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Lipase-catalyzed dynamic kinetic resolution of hemiaminals

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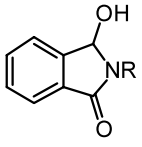
Abstract—The enzymatic dynamic kinetic resolution of *N*-acylhemiaminals by various lipases, namely, lipase PS, lipase AK and lipase QL, has been investigated. The acetylation of racemic *N*-acylhemiaminals with lipases exclusively produced the (*R*)-enantiomers in enantiomerically pure form and quantitative yields.

1. Introduction

Despite the success of the enzyme-catalyzed kinetic resolutions for the generation of a wide range of homochiral building blocks, there is an increasing desire to develop transformations that are not limited by a maximum yield of only 50% of the product. Increasing attention has been paid in recent years to the discovery of dynamic kinetic resolution (DKR) processes in which the reacting isomers are able to undergo rapid interconversion in situ under the reaction conditions.[1–3] DKR reactions can thus result in quantitative yields with enantiomeric excesses (e.e.s) approaching 100%. Recently, Feringa et al. reported that *Candida antarctica* lipase B (CAL-B) mediated the enantioselective transformation of 5-hydroxy-1,5-dihydro-pyrrol-2-ones[4] and the products are utilized as chiral building blocks for various organic syntheses.[5] The 3-hydroxy-2,3-dihydro-isoindolin-1-ones (hemiaminals) are the core unit of a wide range of naturally occurring substances[6] and also building blocks in the synthesis of several bio-active compounds.[7] Recently, we reported the chemical dynamic kinetic resolution of *N*-acylhemiaminals using chiral twisted amides.[8] Herein we present the simple enzymatic acetylation of *N*-acylhemiaminals (Fig. 1) using various lipases (lipase PS, lipase AK and lipase QL) via DKR to give the corresponding enantiomerically pure acetates in quantitative yields.



1a : R = $COCH_3$
1b : R = COC_2H_5
1c : R = COC_3H_7
1d : R = $COCH(CH_3)_2$
1e : R = $COC(CH_3)_3$
1f : R = COPh

Figure 1. *N*-Acylhemiaminals.

2. Results and discussion

2.1. Screening of the enzyme system

Racemic *N*-acylhemiaminals are readily synthesized according to a previously reported procedure.[8] As a screening process, 13 commercially available hydrolytic enzymes were tested with racemic 3-hydroxy-2-pivaloyl-2,3-dihydro-isoindolin-1-one **1e**, which was employed as the substrate in hexane using isopropenyl acetate as an acyl donor. The selection of the enzymes was carried out on the basis of the hydrolytic activity without paying attention to the enantioselectivity.[9] The assay was performed by monitoring the production of the corresponding acetate using thin-layer chromatography (TLC). As a result (Table 1), only three lipases, namely lipase PS, lipase AK and lipase QL, were found to be active in the acetylation of the substrate **1e**, while the other enzymes failed to catalyze the transformation.

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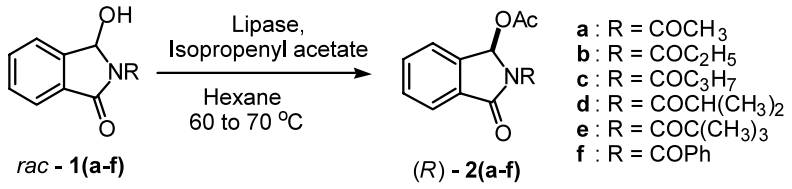
Table 1. Results of screening test for the enzyme system[a]

	Activity[b]		Activity
CAL-A	–	Lipase N	–
CAL-B	–	Lipase M-10	–
LIP-300	–	Lipase PS	+
Lipase A	–	Lipase QL	+
Lipase AY-30	–	PPL	–
Lipase AK	+	RML	–
Lipase F	–		

[a] Reactions were performed on a 5 mg substrate of **1e** for 24 h at 70°C using 5 mg of enzyme in 2 ml of hexane.
[b] –: Little or no reaction by TLC, +: considerable formation of the corresponding acetate by TLC.

2.2. Dynamic kinetic resolution of *N*-acylhemiaminals with lipases

On the basis of preliminary results in the screening test, we then studied the acetylation of the *N*-acylhemiaminals **1(a–f)** with lipases using isopropenyl acetate[10] as an acylating agent in hexane at elevated temperatures (Scheme 1). The e.e.s of the product acetates were determined by HPLC using chiral stationary phases. These results are summarized in Table 2. Lipase PS (entries 1–6) catalyzed the acetylation of *N*-acylhemiaminals to provide the corresponding acetates in quantitative yields with high enantiomeric excess. However, the reaction took a very long time for complete conversion. The lipase AK (entries 7–12) also catalyzed these acetylations in quantitative yields with high e.e.s, but took relatively fewer days for total conversion. Surprisingly, the lipase QL (entries 13–18) mediated acetylations took a significantly shorter time compared to the other lipases to furnish the corresponding enantiomerically pure acetates in quantitative yields. It is also worth noting that the lipase QL reactions were particularly versatile for scaling up. Acetylation can be accomplished by shaking an *N*-acylhemiaminal **1** with the lipase in hexane at 150 rpm and 60°C, followed by filtration to remove the enzyme and finally removal of the solvent. Most of the products were obtained in quantitative yield with >99% e.e. The quantitative yields and excellent high e.e.s obtained in the acetylations clearly confirm that the acetylations apparently proceeded via DKR under the reaction conditions. It is estimated from the present study that the *N*-acylhemiaminal **1** could be racemized presumably due to ring opening at the C3 position.[4b,8]



Scheme 1.

Table 2. Dynamic kinetic resolution of *N*-acylhemiaminals using lipases[a,b]

Entry	Substrate	Lipase[c]	Temp. (°C)	Time (days)	E.e. (%)[d]
1	**1a**	PS	70	6	63
2	**1b**	PS	70	12	95
3	**1c**	PS	70	6	>99
4	**1d**	PS	70	6	>99
5	**1e**	PS	70	6	>99
6	**1f**	PS	70	7	>99
7	**1a**	AK	65	4	63
8	**1b**	AK	65	4	>99
9	**1c**	AK	65	4	97
10	**1d**	AK	65	4	>99
11	**1e**	AK	65	1.5	>99
12	**1f**	AK	65	1.5	>99
13	**1a**	QL	60	1	63
14	**1b**	QL	60	1	>99
15	**1c**	QL	60	1	98
16	**1d**	QL	60	1	>99
17	**1e**	QL	60	1	>99
18	**1f**	QL	60	1	>99

[a] (i) Reactions (entries 1–12) were performed on a 0.1 mmol substrate using 100 mg of enzyme in 3 ml of hexane. (ii) Reactions (entries 13–18) were performed on a 0.5 mmol substrate using 100 mg of enzyme in 10 ml of hexane.
[b] Isolated yield was quantitative in all cases and the acetate products showed satisfactory spectral data.
[c] Lipase AK: *Pseudomonas fluorescens* (Amano); Lipase PS: *Pseudomonas cepacia* (Amano); Lipase QL: *Alcaligenes species* (Meito Sangyo).
[d] Determined by Chiral HPLC (full details in experimental section).

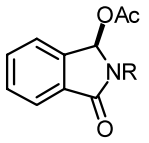
2.3. Enantioselectivity in dynamic kinetic resolution

Theoretically, the e.e.s of the products from the DKR can be enriched to 100%. As can be seen from the results in Table 2, the reaction was found to proceed with high enantioselectivity and the (*R*)-enantiomers were obtained exclusively. However, for the substrate **1a**, the acetylated product was obtained with moderate enantioselectivity under the same reaction conditions. The above observation can be rationalized using an empirical rule[11] for the lipase-catalyzed kinetic resolutions of secondary alcohols. The rule is based on the size difference of the two substituents at the stereogenic centre of the substrates and thus predicts that (*R*)-enantiomers typically react faster with lipases. The fact that (*R*)-enantiomers preferentially form suggests that the lipases recognize the *N*-acyl groups as being larger than a fused benzene ring by applying the empirical rule. Thus, the (*R*)-enantiomer selectivity should increase with increasing size of the *N*-acyl groups. In fact, the substrate **1a** having an *N*-acetyl group showed moderate enantioselectivity, while complete selectivity was attained for the substrates **1(d–f)** having very large *N*-acyl groups.

2.4. Absolute configuration of the products

The absolute configuration of the products was determined by CD spectra according to an empirical rule proposed by Feringa et al.[12] where both signs of the Cotton effects for the n–π* and π–π* absorption bands are important to determine that the absolute configuration and the (–)-enantiomer always has the (*R*)-configuration. The CD/UV spectral data indicated that all the acetate products in the DKR were assigned to the (*R*)-configuration as listed in Table 3.

Table 3. CD and UV data for *N*-acylhemiaminal acetates **2(a–f)** in ethanol



(*R*) - **2(a-f)**

Entry	Compound	R	CD, $\Delta\varepsilon$ (nm)/UV, ε (nm) *N*-acylhemiaminal	
			n–π*	π–π*
1	**2a**	$COCH_3$	+1.72 (237)	−34.2 (207) 17700 (241)
2	**2b**	COC_2H_5	+1.55 (237)	−34.6 (206) 16400 (241)
3	**2c**	COC_3H_7	+1.47 (237)	−33.7 (208) 16400 (242)
4	**2d**	$COCH(CH_3)_2$	+1.07 (240)	−31.5 (209) 15100 (242)
5	**2e**	$COC(CH_3)_3$	+1.40 (243)	−29.4 (208) 15700 (242)
6	**2f**	COPh	+7.93 (243)	−22.2 (210) 21700 (250)

3. Conclusion

In conclusion, we have shown that acetylation of the racemic *N*-acylhemiaminals with lipases (lipase PS, lipase AK and lipase QL) exclusively produce (*R*)-enantiomers in enantiomerically pure form in quantitative yields via DKR. It is important to note that the lipase QL mediated transformations are versatile for large-scale reactions. We believe that this strategy is a useful tool for the synthesis of biologically active molecules.

4. Experimental

4.1. General

^{1}H NMR (270 MHz) and ^{13}C NMR (67 MHz) spectra were measured using a JEOL JNM-GX270 in deuterated chloroform with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded with a Perkin–Elmer 1650-FTIR spectrometer. MS spectra and HRMS were obtained using JEOL JMS-AX500 and JMS-SX102A by EI and FD methods, respectively. Optical rotations were measured with a Jasco DIP-370 polarimeter. HPLC data were obtained using Hitachi 655A and L-7000. The CD spectra were recorded using a Jasco J-820 spectropolarimeter. Flash column chromatography and thin layer chromatography (TLC) for analytical purposes were performed on silica gel, Merck Art. 9385 and 5715, respectively. Melting points were determined using a Yanagimoto 500-D micro melting point apparatus and were uncorrected. All other chemicals were obtained from commercial sources.

All the racemic substrates **1(a–f)** were prepared according to the previous procedure[8] and were characterized as follows.

4.1.1. (±)-2-Acetyl-3-hydroxy-2,3-dihydro-isoindolin-1-one 1a. Colorless solid; mp 162–163°C; IR (KBr): 3409, 2940, 1724, 1692, 1613, 1374, 1358, 1274, 1137, 1065, 750 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.67 (s, 3H), 4.71 (d, J=7.3 Hz, 1H), 6.56 (d, J=3.5 Hz, 1H), 7.56–7.76 (m, 3H), 7.89 (d, J=7.5 Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$): δ 24.97, 80.53, 124.05, 124.07, 124.80, 130.04, 130.43, 134.59, 141.99, 165.93, 172.59; MS m/z: 191 (M^+), 190, 149 (100), 148, 133, 130, 105, 77. Anal. calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.88; H, 4.71; N, 7.28.

4.1.2. (±)-3-Hydroxy-2-propionyl-2,3-dihydro-isoindolin-1-one 1b. Colorless solid; mp 145.5–146.5°C; IR (KBr): 3441, 2980, 2939, 1738, 1679, 1615, 1293, 1235, 1211, 753 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.23 (t, J=7.3 Hz, 3H), 3.11 (q, J=3.2, 7.3 Hz, 2H), 4.77 (d, J=3.5 Hz, 1H), 6.57 (d, J=4.3 Hz, 1H), 7.55–7.72 (m, 3H), 7.88 (d, J=7.5 Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$): δ 8.11, 30.56, 80.61, 124.04, 124.72, 130.19, 130.35, 134.45, 140.06, 165.88, 176.42; MS m/z: 205

(M^+), 187 (100), 149, 133, 132, 105, 77. Anal. calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.24; H, 5.37; N, 6.69.

4.1.3. (±)-2-Butyryl-3-hydroxy-2,3-dihydro-isoindolin-1-one 1c. Colorless solid; mp 71–72.5°C; IR (KBr): 3452, 2969, 1735, 1675, 1614, 1291, 1226, 1067, 756 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.03 (t, $J=7.3$ Hz, 3H), 1.76 (q, $J=7.3$ Hz, 2H), 2.98–3.12 (m, 1H), 4.81 (d, $J=3.7$ Hz, 1H), 6.56 (d, $J=4.0$ Hz, 1H), 7.55–7.75 (m, 3H), 7.87 (d, $J=7.5$ Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$): δ 13.79, 17.63, 38.79, 80.63, 124.03, 124.74, 130.22, 130.36, 134.46, 142.03, 165.83, 175.65; MS m/z: 219 (M^+), 191, 173, 149, 133 (100), 132, 105, 77. Anal. calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.66; H, 5.92; N, 6.22.

4.1.4. (±)-3-Hydroxy-2-isobutyryl-2,3-dihydro-isoindolin-1-one 1d. Colorless solid; mp 84–86°C; IR (KBr): 3412, 2979, 2941, 1721, 1695, 1617, 1354, 1208, 1064, 745 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.24 (d, $J=5.6$ Hz, 3H), 1.27 (d, $J=5.1$ Hz, 3H), 3.8–3.93 (m, 1H), 4.79 (d, $J=7.0$ Hz, 1H), 6.56 (d, $J=3.7$ Hz, 1H), 7.55–7.74 (m, 3H), 7.88 (d, $J=7.5$ Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$): δ 18.47, 18.88, 34.05, 80.87, 123.98, 124.75, 130.29, 130.33, 134.42, 142.03, 165.48, 179.99; MS m/z: 219 (M^+), 218, 201 (100), 173, 148, 133, 132, 105, 77. Anal. calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.92; H, 5.97; N, 6.29.

4.1.5. (±)-3-Hydroxy-2-pivaloyl-2,3-dihydro-isoindolin-1-one 1e. Colorless solid; mp 82–83°C; IR (KBr): 3471, 2975, 2872, 1740, 1667, 1616, 1286, 1183, 1069, 757 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.45 (s, 9H), 4.79 (d, $J=4.0$ Hz, 1H), 6.58 (d, $J=4.0$ Hz, 1H), 7.54–7.73 (m, 3H), 7.87 (d, $J=7.5$ Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$): δ 25.93, 41.64, 82.47, 123.75, 124.78, 130.3, 130.5, 134.23, 142.05, 164.42, 181.23; MS m/z: 233 (M^+), 218, 178 (100), 177, 160, 149, 148, 77. Anal. calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.14; H, 6.49; N, 5.89.

4.1.6. (±)-2-Benzoyl-3-hydroxy-2,3-dihydro-isoindolin-1-one 1f. Colorless solid; mp 105–106°C; IR (KBr): 3420, 3059, 1725, 1667, 1614, 1600, 1332, 1287, 1156, 1062, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.99 (dd, $J=4.3$, 4.6 Hz, 1H), 6.77 (d, $J=4.6$ Hz, 1H), 7.40–7.73 (m, 8H), 7.82 (d, $J=7.5$ Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$): δ 80.96, 124.04, 124.86, 127.69, 128.84, 128.87, 130.44, 132.16, 133.74, 134.58, 142.28, 142.33, 165, 171.19; MS m/z: 148 (M^+), 132, 130, 105 (100), 77. Anal. calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.10; H, 4.51; N, 5.45.

4.2. General procedure for lipase-catalyzed acetylation of *N*-acylhemiaminals

The corresponding *N*-acylhemiaminal (0.5 mmol) was dissolved in hexane (10 ml) containing isopropenyl acetate (0.5 ml) in a 50 ml stoppered Erlenmeyer flask. Lipase (100 mg) was added in one portion to the suspension and stirred on a shaker at 150 rpm at the temperature and time indicated in Table 2. Prior to the addition of the enzyme, the suspension was stirred for 30 min under the same conditions. The reaction was followed by thin layer chromatography (TLC) for the formation of the corresponding acetate. After the completion of the acetylation, the enzyme was filtered through a small pad of Celite-545® and solvent was evaporated under reduced pressure. The crude acetate was purified through a short column of silica gel (eluent: EtOAc/*n*-hexane = 1:4). The pure product was quantitatively obtained. Properties of the products and the determination method of the e.e. are as follows.

4.2.1. (1*R*)-2-Acetyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl acetate 2a. Colorless solid; mp 149–150°C; 63% e.e.; $[\alpha]_D^{25}=-180$ (*c* 1.0, $CHCl_3$); IR (KBr): 2993, 1727, 1709, 1613, 1377, 1359, 1325, 1277, 1225, 1212, 1173, 1026, 761 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 2.12 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 7.55–7.35 (m, 4H, H_{arom} and CH), 7.90 (d, $J=7.5$ Hz, 1H, H_{arom}); ^{13}C NMR (67 MHz, $CDCl_3$): δ 20.68, 24.99, 78.76, 124.69, 124.95, 130.19, 130.89, 134.92, 140.8, 166.39, 169.82, 170.03; MS m/z: 233 (M^+), 190, 174, 132 (100), 130, 104, 77, 76, 43. Anal. calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.74; H, 4.84; N, 5.95.

Enantiomeric excess of **2a** was determined by HPLC (Chiralcel® OD, Daicel Chemical Industries, Ltd., Japan). Detection wavelength (λ): 254 nm; eluent: hexane/*i*-PrOH = 90/10; flow rate: 1.0 ml/min; temperature: 35°C; retention times: 9.35 (*R*) and 11.23 (*S*) min.

4.2.2. (1*R*)-3-Oxo-2-propionyl-2,3-dihydro-1*H*-isoindol-1-yl acetate 2b. Colorless solid; mp 88–91°C; >99% e.e.; $[\alpha]_D^{25}=-191$ (*c* 1.0, $CHCl_3$); IR (KBr): 2988, 2939, 1752, 1710, 1611, 1359, 1246, 1213, 1146, 1013, 763 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.23 (t, $J=7.0$ Hz, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.10 (q, $J=7.29$ Hz, 2H, CH_2), 7.58 to 7.73 (m, 4H, H_{arom} and CH), 7.89 (d, $J=7.29$ Hz, 1H, H_{arom}); ^{13}C NMR (67 MHz, $CDCl_3$): δ 8.03, 20.8, 30.69, 78.89, 124.67, 124.95, 130.35, 130.9, 134.87, 140.86, 166.43, 170.12, 173.83; MS m/z: 247 (M^+), 204, 187, 159, 148, 132 (100), 104, 77, 57, 43. Anal. calcd for $C_{13}H_{13}NO_4$ C, 63.15; H, 5.30; N, 5.67. Found: C, 62.99; H, 5.28; N, 5.61.

Enantiomeric excess of **2b** was determined by HPLC and the conditions were identical to **2a**. Retention times: 7.48 (*R*) and 9.73 (*S*) min.

4.2.3. (1*R*)-2-Butyryl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl acetate 2c. Colorless solid; mp 80–81°C; 98% e.e.; $[\alpha]_D^{25}=-176$ (*c* 1.0, $CHCl_3$); IR (KBr): 2961, 2872, 1742, 1714, 1612, 1377, 1357, 1326, 1237, 1204, 1160, 1148, 1017, 760 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.02 (t, $J=7.29$ Hz, 3H, CH_3), 1.69–1.83 (m, 2H, CH_2), 2.11 (s, 3H, CH_3) 3.04 (t, $J=7.29$ Hz, 2H, CH_2), 7.57 to 7.72 (m, 4H, H_{arom} and CH), 7.88 (d, $J=7.56$ Hz, 1H, H_{arom}); ^{13}C NMR (67 MHz, $CDCl_3$): δ 13.62, 17.45, 20.72, 38.86, 78.82, 124.61, 124.89, 130.31, 130.84, 134.82, 140.76, 166.31, 170.06, 172.92; MS m/z: 261 (M^+), 246, 233, 218, 201, 173, 148, 132 (100), 130, 104, 77, 71, 69, 43. Anal. calcd for $C_{14}H_{15}NO_4$ C, 64.36; H, 5.79; N, 5.36. Found: C, 64.28; H, 5.89; N, 5.31.

Enantiomeric excess of **2c** was determined by HPLC and the conditions were identical to **2a**. Retention times: 6.82 (*R*) and 8.64 (*S*) min.

4.2.4. (1*R*)-2-Isobutyryl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl acetate 2d. Colorless syrup; >99% e.e.; $[\alpha]_D^{25} = -181$ (*c* 1.0, $CHCl_3$); IR (neat): 2978, 2936, 2875, 1746, 1707, 1615, 1469, 1385, 1356, 1242, 1207, 1150, 1020, 758 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.25 (dd, $J = 7.0$ and 7.0 Hz, 6H, CH_3), 2.12 (s, 3H, CH_3) 3.86 (m, 1H, CH), 7.58–7.73 (m, 4H, H_{arom} and CH), 7.89 (d, $J =$ 7.29 Hz, 1H, H_{arom}); ^{13}C NMR (67 MHz, $CDCl_3$): δ 18.22, 19.04, 20.76, 34.19, 79.07, 124.58, 124.94, 130.41, 130.84, 134.81, 140.79, 165.96, 170.06, 177.32; MS *m*/*z*: 261 (M^+), 246, 218, 201, 173, 148, 132 (100), 130, 104, 77, 70, 43; HRMS *m*/*z* 261.1018 (261.1001 calcd for $C_{14}H_{15}NO_4$, M^+).

Enantiomeric excess of **2d** was determined by HPLC and the conditions were identical to **2a**. Retention times: 6.31 (*R*) and 7.51 (*S*) min.

4.2.5. (1*R*)-3-Oxo-2-pivaloyl-2,3-dihydro-1*H*-isoindol-1-yl acetate 2e. Colorless solid; mp 94–95°C; >99% e.e.; $[\alpha]_D^{25} = -165$ (*c* 1.0, $CHCl_3$); IR (KBr): 2982, 1748, 1691, 1614, 1358, 1318, 1229, 1145, 1017, 763 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.44 (s, 9H, $(CH_3)_3$), 2.11 (s, 3H, CH_3) 3.86 (m, 1H, CH), 7.57 to 7.71 (m, 4H, H_{arom} and CH), 7.87 (d, $J = 7.29$ Hz, 1H, H_{arom}); ^{13}C NMR (67 MHz, $CDCl_3$): δ 20.8, 25.99, 41.67, 80.62, 124.33, 124.85, 130.66, 130.78, 134.55, 140.86, 164.97, 170.11, 178.59; MS *m*/*z*: 275 (M^+), 260, 232, 220, 215, 177, 160, 148, 132 (100), 130, 104, 77, 57, 43; HRMS *m*/*z* 275.1169 (275.1158 calcd for $C_{15}H_{17}NO_4$, M^+).

Enantiomeric excess of **2e** was determined by HPLC (Chiralcel® OJ, Daicel Chemical Industries, Ltd., Japan). Detection wavelength (λ): 254 nm; eluent: hexane/*i*-PrOH = 90/10; flow rate: 0.5 ml/min; temperature: 35°C; retention times: 10.5 (*R*) and 11.89 (*S*) min.

4.2.6. (1*R*)-2-Benzoyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl acetate 2f. Colorless solid; mp 125–126.5°C; >99% e.e.; $[\alpha]_D^{25} = -358$ (*c* 1.0, $CHCl_3$); IR (KBr): 3067, 2973, 1745, 1683, 1613,1600, 1329, 1288, 1220, 1146, 1027, 1015, 759 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 2.07 (s, 3H, CH_3) 7.44 to 7.86 (m, 10H, H_{arom} and CH); ^{13}C NMR (67 MHz, $CDCl_3$): δ 20.77, 79.29, 124.74, 125.01, 127.88, 129.25, 130, 130.98, 132.53, 133.74, 134.91, 140.87, 165.30, 168.91, 170.15; MS *m*/*z*: 295 (M^+), 267, 252, 236, 208, 179, 148, 132, 105 (100), 77, 51, 43. Anal. calcd for $C_{17}H_{13}NO_4$ C, 69.15; H, 4.44; N, 4.74. Found: C, 69.04; H, 4.50; N, 4.72.

Enantiomeric excess of **2f** was determined by HPLC (Chiralcel® OC, Daicel Chemical Industries, Ltd., Japan). Detection wavelength (λ): 254 nm; eluent: hexane/*i*-PrOH = 80/20; flow rate: 1 ml/min; temperature: 35°C; retention times: 26.37 (*S*) and 33.71 (*R*) min.

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