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Note

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# Nucleophilic Opening of Donor-Acceptor Cyclopropanes With Indoles via Hydrogen Bond Activation with 1,1,1,3,3,3-Hexafluoroisopropanol

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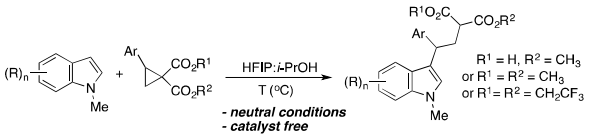



Treatment of donor-acceptor cyclopropanes with the strong hydrogen bond donor, HFIP, activated the cyclopropanes (via presumed hydrogen bonding) towards homo-Michael additions with indoles as the nucleophiles. This reaction proceeds without the need for high-pressure or catalysis.

The field of donor-acceptor cyclopropane chemistry, while well established, has seen a resurgence of activity in recent years as new and innovative use for these compounds are reported.[1] Their use as homo Michael-acceptors makes them important for the functionalization of a variety of nucleophiles[2] while their ability to act as dipolarophiles has made them useful for the synthesis of heterocycles[3] and carbocycles.[4]

Our interest in these species dates back over 20 years ago when we reported that indoles could nucleophilically open cyclopropanes under the influence of a lanthanide triflate (Figure 1).[5] This was the first example of such a reaction and since that time numerous groups have made important developments and improvements. This often involved changing the catalyst, the donor group, or the acceptor group. Our interest in this particular reaction resurfaced in 2011, when we reported that, what we presume to be an internal hydrogen bond, allowed cyclopropane hemimalonates to react with indoles under catalyst-free conditions at high pressures.[6] This sparked our interest in hydrogen bonding as a mode of activation for donor acceptor cyclopropanes. Herein we report the results of a study in which we show that various donor acceptor cyclopropanes react smoothly with indoles under catalyst free conditions in a medium where 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) is either the solvent or co-solvent. At this point, it is important to note that during the preparation of this manuscript an elegant report by the Moran group appeared which delineates similar chemistry.[7] The work herein complements that research.

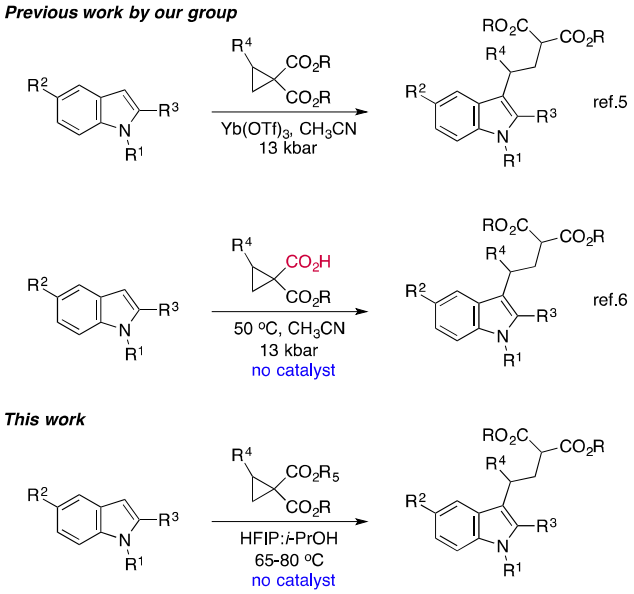
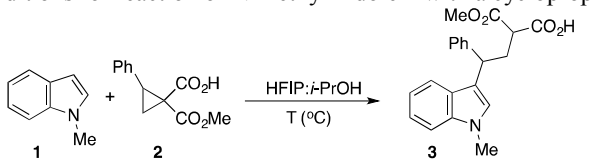



**Figure 1.** Current and related research from our group.

Our research commenced with the use of cyclopropane hemimalonates since they had shown promise in the milieu of hydrogen bonding activation. In the initial experiment (Table 1), cyclopropane **2** was treated with 2 equivalents of N-methyl indole **1** in pure HFIP at 60°C and produced the desired adduct **3** in 46% yield. In a control experiment, acetonitrile as solvent led to no product formation. The suspected need for a hydrogen bonding solvent caused us to examine acetic acid, phenol, and trifluoroethanol as solvents (entries 3,4,and 5). Phenol was chosen since its pKa is similar to HFIP. It is surprising to us that trifluoroethanol produced no product. Interestingly, isopropanol alone (entry 8) yielded some product. Optimized conditions were realized with a 1:1 mixture of HFIP and isopropanol as the reaction medium and a 2-fold excess of the indole (entry 12).

**Table 1.** Optimization of reaction conditions for reaction of N-methyl indole **1** with a cyclopropane hemimalonate **2**.

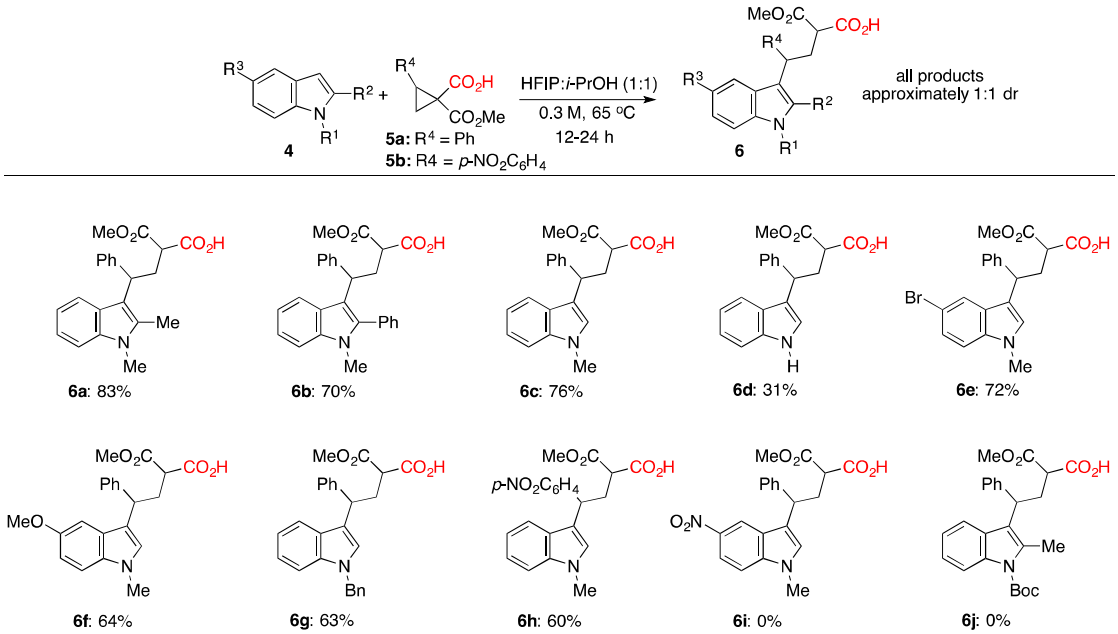



| Entry | **1** (equiv) | **2** (equiv) | HFIP:$^{i}$PrOH | Temp (° C) | Yield **3** (%) |
|---|---|---|---|---|---|
| 1 | 2.0 | 1.0 | 100:0 | 60 | 46 |
| 2 | 2.0 | 1.0 | MeCN | 80 | 0 |
| 3 | 2.0 | 1.0 | AcOH | 110 | 0 |
| 4 | 2.0 | 1.0 | PhOH | 100 | 0 |
| 5 | 2.0 | 1.0 | TFE | 70 | 0 |
| 6 | 1.1 | 1.0 | 100:0 | 60 | 28 |
| 7 | 1.1 | 1.0 | 100:0 | 25 | 19 |
| 8 | 2.0 | 1.0 | $^{i}$PrOH | 40 | 17 |
| 9 | 2.0 | 1.0 | 50:50 | 65 | 56 |
| 10 | 2.0 | 1.0 | 20:80 | 65 | IC* |
| 11 | 2.0 | 1.0 | 50:50 | 65 | 67[a] |
| 12 | 2.0 | 1.0 | 50:50 | 65 | 76[b] |
| 13 | 3.0 | 1.0 | 50:50 | 65 | 70[b] |

[a] Sealed tube [b] Changed purification to aqueous removal of excess indole * Incomplete conversion

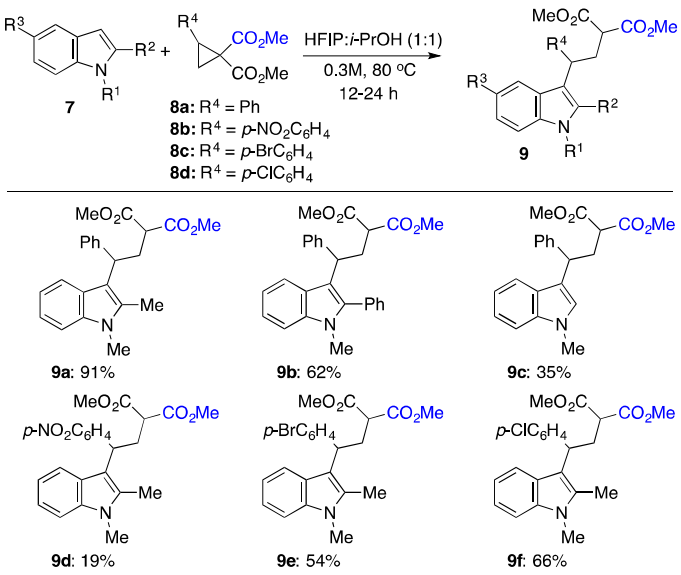
With optimal conditions in hand we turned our attention to a study of substrate performance. Chart 1 shows a series of products prepared. Several things are worthy of note. While N-methyl indole added to cyclopropane **5** in 76% yield (**6c**), indole itself behaved more poorly, producing the adduct **6d** in 31% yield. Substitution at the 2-position of the indole was well tolerated; in fact, 1,2-dimethylindole was the best nucleophile studied (**6a**). Substitution on the benzenoid portion of the indole did not have a significant effect (adducts **6e**, **6f**) except in the case of 5-nitroindole which failed to form adduct **6i** inert under these conditions. As expected N-Boc indole did not react except to undergo Boc removal.[8] Finally, a strong electron withdrawing group on the phenyl ring of the cyclopropane was tolerated, resulting in a 60% yield of **6h**.

**Chart 1:** Substrate scope for the reaction of indoles with cyclopropane hemimalonates.



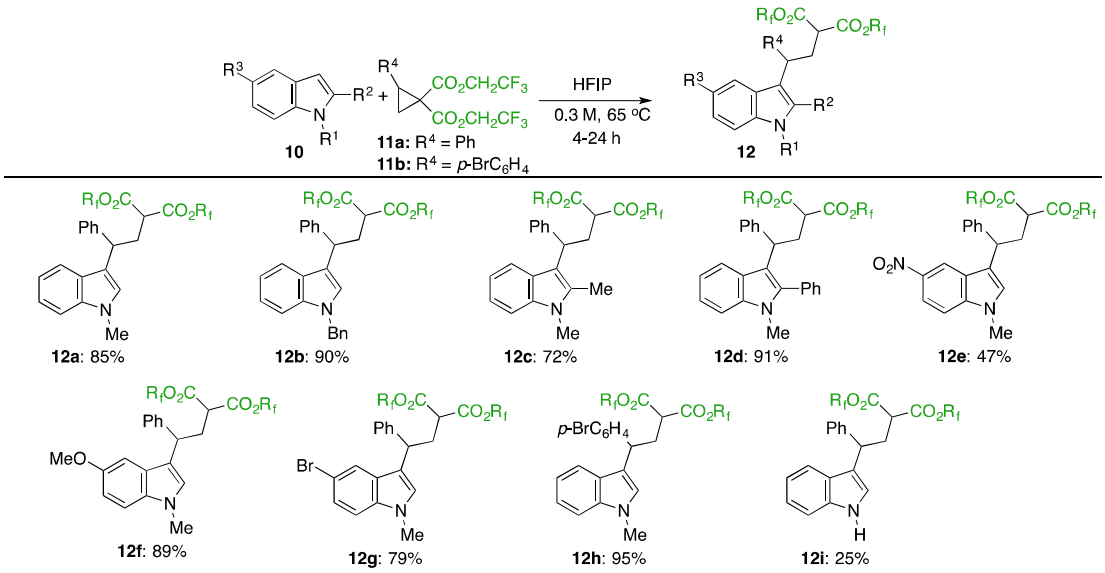

In order to compare the hemimalonates with the parent diesters, cyclopropane **8** was treated with indoles **7** under a variety of conditions (Chart 2). Initially, under the mild conditions used for the hemimalonates, little or no reaction was observed. However, when N-methyl indole was treated with cyclopropane **8** at 80 °C for a prolonged period of time, a 35% yield of adduct **9c** was realized. 2-Substitution, as expected, enhanced the nucleophilicity and improved yields were noted with the 2-methylindole and 2-phenylindole (adducts **9a** and **9b** respectively). When the cyclopropanes bore phenyl groups with electron withdrawing moieties, the expected reduction in yields was observed.

**Chart 2:** Substrate scope for the reaction of indoles with cyclopropane diesters.




With some surprising success employing cyclopropanediesters, we turned our attention to cyclopropanes bearing a geminal bis-trifluoroethyl ester moiety. We, and others, have noted the enhanced reactivity of such cyclopropanes.[9] To our delight, excellent yields were observed in most cases. Chart 3 shows the results. N-methyl indole reacted with cyclopropane **11a** to produce adduct **12a** in 85% yield. In this study we again noted that indole itself resulted in poor yields of adduct **12i**. In contrast to the hemimalonates, 5-nitroindole produced adduct **12e** in 47% yield. The excellent yields for the fluoroethylester-bearing cyclopropanes is certainly a result of the enhanced electron withdrawing nature, however an additional effect could be the interaction of HFIP with the C-F bonds of the cyclopropane. This has been noted by Paquin.[10]

**Chart 3:** Substrate scope for the reaction of indoles with cyclopropane fluoroesters.




The essential role of HFIP as a co-solvent is certainly centered around its excellent ability to act as a hydrogen bond donor. The way in which it does so in this study is somewhat unclear, however several possible modes of activation are shown in Figure 2. In the case of the diesters (**I**), hydrogen bonding to the carbonyl oxygen(s) should provide activation toward nucleophilic attack by the indole. With the cyclopropyl hemimalonate the situation may be more complex (see **II**). An internal hydrogen bond may also be in play in addition to the participation by HFIP. While the fluoroesters are expected to be electron withdrawing, a fluorine hydrogen bond (as noted by Paquin[10])would make them even more so (see **III**). In addition to enhancing the electron withdrawing nature of

the ester moieties, hydrogen bonding may serve to stereoelectronically align the carbonyls to accept the impending negative charge upon ring opening.

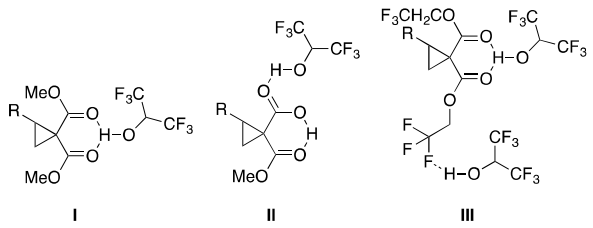



**Figure 2.** Possible hydrogen bonding motifs for donor-acceptor cyclopropanes in HFIP.

In conclusion, we have reported a simple and catalyst free method for the activation of donor-acceptor cyclopropanes with hexafluoroisopropanol, and the subsequent addition of indoles. Both fluoroesters **11** and hemi-malonates **8** were found to be more reactive under these conditions with fluoroesters providing excellent yields of adducts. Future work will examine other ring-opening and annulation reactions under similar reaction conditions.

## Experimental Section

**General Information.** Reaction flasks were oven-dried at 110 °C and cooled in a desiccator prior to use. All cyclopropane opening reactions were conducted in sealed tubes that had been flushed with argon before the addition of reagents unless otherwise indicated. The tubes were sealed with a Teflon stopper and capped with an aluminum crimping cap. All chemicals were of reagent quality and used as obtained from commercial sources. HFIP was purchased from Oakwood Chemical and dried with 3Å molecular sieves. Isopropanol was purchased as distilled in glass from Caledon Scientific and stored over 3Å molecular sieves. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS mass spectrometer using electron impact ionization. Dichloromethane (DCM), acetonitrile (MeCN) and tetrahydrofuran (THF) were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. All other reagents and solvents were used as purchased from Aldrich, Alfa Aesar (VWR), or Caledon. Reaction progress was followed by thin layer chromatography (TLC) (Merck, TLC Silica gel 60 F254) visualizing with UV light, and the plates were developed using acidic *p*-anisaldehyde. Column chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh). All columns were performed using Still's procedure for flash chromatography.[11] IR spectra were acquired using a PerkinElmer Spectrum Two FT-IR. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. NMR experiments were performed on either a Bruker AvIII 400 or Inova 600 instrument and samples were obtained in $CDCl_3$ (referenced to 7.25 ppm for $^1H$ and 77.0 ppm for $^{13}C$). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, m = multiplet, br = broad.

**General Experimental Procedure for the Synthesis of Indole Starting Materials**
Commercially available indole starting materials were used as purchased. When not available the substrates were obtained by *N*-methylation or alkylation of the parent indole following literature procedures and then confirmed by comparison to reported characterization data for these compounds. Methylated/alkylated indoles were synthesized following literature procedures [12,13,14] using the following conditions: Desired indole (1 equiv.) was dissolved in dry THF or DMF in an argon flushed flask to give a 0.3 M solution. NaH (60% dispersed in mineral oil, 1.5 eq) was added portion wise at 0 °C and then the reaction septum was returned. The flask was evacuated and placed under argon once more. The reaction was warmed to room temperature and stirred for 1.5 h. At which point, the reaction was cooled again to 0 °C and MeI (1.3 equiv.) or BnBr (1.1 eq) was added dropwise via syringe. The reactions were allowed to stir at room temperature until TLC analysis confirmed consumption of starting materials, or until 24 h had passed. Water was added to quench the reaction, and then extracted 3x with $Et_2O$. The organic layers were combined and washed 1x with brine, and then dried using $MgSO_4$. Upon filtering and concentrating, the crude mixture was purified via flash column chromatography (EtOAc:Hex) and pure product was collected.

**Synthesis of Cyclopropane Starting Materials**

All diester and hemimalonate cyclopropanes were synthesized via literature methods and confirmed by comparison to the reported characterization data: **5a-5b**[6], **8a-d** [12&13], **11a-11b**[9d]

**General Experimental Procedure: Nucleophilic Opening of Hemimalonate Cyclopropanes (6a-h) (GP1)**
To an argon flushed sealed tube was added cyclopropane (1 equiv.), indole substrate (2 equiv.) and 50:50 *i*-PrOH:HFIP for a concentration of 0.2 M. The tube was sealed and submerged into an oil bath at 65-70°C and left to react for 12-24 h. Upon confirmation of starting material consumption *via* TLC, the reactions were poured into a round bottom flask, rinsed with DCM and then concentrated *in vacuo*. The crude mixture was subjected to flash column chromatography using appropriate eluent system of either AcOH:MeOH:DCM or AcOH:EtOAc:Hex. In some cases (indicated below), instead of a column, the crude material was taken up in 2M NaOH, extracted with $Et_2O$ or DCM 3x to remove excess indole. The collected aqueous fraction was then acidified with concentrated HCl (very slowly, with cooling if needed) to a pH of 1. The resulting acidic aqueous layer was then extracted with 3x EtOAc, organic fractions combined, washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to yield purified product.

***(6a) 4-(1,2-dimethyl-1H-indol-3-yl)-2-(methoxycarbonyl)-4-phenylbutanoic acid*** Following **GP1**, CP **5a** (0.05 g, 0.23 mmol), 1,2-dimethylindole (0.066 g, 0.45 mmol) in 1.2 mL of HFIP:$^i$PrOH was reacted for 20 h. The reaction was concentrated *in vacuo* and then taken up in 1M NaOH and placed into a separatory funnel. Extractions using DCM 3x and monitoring by TLC showed that all indole had been removed from the aqueous phase. The basic aqueous layer was then carefully acidified with concentrated HCl to pH =1 and extracted with DCM 3x. The organic layers were washed with brine 1x and then dried with $MgSO_4$. Upon filtering and concentrating *in vacuo* the pure product **6a** was isolated as a white solid (0.069 g, 83% yield). Rf = 0.26 30% EtOAc:1% AcOH: 69% Hex. Characterization data for this compound matched literature reports.[6] **$^1$H NMR (400 MHz, Chloroform-*d*) δ** mixture of diastereomers = 7.46 (t, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.23-7.21 (m, 3H), 7.16 – 7.07 (m, 2H), 7.01 – 6.95 (m, 1H), 4.36 – 4.26 (m, 1H), 3.65 3.62 and 3.56 (s, 6 H total), 3.36 – 3.29 (m, 1H), 2.97 – 2.86 (m, 2H), 2.33 and 2.32 (s, 3H total)

***(6b) 2-(methoxycarbonyl)-4-(1-methyl-2-phenyl-1H-indol-3-yl)-4-phenylbutanoic acid*** Following **GP1**, hemimalonate CP **5a** (0.05 g, 0.23 mmol), 2-phenyl-1-methylindole (0.10 g, 0.48 mmol) in 1.2 mL of HFIP:$^i$PrOH was reacted for 16 h. The reaction was concentrated *in vacuo* and purified directly via flash column chromatography. The pure product was isolated as a white solid (0.072 g, 70%). MP = 165-169 °C Rf = 0.37 40% EtOAc: 1% AcOH: 59% Hex. **$^1$H NMR (599 MHz, $CDCl_3$)** mixture of diastereomers **δ =** 7.63 (t, *J* = 8.2 Hz, 1H), 7.45 – 7.26 (m, 8H), 7.20 – 7.05 (m, 5H), 4.13 (m, 1H), 3.56 and 3.55 (s, 3H), 3.46 (s, 3H), 3.29 – 3.21 (m, 1H), 2.92 – 2.71 (m, 2H) **$^{13}$C NMR** mixture of diastereomers **(101 MHz, $CDCl_3$) δ** 175.21, 174.89, 171.58, 169.47, 169.43, 144.59, 144.50, 139.73, 139.72, 137.73, 137.67, 134.16, 131.59, 131.55, 130.95, 130.91, 129.19, 128.52, 128.49, 128.45, 128.42, 128.02, 127.78, 127.74, 126.38, 126.34, 126.15, 121.84, 121.75, 120.72, 120.69, 119.70, 119.62, 112.64, 112.42, 109.76, 109.70, 77.48, 77.36, 77.16, 76.84, 52.62, 52.50, 52.47, 50.50, 50.29, 40.36, 40.30, 39.92, 34.18, 33.90, 31.01, 30.95, 21.19. **IR (cm$^{-1}$)** 2954, 1743, 1694, 1468, 1433, 1290, 1146, 744, 699 **HRMS (EI)** m/z: [$M^+$] Calcd for $C_{27}H_{25}NO_4$ 427.1784; Found 427.1775

***(6c) 2-(methoxycarbonyl)-4-(1-methyl-1H-indol-3-yl)-4-phenylbutanoic acid*** Following **GP1**, hemimalonate CP **5a** (0.10 g, 0.46 mmol), 1-methylindole (0.126 g, 0.92 mmol) in 2.4 mL of HFIP:$^i$PrOH was reacted for 20 h. The reaction was concentrated *in vacuo* and taken up in 1M NaOH and followed **GP2** extraction work up. The pure product was isolated as an off-white solid (0.12 g, 76 % yield) Rf = 0.47 1% AcOH:1% MeOH: 98% DCM. Characterization data for this compound matched literature reports.[6] **$^1$H NMR (400 MHz, Chloroform-*d*)** mixture of diastereomers **δ =** 9.91 (br.s, 1H), 7.45 (m, 1H), 7.36 – 7.26 (m, 4H), 7.22 – 7.15 (m, 3H), 7.02 (m, 1H), 6.90 and 6.88 (s, 1H total), 4.26 (m, , 1H), 3.74 and 3.68 (s, 6H total), 3.44 (m,1H), 2.85m, 1H), 2.71 – 2.58 (m, 1H)

***(6d) 4-(1H-indol-3-yl)-2-(methoxycarbonyl)-4-phenylbutanoic acid*** Following **GP1**, hemimalonate CP **5a** (0.05 g, 0.23 mmol), indole (0.054 g, 0.46 mmol) in 1.2 mL HFIP:$^i$PrOH was reacted for 20 h. The crude mixture was concentrated *in vacuo* and purified by flash column chromatography. Rf = 0.32 1% AcOH:1% MeOH: 98% DCM. The product was isolated as a yellow oil (0.024 g, 31%). Even after multiple purification attempts characterization data was unclean but had matching results to reported literature.[6]

***(6e) 4-(5-bromo-1-methyl-1H-indol-3-yl)-2-(methoxycarbonyl)-4-phenylbutanoic acid*** Following **GP1**, hemimalonate CP **5a** (0.075g, 0.34 mmol), 5-bromo-1-methylindole (0.14 g, 0.68 mmol) in 1.7 mL HFIP:$^i$PrOH were heated for 30 h. The crude mixture was subjected to the extraction method of purification as described in **GP1**. The resultant solid from the extractions was further purified by recrystallization in pentane/DCM to yield pure product as a pale yellow solid (0.10 g, 72%). Rf = 0.5 1% AcOH: 1% MeOH: 98% DCM. Characterization data for this compound matched literature results.[6] **$^1$H**

**NMR (400 MHz, Chloroform-*d*)** mixture of diastereomers **δ =** 7.54 (m, 1H), 7.31 – 7.27 (m, 4H), 7.25 – 7.18 (m, 2H), 7.13 and 7.11 (s, 1H total), 6.92 and 6.89 (s, 1H total), 4.21-4.12 (m, 1H), 3.76 and 3.73 and 3.72 and 3.69 (s, 6H total), 3.44 – 3.37 (m, 1H), 2.85 – 2.71 (m, 1H), 2.68 – 2.54 (m, 1H)

***(6f) 4-(5-methoxy-1-methyl-1H-indol-3-yl)-2-(methoxycarbonyl)-4-phenylbutanoic acid*** Following **GP1**, hemimalonate CP **5a** (0.05 g, 0.23 mmol), 5-methoxy-1-methylindole (0.074 g, 0.46 mmol) in 1.2 mL of HFIP:$^{i}$PrOH was reacted for 16 h. The reaction was concentrated *in vacuo* and purified directly via flash column chromatography. The pure product was isolated as a white foam (0.056 g, 64%) Rf = 0.27 40% EtOAc: 1% AcOH: 59% Hex. **$^{1}$H NMR (400 MHz, $CDCl_3$)** mixture of diastereomers **δ =** 7.34 – 7.26 (m, 4H), 7.19 (t, *J* = 7.0 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 6.88 (m, 1H), 6.86 – 6.79 (m, 2H), 4.19 (m, 1H), 3.76 and 3.67 (s, 3H total), 3.74 and 3.73 (3H total), 3.70 (s, 3H), 3.43 (m, 1H), 2.83 (m, 1H), 2.67 – 2.55 (m, 1H) **$^{13}$C NMR (101 MHz, $CDCl_3$)** mixture of diastereomers **δ =** 174.7**,** 169.9, 153.8, 143.4, 132.8, 128.7, 128.5, 128.1, 126.9, 126.7, 116.6, 112.0, 110.1, 101.6, 101.5, 56.0, 52.8, 50.0, 40.8, 35.1 33.0. **IR (cm$^{-1}$)** 2949, 1732, 1490, 1451, 1212, 1035, 792, 700, 587 **HRMS (EI)** m/z: [$M^+$] Calcd for $C_{22}H_{23}NO_5$ 381.1576; Found 381.1574

***(6g) 4-(1-benzyl-1H-indol-3-yl)-2-(methoxycarbonyl)-4-phenylbutanoic acid*** Following **GP1**, hemimalonate CP **5a** (0.05 g, 0.23 mmol), 1-benzylindole (0.095 g, 0.46 mmol) in 1.2 mL of HFIP:$^{i}$PrOH was reacted for 16 h. The reaction was concentrated *in vacuo* and purified directly via flash column chromatography. The pure product was isolated as a white solid (0.062 g, 63%) Rf = 0.31 30% EtOAc: 1% AcOH: 69% Hex. Characterization data for this compound matched literature reports.[6] **$^{1}$H NMR (400 MHz, Chloroform-*d*)** mixture of diastereomers **δ =** 7.45 (m, 2H), 7.36 – 7.25 (m, 7H), 7.23 – 7.15 (m, 3H), 7.15 – 7.06 (m, 3H), 7.04 – 6.96 (m, 2H), 5.28 (m, 1H), 4.28 (m, 1H), 3.73 and 3.66 (s, 3H total), 3.44 – 3.39 (m, 1H), 2.91 – 2.78 (m, 1H), 2.70 – 2.57 (m, 1H)

***(6h) 2-(methoxycarbonyl)-4-(1-methyl-1H-indol-3-yl)-4-(4-nitrophenyl)butanoic acid*** Following **GP1**, hemimalonate CP **5b** (0.05 g, 0.19 mmol), 1-methylindole (0.05 g, 0.38 mmol) in 0.65 mL of HFIP:$^{i}$PrOH was reacted for 24 h. The reaction was concentrated *in vacuo* and purified directly via flash column chromatography. The pure product was isolated as a yellow foam (0.044 g, 64%) Note: Compound 6h is light sensitive and decomposed upon $^{13}$C NMR data acquisition as evidenced by a color change. Rf = 0.28 40% EtOAc: 1% AcOH:1% MeOH: 58% Hex. **$^{1}$H NMR (599 MHz, Chloroform-*d*)** mixture of diastereomers **δ** 8.07 (d, *J* = 8.7 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 2H), 7.37 (m, 3H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.95 – 6.88 (m, 1H), 6.86 (m, 1H), 4.27 (t, *J* = 7.7 Hz, 1H), 3.67 (apparent d, *J* = 3.2 Hz, 1.5H), 3.25 (s, 1.3H), 3.63 and 3.61 (s, 3H), 3.32 (t, *J* = 8.7 Hz, 1H), 2.81 – 2.64 (m, 1H), 2.55 (m, 1H) **$^{13}$C NMR (101 MHz, $CDCl_3$)** mixture of diastereomers **δ** 177.61, 174.75, 171.42, 169.44, 151.62, 146.81, 141.78, 137.52, 130.12, 128.87, 128.46, 126.86, 126.40, 123.98, 123.63, 122.32, 119.47, 119.17, 115.00, 109.63, 52.95, 49.80, 40.54, 37.36, 34.59, 32.98, 21.47, 20.84.

**IR (cm$^{-1}$)** 2953, 1733, 1706, 1598, 1514, 1344, 1287, 1152, 855, 737 **HRMS (EI)** m/z: [$M^+$] Calcd for $C_{21}H_{20}N_2O_6$ 396. 1321; Found 396.1325

**General Experimental Procedure: Nucleophilic Opening of Bis-dimethylester Cyclopropanes (9a-f) (GP2)**
To an argon flushed sealed tube was added cyclopropane (1 equiv.), indole substrate (3 equiv.) and HFIP for a concentration of 0.3 M. The tube was sealed off and submerged into an oil bath at 80 °C and left to react for 12-24 h. Upon confirmation of starting material consumption *via* TLC, the reaction was poured into a round bottom flask, rinsed with DCM and then concentrated down *in vacuo*. The crude material was directly subjected to flash column chromatography using appropriate eluent system of EtOAc:Hex to isolate purified material.

***(9a) dimethyl 2-(2-(1,2-dimethyl-1H-indol-3-yl)-2-phenylethyl)malonate*** Following **GP2**, CP **8a** (0.05 g, 0.21 mmol) and 1,2-dimethylindole (0.093g, 0.64 mmol) in HFIP (0.7 mL) were subjected to heat for 29 h. The crude material was purified via flash column chromatography 20%EtOAc:80%Hex to collect a white solid (0.073 g, 91%). MP = 81-83 °C Rf = 0.24 (20%EtOAc:80%Hex) **$^{1}$H NMR (599 MHz, Chloroform-*d*) δ** = 7.46 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.33 (m, 2H), 7.25 – 7.20 (m, 3H), 7.16 – 7.10 (m, 2H), 7.00 – 6.96 (m, 1H), 4.28 (t, *J* = 8.3 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 3.53 (s, 3H), 3.30 (dd, *J* = 8.0, 6.8 Hz, 1H), 2.89 (m, 2H), 2.32 (s, 3H). **$^{13}$C NMR (101 MHz, $CDCl_3$) δ** = 170.1, 170.0, 144.3, 137.1, 134.3, 128.4, 127.7, 126.7, 126.1, 120.6, 119.6, 119.0, 111.2, 108.8, 52.6, 52.5, 50.6, 39.7, 33.5, 29.7, 10.7. **IR (cm$^{-1}$)** 2950, 1748, 1724, 1472, 1431, 1249, 1229, 1147,1033, 999 **HRMS (EI)** m/z: [$M^+$] Calcd for $C_{23}H_{25}NO_4$, 379.1784; Found 379.1786

***(9b) dimethyl 2-(2-(1-methyl-2-phenyl-1H-indol-3-yl)-2-phenylethyl)malonate*** Following **GP2**, CP **8a** (0.037 g, 0.16 mmol) and 2-phenyl-1-methylindole (0.036g, 0.17 mmol, 1.1 equiv) in HFIP (0.5 mL) were subjected to heat for 24 h. The crude material was purified via flash column chromatography 20%EtOAc:80%Hex to collect a white solid (0.044 g, 62%). MP=

119-120 °C Rf = 0.32 (20%EtOAc:80%Hex). **$^1$H NMR (400 MHz, Chloroform-*d*) δ** = 7.67 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.43 (m, 3H), 7.37 (t, *J* = 7.9 Hz, 3H), 7.33 – 7.29 (m, 2H), 7.26 (m, 3H), 7.21 – 7.15 (m, 1H), 7.12 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 4.08 (dd, *J* = 10.7, 5.8 Hz, 1H), 3.56 (s, 3H), 3.48 (s, 3H), 3.45 (s, 3H), 3.24 (dd, *J* = 9.2, 5.5 Hz, 1H), 2.91 – 2.72 (m, 2H). **$^{13}$C NMR (101 MHz, $CDCl_3$) δ** = 169.9, 169.8, 144.7, 139.6, 137.7, 131.7, 131.0, 128.4, 127.8, 126.4, 126.1, 121.8, 120.8, 119.6, 112.8, 109.7, 52.4, 50.6, 40.5, 34.2, 31.0. **IR (cm$^{-1}$)** 3026, 2953, 1731, 1467, 1435, 1215, 1153, 701 **HRMS (EI)** m/z: [$M^+$] Calcd for $C_{28}H_{27}NO_4$ 441.1940; Found 441.1948

***(9c) dimethyl 2-(2-(1-methyl-1H-indol-3-yl)-2-phenylethyl)malonate*** Following **GP2**, CP **8a** (0.05 g, 0.21 mmol) and 1-methylindole (0.083g, 0.63 mmol) in HFIP (0.7 mL) were subjected to heat for 48 h. The crude material was purified via flash column chromatography 20%EtOAc:80%Hex to collect a clear oil (0.026 g, 35%). Rf = 0.24 (20%EtOAc:80%Hex). Characterization data matched literature reports.[15] **$^1$H NMR (599 MHz, Chloroform-*d*) δ** = 7.45 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.34 – 7.25 (m, 5H), 7.19 (m, 2H), 7.02 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.88 (s, 1H), 4.22 (t, *J* = 7.9 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.67 (s, 3H), 3.41 (dd, *J* = 8.0, 6.6 Hz, 1H), 2.83 (ddd, *J* = 13.6, 8.0, 7.0 Hz, 1H), 2.62 (ddd, *J* = 13.6, 8.8, 6.7 Hz, 1H) **$^{13}$C NMR (101 MHz, $CDCl_3$) δ** = 170.0, 143.6, 137.4, 128.7, 128.1, 127.3, 126.6, 126.2, 121.8, 119.6, 119.0, 117.3, 109.3, 52.7, 52.6, 50.2, 40.7, 35.1, 32.8. **IR(cm$^{-1}$)** 2952, 1754, 1488, 1282, 1159, 974

***(9d) dimethyl 2-(2-(1,2-dimethyl-1H-indol-3-yl)-2-(4-nitrophenyl)ethyl)malonate*** Following **GP2**, CP **8b** (0.022 g, 0.08 mmol) and 1,2-dimethylindole (0.034g, 0.24 mmol) in HFIP (0.3 mL) were subjected to heat for 25 h. The crude material was purified via flash column chromatography 30%EtOAc:70%Hex to collect a yellow oil (0.07 g, 19%). Rf = 0.2 (30%EtOAc:70%Hex). **$^1$H NMR (400 MHz, Chloroform-*d*) δ** = 8.09 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 4.4 Hz, 1H), 7.14 (t, *J* = 8.1 Hz, 1H), 7.02 – 6.97 (m, 1H), 4.37 (t, *J* = 8.1 Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.54 (s, 3H), 3.27 (dd, *J* = 8.1, 6.7 Hz, 1H), 2.88 (dd, *J* = 9.0, 6.7 Hz, 1H), 2.32 (s, 3H) **$^{13}$C NMR (101 MHz, $CDCl_3$) δ** = 169.9, 169.6, 152.1, 146.4, 137.2, 134.7, 128.5, 126.2, 123.7, 121.1, 119.5, 119.0, 109.6, 109.1, 52.7, 52.6, 50.2, 39.6, 33.0, 29.8, 10.7. **IR (cm$^{-1}$)** 2952, 1732, 1596, 1516, 1471, 1434, 1344, 1251, 1230, 853 **HRMS (EI)** m/z: [$M^+$] Calcd for $C_{23}H_{24}N_2O_6$ 424.1634; Found 424.1631

***(9e) dimethyl 2-(2-(4-bromophenyl)-2-(1,2-dimethyl-1H-indol-3-yl)ethyl)malonate*** Following **GP2**, CP **8c** (0.050 g, 0.16 mmol) and 1,2-dimethylindole (0.070g, 0.48 mmol) in HFIP (0.55 mL) were subjected to heat for 24 h. The crude material was purified via flash column chromatography 20%EtOAc:80%Hex to collect a viscous yellow oil (0.039 g, 54%). Rf = 0.26 (20%EtOAc:80%Hex). **$^1$H NMR (400 MHz, Chloroform-*d*) δ =** 7.43 (d, *J* = 7.9 Hz, 2H), 7.40 – 7.35 (m, 2H), 7.31 – 7.26 (m, 2H), 7.23 (s, 1H), 7.20 – 7.12 (m, 1H), 7.02 (m, 1H), 4.26 (t, *J* = 8.1 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.57 (s, 3H), 3.30 (t, *J* = 7.9 Hz, 1H), 2.88 (m, 2H), 2.34 (s, 3H). **$^{13}$C NMR (101 MHz, $CDCl_3$) δ** = 170.0, 169.8, 143.4, 137.1, 134.4, 131.4, 129.5, 126.4, 120.8, 119.9, 119.3, 119.2, 110.5, 108.9, 52.6, 52.5, 50.4, 39.1, 33.3, 29.8, 10.6. **IR (cm$^{-1}$)** 2947, 1730, 1433, 1368, 1222, 1150, 735, 691 **HRMS (EI)** m/z: [$M^+$] Calcd for $C_{23}H_{24}BrNO_4$ 457.0889; Found 457.0889

***(9f) dimethyl 2-(2-(4-chlorophenyl)-2-(1,2-dimethyl-1H-indol-3-yl)ethyl)malonate*** Following **GP2**, CP **8d** (0.050 g, 0.19 mmol) and 1,2-dimethylindole (0.081g, 0.59 mmol) in HFIP (0.6 mL) were subjected to heat for 48 h. The crude material was purified via flash column chromatography 20%EtOAc:80%Hex to collect a clear oil (0.051 g, 66%). Rf = 0.23 (20%EtOAc:80%Hex). **$^1$H NMR (400 MHz, Chloroform-*d*) δ** 7.44 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.27 (m, 3H), 7.26 – 7.22 (m, 2H), 7.20 – 7.14 (m, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 4.29 (t, *J* = 8.1 Hz, 1H), 3.77 (s,3H), 3.70 (s, 3H), 3.58 (s, 3H), 3.31 (dd, *J* = 7.9, 6.9 Hz, 1H), 2.89 (m, 2H), 2.35 (s, 3H) **$^{13}$C NMR (101 MHz, $CDCl_3$) δ** = 170.0, 169.8, 142.8, 137.1, 134.4, 131.8, 129.1, 128.4, 126.4, 120.8, 119.3, 119.2, 110.6, 108.9, 52.6, 52.5, 50.4, 39.1, 33.3, 29.7, 10.6. **IR (cm$^{-1}$)** 2951, 1731, 1490, 1471, 1434, 1250, 1151, 1013 **HRMS (EI)** m/z: [$M^+$] Calcd for $C_{23}H_{24}ClNO_4$ 413.1394; Found 413.1393

**General Experimental Procedure: Nucleophilic Opening of Bis-trifluoroethylester Cyclopropanes (12a-i) (GP3)**
To an argon flushed sealed tube was added cyclopropane (1 equiv.), indole substrate (3 equiv.) and HFIP for a concentration of 0.3 M. The tube was sealed off and submerged into an oil bath at 80 °C and left to react for 8-24 h. Upon confirmation of starting material consumption *via* TLC, the reaction was poured into a round bottom flask, rinsed with DCM and then concentrated down *in vacuo*. The crude material was directly subjected to flash column chromatography using appropriate eluent system of EtOAc:Hex to isolate purified material.

***(12a) bis(2,2,2-trifluoroethyl) 2-(2-(1-methyl-1H-indol-3-yl)-2-phenylethyl)malonate*** Following **GP3**, CP **11a** (0.05 g, 0.13 mmol) and 1-methylindole (0.053g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 24 h. The crude material was purified via flash column chromatography 12%EtOAc:88% Hexanes to collect a clear oil (0.057 g, 85%). Rf = 0.38 12% EtOAc:88% Hexanes. **$^{1}$H NMR (400 MHz, $CDCl_3$) δ =** 7.47 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.27 (m, 5H), 7.24 – 7.18 (m, 2H), 7.09 – 7.01 (m, 1H), 6.88 (s, 1H), 4.57 – 4.38 (m, 4H), 4.26 (t, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 3.60 (t, *J* = 7.2 Hz, 1H), 2.96 – 2.85 (m, 1H), 2.76 – 2.65 (m, 1H). **$^{19}$F NMR (376 MHz, Chloroform-*d*) δ =** -73.74 (t, *J* = 7.3 Hz, 3F) -73.75 (t, *J* = 7.6 Hz, 3F). **$^{13}$C NMR (101 MHz, $CDCl_3$) δ =** 167.3, 143.0, 137.5, 128.8, 128.0, 127.1, 126.9, 126.4, 122.7 (q, $^{1}J_{C\text{-}F}$= 277 Hz), 122.7 (q, $^{1}J_{C\text{-}F}$= 277 Hz), 122.0, 119.6, 119.2, 116.5, 109.4, 61.16 (q, $^{2}J_{C\text{-}F}$ = 37 Hz), 49.7, 40.7, 34.8, 32.9. **IR (cm$^{-1}$)** 3028, 1754, 1410, 1281, 1216, 1164, 1136, 977, 703 **HRMS (EI)** m/z: [$M^+$] Calcd for $C_{24}H_{21}F_6NO_4$ 501.1375; Found 501.1372

***(12b) bis(2,2,2-trifluoroethyl) 2-(2-(1-benzyl-1H-indol-3-yl)-2-phenylethyl)malonate*** Following **GP3**, CP **11a** (0.05 g, 0.13 mmol) and 1-benzylindole (0.084g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 8 h. The crude material was purified via flash column chromatography 10%EtOAc:90%Hex to collect a clear oil (0.070 g, 90%). Rf = 0.23 (10%EtOAc:90%Hex). **$^{1}$H NMR (400 MHz, Chloroform-*d*) δ** 7.47 (d, *J* = 7.9 Hz, 1H), 7.35 – 7.25 (m, 7H), 7.22 (dt, *J* = 8.6, 2.8 Hz, 2H), 7.18 – 7.09 (m, 3H), 7.04 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.99 (s, 1H), 5.29 (s, 2H), 4.57 – 4.38 (m, 4H), 4.28 (t, *J* = 8.0 Hz, 1H), 3.62 – 3.55 (m, 1H), 2.91 (dt, *J* = 14.1, 7.5 Hz, 1H), 2.71 (ddd, *J* = 13.9, 8.8, 6.8 Hz, 1H). **$^{19}$F NMR (376 MHz, Chloroform-*d*) δ** = -73.72 (t, *J* = 8.1 Hz, 3F), -73.75 (t, *J*= 8.4 Hz, 3F). **$^{13}$C NMR (101 MHz, $CDCl_3$) δ =** 167.3, 167.2, 142.8, 137.5, 137.0, 128.8, 128.7, 127.9, 127.7, 127.3, 126.8, 126.7, 125.6, 122.6 (q, $^{1}J_{C\text{-}F}$ = 278 Hz), 122.5 (q, $^{1}J_{C\text{-}F}$ = 277 Hz), 122.2, 119.6, 119.4, 117.2, 109.9, 61.04 (q, $^{2}J_{C\text{-}F}$ = 37 Hz), 50.1, 49.5, 40.7, 34.7. **IR (cm$^{-1}$)** 3030, 1753, 1453, 1280, 1216, 1165, 977, 908 **HRMS (EI)** m/z: [$M^+$] Calcd for $C_{30}H_{25}F_6NO_4$ 577.1688; Found 577.1688

***(12c) bis(2,2,2-trifluoroethyl) 2-(2-(1,2-dimethyl-1H-indol-3-yl)-2-phenylethyl)malonate*** Following **GP3**, CP **11** (0.05 g, 0.13 mmol) and 1,2-dimethylindole (0.059g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 18 h. The crude material was purified via flash column chromatography 12.5%EtOAc:87.5%Hex to collect a clear oil (0.050 g, 72%). Rf = 0.47 20%EtOAc:80% Hexanes. **$^{1}$H NMR (400 MHz, Chloroform-*d*) δ** = 7.50 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.30 – 7.22 (m, 3H), 7.20 – 7.11 (m, 2H), 7.02 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 4.50 (m, 2H (two overlapping dq unresolved)), 4.35 – 4.12 (m, 1H), 3.66 (s, 3H), 3.51 (dd, *J* = 9.3, 5.2 Hz, 1H), 3.07 – 2.87 (m, 2H), 2.32 (s, 3H). **$^{19}$F NMR (376 MHz, Chloroform-*d*) δ =** -73.71 (dt, *J* = 8.3, 4.2 Hz, 3F), -73.87 (dt, *J* = 8.3, 0.9 Hz, 3F). **$^{13}$C NMR (101 MHz, Chloroform-*d*) δ** = 167.3, 143.9, 137.1, 134.7, 128.5, 127.6, 126.5, 126.3, 122.7 (q, $^{1}J_{C\text{-}F}$= 277 Hz), 122.6 (q, $^{1}J_{C\text{-}F}$= 278 Hz), 120.8, 119.4, 119.3, 110.3, 109.0, 61.1 (q, $^{2}J_{C\text{-}F}$ = 36 Hz), 60.9 (q, $^{2}J_{C\text{-}F}$ = 37 Hz), 50.0, 39.9, 33.4, 29.8, 10.5 **IR (cm$^{-1}$)** 2941, 1753, 1409, 1280, 1162, 976, 700, 561 **HRMS (EI)** m/z: [$M^+$] Calcd for $C_{25}H_{23}F_6NO_4$ 515.1531; Found 515.1525

***(12d) bis(2,2,2-trifluoroethyl) 2-(2-(1-methyl-2-phenyl-1H-indol-3-yl)-2-phenylethyl)malonate*** Following **GP3**, CP **11a** (0.050 g, 0.13 mmol) and 2-phenyl-1-methylindole (0.084g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 4 h. The crude material was purified via flash column chromatography 10%EtOAc:90%Hex to collect a clear oil (0.071 g, 91%). Rf = 0.32 (15%EtOAc:85%Hex). **$^{1}$H NMR (599 MHz, Chloroform-*d*) δ =** 7.62 (d, *J* = 8.0 Hz, 1H), 7.42 (m, 3H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.27 – 7.22 (m, 5H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 4.30 (dq, *J* = 12.6, 8.4 Hz, 1H), 4.19 (dq, *J* = 12.5, 8.3 Hz, 1H), 4.15 – 4.08 (m, 2H), 4.00 (dq, *J* = 12.6, 8.3 Hz, 1H), 3.56 (s, 3H), 3.39 (dd, *J* = 8.9, 5.4 Hz, 1H), 2.94 (ddd, *J* = 13.9, 11.5, 5.4 Hz, 1H), 2.80 (ddd, *J* = 14.1, 8.9, 5.4 Hz, 1H). **$^{19}$F NMR (376 MHz, Chloroform-*d*) δ** -73.74 (t, *J* = 8.3 Hz, 3F), -73.88 (t, *J* = 8.9 Hz, 3F). **$^{13}$C NMR (151 MHz, cdcl$_3$) δ** 167.0, 166.8, 144.1, 139.7, 137.6, 131.4, 130.8, 128.5, 128.4, 128.4, 127.6, 126.2, 126.1, 122.51 (q, $^{1}J_{C\text{-}F}$ = 277 Hz), 122.4 (q, $^{1}J_{C\text{-}F}$ = 277 Hz) 121.8, 120.5, 119.7, 111.8, 109.7, 60.9 (q, $^{2}J_{C\text{-}F}$ = 36 Hz, ), 60.7 (q, $^{2}J_{C\text{-}F}$ = 38 Hz), 49.9, 40.4, 33.9, 30.9. **IR (cm$^{-1}$)** 3091, 2940, 1774, 1756, 1279, 1240, 1165, 1138, 970, 742, 699, 648 **HRMS (EI)** m/z: [$M^+$] Calcd for $C_{30}H_{25}F_6NO_4$ 577.1688; Found 577. 1693

***(12e) bis(2,2,2-trifluoroethyl) 2-(2-(1-methyl-5-nitro-1H-indol-3-yl)-2-phenylethyl)malonate*** Following **GP3**, CP **11a** (0.05 g, 0.13 mmol) and 5-nitro-1-methylindole (0.071g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 20 h. The crude material was purified via flash column chromatography 40%EtOAc:60%Hex to collect a yellow solid (0.035 g, 47%). MP = 78-81 °C Rf = 0.28 40%EtOAc:60% Hexanes. **$^{1}$H NMR (400 MHz, Chloroform-*d*) δ =** 8.36 (d, *J* = 2.1 Hz, 1H), 8.09 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.37 – 7.26 (m, 6H), 7.06 (s, 1H), 4.65 – 4.40 (m, 4H), 4.26 (dd, *J* = 9.0, 6.9 Hz, 1H), 3.81 (s, 3H), 3.54 (dd, *J* = 7.9, 6.6 Hz, 1H), 2.84 (m, 1H), 2.70 (ddd, *J* = 14.0, 9.2, 6.6 Hz, 1H). **$^{19}$F NMR (376 MHz, Chloroform-*d*) δ = -** 73.69 – -73.87 (m, 6F). **$^{13}$C NMR (101 MHz, $CDCl_3$) δ** = 167.1, 141.9, 141.5, 140.1, 129.2, 129.1, 127.9, 127.5, 126.4, 122.7 (q, $^{1}J_{C\text{-}F}$=277.5 Hz), 122.6 (q, $^{1}J_{C\text{-}F}$= 277.3 Hz) 120.0, 117.9, 116.8, 109.4, 61.30 (q, $^{2}J_{C\text{-}F}$ = 37.2 Hz), 49.4, 40.4, 34.7,

33.4. **IR (cm$^{-1}$)** 2940, 1758, 1488, 1322, 1283, 1160, 1064, 973 **HRMS (EI)** m/z: [M$^+$] Calcd for $C_{24}H_{20}F_6N_2O_6$ 546.1226; Found 546.1226

***(12f) bis(2,2,2-trifluoroethyl) 2-(2-(5-methoxy-1-methyl-1H-indol-3-yl)-2-phenylethyl)malonate*** Following **GP3**, CP **11a** (0.05 g, 0.13 mmol) and 5-methoxy-1-methylindole (0.065g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 18 h. The crude material was purified via flash column chromatography 12.5%EtOAc:87.5%Hex to collect a clear oil (0.0632 g, 89%). Rf = 0.34 20%EtOAc:80% Hexanes. **$^1$H NMR (400 MHz, Chloroform-*d*) δ =** 7.33 – 7.29 (m, 4H), 7.22 (ddd, *J* = 8.6, 4.8, 3.3 Hz, 1H), 7.16 (d, *J* = 9.1 Hz, 1H), 6.90 – 6.82 (m, 3H), 4.58 – 4.40 (m, 4H), 4.19 (t, *J* = 8.0 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.59 (t, *J* = 7.2 Hz, 1H), 2.88 (dt, *J* = 14.1, 7.5 Hz, 1H), 2.68 (ddd, *J* = 14.0, 8.7, 6.8 Hz, 1H) **$^{19}$F NMR (376 MHz, Chloroform-*d*) δ** = -73.73 (t, *J* = 8.7 Hz, 3F), -73.76 (t, *J*= 8.6 Hz, 3F). **$^{13}$C NMR (101 MHz, CDCl$_3$) δ** = 167.4, 167.3, 153.9, 143.0, 132.9, 128.8, 128.0, 127.4, 126.9, 122.7 (q, $^1J_{C\text{-}F}$= 277 Hz), 116.0, 112.1, 110.2, 101.5, 61.15 (q, $^2J_{C\text{-}F}$ = 37 Hz), 55.9, 49.6, 40.7, 34.7, 33.0. **IR (cm$^{-1}$)** 2945, 1753, 1623, 1491, 1280, 1162, 1136, 1058, 701 **HRMS (EI)** m/z: [M$^+$] Calcd for $C_{25}H_{23}F_6NO_5$ 531.1481; Found 531.1483

***(12g) bis(2,2,2-trifluoroethyl) 2-(2-(5-bromo-1-methyl-1H-indol-3-yl)-2-phenylethyl)malonate*** Following **GP3**, CP **11a** (0.05 g, 0.13 mmol) and 5-bromo-1-methylindole (0.085g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 16 h. The crude material was purified via flash column chromatography 15%EtOAc:85%Hex to collect a pale-yellow oil (0.062 g, 79%). Rf = 0.40 15% EtOAc:85% Hexanes. **$^1$H NMR (400 MHz, Chloroform-*d*) δ** = 7.45 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.26 (m, 4H), 7.23 – 7.17 (m, 2H), 7.03 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.87 (s, 1H), 4.56 – 4.37 (m, 4H), 4.24 (t, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 3.58 (t, *J* = 7.2 Hz, 1H), 2.88 (dt, *J* = 14.1, 7.5 Hz, 1H), 2.69 (ddd, *J* = 14.0, 8.6, 7.0 Hz, 1H). **$^{19}$F NMR (376 MHz, Chloroform-*d*) δ =** -73.73 (t, *J* = 7.6 Hz, 3F), -73.76 (t, *J*= 8.2 Hz, 3F). **$^{13}$C NMR (101 MHz, CDCl$_3$) δ =** 167.3, 143.0, 137.5, 128.8, 128.0, 127.1, 126.9, 126.4, 122.7 (q, $^1J_{C\text{-}F}$ = 277 Hz), 122.6 (q, $^1J_{C\text{-}F}$= 277 Hz), 122.0, 119.6, 119.2, 116.5, 109.4, 61.17 (q, $^2J_{C\text{-}F}$ = 37 Hz), 49.7, 40.7, 34.8, 32.9. **IR (cm$^{-1}$)** 2935, 1753, 1411, 1279, 1162, 976, 703, 664 **HRMS (EI)** m/z: [M$^+$] Calcd for $C_{24}H_{20}BrF_6NO_4$ 579.0478; Found 579.0478

***(12h) bis(2,2,2-trifluoroethyl) 2-(2-(4-bromophenyl)-2-(1-methyl-1H-indol-3-yl)ethyl)malonate*** Following **GP3**, CP **11b** (0.050 g, 0.11 mmol) and 1-methylindole (0.044g, 0.33 mmol) in HFIP (0.4 mL) were subjected to heat for 24 h. The crude material was purified via flash column chromatography 15%EtOAc:85%Hex to collect a clear oil (0.061 g, 95%). Rf = 0.35 (15%EtOAc:85%Hex). **$^1$H NMR (400 MHz, Chloroform-*d*) δ** = 7.45 – 7.37 (m, 3H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.24 – 7.15 (m, 3H), 7.08 – 7.01 (m, 1H), 6.88 (s, 1H), 4.61 – 4.36 (m, 4H), 4.21 (t, *J* = 8.0 Hz, 1H), 3.76 (s, 3H), 3.57 (t, *J* = 7.2 Hz, 1H), 2.86 (dt, *J* = 14.0, 7.6 Hz, 1H), 2.66 (ddd, *J* = 14.0, 8.1, 7.2 Hz, 1H). **$^{19}$F NMR (376 MHz, Chloroform-*d*) δ** = -73.73 (t, *J* = 8.2 Hz, 3F), -73.74 (t, *J* = 7.5 Hz, 3F) **$^{13}$C NMR (101 MHz, CDCl$_3$) δ** = 167.3, 167.2, 142.2, 137.5, 131.9, 129.7, 126.9, 126.4, 122.7 (q, $^1J_{C\text{-}F}$ = 277 Hz), 122.2, 120.7, 119.4, 115.7, 109.5, 61.20 (q, $^2J_{C\text{-}F}$ = 37 Hz), 49.5, 40.1, 34.6, 32.9. **IR (cm$^{-1}$)** 3422**,** 2945, 1754, 1411, 1279, 1162, 976, 701, 664 **HRMS** m/z: [M$^+$] Calcd for $C_{24}H_{20}BrF_6NO_4$ 579.0480; Found 579.0454

***(12i) bis(2,2,2-trifluoroethyl) 2-(2-(1H-indol-3-yl)-2-phenylethyl)malonate*** Following **GP3**, CP **11a** (0.050 g, 0.13 mmol) and indole (0.047g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 24 h. The crude material was purified via flash column chromatography 20%EtOAc:80%Hex to collect a clear oil (0.017 g, 25%). Rf = 0.23 (20%EtOAc:80%Hex). **$^1$H NMR (400 MHz, Chloroform-*d*) δ** = 8.02 (s, br, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.37 – 7.27 (m, 5H), 7.24 – 7.13 (m, 2H), 7.08 – 7.00 (m, 2H), 4.59 – 4.38 (m, 4H), 4.26 (t, *J* = 8.0 Hz, 1H), 3.58 (t, *J* = 7.2 Hz, 1H), 2.90 (dt, *J* = 14.0, 7.5 Hz, 1H), 2.70 (ddd, *J* = 14.0, 8.7, 6.9 Hz, 1H) **$^{19}$F NMR (376 MHz, Chloroform-*d*) δ** = -73.75 (q, *J* = 8.9 Hz) **$^{13}$C NMR (101 MHz, CDCl$_3$) δ** 167.4, 167.3, 142.8, 136.7, 128.8, 128.0, 127.0, 126.7, 122.7 (q, $^1J_{C\text{-}F}$ = 277 Hz), 122.5, 121.5, 119.8, 119.5, 118.2, 111.3, 61.17 (q, $^2J_{C\text{-}F}$ = 37 Hz), 49.7, 40.7, 34.7. **IR (cm$^{-1}$)** 3422, 1752, 1457, 1413, 1281, 1165, 977 **HRMS (EI)** m/z: [M$^+$] Calcd for $C_{23}H_{19}F_6NO_4$ 487.1218; Found 487.1219

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**Supporting Information Available:** $^{1}H$, $^{19}F$ and $^{13}C$ NMR spectra are available all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.


[1] Selected reviews on donor-acceptor cyclopropanes see: a) Pagenkopf, B.L.; Vemula, N. Cycloadditions of Donor–Acceptor Cyclopropanes and Nitriles. *Eur. J. Org. Chem* 2017, *18*, 2561-2567. b) Gharpure, S.J.; Nanda, L.N. Application of Oxygen/Nitrogen Substituted Donor-Acceptor Cyclopropanes in the Total Synthesis of Natural Products. *Tetrahedron Lett.* 2017, *58*, 711-720. c) Cavitt, M.A.; Phun, L.H.; France, S. Intramolecular Donor–Acceptor Cyclopropane Ring-Opening Cyclizations. *Chem. Soc. Rev.* 2014, *43*, 804-818. d) Schneider, T.F.; Kaschel, J.; Werz, D. A New Golden Age for Donor–Acceptor Cyclopropanes. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504-5523 e) Lebold, T.P.; Kerr. M.A. Intramolecular Annulations of Donor–Acceptor Cyclopropanes. *Pure Appl. Chem.* **2010**, *82*, 1797-1812 f) Ming, Y.; Pagenkopf, B.L. Recent Advances in Donor-Acceptor (DA) Cyclopropanes. *Tetrahedron* **2005**, *61*, 321-347.

[2] a) Budynina, E.M.; Ivanov, K.L.; Sorokin, I.D.; Melnikov, M.Y. Ring Opening of Donor–Acceptor Cyclopropanes with N-Nucleophiles. *Synthesis* 2017, *49*, 3035-3068. b) Wales, S.M.; Walker, M.M.; Johnson, J.S. Asymmetric Synthesis of Indole Homo-Michael Adducts via Dynamic Kinetic Friedel–Crafts Alkylation with Cyclopropanes. *Org. Lett.* **2013**, *15*, 2558-2561.

[3] a) Humenny, W.J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr. M.A. Multicomponent Synthesis of Pyrroles from Cyclopropanes: A One-Pot Palladium (0)-Catalyzed Dehydrocarbonylation/Dehydration. *Angew. Chem. Int. Ed.* **2012**, 51, 11088-11091. b) Xiao, J-A.; Li, J.; Xia, P-J.; Zhou, Z-F.; Deng, Z-X.; Xiang, H-Y.; Chen, X-Q.; Yang, H. Diastereoselective Intramolecular [3 + 2]-Annulation of Donor–Acceptor Cyclopropane with Imine-Assembling Hexahydropyrrolo[3,2-*c*]quinolinone Scaffolds. *J. Org. Chem.* **2016**, *81*, 11185-11194. c) Leduc, A.B.; Lebold, T.P.; Kerr, M.A. Synthesis of Tetrahydropyrans from Propargyl Alcohols and 1,1-Cyclopropanediesters: A One-Pot Ring-Opening/Conia-ene Protocol. *J. Org. Chem.* **2009**, *74*, 8414-8416. d) Carson, C.A.; Kerr, M.A. Heterocycles from Cyclopropanes: Applications in Natural Product Synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3051-3060. e) Pohlhaus, P.D.; Sanders, S.D.; Parsons, A.T.; Li, W.; Johnson, J.S. Scope and Mechanism for Lewis Acid-Catalyzed Cycloadditions of Aldehydes and Donor−Acceptor Cyclopropanes: Evidence for a Stereospecific Intimate Ion Pair Pathway. *J. Am. Chem. Soc.* **2008**, *130*, 8642-8650.

[4] Huck, G.K.; Emmet, M.R.; Kerr, M.A. Carbocycles from Donor-Acceptor Cyclopropanes. *Org. Biomol. Chem.* **2015**, *13*, 655-671.

[5] Harrington, P.; Kerr, M.A. The High Pressure Reaction of Cyclopropanes with Indoles Catalyzed by Ytterbium Triflate. *Tetrahedron Lett.* **1997**, *38*, 5949-5952.

[6] Emmett, M.R.; Kerr. M.A. Nuclleophilic Ring Opening of Cyclopropane Hemimalonates Using Internal Brønsted Acid Activation. *Org. Lett.* **2011**, *13*, 4180-4183.

[7] Richmond, E.; Vukovic, V.D.; Moran, J. Nucleophilic Ring Opening of Donor–Acceptor Cyclopropanes Catalyzed by a Brønsted Acid in Hexafluoroisopropanol. *Org. Lett.* **2018**, 20, 574-577.

[8] Choy, J.; Jaime-Figueroa, S.; Jiang, L.; Wagner, P. Novel Practical Deprotection of N-Boc Compounds Using Fluorinated Alcohols. *Synth. Commun.* **2008**, *38*, 3840-3853.

[9] a) Preindl, J.; Chakrabarty, S.; Waser, J. Dearomatization of electron poor six-membered N-heterocycles through [3 + 2] annulation with aminocyclopropanes. *Chem. Sci.* **2017**, *8*, 7112-7118. b) Wang, Z-H.; Zhang, H-H.; Wang, D-M; Xu, P-F.; Luo, Y-C. Lewis acid catalyzed diastereoselective [3+4]-annulation of donor–acceptor cyclopropanes with anthranils: synthesis of tetrahydro-1-benzazepine derivatives. *Chemical Commun.* **2017**, *53*, 8521-8524. c) Laugeois, M.; Ling, J.; Ferard, C.; Michelet, V.; Ratovelomanana-Vidal, V.; Vitale, M. R. Palladium(0)-Catalyzed Dearomative [3 + 2] Cycloaddition of 3-Nitroindoles with Vinylcyclopropanes: An Entry to Stereodefined 2,3-Fused Cyclopentannulated Indoline Derivatives. *Org. Lett.* **2017**, *19*, 2266-2269. d) Curiel Tejeda, J. E.; Irwin, L. C.; Kerr, M. A. Annulation Reactions of Donor–Acceptor Cyclopropanes with (1-Azidovinyl)benzene and 3-Phenyl-2*H*-azirine. *Org. Lett.* **2016**, *18*, 4738-4741 e) Serrano, E.; de Nanteuil, F.; Waser, J. Diester-Substituted Aminocyclopropanes: Synthesis and Use in [3+2] Annulation Reactions. *Synlett* **2014**, *25*, 2285-2288. f) de Nanteuil, F.; Loup, J.; Waser, J. Catalytic Friedel–Crafts Reaction of Aminocyclopropanes. *Org. Lett.* **2013**, *15*, 3738-3741. .

[10] a) Hamel, J-D.; Beaudoin, M.; Cloutier, M.; Paquin, J-F. Hydrogen-Bond-Promoted Friedel–Crafts Reaction of Secondary Propargylic Fluorides: Preparation of 1-Alkyl-1-aryl-2-alkynes. *Synlett* **2017**, *28*, 2823-2828 b) Champagne, P. A.; Benhassine, Y.; Desroches, J.; Paquin, J. F. Friedel–Crafts Reaction of Benzyl Fluorides: Selective Activation of CF Bonds as Enabled by Hydrogen Bonding *Angew. Chem. Int. Ed.* **2014**, *53*, 13835–13839.

[11] Still, W.C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923-2925.

[12] Tolnai, G.L.; Ganss, S.; Brand, J.P.; Waser, J. C2-Selective Direct Alkynylation of Indoles. *Org. Lett.*, **2012**, *15*, 112-115.

[13] Klare, H.F.T.; Oestreich, M.; Ito, J-i.; Nishiyama, H.; Ohki, Y.; Tatsumi, K. Cooperative Catalytic Activation of Si−H Bonds by a Polar Ru−S Bond: Regioselective Low-Temperature C−H Silylation of Indoles under Neutral Conditions by a Friedel−Crafts Mechanism. *J. Am. Chem. Soc.*, **2011**, *133*, 3312–3315.
[14] (a) Johansen, M.B.; Kerr, M.A. Direct Functionalization of Indoles: Copper-Catalyzed Malonyl Carbenoid Insertions. *Org. Lett.* **2010**, *12*, 4956-4959. (b) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. Cycloadditions of Aromatic Azomethine Imines with 1,1-Cyclopropane Diesters. *Org.Lett.* **2008**,*10*, 689.
[15] Dulin, C.C.; Murphy, K.L.; Nolin, K.A. Calcium-catalyzed Friedel-Crafts Addition of 1-methylindole to Activated Cyclopropanes. *Tetrahedron Lett.* **2014**, *55*, 5280-5282.