6, 172.4, 173.9, 174.8, 195.8, 195.9; HRMS (ESI-TOF) *m/z*: calcd for $C_{26}H_{29}NO_7$ $[M+Na]^+$ 490.1842; found 490.1835.

***tert*-Butyl-(*R*)-3-((*R*)-1-ethoxy-4-(2-methoxyphenyl)-1,4-dioxobutan-2-yl)-2-oxoindoline-1-carboxylate (3p):** Semi-solid; 89% yield; $[\alpha]_D^{25}$= -17.9 (*c* 0.20, $CHCl_3$); 89% (83%) *ee*; 59:41 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 95:5, 1 mL/min, 254 nm, (Isomer A) t_R = 19.0 min (major), t_R = 35.3 min (minor) and (Isomer B) t_R = 25.1 min (minor) and t_R = 28.5 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.85 (m, 1H), 7.69-7.73 (m, 1H), 7.43-7.47 (m, 1H), 7.29-7.32 (m, 2H), 7.12-7.17 (m,1H), 6.92-7.00 (m, 2H), 3.91-4.12 (m, 4H), 3.83-3.86 (m, 3H), 3.54-3.76 (m, 1H), 3.46 (dd, *J* = 6.40 Hz, *J* = 18.5 Hz, 1H), 3.02 (dd, *J* = 4.40 Hz, *J* = 17.8 Hz, 1H), 1.63-1.64 (m, 9H), 1.05-1.34 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.73, 13.82, 41.98, 42.05, 42.17, 42.43, 46.11, 47.34, 55.44, 55.50, 61.11, 61.45, 84.19, 84.31, 111.5,111.6, 114.8, 114.9, 120.6, 120.7, 123.8, 130.5, 130.6, 133.7, 133.8, 140.3, 140.7, 149.2, 158.6, 158.8, 171.5, 172.5, 174.0, 174.8, 198.9; HRMS (ESI-TOF) *m/z*: calcd for $C_{26}H_{29}NO_7$ $[M+Na]^+$ 490.1842; found 490.1824.

***tert*-Butyl-(*R*)-3-((*R*)-1-ethoxy-1,4-dioxo-4-(*p*-tolyl)butan-2-yl)-2-oxoindoline-1-carboxylate (3q):** White solid; 90% yield; $[\alpha]_D^{25}$= -9.99 (*c* 0.20, $CHCl_3$); 96% (97%) *ee*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 90:10, 1 mL/min, 254 nm, (Isomer A) t_R = 9.24 min (major), t_R = 18.1 min (minor) and (Isomer B) t_R = 12.5 min (minor) and t_R = 14.2 min (major)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83-7.85 (m, 3H), 7.29-7.34 (m, 2H), 7.23-7.25 (m, 2H), 7.12-7.18 (m, 1H), 3.98-4.15 (m, 3H), 3.91 (d, *J* = 3.24 Hz, 1H), 3.57-3.78 (m, 1H), 3.45 (dd, *J* = 18.04 Hz, *J* = 6.48 Hz, 1H), 2.67 (dd, *J* = 17.24 Hz, *J* = 4.08 Hz, 1H), 2.39 (s, 3H), 1.63-1.65 (m, 9H), 1.08-1.12 (m, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 13.79, 21.67, 28.16, 35.95, 36.87, 41.49, 42.04, 45.86, 47.31, 61.32, 61.34, 84.32, 84.56, 114.9, 115.1, 123.6, 123.7, 124.4, 124.5, 125.1, 125.9, 128.2, 128.5, 128.7, 129.2, 129.3, 133.9, 134.0, 144.1, 144.2, 149.1, 149.2, 171.5, 172.3, 173.9, 174.8, 196.9, 197.1; HRMS (ESI-TOF) *m/z*: calcd for $C_{26}H_{29}NO_6$ $[M+Na]^+$ 474.1893; found 474.1867.

***tert*-Butyl-(*R*)-3-((*R*)-1-ethoxy-4-(naphthalen-2-yl)-1,4-dioxobutan-2-yl)-2-oxoindoline-1-carboxylate (3r):** Light brown solid; 88% yield; $[\alpha]_D^{25}$= -15.0 (*c* 0.20, $CHCl_3$); 95% (95%) *ee*; 66:34 *dr*; HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 82:18, 1 mL/min, 254 nm, (Isomer A) t_R = 9.56 min (major), t_R = 17.6 min (minor) and (Isomer B) t_R = 11.8 min (minor) and t_R = 15.9 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47, (s, 1H), 7.95-8.03 (m, 2H), 7.83-7.91 (m, 3H), 7.52-7.62 (m, 3H), 7.31-7.36 (m, 2H), 7.14-7.20 (m, 1H), 4.22 (d, *J* = 3.72 Hz, 1H), 4.05-4.14 (m, 3H), 3.98 (d, *J* = 3.2 Hz, 1H), 3.87-3.93 (m, 1H), 3.63 (dd, *J* = 6.52 Hz, *J* = 17.9 Hz, 1H), 2.82 (dd, *J* = 3.88 Hz, *J* = 17.1 Hz, 1H), 1.64-1.67 (m, 9H), 1.10-1.13 (m, 3H); 13C NMR (100 MHz, CDCl3) δ 13.82, 28.11, 36.07, 37.10, 41.56, 42.12, 45.93, 47.37, 61.38, 61.44, 84.37, 84.65, 123.6, 123.7, 123.8, 123.9, 124.4, 124.6, 125.0, 125.9, 126.8, 127.8,128.4, 128.5, 128.6, 128.9, 129.6, 129.7, 129.9, 130.0, 140.3, 140.5, 149.2, 171.6, 172.4, 174.1, 174.9, 197.3, 197.4; HRMS (ESI-TOF) *m/z*: calcd for $C_{29}H_{29}NO_6$ $[M+Na]^+$ 510.1893; found 510.1944.

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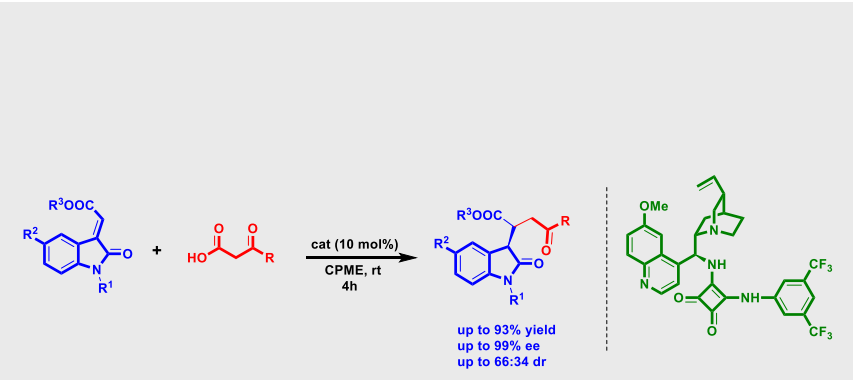

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Page No. – Page No.

Organocatalytic asymmetric decarboxylative addition of *β*-ketoacids to methyleneindolinones derivatives