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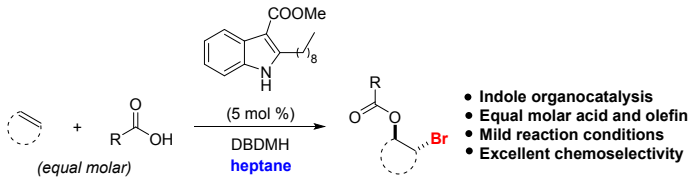
Lipophilic Indole-Catalyzed Intermolecular Bromoesterification of Olefins in Nonpolar Media

Yao Shi,[†] Jonathan Wong,[†] Zhihai Ke, Ying-Yeung Yeung**

Department of Chemistry, The Chinese University of Hong Kong, Shatin, NT, Hong Kong (China)



ABSTRACT: An environmentally-benign and highly versatile catalytic protocol has been successfully applied in the intermolecular bromoesterification between various olefins and carboxylic acids. The use of a highly lipophilic indole catalyst and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the bromine source allows the reaction to proceed in heptane via a solid-liquid phase transfer mechanism, affording the corresponding bromoester products in good-to-excellent yields.

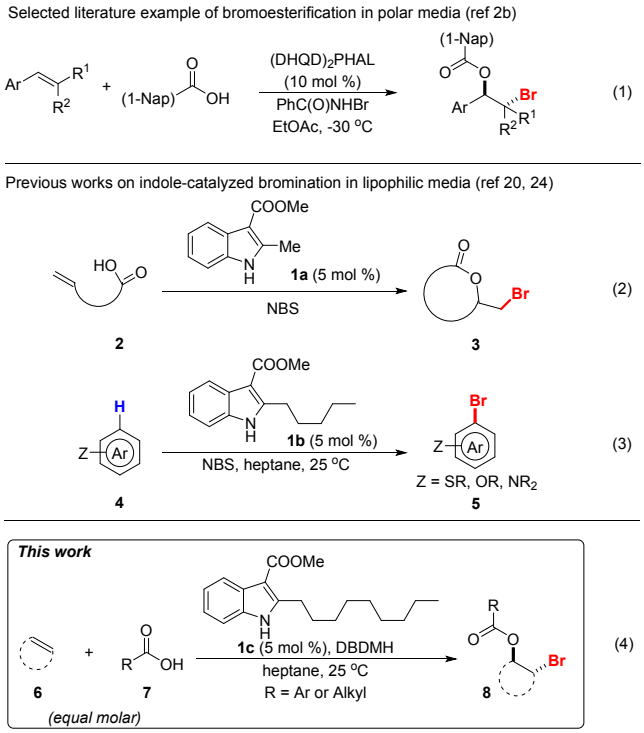
1. INTRODUCTION

Electrophilic halofunctionalization of alkenes is a powerful organic transformation, permitting the simultaneous introduction of a halogen and an additional functional group across the olefinic substrates. The resultant 1,2-halofunctionalized compounds are valuable building blocks that can easily be manipulated by nucleophilic substitution of the halogen.[1–4] Olefinic halofunctionalizations such as haloetherifications,[5–11] haloamidations,[12–15] halo-dearomatization[16] and haloesterifications[2–4,17–20] are well-documented. Amongst these reactions, intermolecular haloesterification is challenging with a low efficiency partly due to the weak nucleophilicity of the carboxylate group. Practically, super-stoichiometric amounts of carboxylic acid is often required to compensate the low reaction efficiency.[3,4] In addition, these reactions are typically run in environmentally unfriendly solvents such as methylene chloride and chloroform. A seminal work on the asymmetric bromoesterification of unactivated olefins was reported by Shi in which the reactions proceeded smoothly with catalyst $(DHQD)_2PHAL$ in ethyl acetate (Scheme 1, eq 1).[2b]. Recently, Borhan[19a] and Christmann[19b] independently reported elegant examples of intermolecular asymmetric haloesterifications of assisting group-containing olefins and the assisting groups were found to be crucial in facilitating the introduction of ester groups.

In our previous research efforts regarding the bromolactonization of olefinic acids **2**,[20] we have demonstrated that indole-based catalyst **1a** allowed the reaction to proceed efficiently in green lipophilic solvents such as heptane[21] via a solid-liquid phase transfer mechanism (Scheme 1, eq 2).[22,23] Very recently, we re-engineered indole **1a** to the more lipophilic catalyst **1b**, which was found to be very potent in promoting the aromatic bromination of various anisole, thioanisole and aniline-type substrates **4** (Scheme 1, eq 3).[24] Herein, we are pleased to disclose our recent success in the application of the indole catalytic protocol to the intermolecular

bromoesterification of olefinic substrates **6** in nonpolar media with equimolar amount of the carboxylic acids **7** as the nucleophilic partners (Scheme 1, eq 4).

Scheme 1. Lipophilic Indole-based Catalysis in Bromination

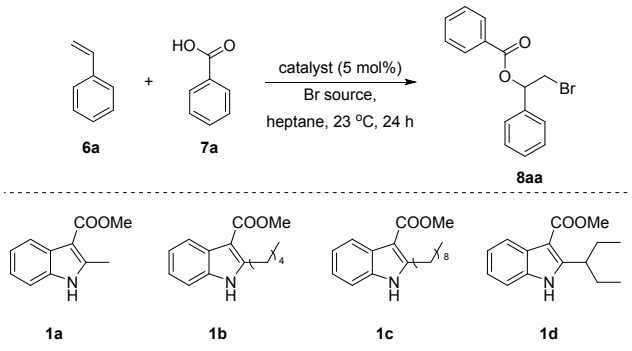


2. RESULTS AND DISCUSSION

The investigation began with the intermolecular bromoesterification of styrene (**6a**) in heptane. 1,3-Dibromo-5,5-hydantoin (DBDMH) and benzoic acid (**7a**) were used as the halogen source and the nucleophilic partner, respectively. A series of lipophilic indole-based catalysts **1a-d** were examined and the results are summarized in Table 1. The reaction was sluggish when no catalyst was applied (Table 1, entry 1). Some common catalysts for electrophilic halogenations[25–28] including Lewis base (Ph_3PS), Lewis acid ($FeCl_3$), Brønsted acid (HCl), and Brønsted base (Na_2CO_3) catalysts were examined and these reactions gave inferior yields of the desired bromoester product **8aa** as compared to the lipophilic indole catalysts **1** (entries 2–5). For the

case with HCl as the catalyst, significant amounts of vicinal dibrominated side product was detected. Indole **1a** (5 mol%), which was found to be effective in promoting the bromolactonization of olefinic acids,[20] could catalyze the intermolecular bromoesterification of **6a** and **7a** to give bromoester **8aa** with moderate yield, attributable to the moderate solubility of **1a** (entry 6). To our delight, dramatic improvement of the efficiency was observed when indole **1c** was used, giving the desired product **8aa** in 85% yield (entry 8). This increase in activity could be congruent with an increase in lipophilicity and hence catalyst solubility conferred upon by the length of the alkyl chain attached at the C(2) position of the indole system. The reaction was found to be sensitive to the lipophilicity of the catalyst; indole catalyst **1b** that has a relatively shorter hydrocarbon side-chain returned a considerable drop in yield (entry 7). Diminishment of the reaction efficiency was observed when the sterically hindered indole **1d** was applied instead of **1c** (entry 9). The performance of DBDMH was found to be superior to *N*-bromosuccinimide (NBS) (entry 10), which can be ascribed to the higher reactivity of DBDMH.

Table 1. Reaction Optimization[a]



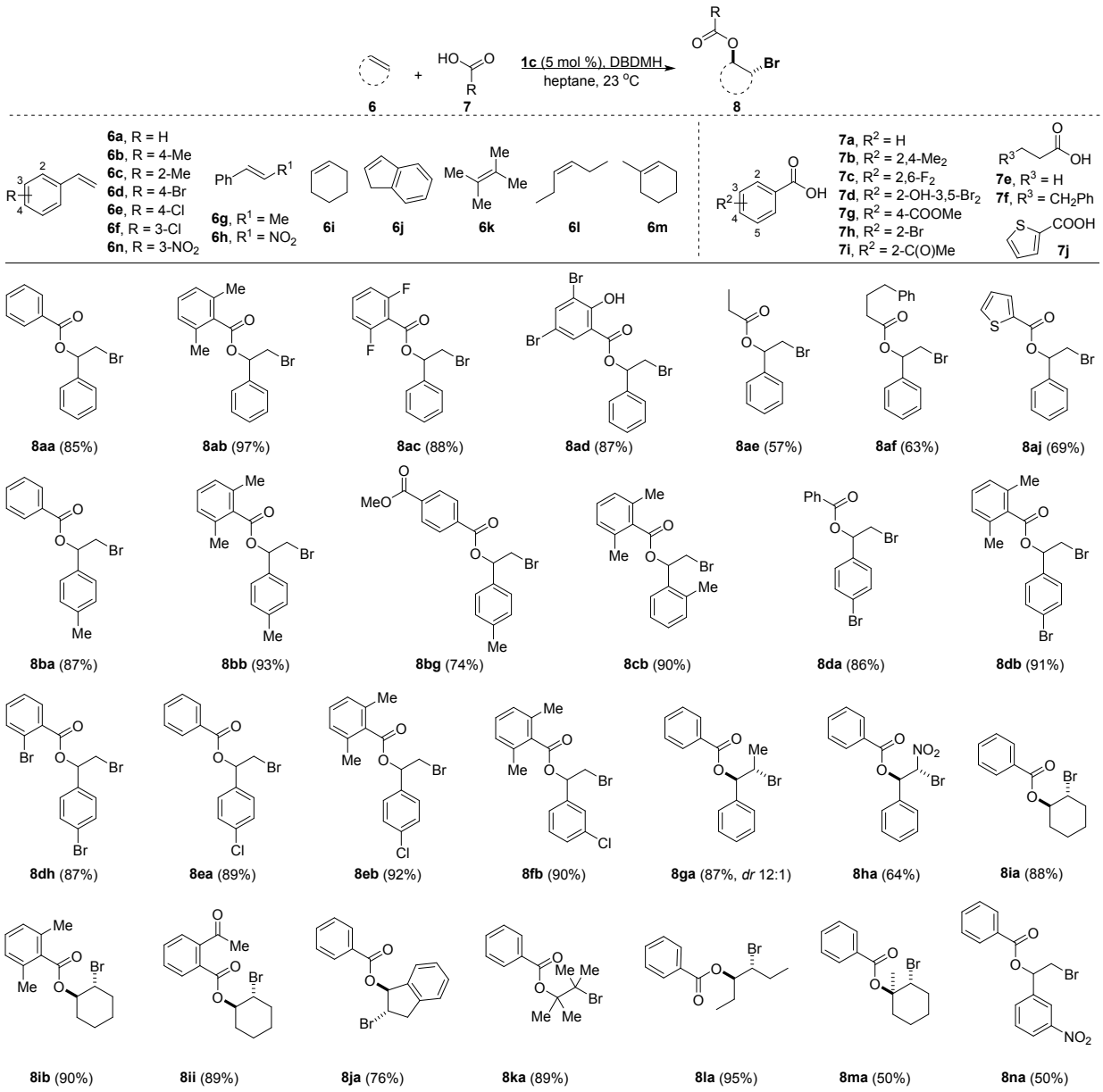
entry	Br source	catalyst	yield (%)
1	DBDMH	-	11
2	DBDMH	Ph_3PS	31
3	DBDMH	$FeCl_3$	24

4[b]	DBDMH	HCl	12
5	DBDMH	Na_2CO_3	22
6	DBDMH	**1a**	35
7	DBDMH	**1b**	61
8	DBDMH	**1c**	85
9	DBDMH	**1d**	40
10	NBS	**1c**	trace

[a] Reactions were carried out with styrene (**6a**) (0.36 mmol), benzoic acid (**7a**) (0.3 mmol), catalyst (5 mol%), and Br source (0.315 mmol) in *n*-heptane (1.0 mL) at 23 °C in the absence of light for 24 h. [b] Olefinic dibromination of styrene (**6a**) was observed.

With the optimized reaction conditions in hand, the substrate scope of the intermolecular bromoesterification reaction catalyzed by indole catalyst **1c** was investigated (Table 2). Benzoic acid derivatives **7** carrying electron donating or withdrawing substituents with styrene (**6a**) as the reacting partner gave the corresponding bromoesters **8aa-8ad** with excellent yields. In all cases, the reactions were regioselective for the Markovnikov product and no aromatic bromination side products were observed. The sterically demanding 2,6-disubstituted benzoic acid **7b** was well tolerated, giving **8ab** in 97% yield. 3,5-dibromo-2-hydroxybenzoic acid (**7d**) underwent preferential nucleophilic attack from the carboxylate group to yield bromoester **8ad**, attributed to the intramolecular hydrogen-bonding which could favor the nucleophilic attack of the carboxylate.[29] Other aliphatic acids such as **7e**, **7f** and heterocyclic acid such as 2-thiophenecarboxylic acid (**7j**) were also found to react smoothly under these conditions to give **8ae**, **8af** and **8aj**, respectively. However, 4-nitrobenzoic acid and 4-methylcinnamic acid gave sluggish reactions with very low conversions (<5%).

Table 2. Substrate Scope[a]



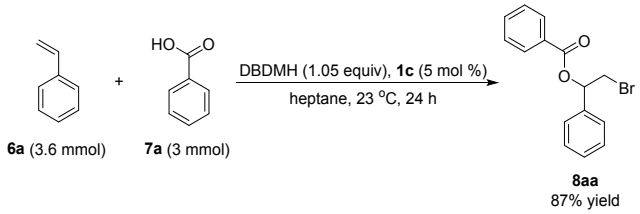
[a] Reactions were carried out with **6** (0.36 mmol), **7** (0.3 mmol), catalyst **1c** (0.015 mmol), and DBDMH (0.315 mmol) in *n*-heptane (1 mL) for 24 h at 23 °C in the absence of light.

Styrene derivatives carrying electron rich substituents on the aromatic ring such as 4-methylstyrene (**6b**) and 2-methylstyrene (**6c**) reacted with benzoic derivatives to give the

corresponding bromoesters **8ba**, **8bb**, **8bg**, and **8cb** in good-to-excellent yields. Olefins with electron-deficient substituents such as 4-bromo, 4-chloro, and 3-chlorostyrene (**6d**, **6e**, and **6f**, respectively) also worked well under the mild and pH neutral conditions, furnishing bromoesters **8da**, **8db**, **8dh**, **8ea**, **8eb** and **8fb** in excellent yields. β-Substituted styrene derivatives such as *trans*-1-phenyl-1-propene (**6g**) and *trans*-1-nitro-2-phenylethylene (**6h**) reacted with benzoic acid (**7a**) to give bromoesters **8ga** (*dr* 12:1) and **8ha** in 87% and 64% yields, respectively. The decrease in yield was consistent with the strong electron-withdrawing nature of the nitro substituent in **6h**, which could deactivate the olefin towards bromination. Other olefinic partners such as cyclohexene (**6i**), indene (**6j**), 2,3-dimethyl-2-butene (**6k**) and *cis*-3-hexene (**6l**) were also subjected to the reaction, producing bromoesters **8ii**, **8ja**, **8ka**, and **8la**, respectively, in appreciable conversions. The reaction with the bulkier trisubstituted olefin 1-methyl-1-cyclohexene (**6m**) gave bromoester **8ma** in 50% yield. The use of a highly electron-deficient olefin **6n** still gave the desired product **8na** in 50% yield. However, reactions using methyl cinnamate/acrylate or 2-vinylpyridine were sluggish. 1-Hexene was also examined but low reaction yield (c.a. 10%) and regioselectivity (3:2) were observed.

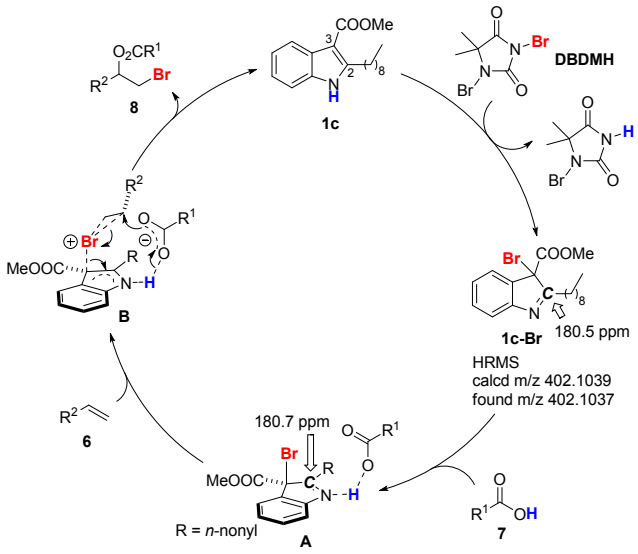
The indole-catalyzed bromoesterification could also be scaled up while retaining regioselectivity and yield. For example, the scaled-up reaction using styrene (**6a**) (3.6 mmol) and benzoic acid (**7a**) (3 mmol), produced **8aa** in 87% yield (Scheme 2).

Scheme 2. Scale-up Reaction



Based on our previous experience on the indole-catalyzed bromination reactions,[20,24,30] we believe that indole **1c** might react with DBDMH to give the 3-bromoindole[16] active species **1c-Br** through a solid-liquid phase transfer mechanism (Scheme 3). The existence of **1c-Br** was evidenced by NMR and HRMS analysis. Unlike other intermolecular bromoesterification reaction, the indole catalytic protocol does not require excess amount of carboxylic acid.[3,4] We speculate that the active species **1c-Br** might interact with the carboxylic acid which could facilitate the reaction. Thus, an ^{13}C NMR experiment on a 1:1 mixture of **1c-Br** and benzoic acid (**7a**) was conducted and a measurable downfield-shift of the C(2) signal was observed (Figure 1). A possible explanation is that the Schiff base in **1c-Br** might interact with the acidic proton of benzoic acid (**7a**) to give species **A**, which would lead to the deshielding of the C(2) in **1c-Br**. Subsequently, the olefinic substrate **6** might then be brominated to give the corresponding bromiranium species **B**, which could be attacked by the carboxylate group in a Markovnikov-fashion to yield product **8**. The high reaction efficiency by just employing an equal molar of olefinic substrates **6** and carboxylic acids **7** could be attributed to the close proximity of the bromiranium ion and the carboxylate group in the putative species **B**. However, a more detailed study is needed in order to elucidate a clearer mechanistic picture.

Scheme 3. A Plausible Reaction Mechanism



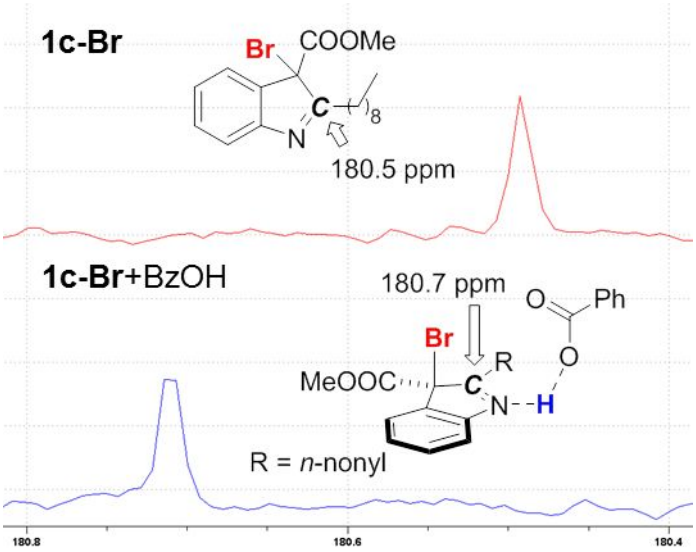


Figure 1. ^{13}C NMR study on a 1:1 mixture of 1c-Br and benzoic acid (7a) [the C(2) signal of 1c-Br]

3. CONCLUSIONS

In summary, we have developed an efficient electrophilic intermolecular bromoesterification between various olefins and carboxylic acids, using a lipophilic indole as a solid-liquid phase

transfer catalyst, DBDMH as the bromine source, and the lipophilic green solvent, heptane, as the reaction media. This process is highly regioselective, producing the corresponding 1,2-bromoester products with good to excellent yields. Mechanistic studies suggest that a 3-bromoindole intermediate may act as the active electrophilic brominating species with a mechanism analogous to that previously reported by our group. Thus far, we have successfully applied the indole-catalyzed electrophilic bromination protocol to bromolactonization, aromatic bromination and intermolecular bromoesterification reactions. As such, this bromination protocol may represent a highly general method for various bromination reactions, and applications in other reactions and their asymmetric variants are currently being investigated.

EXPERIMENTAL SECTION

General Information.

All reactions requiring anhydrous conditions were conducted by standard procedures under nitrogen atmosphere. Commercially available reagents were used as received. The solvents were dried over a solvent purification system from Innovative Technology. Melting points were determined on a BÜCHI B-540b melting point apparatus. ^{1}H NMR, $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker AMX500 (500 MHz) spectrometer or a Bruker AMX400 (400 MHz) spectrometer. Proton and carbon chemical shifts are reported in parts per million (ppm) values downfield from TMS (δ 0.00) and referenced to residual protons in NMR solvents ($CDCl_3$ at δ 7.26, CD_2Cl_2 at δ 5.36) or carbon signals in NMR solvent ($CDCl_3$ at δ 77.16, CD_2Cl_2 at δ 55.42). High resolution mass spectra were obtained on a Thermo Finnigan MAT95XL Magnetic Sector Mass Spectrometer (ionization mode: EI) or a Thermo Q Exactive Hybrid Quadrupole-Orbitrap Mass Spectrometer (ESI). Analytical thin layer chromatography (TLC) was performed with

Merck pre-coated TLC plates, silica gel 60F-254, layer thickness 0.25 mm. Flash chromatography separations were performed on Merck 60 (0.040-0.063 mm) mesh silica gel.

Representative procedure for the synthesis of indole catalyst 1c. A mixture of methyl 3-oxododecanoate (1 mmol), aniline (1.5 mmol) and acetic acid (0.1 mmol) in a 5 mL eggplant-shaped flask was placed in an ultrasound bath under sonication at 22 ^{o}C for ~3 h and the reaction was monitored by TLC. Upon completion of the reaction, the product mixture was diluted with EtOH (5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was briefly purified by column chromatography through silica gel (hexanes/ethyl acetate 20:1) to give the corresponding enamine, methyl 3-(phenylamino)dodec-2-enoate, which was used immediately in the next step.

A solution of the methyl 3-(phenylamino)dodec-2-enoate (1.0 mmol) in DMF (3 mL) was transferred with a syringe into a 50 mL resealable tube containing $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 10 mol%), $Cu(OAc)_2$ (0.54 g, 3.0 mmol, 3.0 equiv), K_2CO_3 (0.41 g, 3.0 mmol, 3.0 equiv), DMF (7 mL) and a magnetic stir bar (Teflon-coated) under a nitrogen atmosphere. The resealable tube was degassed by evacuation under high vacuum and refilled with nitrogen gas. The step was repeated three times before closing the screw cap tightly. The resealable tube was then placed in a preheated oil bath at 140 ^{o}C and allowed to stir for 1 h (no more enamine substrate detectable by TLC). The product mixture was allowed to cool to room temperature then filtered through a thin plug of celite eluted with EtOAc (3 x 10 mL). The filtrate was washed with saturated aqueous NH_4Cl (5 mL) and brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography through silica gel (hexanes/ethyl acetate 10:1) to give indole **1c**. **1a**, **1b**, and **1d** were prepared according to above procedure starting from the corresponding β-ketoesters.

*Methyl 2-pentyl-indole-3-carboxylate (**1b**)*. Yield: 87%, 214 mg; Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (s, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.18−7.24 (m, 2H), 3.95 (s, 3H), 3.14 (t, J = 7.8 Hz, 2H), 1.68−1.73 (m, 2H), 1.29−1.34 (m, 4H), 0.86 (t, J = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.7, 149.1, 134.7, 127.2, 122.3, 121.7, 121.3, 110.8, 103.5, 50.8, 31.6, 29.0, 28.0, 22.4, 14.0. HRMS (EI) m/z: $[M]^+$ calcd for $C_{15}H_{19}NO_2$ 245.1410, found 245.1414.

*Methyl 2-decyl-indole-3-carboxylate (**1c**)*. Yield: 85%, 257 mg; Orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.16 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.17−7.24 (m, 2H), 3.95 (s, 3H), 3.14 (t, J = 7.6 Hz, 2H), 1.67−1.74 (m, 2H), 1.22−1.33 (m, 12H), 0.89 (t, J = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.8, 149.3, 134.7, 127.2, 122.3, 121.6, 121.3, 110.9, 103.4, 50.8, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 28.0, 22.7, 14.4. HRMS (EI) m/z: $[M]^+$ calcd for $C_{19}H_{27}NO_2$ 301.2036, found 301.2033.

*Methyl 2-ethylpropyl-indole-3-carboxylate (**1d**)*. Yield: 85%, 209 mg; Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.31 (s, 1H), 8.24 (d, J = 5.3 Hz, 1H), 7.41 (s, 1H), 7.28 (s, 2H), 4.01 (s, 4H), 1.76−1.87 (m, 4H), 0.92 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.1, 151.8, 135.0, 127.0, 122.3, 121.5, 110.9, 105.0, 50.8, 40.0, 29.7, 27.8, 11.9. HRMS (EI) m/z: $[M]^+$ calcd for $C_{15}H_{19}NO_2$ 245.1410, found 245.1412.

General Procedure for the intermolecular bromoesterification reactions.

1,3-dibromo-5,5-dimethydantoin (90 mg, 0.315 mmol) was added to a mixture of alkene **6** (0.36 mmol), carboxylic acid **7** (0.3 mmol) and indole catalyst **1c** (4.52 mg, 0.015 mmol) in heptane (1.0 mL) at 23 ^{o}C in the absence of light. The resultant mixture was allowed to stir at 23 ^{o}C and the reaction was monitored by TLC. The product mixture was concentrated under

reduced pressure and the residue was purified by flash column chromatography through silica gel (hexanes/ethyl acetate 10:1) to give the corresponding product **8**.

*2-bromo-1-phenylethyl benzoate (**8aa**)*. Yield: 85%, 78 mg; Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 7.3 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.49−7.53 (m, 4H), 7.37−7.45 (m, 3H), 6.26−6.29 (m, 1H), 3.84−3.88 (m, 1H), 3.76−3.80 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.5, 137.8, 133.4, 130.0, 129.8, 129.0, 128.9, 128.6, 126.6, 75.4, 34.6. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{15}H_{13}BrO_2Na$ 326.9991, found 326.9995.

*2-bromo-1-phenylethyl 2,6-dimethylbenzoate (**8ab**)*. Yield: 97%, 97 mg; Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.48 (m, 5H), 7.21 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.6 Hz, 2H), 6.27−6.31 (m, 1H), 3.67−3.71 (m, 1H), 3.78−3.83 (m, 1H), 2.28 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.1, 137.6, 135.0, 133.5, 129.5, 129.2, 128.9, 127.6, 127.0, 76.2, 33.9, 19.9. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{17}H_{17}BrO_2Na$ 355.0304, found 355.0304.

*2-bromo-1-phenylethyl 2,6-difluorobenzoate (**8ac**)*. Yield: 88%, 90 mg; Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.48 (m, 6H), 6.97 (t, J = 8.3 Hz, 2H), 6.27 (dd, J = 8.0, 4.7 Hz, 1H), 3.78 (dd, J = 11.0, 8.1 Hz, 1H), 3.70 (dd, J = 11.0, 4.7 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.3, 161.0 (d, $^1J_{C\text{-}F}$ = 256 Hz), Hz, 160.4, 137.1, 133.3 (t, $^3J_{C\text{-}F}$ = 10.5 Hz), 128.9 (d, $^2J_{C\text{-}F}$ = 25 Hz), 126.7, 112.2 (d, $^2J_{C\text{-}F}$ = 25 Hz), 112.1, 76.7, 33.8. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{15}H_{11}BrF_2O_2Na$ 362.9803, found 362.9808.

*2-bromo-1-phenylethyl 3,5-dibromo-2-hydroxybenzoate (**8ad**)*. Yield: 87%, 125 mg; Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.16 (s, 1H), 8.06 (d, J = 2.4 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.39−7.43 (m, 5H), 6.20−6.23 (m, 1H), 3.81−3.86 (m, 1H), 3.70−3.74 (m, 1H). ^{13}C{^{1}H}

NMR (100 MHz, $CDCl_3$): δ 167.8, 157.8, 141.5, 136.6, 131.5, 129.6, 129.2, 126.6, 114.3, 112.6, 111.1, 33.5. HRMS (EI) m/z: $[M]^+$ calcd for $C_{15}H_{11}Br_3O_3$ 477.8232, found 477.8231.

*2-bromo-1-phenylethyl propionate (**8ae**)*. Yield: 57%, 44 mg; Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.40 (m, 5H), 5.99−6.01 (m, 1H), 3.59−3.68 (m, 2H), 2.38−2.50 (m, 2H), 1.18 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.3, 137.9, 128.9, 128.8, 126.6, 74.7, 34.5, 27.7, 9.2. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{11}H_{13}BrO_2Na$ 278.9991, found 278.9994.

*2-bromo-1-phenylethyl 4-phenylbutanoate (**8af**)*. Yield: 63%, 66 mg; Yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.32−7.41 (m, 5H), 7.26−7.30 (m, 2H), 7.21 (d, J = 7.4 Hz, 1H), 7.17 (d, J = 7.4, 2H), 6.00−6.02 (m, 1H), 3.59−3.68 (m, 2H), 2.66 (t, J = 7.6 Hz, 2H), 2.37−2.49 (m, 2H), 1.97−2.03 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 172.4, 141.4, 137.9, 129.0, 128.9, 128.6, 128.5, 126.7, 126.1, 74.9, 35.2, 34.5, 33.7, 26.6. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{18}H_{19}BrO_2Na$ 369.0461, found 369.0461.

*2-bromo-1-phenylethyl thiophene-2-carboxylate (**8aj**)*. Yield: 69%, 64 mg; Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (dd, J = 3.8, 1.2 Hz, 1H), 7.60 (dd, J = 5.0, 1.2 Hz, 2H), 7.33−7.45(m, 5H), 7.13 (dd, J = 4.9, 3.9 Hz, 2H), 3.69−3.81 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 161.0, 137.6, 134.1, 133.1, 133.0, 129.0, 128.8, 127.9, 126.6, 75.5, 34.3. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{13}H_{11}BrO_2SNa$ 334.9535, found 334.9532.

*2-bromo-1-(p-tolyl)ethyl benzoate (**8ba**)*. Yield: 87%, 83 mg; Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 7.3 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.21−6.24 (m, 1H), 3.81−3.86 (m, 1H), 3.72−3.76

(m, 1H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.5, 138.8, 134.9, 133.3, 129.9, 129.5, 128.5, 126.6, 75.4, 34.6, 21.3. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{16}H_{15}BrO_2Na$ 341.0147, found 341.0148.

*2-bromo-1-(p-tolyl)ethyl 2,6-dimethylbenzoate (**8bb**)*. Yield: 93%, 97 mg; Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, J = 8.0 Hz, 2H), 7.20 (t, J = 8.0 Hz, 3H), 7.03 (d, J = 7.6 Hz, 2H), 6.22−6.26 (m, 1H), 3.75−3.80 (m, 1H), 3.64−3.67 (m, 1H), 2.38 (s, 3H), 2.26 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.1, 139.1, 135.1, 134.7, 133.6, 129.6, 129.5, 127.6, 127.0, 76.1, 34.0, 21.4, 19.9. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{18}H_{19}BrO_2Na$ 369.0461, found 369.0454.

*2-bromo-1-(p-tolyl)ethyl methyl terephthalate (**8bg**)*. Yield: 74%, 84 mg; Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.10−8.17 (m, 4H), 7.33 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H), 6.17-6.20 (m, 1H), 3.95 (s, 3H), 3.79−3.84 (m, 1H), 3.69−3.73 (m, 1H), 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.3, 164.8, 139.1, 134.6, 134.3, 133.7, 129.9, 129.7, 129.6, 126.6, 76.0, 52.6, 34.4, 21.4. HRMS (EI) m/z: $[M]^+$ calcd for $C_{18}H_{17}BrO_4$ 376.0305, found 376.0305.

*2-bromo-1-(o-tolyl)ethyl 2,6-dimethylbenzoate (**8cb**)*. Yield: 90%, 94 mg; Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 7.2 Hz, 1H), 7.21−7.29 (m, 4H), 7.06 (d, J = 7.6 Hz, 2H), 6.50−6.53 (m, 1H), 3.74−3.80 (m, 1H), 3.61−3.64 (m, 1H), 2.57 (s, 3H), 2.30 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.1, 136.2, 135.7, 135.0, 133.6, 130.9, 129.5, 128.9, 127.6, 126.4, 126.0, 73.1, 33.3, 19.9, 19.4. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{18}H_{19}BrO_2Na$ 369.0461, found 369.0459.

*2-bromo-1-(4-bromophenyl)ethyl benzoate (**8da**)*. Yield: 86%, 99 mg; Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 7.2 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.46−7.54 (m, 4H), 7.33 (d, J = 8.4 Hz, 2H), 6.15−6.18 (m, 1H), 3.69−3.81 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.4, 136.8, 133.6, 132.0, 129.9, 129.8, 129.5, 128.6, 128.4, 123.0, 74.7, 34.2. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{15}H_{12}Br_2O_2Na$ 406.9076, found 406.9075.

*2-bromo-1-(4-bromophenyl)ethyl 2,6-dimethylbenzoate (**8db**)*. Yield: 91%, 113 mg; Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.6 Hz, 2H), 6.22−6.25 (m, 1H), 3.73−3.78 (m, 1H), 3.63−3.67 (m, 1H), 2.28 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.9, 136.6, 135.0, 132.2, 132.0, 129.6, 128.7, 127.7, 123.2, 75.3, 33.5, 19.9. HRMS (EI) m/z: $[M]^+$ calcd for $C_{17}H_{16}Br_2O_2$ 411.9491, found 411.9495.

*2-bromo-1-(4-bromophenyl)ethyl 2-bromobenzoate (**8dh**)*. Yield: 87%, 121 mg; Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89−7.91 (m, 1H), 7.67 (d, J = 6.9 Hz, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.33-7.41 (m, 4H), 6.15−6.18 (m, 1H), 3.75−3.80 (m, 1H), 3.68−3.71 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.8, 136.3, 134.7, 133.2, 132.1, 131.8, 131.3, 128.6, 127.4, 123.2, 122.1, 75.6, 33.8. HRMS (EI) m/z: $[M]^+$ calcd for $C_{15}H_{11}Br_3O_2$ 461.8283, found 461.8286.

*2-bromo-1-(4-chlorophenyl)ethyl benzoate (**8ea**)*. Yield: 89%, 91 mg; Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.36−7.41 (m, 4H), 6.17−6.20 (m, 1H), 3.77−3.81 (m, 1H), 3.70−3.74 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.4, 136.3, 134.8, 133.6, 129.9, 129.6, 129.1, 128.6, 128.1, 74.7, 34.2. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{15}H_{12}BrClO_2Na$ 362.9580, found 362.9591.

*2-bromo-1-(4-chlorophenyl) ethyl 2,6-dimethylbenzoate (**8eb**)*. Yield: 92%, 102 mg; Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (m, 4H), 7.22 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.6 Hz, 2H), 6.22−6.26 (m, 1H), 3.73−3.79 (m, 1H), 3.63−3.67 (m, 1H), 2.27 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.9, 136.1, 135.0, 133.2, 129.7, 129.1, 128.4, 127.7, 75.3, 33.5, 19.9. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{17}H_{16}BrClO_2Na$ 390.9893, found 390.9896.

*2-bromo-1-(3-chlorophenyl)ethyl 2,6-dimethylbenzoate (**8fb**)*. Yield: 90%, 99 mg; Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.34−7.37 (m, 3H), 7.22 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.6 Hz, 2H), 6.21−6.24 (m, 1H), 3.73−3.78 (m, 1H), 3.64−3.68 (m, 1H), 2.28 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.9, 139.6, 135.1, 134.8, 133.2, 130.2, 129.7, 129.4, 127.7, 127.2, 125.3, 75.3, 33.5, 19.9. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{17}H_{16}BrClO_2Na$ 390.9893, found 390.9892.

*2-bromo-1-phenylpropyl benzoate (**8ga**)*. Yield: 87%, 83 mg; Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.2 Hz, 1H), 7.45−7.51 (m, 4H), 7.34−7.40 (m, 3H), 6.21−6.23 (m, 1H), 4.50−4.54 (m, 1H), 1.75 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.3, 137.1, 133.4, 130.0, 128.7, 128.6, 128.5, 127.2, 78.8, 50.4, 21.0. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{16}H_{15}BrO_2Na$ 341.0148, found 341.0145.

*2-bromo-2-nitro-1-phenylethyl benzoate (**8ha**)*. Yield: 64%, 67 mg; Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 13.7 Hz, 1H), 7.54−7.61 (m, 2H), 7.45−7.51 (m, 2H), 7.37−7.43 (m, 3H), 7.26−7.28 (m, 2H), 5.87−5.91 (m, 1H), 5.01−5.05 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 139.2, 137.2, 132.2, 131.9, 130.1, 129.5, 129.4, 129.3, 129.1, 127.2, 82.3, 47.4. HRMS (EI) m/z: $[M]^+$ calcd for $C_{15}H_{12}BrNO_4$ 348.9944, found 348.9944.

*2-bromocyclohexyl benzoate (**8ia**)*. Yield: 88%, 75 mg; Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 5.10−5.16 (m, 1H), 4.12−4.18 (m, 1H), 2.38−2.42 (m, 1H), 2.25−2.31 (m, 1H), 1.89−1.99 (m, 3H), 1.75−1.81 (m, 2H), 1.53−1.56 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.7, 133.2, 130.3, 129.8, 128.5, 76.5, 52.8, 35.7, 31.2, 25.5, 23.4. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{13}H_{15}BrO_2Na$ 305.0148, found 305.0150.

*2-bromocyclohexyl 2,6-dimethylbenzoate (**8ib**)*. Yield: 90%, 84 mg; Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 2H), 5.17−5.23 (m, 1H), 4.00−4.07 (m, 1H), 2.38−2.42 (m, 8H), 1.89−1.99 (m, 1H), 1.74−1.83 (m, 2H), 1.46−1.57 (m, 2H), 1.29−1.38 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.1, 134.7, 134.0, 129.3, 127.6, 76.8, 52.5, 36.2, 31.7, 25.8, 23.5, 19.8. HRMS (ESI-Q-orbitrap) m/z: $[2M+Na]^+$ calcd for $C_{30}H_{38}Br_2O_4Na$ 645.1011, found 645.1009.

*2-bromocyclohexyl 2-acetylbenzoate (**8ii**)*. Yield: 89%, 87 mg; Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 7.4 Hz, 1H), 7.47−7.56 (m, 2H), 7.41 (d, J = 7.4 Hz, 1H), 5.06−5.11 (m, 1H), 4.05−4.11 (m, 1H), 2.54 (s, 3H), 2.27−2.37 (m, 2H), 1.84−1.94 (m, 3H), 1.70−1.78 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.1, 142.3, 132.0, 130.2, 129.7, 129.2, 126.6, 52.6, 35.7, 30.9, 25.5, 24.1, 23.3. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{15}H_{17}BrO_3Na$ 347.0253, found 347.0253.

*2-bromo-2,3-dihydro-1H-inden-1-yl benzoate (**8ja**)*. Yield: 76%, 72 mg; Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 7.4 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.27−7.48 (m, 6H), 6.59 (d, J = 3.6 Hz, 1H), 4.65−4.68 (m, 1H), 3.77−3.83 (m, 1H), 3.33−3.38 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.1, 141.4, 138.5, 133.5, 130.0, 129.9, 129.7, 128.6,

127.8, 126.1, 125.0, 84.6, 50.0, 41.7. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{16}H_{13}BrO_2Na$ 338.9991, found 338.9995.

*3-bromo-2,3-dimethylbutan-2-yl benzoate (**8ka**)*. Yield: 89%, 76 mg; Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.04−8.06 (m, 2H), 7.53−7.57 (m, 1H), 7.42−7.46 (m, 2H), 1.94 (s, 6H), 1.84 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.3, 132.9, 131.8, 129.7, 128.5, 86.5, 73.1, 30.0, 21.9. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{13}H_{17}BrO_2Na$ 307.0304, found 307.0319.

*4-bromohexan-3-yl benzoate (**8la**)*. Yield: 95%, 81 mg; Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 7.7 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 5.17 (td, J = 6.7, 3.1 Hz, 1H), 4.09−4.13 (m, 1H), 1.82−1.96 (m, 4H), 1.08 (t, J = 7.3 Hz, 3H), 0.97 (t, J = 7.3Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.1, 133.3, 130.0, 129.9, 128.6, 76.7, 59.5, 28.9, 25.8, 12.7, 9.9. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{13}H_{17}BrO_2Na$ 307.0304, found 307.0304.

*2-bromo-1-methylcyclohexyl benzoate (**8ma**)*. Yield: 50%, 45 mg; Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 7.7 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 4.86 (dd, J = 8.4, 3.9 Hz, 1H), 2.46−2.50 (m, 1H), 2.05-2.10 (m, 1H), 1.94−2.01 (m, 1H), 1.69−1.82 (m, 5H), 1.45−1.58 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.4, 132.9, 131.5, 129.7, 128.5, 84.1, 57.9, 34.3, 33.2, 31.1, 23.7, 22.1. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{14}H_{17}BrO_2Na$ 319.0304, found 319.0305.

*2-bromo-1-(3-nitrophenyl)ethyl benzoate (**8na**)*. Yield: 50%, 53 mg; Colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.34 (t, J = 1.9 Hz, 1H), 8.23 (dq, J = 8.2, 1.1 Hz, 1H), 8.12 (dd, J = 8.3, 1.3 Hz, 2H), 7.80 (d, J = 7.8 Hz, 1H), 7.58−7.64 (m, 2H), 7.49 (t, J = 7.8 Hz, 2H), 6.29 (dd, J =

6.6, 5.4 Hz 1H), 3.77−3.85 (m, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 165.3, 148.6, 139.9, 133.9, 133.0, 130.0, 129.9, 128.8, 123.9, 121.8, 74.1, 33.9. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{15}H_{12}BrNO_4Na$ 371.9842, found 371.9840.

Procedure for the preparation compound 1c-Br.

1,3-Dibromo-5,5-dimethylhydantoin (20.9 mg, 0.073 mmol, 1.1 equiv) was added to a mixture of indole catalyst **1c** (0.066 mmol, 16.3 mg, 1.0 equiv) in dichloromethane (0.22 mL) at 23 °C and allowed to stir for 15 minutes in the absence of light. The product mixture was then concentrated under reduced pressure and the yellow solid residue was diluted in hexanes. The solution was filtered and concentrated under reduced pressure to give compound **1c-Br** as a yellow oil with 79% yield.

*Methyl 3-bromo-2-nonyl-3H-indole-3-carboxylate (**1c-Br**)*. Yield: 79%, 20 mg; Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, J = 7.5, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 3.76 (s, 3H), 2.92−2.99 (m, 1H), 2.73−2.80 (m, 1H), 1.83−1.94 (m, 2H), 1.25−1.46 (m, 12 H), 0.88 (t, J = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 180.5, 166.6, 153.6, 136.4, 131.0, 126.8, 124.5, 121.1, 60.2, 54.2, 32.0, 30.3, 29.65, 29.59, 29.53, 29.4, 26.7, 22.8, 14.3. HRMS (ESI-Q-orbitrap) m/z: $[M+Na]^+$ calcd for $C_{19}H_{26}BrNO_2Na$ 402.1039, found 402.1037.

ASSOCIATED CONTENT

Supporting Information

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: chmkz@cuhk.edu.hk; yyyeung@cuhk.edu.hk

Notes

The authors declare no competing financial interest.

†These authors contributed equally in this project.

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