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Lanthanum(III)-Catalyzed Three-Component Reaction of Coumarin-3-carboxylates for the Synthesis of Indolylmalonamides and Analysis of Their Photophysical Properties

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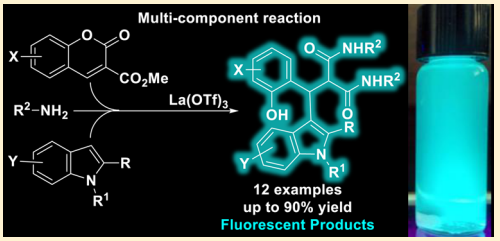
Supporting Information

ABSTRACT: New methodology has been developed for the Lewis acid catalyzed synthesis of malonamides. First, the scandium(III)-catalyzed addition of diverse nucleophiles (e.g., indoles, *N*,*N*-dimethyl-*m*-anisidine, 2-ethylpyrrole, and 2-methylallylsilane) to coumarin-3-carboxylates has been developed to afford chromanone-3-carboxylates in high yields as a single diastereomer. Upon investigating a subsequent lanthanum(III)-catalyzed amidation reaction, a new multicomponent reaction was designed by bringing together coumarin-3-carboxylates with indoles and amines to afford indolylmalonamides, which were identified to exhibit fluorescent properties. The photophysical properties for selected compounds have been analyzed, including quantum yield, molar absorptivity, and Stokes shift. Synthetic studies of several reaction byproducts involved in the network of reaction equilibria for the three-component reaction provide mechanistic insight for the development of this methodology.



INTRODUCTION

Multicomponent reactions (MCRs) are an efficient and powerful tool for organic synthesis.[1−4] MCRs combine three or more building blocks in a single operation for the synthesis of structurally diverse molecules with applications for the discovery of new pharmaceutical leads, agrochemicals, and other useful organic compounds.[5−7] These processes have the advantages of being operationally simple and atom economical and can reduce waste and energy consumption compared to stepwise syntheses. The challenge to develop a successful MCR requires orchestrating a series of reactions that channel into a major product without formation of significant side products.[8] While thermal processes have dominated the history of MCRs, many recent discoveries have been enabled using catalysts to activate new substrates for MCRs and provide high selectivity under mild reaction conditions.[9−15] Examples of catalysts used for MCRs include rare earth salts such as La(OTf)$_3$, CAN, and Yb(OTf)$_3$.[16]

Here we describe the development of a Sc(III)-catalyzed addition of nucleophiles to coumarin-3-carboxylates where we recognized the opportunity to design a La(III)-catalyzed three-component reaction (3CR) involving indoles, amines, and coumarin-3-carboxylates for the synthesis of indolylmalonamides (Figure 1A). Many traditional MCRs utilize imine or isocyanide substrates;[16] however, MCRs incorporating indoles are desirable because these important heterocycles are found in many natural products and medicinally relevant compounds.[17−19] Furthermore, the malonamide motif is useful for various applications in medicinal and industrial chemistry (Figure 1B), including ligands for copper[20] and lanthanides,[21−23] actinide chelators for nuclear waste sequestration,[24−26] and medicinal compounds such as opioid κ agonists[27] and 1,5-benzodiazepinedione derivatives.[28,29]

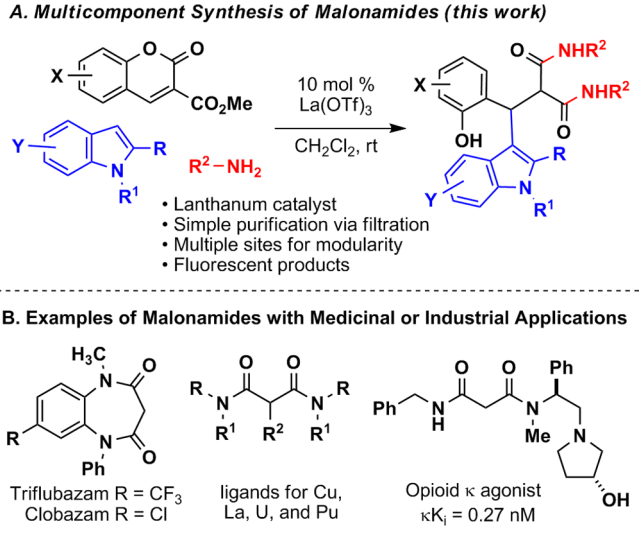


Figure 1. (A) Multicomponent synthesis of malonamides. (B) Examples of malonamides with medicinal or industrial applications.

In addition to these applications, our results presented here also demonstrate the fluorescence properties of indolylmalonamides.

Coumarin-3-carboxylates such as **1** are useful 1,3-dicarbonyl electrophiles; however, they are also challenging substrates that often require longer reaction times and afford products in lower yields compared to related dicarbonyl substrates investigated in methodology development.[30−33] We have previously reported

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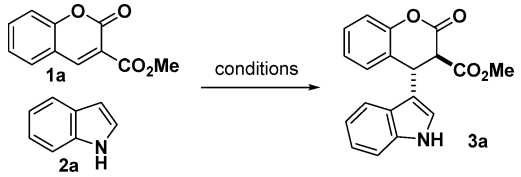
examples of oxazole cyclizations and an allylsilane carboannulation using coumarin-3-carboxylates with Ti(IV) and Sc(III) Lewis acids.[31,32] Two examples of an indole addition to ethyl coumarin-3-carboxylate have been achieved previously, initially using a urea palladacycle catalyst[30] and more recently with $Sc(OTf)_3$/sodium dodecyl sulfate (SDS) in water.[33] Indolylchromanones and other indolylmalonates can be accessed via the three-component Yonemitsu reaction[34,35] of aldehydes, indoles, and Meldrum's acid.[36] Recently, catalyst-free tandem Michael addition/decarboxylation of coumarin-3-carboxylic acid and thiocoumarin-3-carboxylic acid with indole has also been reported.[37] In our studies to expand the utility of coumarin-3-carboxylates, we sought to develop general methodology for the Sc(III)-catalyzed addition of indoles, methallyltrimethylsilane, and *N,N*-dimethyl-*m*-anisidine to coumarin-3-carboxylates and also demonstrate that both esters can be utilized in further transformations that are desirable for medicinal compounds.

RESULTS AND DISCUSSION

In our initial studies for the Sc(III)-catalyzed addition of indoles to methyl coumarin-3-carboxylate, we obtained indolylchromanone **3a** as the thermodynamically favored *trans*[38] diastereomer in 88% yield using dichloromethane with 10 mol % of $Sc(OTf)_3$ as a catalyst (Table 1, entry 1). Solvent, concentration, and temperature were investigated (Table 1, entries 1−4), and conditions with increased concentration and heating to 50 °C improved the reaction rate significantly (54 vs 12 h). Conditions using toluene were selected to accommodate a substrate scope with a wide range of solubilities and melting points. The reaction was effectively catalyzed with other scandium salts ($ScCl_3$) with excellent diastereoselectivity maintained (Table 1, entry 5). The reaction was also catalyzed by other rare earth salts, such as $Y(OTf)_3$. A decrease in product formation was observed within a series of lanthanide catalysts, i.e. Sc > Y > La, correlating with decreasing Lewis acidity[39] (Table 1, entry 2 vs entries 6 and 7).

Table 1. Reaction Optimization for the Addition of Indole to Methyl Coumarin-3-carboxylate[a]



entry	conditions	yield (%)[b,c]
1	$Sc(OTf)_3$, CH_2Cl_2, rt, 54 h[d]	88[e]
2	$Sc(OTf)_3$, PhMe, 50 °C, 12 h	85[e]
3	$Sc(OTf)_3$, neat, rt, 24 h	60
4	$Sc(OTf)_3$, neat, 50 °C, 12 h	81
5	$ScCl_3$, PhMe, 50 °C, 12 h	63
6	$Y(OTf)_3$, PhMe, 50 °C, 12 h	38
7	$La(OTf)_3$, PhMe, 50 °C, 12 h	6
8	$TiCl_4$, PhMe, 50 °C, 12 h	77
9	no catalyst, PhMe, 50 °C, 12 h	0

[a]Reactions performed under argon with 0.1 mmol of coumarin **1a**, 0.3 mmol of indole **2a**, and 0.1 mL of PhMe unless otherwise indicated. Molecular sieves were not necessary when the vial was dried and purged with argon. [b]Determined using ^1H NMR spectroscopy; see Experimental Section for details. [c]Only the *trans*-diastereomer is observed for all reaction conditions. [d]Performed in 0.5 mL of CH_2Cl_2. [e]Isolated yield.

Using $TiCl_4$ resulted in low conversion (Table 1, entry 8). No product was observed in the absence of a Lewis acid (Table 1, entry 9). In general, 3 equiv of indole were optimal for higher yields and lower reaction times. Using either 2 or 1 equiv of indole afforded 83% and 65% yields, respectively. The *trans*-chromanone product was observed as a single diastereomer under all reaction conditions.

The scope of coumarin-3-carboxylate **1** and nucleophiles was examined (Figure 2). The reaction proceeds in good yield with both electron-withdrawing and -donating groups on either coumarin-3-carboxylate (Figure 2, **3g** and **3h**) or indole substrates (Figure 2, **3e** and **3d**). Both *N*-H and *N*-methylindoles were effective nucleophiles (Figure 2, **3a** vs **3c** and **3b** vs **3f**). The reaction of *tert*-butyl coumarin-3-carboxylate also proceeds with no loss of the *tert*-butyl group or decarboxylation observed under the reaction conditions (Figure 2, **3i**). The reactivity observed for

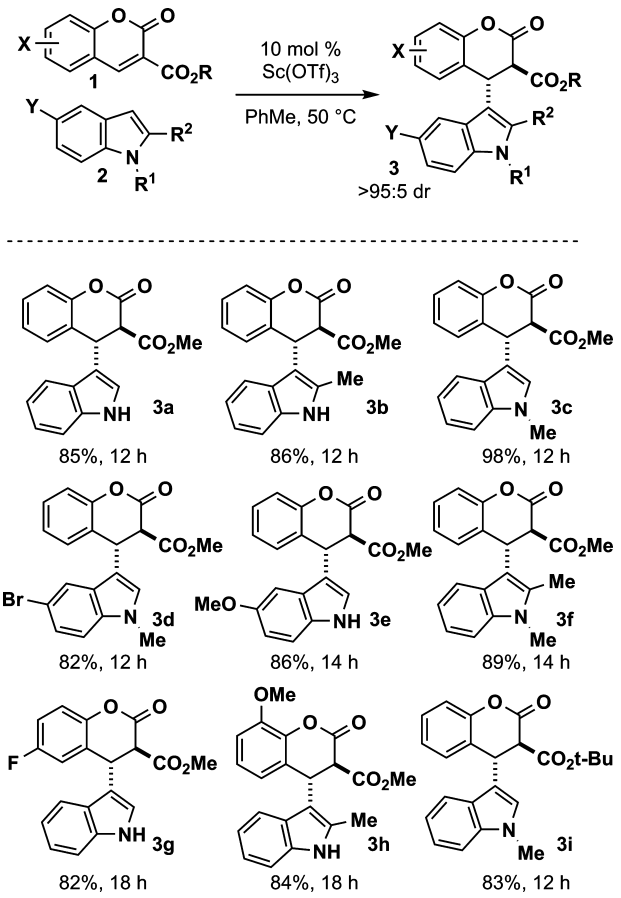


Figure 2. Scope of indole additions to coumarin-3-carboxylates.

indole also applies to other nucleophiles[40] such as 2-methylallyltrimethylsilane, *N,N*-dimethyl-*m*-anisidine, and 2-ethylpyrrole, yielding substituted chromanones **4**, **5**, and **6**, respectively (eqs 1−3). In the case of the methallylsilane, the reaction proceeds rapidly with a 93% yield achieved within 3 h.

We planned to elaborate the chromanone scaffold by transformation of the methyl carboxylate, but instead discovered a novel route to malonamides **7** using La(III)-catalyzed amidation conditions developed by Ohshima and co-workers.[41] Although amidation of the external methyl carboxylate was initially expected to afford chromane-3-carboxamide **8**, we observed amidation of both the exocyclic ester and the chromanone ring to afford malonamide **7a** in 61% yield (eq 4).

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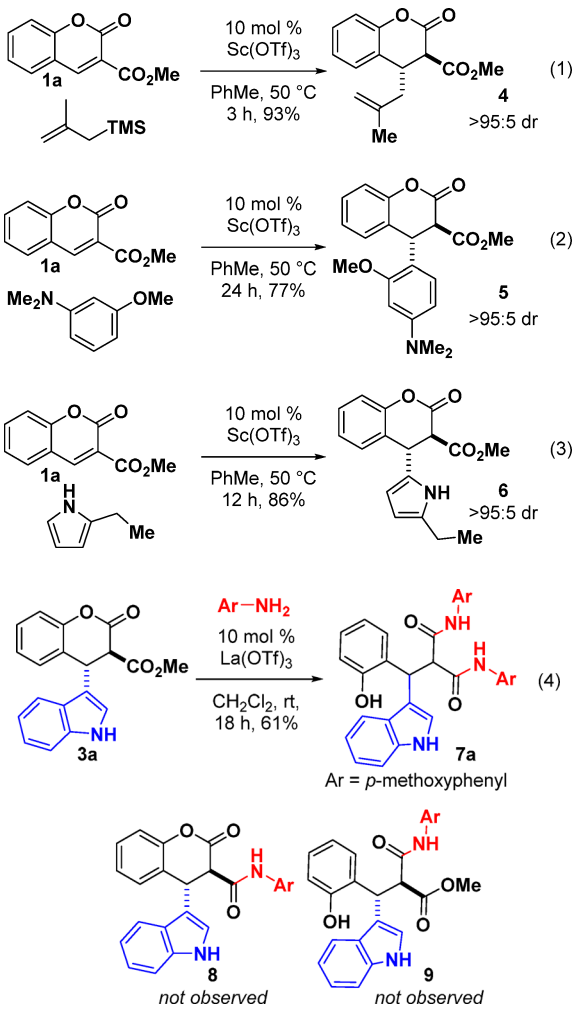


No product resulting from single amidation (e.g., **8** or **9**) was observed (eq 4). Various amines, including ethanolamine, are effective in the amidation reaction to afford highly functionalized malonamides (i.e. **7a** and **10**–**12**) with good yields (Figure 3).

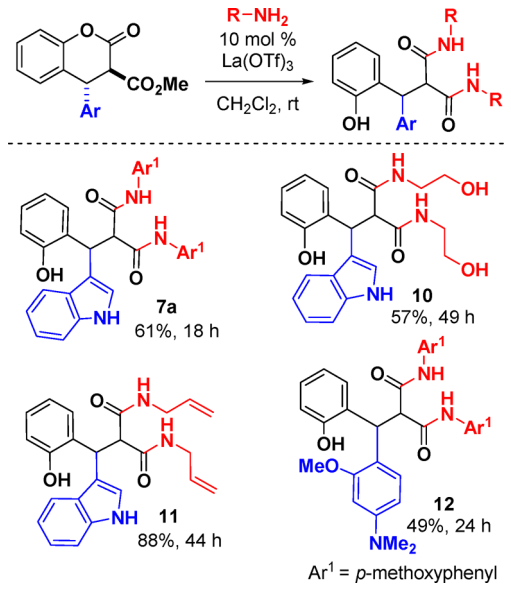
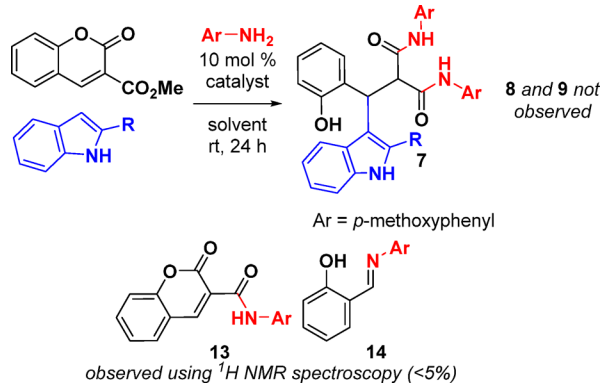


Figure 3. Scope of $La(OTf)_3$-catalyzed amidation to form malonamides.

With the effective amidation of indolylchromanone, we recognized the opportunity to design a new one-pot, three-component process for malonamide synthesis because rare earth catalysts are used for both reactions. Initial investigations using scandium salts as catalysts afforded <5% of the malonamide product, and only starting materials were observed (Table 2, entry 1), attributed to the amine inhibiting the catalytic ability of the scandium Lewis acid in the indole addition to coumarin-3-carboxylate.[41] However, we identified that $La(OTf)_3$ was effective at catalyzing both the indole addition and the amidation in a one-pot, multicomponent reaction to afford the desired indolylmalonamides (Table 2, entries 2 and 3) with minimal side products observed. Amides **8** and **9** were not observed under any conditions; however, the formation of small amounts (<5%) of the coumarin carboxamide (**13**) and imine (**14**) was observed using ^{1}H NMR spectroscopy.[42] A decreased yield was observed for other Lewis acids, such as $Y(OTf)_3$ and $TiCl_4$ (Table 2, entries 4 and 5).

Table 2. Optimization and Solvent Effects for the Malonamide 3CR[a]



entry	R	catalyst	solvent	yield (%)[b]
1	Me	$Sc(OTf)_3$	CH_2Cl_2	<5
2	H	$La(OTf)_3$	CH_2Cl_2	64
3	Me	$La(OTf)_3$	CH_2Cl_2	90
4	Me	$Y(OTf)_3$	CH_2Cl_2	38
5	Me	$TiCl_4$	CH_2Cl_2	39
6	Me	$La(OTf)_3$	PhMe	90
7	Me	$La(OTf)_3$	iPrOH	77
8	Me	$La(OTf)_3$	CH_3CN	74
9	Me	$La(OTf)_3$	THF	70

[a]All reactions performed under argon with 0.1 mmol of coumarin **1a**, 0.3 mmol of indole, 0.3 mmol of amine, 10 mol % of Lewis acid, and 0.1 M solvent for 24 h. [b]Yield determined using ^{1}H NMR spectroscopy with phenylTMS as an internal standard; see Experimental Section for details.

The indolylmalonamide product precipitates in dichloromethane, allowing the product to be collected using simple filtration, which we expect is a key feature in driving the reaction forward. A solvent screen was performed to analyze solvent effects on product yield (Table 2, entries 6–10). The 3CR proceeds in toluene with comparable yield (Table 2, entry 6), and only slight reductions in yield were observed for acetonitrile, tetrahydrofuran, and isopropanol (Table 2, entries 7–9). Due to the precipitation of the malonamide product in CH_2Cl_2 and favorable solubility of any side products and starting materials, the highest yield and purity were observed when the product is isolated from CH_2Cl_2.

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The 3CR tolerates variation on the coumarin and indole components, and both aromatic and alkyl amines could be utilized. The 3CR proceeds in good yields ranging from 47% to 85% with aromatic amines, electron-rich indoles, and coumarin-3-carboxylates (Figure 4). The use of electron-rich indoles favors

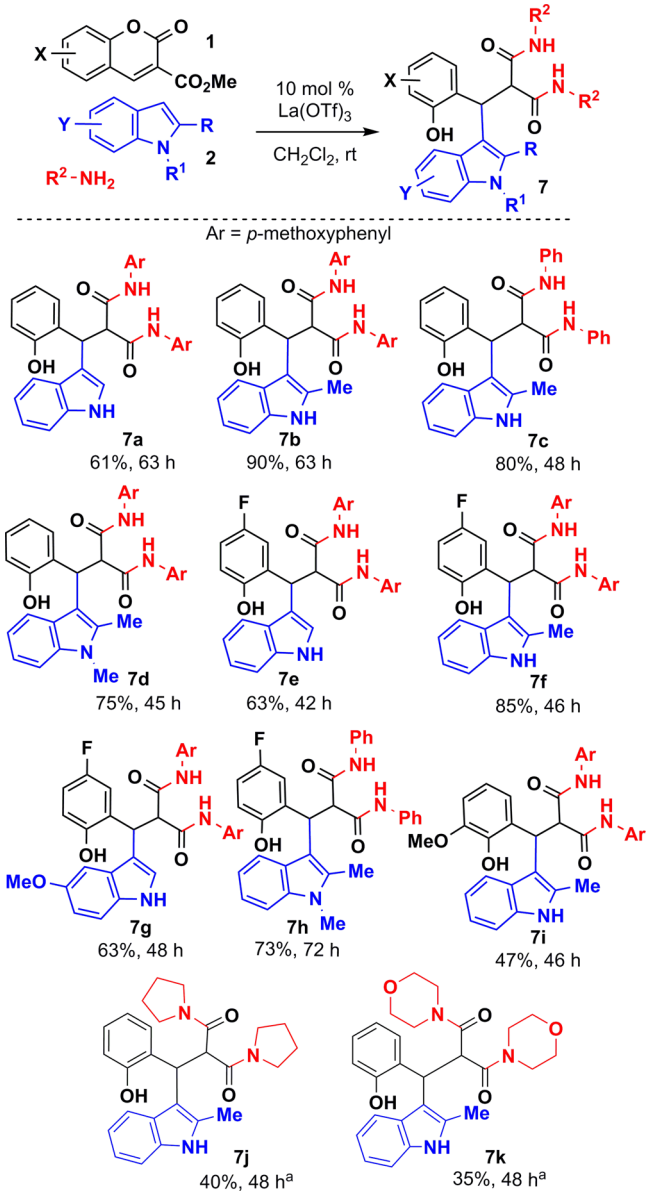
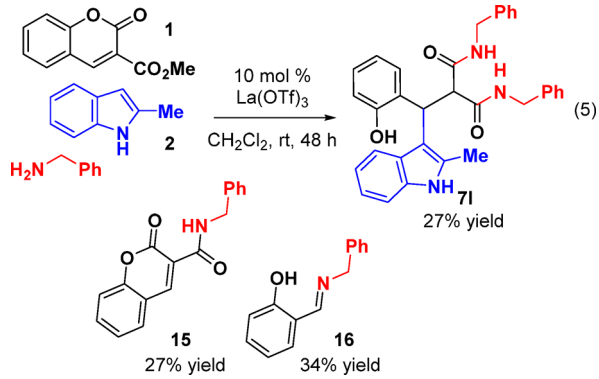


Figure 4. Scope in the multicomponent synthesis of malonamides. [a]Reactions were performed in toluene at 50 °C.

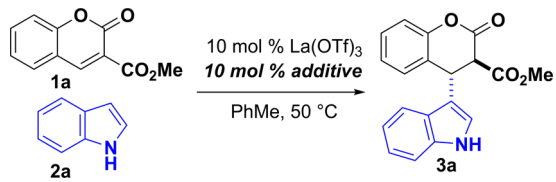
product formation and increases yield by reducing the amount of byproducts observed. Electron-neutral or -poor coumarin-3-carboxylates proceed to give the highest yields, but electron-rich coumarin-3-carboxylates were tolerated (**7i** vs **7b** and **7f**). The highest yields for the 3CR were observed while using aromatic amines such as *p*-anisidine and aniline due to a favorable balance of nucleophilicity (**7c** and **7h**, Figure 4). The 3CR also proceeds with secondary cyclic amines such as pyrrolidine and morpholine (**7j** and **7k**, Figure 4). In these cases, heating to 50 °C was required to attain significant amounts of the desired malonamide. When a primary amine such as benzylamine was employed, malonamide product **7l** was observed, albeit with a lower yield of 27% because significant amounts of benzyl carboxamide **15** and benzyl imine **16** were also formed in the 3CR (eq 5). Dibenzylamine was also tested as a reactant in the 3CR as a comparison; however, malonamide product was observed even with heating to 50 °C (not shown). This amidation reactivity matches the previous report from the Ohshima group, who observed that the lanthanum(III)-catalyzed amidation of esters is sensitive to sterics. When other nucleophiles were investigated in the 3CR, the reaction favored formation of byproducts **13** and **14**, even with very active nucleophiles such as 2-methylallylTMS.



(5)

The success of the La(OTf)$_3$ as a catalyst for this MCR is unexpected based on the fact that this metal salt showed no catalytic activity for the indole conjugate addition (Table 1, 6% with La vs 85% with Sc). The success of lanthanum as a catalyst for this 3CR can be potentially attributed to the importance of atomic radii and coordination number where increasing substrate coordination can enhance catalytic activity.[43] We also hypothesized that there are reaction components, such as the malonamide product or a byproduct (e.g., **13** and **14**), formed during the progress of the reaction that may serve as a ligand to enhance the activity of the lanthanum salt. Coumarin-3-carboxamide **13** and imine **14** were both independently synthesized[44] and investigated as additives to enhance the activity of the lanthanum catalyst for the indole conjugate addition reaction (Table 3). These investigations revealed that addition of 10 mol % of imine **14** to the reaction increases the yield of the indole conjugate addition (6% vs 35%), providing support for the hypothesis that a component formed in the

Table 3. Effect of Additives on Yield of 3[a]



entry	additive	time (h)	yield (%)[b]
1	–	12	6
2	**14**	12	35
3	**13**	12	4
4	**13** + **14**	24	41
5	**7b**	24	7
6	**14** + **7b**	24	31

[a]All reactions performed under argon with 0.1 mmol of coumarin **1a**, 0.3 mmol of indole, 10 mol % of La(OTf)$_3$, and 0.1 M PhMe. [b]Yield determined using ^{1}H NMR spectroscopy for analysis of the unpurified reaction mixture with hexamethylcyclotrisiloxane as an internal standard.

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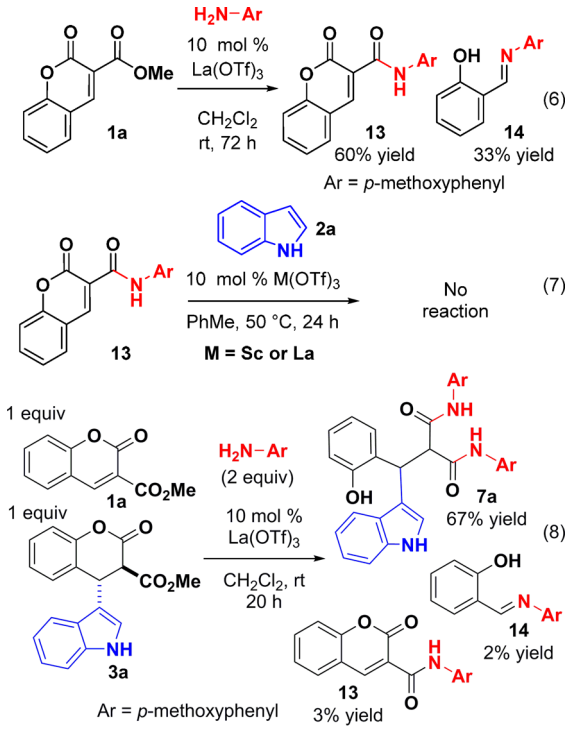
reaction mixture may be acting as a ligand to activate the lanthanum catalyst (Table 3, entry 1 vs 2). The addition of amide **13** or an indolylmalonamide such as **7b** did not increase the yield for the conjugate addition reaction, and combinations with imine **14** did not provide any further increases (Table 3, entries 3–6).[45]

The mechanistic details leading to selective formation of malonamides in the 3CR were investigated. Coumarin-3-carboxamide **13** was independently synthesized and tested as a substrate for the indole addition (eqs 6 and 7). In the absence of



indole, the lanthanum(III)-catalyzed amidation of **1a** proceeds to afford carboxamide **13** in 60% yield, with a significant amount (33% yield) of imine **14** also observed (eq 6). The addition of indole was investigated directly with carboxamide **13**, and no reaction was observed using either scandium or lanthanum catalysts (eq 7). In order to understand the factors leading to the favorable formation of indolylmalonamides over coumarin-3-carboxamide in the 3CR, a competition experiment was performed (eq 8). If both coumarin-3-carboxylate **1a** and indolylchromanone **3a** are present, the amidation of the indolylchromanone is favored over formation of **13** and **14**. This result helps indicate why the 3CR product is observed in much higher yields than **13** and **14**.

The catalytic cycle shown in Figure 5 describes the mechanism for the La(III)-catalyzed synthesis of indolylmalonamides and summarizes the network of competing side pathways for the reactants in the 3CR. The proposed mechanism is initiated by activation of the lanthanum salt upon complexation under the reaction conditions, e.g. with a ligand such as imine **14**. The activation of coumarin-3-carboxylate **1a** occurs upon coordination of $La(OTf)_2$·L to the 1,3-dicarbonyl. Indole addition must proceed faster than amidation because limited quantities of coumarin-3-carboxamide **13** are observed. In the case of less reactive indoles, the yield of malonamide decreases (vide supra) as the amidation reaction begins to compete more effectively with the indole addition pathway. Upon formation of indolylchromanone **3**, consecutive amidation reactions occur at the chromanone ring and exocyclic ester to afford malonamide **7a**. Here amidation favors formation of malonamide products over formation of **13** and **14**. The 3CR requires balance between the relative nucleophilicities of the indole and the amine, where the indole must be sufficiently nucleophilic to out-compete the amidation of the coumarin-3-carboxylate to favor formation of indolylchromanone first. In the case of nonaromatic primary amines with enhanced nucleophilicity, the amidation of **1a** can out-compete the indole addition and a low yield of malonamide is observed. Using ^{19}F and ^{1}H NMR spectroscopy to monitor the reaction shows early formation of product **7** with no accumulation of ester **3** or amide **9**. Peaks associated with coumarin carboxylate **1** are observed to shift and broaden upon addition of catalyst, indicating that complexation and consumption of **1a** occurs immediately. Formation of imine **14** was also observed, albeit as a very broad NMR signal attributed to chelation with the lanthanum salt.

During our studies, we observed that indolylmalonamide products such as **7** have notable fluorescence when exposed to longwave UV light (366 nm) (Figure 6A). We have performed initial studies to evaluate and compare the photophysical properties of chromanone **3a** and malonamides **7b** and **7g**. The excitation and emission spectra show absorption maxima in the range of 262 to 284 nm and maximum emission in the range of 341 to 376 nm, with Stokes shifts corresponding to a range of 79–94 nm (Figure 6, Table 4).[46] A large Stokes shift is often desirable for fluorophores because it can reduce the reabsorption of photons which decrease fluorescence.[47] Favorable molar absorptivities (ε, M^{-1} cm^{-1}) were measured for all compounds. Although the compounds were observed to be fluorescent, the indolylmalonamides exhibited low quantum yields, which we attribute in part to the quenching of the indole fluorescence by adjacent amides.[48] No significant difference in quantum yield was

Table 4. Photophysical Properties of Selected Compounds[a]

compound	solvent	λ_{abs}max (nm)	λ_{em}max (nm)	Stokes shift (nm)	ε[b] (M^{-1} cm^{-1})	Φ
3a	DMSO	284	376	92	2.7×10^3	0.0094
7b	DMSO	266	360	94	3.1×10^4	0.013
7b	MeOH	258	350	92	3.5×10^4	0.0094
7g	DMSO	262	341	79	4.1×10^4	0.018
(L)-Trp[c]	H_2O	278	352	74	3.4×10^3	0.14
indole[c]	H_2O	270	355	85	6.4×10^3	0.47

[a]Absorption intensities and molar absorptivity (ε, M^{-1} cm^{-1}) were measured using UV–vis spectroscopy in the solvent indicated at μM concentrations. Emission intensities and quantum yields (Φ) were determined using a spectrophotometer in the solvent indicated at μM concentrations using (L)-tryptophan in water (Φ = 0.14) as a reference standard.[49] [b]Molar absorptivity (ε, M^{-1} cm^{-1}) was calculated at λ_{abs}max. [c]Literature values included for comparison.[50,49]

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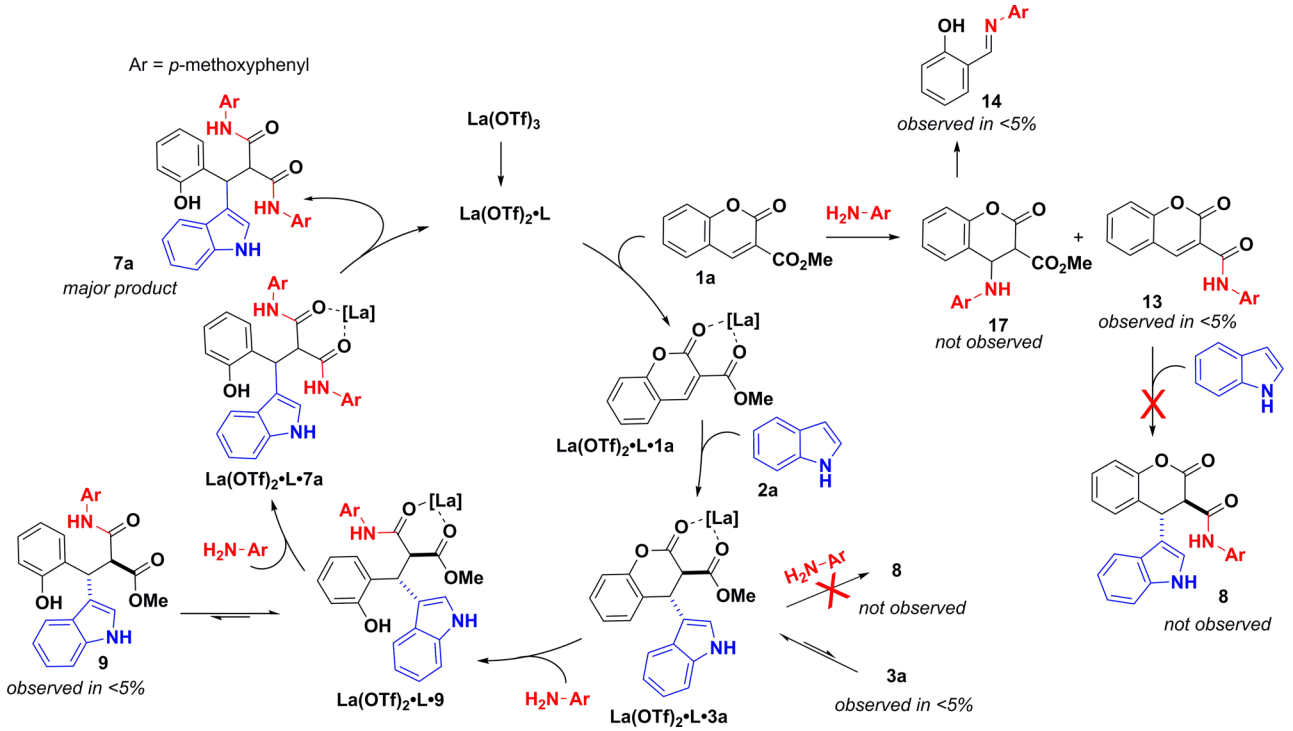

Figure 5. Proposed catalytic cycle and mechanism for the malonamide 3CR.

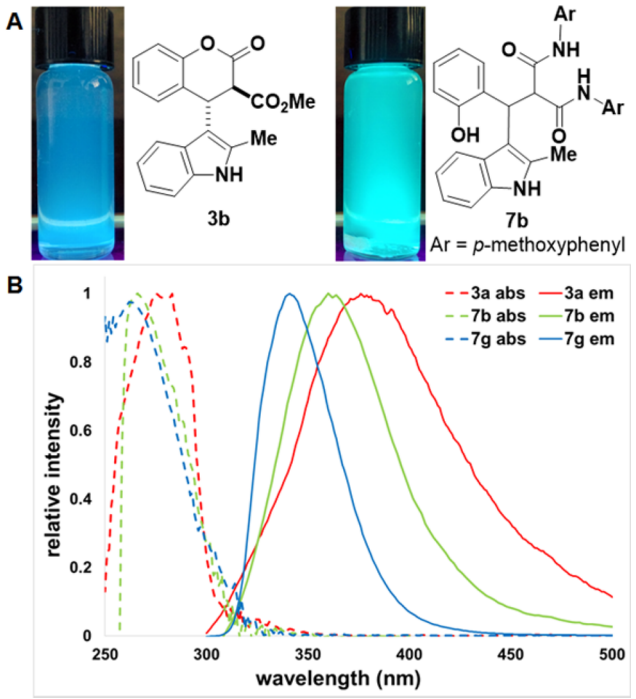

Figure 6. (A) Samples of **3b** and **7b** dissolved in DMSO fluorescing under long-wave UV light (366 nm). (B) Absorption (dashed) and emission (solid) spectra of **3a**, **7b** (in DMSO), and **7g** measured in DMSO or MeOH (see Table 4). Spectra are normalized to the same height at the maximum.

observed during initial investigations of solvent effects (**7b**, DMSO vs MeOH, Table 4).

In addition to indole fluorescence, the aryl malonamide component may contribute to the fluorescent properties, and we hypothesized that small quantities of a tautomer[51] may provide extended conjugation to enhance fluorescence. To assess this hypothesis, N^1,N^3-bis(4-methoxyphenyl)malonamide was synthesized and also observed to be fluorescent under long-wave UV (366 nm). However, we have not observed any evidence that would support formation of the enol tautomer.[52] Using ^{1}H NMR spectroscopy, only the diketo tautomer has been observed for N^1,N^3-bis(4-methoxyphenyl)malonamide and malonamides such as **7**. While the observed fluorescence of N^1,N^3-bis(4-methoxyphenyl)malonamide supports an initial hypothesis for the source of fluorescence, further studies are needed to confirm the structural features that dictate fluorescence.

In conclusion, we have designed a novel lanthanum(III)-catalyzed three-component reaction for the efficient synthesis of indolylmalonamides that demonstrate interesting photophysical properties. The opportunity to develop this 3CR was recognized during the development of stepwise methodology for the scandium-catalyzed addition of nucleophiles to coumarin-3-carboxylates based on the coupling of two rare earth metal-catalyzed reactions. Both the 3CR and the stepwise processes proceed with consecutive amidation of the exocyclic ester and ring-opening amidation of the chromanone for rapid assembly of highly functionalized malonamides. Synthetic studies suggest that an imine byproduct may enhance the catalytic activity of the lanthanum salt in the 3CR. The mechanistic studies and minimal formation of side products showcase the role of a catalyst to orchestrate a series of reactions to discover new MCRs. Selected compounds were analyzed for their photophysical properties including quantum yields (Φ) and molar absorptivity (ε). These compounds exhibit a large Stokes shift and high molar absorptivity which may lend them to useful applications. Enabled by this synthetic methodology, a more detailed study of the structural features responsible for the fluorescent properties of indolylmalonamides is currently underway.

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EXPERIMENTAL SECTION

General Information. Commercially available reagents were obtained from commercial sources and used without further purification unless indicated. *p*-Anisidine was recrystallized from aqueous ethanol and then dried under vacuum at 40 °C for 2 days; other amines were distilled over CaH; 2-methylindole was recrystallized from toluene. Indole starting materials were stored in amber bottles or wrapped in foil. Anhydrous CH_2Cl_2 and PhMe solvents were dispensed from a solvent purification system that passes solvent through two columns of anhydrous neutral alumina. Except for coumarin-3-carboxylate **1b**, all coumarin-3-carboxylate reagents were synthesized according to literature procedures.[53] Lanthanum(III) triflate [$La(OTf)_3$], min. 97%, and scandium(III) chloride [$ScCl_3$] were purchased from Strem Chemicals, Inc. Scandium(III) triflate [$Sc(OTf)_3$], min 97%, was purchased from Strem Chemicals, Inc. or Thermo Fisher Scientific, Inc. $ScCl_3(THF)_3$ was synthesized according to literature procedure.[54] The following abbreviations are used throughout: toluene (PhMe), ethyl acetate (EtOAc), dimethyl sulfoxide (DMSO), diastereomeric ratio (dr), melting point (mp). All reactions were performed in vacuum and heat or flame-dried and Ar-purged glassware (including 8- and 4-mL vials fitted with PTFE closure) unless noted otherwise. 4 Å molecular sieves <50 μm were activated under high vacuum and heating with a heat gun under vacuum for 15 min. All ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature at 600 mHz and 150 mHz, respectively. The ^{1}H spectral data are reported as follows: chemical shift in ppm downfield from tetramethylsilane internal standard, or downfield from tetramethylsilane with the solvent reference employed as the internal standard from DMSO-d_6, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; s, septet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; td, triplet of doublets; and b, broadened), coupling constant (Hz), and integration. ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane with the solvent reference employed as the internal standard (deuterochloroform ($CDCl_3$) at 77.16 ppm or deuterodimethyl sulfoxide (DMSO-d_6) at 39.5 ppm). Infrared spectra were recorded neat on an ATI-FTIR spectrometer.

Compounds were analyzed for HRMS on an orbitrap spectrometer using electrospray ionization in the positive ion mode at >60 000 resolution and using typical ESI source values. These settings result in mass accuracies <5 ppm. Samples were analyzed via flow injection analysis by injecting 5 μL samples into a stream of 50% acetonitrile and 50% aqueous solution of 0.1% formic acid, flowing at 200 μL/min. When indicated, the progress of reactions was monitored by analytical thin layer chromatography using glass or aluminum plates precoated with silica gel 60 F254 and visualized with UV light. Flash chromatography was performed using either silica gel 60 Å (0.035–0.070 mm) or silica gel 150 Å grade 62 (60–200 mesh). Melting points were recorded using an automated melting point apparatus with digital image processing technology (ramp rate of 1 °C/min and melt range of 100–300 °C). Samples were prepared in (1.5–1.8) × 90 mm capillary tubes. The melting points provided are the final melting points recorded by the instrument.

General Procedure for Synthesis of Methyl Coumarin-3-carboxylates. Coumarin-3-carboxylates **1** were synthesized according to literature proceedure.[1] Salicylaldehyde (1.0 equiv, 5.0 mmol), malonate (1.0 equiv, 5.0 mmol), 4-methylpiperidine (0.13 equiv, 0.63 mmol), and acetic acid (1 drop) were combined with 2.5 mL of toluene in a 25 mL round-bottom flask. The solution was heated to reflux with stirring for 12 h. The solution was then cooled to room temperature, allowing the product to crystallize out of solution. The crystalline product was collected by vacuum filtration and washed with 3 × 5 mL of diethyl ether to yield the coumarin-3-carboxylate product; no further purification was required.

*Methyl 6-Fluoro-2-oxo-2H-chromene-3-carboxylate (**1b**).* Prepared from 5-fluorosalicylaldehyde (0.70 g), dimethyl malonate (0.63 mL), 4-methylpiperidine (74 μL), and acetic acid (1 drop) to yield colorless square crystals, mp = 147–149 °C (0.60 g, 54% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.40–7.33 (m, 2H), 7.30 (dd, J = 7.5, 2.7 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.3, 158.7 (d, J^1_{CF} = 245.9 Hz), 156.2, 151.3 (d, J^4_{CF} = 1.7 Hz), 147.9 (d, J^4_{CF} = 2.9 Hz), 122.0 (d, J^2_{CF} = 24.5 Hz), 119.1, 118.5 (d, J^3_{CF} = 8.2 Hz), 118.4 (d, J^3_{CF} = 9.1 Hz), 114.1 (d, J^2_{CF} = 23.8 Hz), 53.0. IR (neat, selected peaks): 3060, 2952, 1733, 1706 cm^{-1}. Exact mass calculated for $C_{11}H_8FO_4$ $[M + H]^+$, 223.0401; found, 223.0410.

General Procedure for the Sc(III)-Catalyzed Synthesis of Indolylchromanones. Coumarin-3-carboxylate **1** (1.0 equiv, 0.20 mmol), indole **2** (3.0 equiv, 0.60 mmol), and 0.2 mL of anhydrous toluene were added to a flame-dried 4 mL vial, followed by the addition of scandium triflate (0.10 equiv, 0.020 mmol). The vial was then purged with Ar and wrapped with parafilm. The mixture was stirred at 50 °C until complete as judged by TLC (1% EtOAc/CH_2Cl_2). Upon completion, the reaction mixture was passed through a plug of silica gel, and the eluent was concentrated in vacuo. The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopic analysis of the unpurified material. The resulting residue was purified via flash column chromatography (gradient of 0% to 2% EtOAc/CH_2Cl_2) to yield the product (**3**) as a colorless foam. Indolylchromanone products change in product appearance (from colorless to red in clear vials), but no degradation was observed after 1 year of storage at ambient temperature.

*Methyl 4-(1H-Indol-3-yl)-2-oxochromane-3-carboxylate (**3a**).* Prepared from methyl coumarin-3-carboxylate (66 mg), indole (0.11 g), scandium triflate (15 mg), and 0.3 mL of dry PhMe for 12 h. The product was isolated as a colorless foam, mp = 180–184 °C (88 mg, 85% yield, >95:5 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.32 (dd, J = 7.4 Hz, 1H), 7.23 (dd, J = 7.6 Hz, 1H), 7.17 (d, J = 8.1 Hz, 1H), 7.15–7.06 (m, 3H), 6.81 (d, J = 2.5 Hz, 1H), 5.06 (d, J = 7.2 Hz, 1H), 4.23 (d, J = 7.2 Hz, 1H), 3.65 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 164.9, 150.7, 136.9, 128.9, 128.7, 125.2, 125.1, 123.8, 123.5, 122.3, 119.6, 118.5, 116.8, 112.2, 111.8, 53.0, 52.9, 36.4. IR (neat, selected peaks): 3389, 2950, 1754, 1731 cm^{-1}. Exact mass calculated for $C_{19}H_{16}NO_4$ $[M + H]^+$, 322.1074; found, 322.1074.

*Methyl 4-(2-Methyl-1H-indol-3-yl)-2-oxochromane-3-carboxylate (**3b**).* Prepared from methyl coumarin-3-carboxylate (62 mg), 2-methylindole (0.12 g), and scandium triflate (18 mg) for 12 h. The product was isolated as a colorless foam, mp = 176–181 °C with decomposition (87 mg, 86% yield, >95:5 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.33–7.27 (m, 2H), 7.17 (dd, J = 8.1, 1.2 Hz, 1H), 7.11 (ddd, J = 8.1, 6.6, 1.6 Hz, 1H), 7.01–6.92 (m, 4H), 6.89 (d, J = 7.8 Hz, 1H), 5.02 (d, J = 12.9 Hz, 1H), 4.23 (d, J = 12.9 Hz, 1H), 3.59 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 165.3, 150.9, 135.7, 134.4, 128.8, 128.6, 126.0, 124.9, 123.9, 121.4, 119.6, 118.9, 116.8, 110.8, 106.1, 52.7, 51.9, 35.2, 11.9. IR (neat, selected peaks): 3390, 2948, 1756, 1732 cm^{-1}. Exact mass calculated for $C_{20}H_{17}NNaO_4^+$ $[M + Na]^+$, 358.1055; found, 358.1060.

*Methyl 4-(1-Methyl-1H-indol-3-yl)-2-oxochromane-3-carboxylate (**3c**).* Prepared from methyl coumarin-3-carboxylate (65 mg), 1-methylindole (0.12 mL), scandium triflate (15 mg), and 0.3 mL of dry PhMe for 12 h. The product was isolated as a yellow solid, mp = 163–165 °C (0.10 g, 98% yield, >95:5 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 1H), 7.35–7.29 (m, 2H), 7.25 (d, J = 7.7 Hz, 1H), 7.19–7.06 (m, 4H), 6.64 (s, 1H), 5.04 (d, J = 6.7 Hz, 1H), 4.21 (d, J = 6.7 Hz, 1H), 3.68 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.7, 164.5, 151.0, 137.6, 129.1, 128.9, 127.6, 125.9, 125.2, 124.0, 122.3, 119.7, 118.8, 117.1, 111.6, 109.9, 53.3, 53.1, 36.5, 32.9. IR (neat, selected peaks): 2951, 1763, 1741, 1585 cm^{-1}. Exact mass calculated for $C_{20}H_{18}NO_4^+$ $[M + H]^+$, 336.1230; found, 336.1227.

*Methyl 4-(5-Bromo-1-methyl-1H-indol-3-yl)-2-oxochromane-3-carboxylate (**3d**).* Prepared from methyl coumarin-3-carboxylate (62 mg), 5-bromo-1-methylindole (0.17 g), scandium triflate (20 mg), and 0.3 mL of dry PhMe for 12 h. The product was isolated as a red solid, mp = 137–137 °C (96 mg, 82% yield, >95:5 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.34–7.29 (m, 2H), 7.16 (d, J = 8.8, 1H), 7.15 (d, J = 8.1, 1H), 7.12–7.07 (m, 2H), 6.64 (s, 1H), 4.96 (d, J = 6.8 Hz, 1H), 4.14 (d, J = 6.8 Hz, 1H), 3.64 (m, 6H, NMe and CO_2Me overlapping). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 164.3, 150.9, 136.2, 129.3, 128.8, 128.7, 127.5, 125.24, 125.20, 123.5, 121.2, 117.1, 113.1, 111.4, 111.2, 53.2, 53.1, 36.2, 33.0. IR (neat, selected peaks): 2918, 1760, 1740, 1558

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cm^{-1}. Exact mass calculated for $C_{20}H_{16}BrNNaO_4$ $[M + Na]^+$, 436.0160; found, 436.0162.

*Methyl 4-(5-Methoxy-1H-indol-3-yl)-2-oxochromane-3-carboxylate (**3e**).* Prepared from methyl coumarin-3-carboxylate (63 mg), 5-methoxyindole (0.14 g), scandium triflate (15 mg), and 0.3 mL of dry PhMe for 14 h. The product was isolated as a colorless solid, mp = 167−168 °C (87 mg, 81% yield, >95:5 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.32 (dd, J = 7.8 Hz, 1H), 7.28 (d, J = 9.5 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 7.10 (dd, J = 7.5 Hz, 1H), 6.92−6.87 (m, 2H), 6.79 (d, J = 2.5 Hz, 1H), 5.01 (d, J = 7.2 Hz, 1H), 4.19 (d, J = 7.2 Hz, 1H), 3.81 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 164.7, 154.4, 151.0, 131.9, 129.2, 128.9, 126.0, 125.2, 123.9, 117.1, 112.8, 112.7, 112.6, 100.9, 56.1, 53.1, 53.0, 36.5. IR (neat, selected peaks): 3375, 2954, 1736, 1585 cm^{-1}. Exact mass calculated for $C_{20}H_{18}NO_5^+$ $[M + H]^+$, 352.1179; found, 352.1177.

*Methyl 4-(1,2-Dimethyl-1H-indol-3-yl)-2-oxochromane-3-carboxylate (**3f**).* Prepared from methyl coumarin-3-carboxylate (1.0 equiv, 0.20 mmol, 41 mg), 1,2-dimethylindole (3.0 equiv, 0.60 mmol, 92 mg), scandium triflate (0.10 equiv, 0.020 mmol, 10 mg), and 0.2 mL of dry PhMe for 14 h. To the crude reaction mixture, 2 mL of methanol were added and the product crashed out of solution. The product was then collected via vacuum filtration to yield **3f** as a colorless crystalline solid, mp = 206−207 °C (62 mg, 89% yield, >95:5 dr). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.41 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 7.7 Hz, 1H), 7.20 (dd, J = 8.1, 0.8 Hz, 1H), 7.08−7.03 (m, 2H), 6.98 (ddd, J = 7.6, 0.8 Hz, 1H), 6.82 (dd, J = 7.5 Hz, 1H), 6.64 (d, J = 7.6 Hz, 1H), 5.06 (d, J = 13.3 Hz, 1H), 4.64 (d, J = 13.3 Hz, 1H), 3.70 (s, 3H), 3.50 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.9, 165.4, 150.7, 136.9, 136.5, 128.5, 127.8, 124.8, 124.7, 124.4, 120.3, 118.9, 118.5, 116.4, 109.5, 104.7, 52.2, 51.4, 34.6, 29.5, 10.0. IR (neat, selected peaks): 2958, 1760, 1742, 1610 cm^{-1}. Exact mass calculated for $C_{21}H_{20}NO_4$ $[M + H]^+$, 350.1387; found, 350.1382.

*Methyl 6-Fluoro-4-(1H-indol-3-yl)-2-oxochromane-3-carboxylate (**3g**).* Prepared from methyl 6-fluoro-coumarin-3-carboxylate (68 mg), indole (0.11 g), scandium triflate (19 mg), and 0.3 mL dry PhMe for 18 h. The product was isolated as a colorless foam, mp = 151−152 °C (85 mg, 82% yield, >95:5 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.45 (dd, J = 8.0, 0.7 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.23 (ddd, J = 8.2, 7.2, 1.0 Hz, 1H), 7.14−7.10 (m, 2H), 7.00 (ddd, J = 8.4, 3.0 Hz, 1H), 6.84−6.79 (m, 2H), 5.01 (d, J = 7.7 Hz, 1H), 4.20 (d, J = 7.7 Hz, 1H), 3.64 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 164.4, 159.5 (d, J^1_{CF} = 244.7 Hz), 146.9 (d, $J J^4_{CF}$ = 2.6 Hz), 136.8, 125.2, 123.3, 122.9, 120.3, 118.7, 125.9 (d, J^3_{CF} = 7.8 Hz), 118.4 (d, J^3_{CF} = 8.5 Hz), 116.0 (d, J^2_{CF} = 23.7 Hz), 115.4 (d, J^2_{CF} = 24.6 Hz), 112.1, 111.9, 53.2, 52.7, 36.5. IR (neat, selected peaks): 3413, 2952, 1758, 1732 cm^{-1}. Exact mass calculated for $C_{19}H_{15}FNO_4$ $[M + H]^+$, 340.0980; found, 340.0982.

*Methyl 4-(1H-Indol-3-yl)-8-methoxy-2-oxochromane-3-carboxylate (**3h**).* Prepared from methyl 8-methoxy-coumarin-3-carboxylate (73 mg), indole (0.13 mg), scandium triflate (16 mg), and 0.3 mL of dry PhMe for 18 h. The product was isolated as a colorless solid, mp = 197−200 °C (97 mg, 85% yield, >95:5 dr). ^{1}H NMR (600 MHz, $CDCl_3$-*d*) δ 8.16 (s, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.09 (dd, J = 7.5 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.95−6.87 (m, 3H), 6.45 (d, J = 7.1 Hz, 1H), 5.00 (d, J = 12.9 Hz, 1H), 4.24 (d, J = 12.9 Hz, 1H), 3.92 (s, 3H), 3.54 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 164.4, 147.5, 140.1, 135.7, 134.4, 126.1, 125.2, 124.6, 121.3, 119.9, 119.5, 118.8, 111.5, 110.8, 106.2, 56.2, 52.6, 51.7, 35.3, 11.9. IR (neat, selected peaks): 3342, 2953, 1762, 1745 cm^{-1}. Exact mass calculated for $C_{21}H_{20}NO_5$ $[M + H]^+$, 366.1336; found, 366.1341.

*tert-Butyl 4-(1-Methyl-1H-indol-3-yl)-2-oxochromane-3-carboxylate (**3i**).* Prepared from *tert*-butyl coumarin-3-carboxylate (76 mg), 1-methylindole (0.12 mL), scandium triflate (16 mg), and 0.3 mL of dry PhMe for 12 h. The product was isolated as a white solid, mp = 130−131 °C (96 mg, 83% yield, >95:5 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 7.9 Hz, 1H), 7.31 (dd, J = 7.7 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.24 (dd, J = 7.5 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.18−7.11 (m, 2H), 7.09 (dd, J = 7.4 Hz, 1H), 6.56 (s, 1H), 4.95 (d, J = 5.2 Hz, 1H), 4.10 (d, J = 5.2 Hz, 1H), 3.62 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 165.0, 151.4, 137.5, 129.0, 128.8, 127.3, 126.0, 124.9, 124.3, 122.3, 119.6, 118.7, 116.9, 111.9, 109.8, 83.2, 54.5, 37.3, 32.8, 27.6. IR (neat, selected peaks): 2940, 1772, 1759, 1719 cm^{-1}. HRMS (ESI) mass calculated for $C_{23}H_{24}NO_4$ $[M + H]^+$, 378.1700; found, 378.1693.

*Methyl 4-(2-Methylallyl)-2-oxochromane-3-carboxylate (**4**).* Prepared from coumarin-3-carboxylate (41 mg), methallyltrimethylsilane (0.10 mL), scandium triflate (10 mg), and 0.3 mL of dry PhMe for 3 h. The product was isolated as a white solid, mp = 146−150 °C (49 mg, 93% yield, >95:5 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (ddd, J = 8.2, 7.7, 1.2 Hz, 1H), 7.19 (dd, J = 7.7, 1.2 Hz, 1H), 7.11 (ddd, J = 7.7 1.1 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 4.92 (s, 1H), 4.72 (s, 1H), 3.87 (d, J = 1.8 Hz, 1H), 3.60 (s, 3H), 3.56 (ddd, J = 10.4, 5.9, 1.8 Hz, 1H), 2.31 (dd, J = 14.1, 5.9 Hz, 1H), 2.19 (dd, J = 14.1, 10.4 Hz, 1H), 1.78 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.9, 164.0, 150.7, 140.6, 129.0, 128.5, 125.0, 124.1, 117.1, 115.2, 53.2, 50.4, 43.3, 37.8, 22.1. IR (neat, selected peaks): 2961, 2912, 1772, 1734 cm^{-1}. Exact mass calculated for $C_{15}H_{17}O_4^+$ $[M + H]^+$, 261.1121; found, 261.1120.

*Methyl 4-(4-(Dimethylamino)-2-methoxyphenyl)-2-oxochromane-3-carboxylate (**5**).* Prepared from coumarin-3-carboxylate **1a** (65 mg), *N*,*N*-dimethyl-*m*-anisidine (0.13 mL), scandium triflate (18 mg), and 0.3 mL of dry PhMe for 24 h. The product was isolated as a white solid, mp = 158−160 °C (87 mg, 77% yield, >95:5 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (ddd, J = 7.9, 6.9, 1.6 Hz, 1H), 7.11 (dd, J = 8.2, 1.0 Hz, 1H), 7.07 (ddd, J = 7.5, 1.1 Hz, 1H), 7.02 (dd, J = 7.6, 1.2 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 6.24 (d, J = 2.4 Hz, 1H), 6.18 (dd, J = 8.5, 2.4 Hz, 1H), 4.88 (d, J = 5.9 Hz, 1H), 4.19 (d, J = 5.9 Hz, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 2.93 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 164.8, 157.7, 151.6, 151.1, 129.3, 128.6, 128.5, 124.8, 124.1, 116.6, 113.8, 104.5, 96.0, 55.0, 52.8, 52.0, 40.4, 39.4. IR (neat, selected peaks): 2953, 2933, 1765, 1739 cm^{-1}. Exact mass calculated for $C_{20}H_{22}NO_4^+$ $[M + H]^+$, 356.1492; found, 356.1495.

*Methyl 4-(5-Ethyl-1H-pyrrol-2-yl)-2-oxochromane-3-carboxylate (**6**).* Prepared from methyl coumarin-3-carboxylate (59.3 mg), 2-ethylpyrrole (95 mg), scandium triflate (15 mg), and 0.3 mL of dry PhMe for 12 h. The product was isolated as a brown oil (74.6 mg, 73% yield, >95:5 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.31 (ddd, J = 8.0, 1.7 Hz, 1H), 7.18 (dd, J = 7.6, 1.3 Hz, 1H), 7.14 (dd, J = 7.4, 1.0 Hz, 1H), 7.11 (dd, J = 8.0, 0.8 Hz, 3H), 5.85 (dd, J = 3.0 Hz, 1H), 5.81 (dd, J = 3.0 Hz, 1H), 4.71 (d, J = 6.9 Hz, 1H), 4.03 (d, J = 6.9 Hz, 1H), 3.66 (s, 3H), 2.54 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 164.2, 150.8, 135.2, 129.4, 128.5, 126.0, 125.3, 123.3, 117.3, 107.1, 105.1, 53.2, 53.0, 38.2, 20.9, 13.5. IR (neat, selected peaks): 3457, 2948, 1763 1742 cm^{-1}. Exact mass calculated for $C_{17}H_{18}NO_4^+$ $[M + H]^+$, 300.1230; found, 300.1240.

General Procedure for the Preparation of Indolylmalonamides from Indolylchromanones. Indolylchromanone **3** (1.0 equiv), amine (3.0 equiv), and CH_2Cl_2 (1.0 M) were added to a flame-dried 4 mL vial, followed by the addition of lanthanum triflate (0.10 equiv). The vial was then purged with Ar and wrapped in parafilm. The mixture stirred at room temperature until the indolylchromanone **3** was judged to be consumed according to TLC (1% EtOAc/CH_2Cl_2). The solids were collected via vacuum filtration on grade 1 Whatman filter paper and washed with 3 × 2 mL of CH_2Cl_2 to isolate the indolylmalonamide **7** as a colorless solid; no further purification was typically required.

*N^1,N^3-Bis(2-hydroxyethyl)-2-((2-hydroxyphenyl)(1H-indol-3-yl)-methyl)malonamide (**10**).* Prepared from **3a** (1.0 equiv, 0.22 mmol, 50 mg), ethanolamine (3.0 equiv, 0.66 mmol, 9.6 μL), lanthanum triflate (0.050 equiv, 0.010 mmol, 5.1 mg), and 0.2 mL CH_2Cl_2. After 49 h, the product was isolated as a colorless solid, mp = 200−206 °C with decomposition (38 mg, 57% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.72 (s, 1H), 9.31 (s, 1H), 8.05 (t, J = 5.5 Hz, 1H), 7.62−7.56 (m, 2H), 7.31 (s, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 6.98 (dd, J = 7.5 Hz, 1H), 6.91−6.84 (m, 2H), 6.71 (d, J = 8.1 Hz, 1H), 6.63 (dd, J = 7.5 Hz, 1H), 5.23 (d, J = 12.3 Hz, 1H), 4.63 (t, J = 5.5 Hz, 1H), 4.27 (d, J = 12.3 Hz, 1H), 3.40 (s, 1H), 3.27−2.91 (m, 8H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.3, 168.7, 154.8, 136.2, 129.5, 127.4, 127.0, 122.1, 121.1, 119.5, 119.1, 118.4, 116.9, 115.7, 111.4, 60.1, 59.9, 58.5, 41.9, 41.7, 36.0. IR (neat, selected peaks): 3332, 3266, 2878, 1653, 1580 cm^{-1}. Exact mass calculated for $C_{22}H_{26}N_3O_5^+$ $[M + H]^+$, 412.1867; found, 412.1867.

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*N^1,N^3-Diallyl-2-((2-hydroxyphenyl)(1H-indol-3-yl)methyl)-malonamide (**11**).* Prepared from **3a** (1.0 equiv, 0.42 mmol, 0.13 g), allylamine (3.0 equiv, 1.3 mmol, 72 mg), lanthanum triflate (0.010 equiv, 0.021 mmol, 12 mg), and CH_2Cl_2 (0.5 mL). After 26 h, the reaction mixture was purified via flash column chromatography (gradient of 20% to 75% EtOAc/CH_2Cl_2, followed by a gradient of 0% to 10% MeOH/CH_2Cl_2) to yield **11** as a pink chalky solid, mp = 183−184 °C (0.14 g, 88% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.74 (s, 1H), 9.37 (s, 1H), 8.11 (t, J = 5.8 Hz, 1H), 7.64 (t, J = 5.8 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.20 (dd, J = 7.6, 1.0 Hz, 1H), 6.98 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 6.90−6.85 (m, 2H), 6.70 (dd, J = 8.0, 1.0 Hz, 1H), 6.63 (ddd, J = 7.5, 1.1 Hz, 1H), 5.65−5.50 (m, 2H), 5.28 (d, J = 12.3 Hz, 1H), 4.92−4.87 (m, 3H), 4.84 (dq, J = 17.2, 1.8 Hz, 1H), 4.35 (d, J = 12.3 Hz, 1H), 3.62−3.55 (m, 3H), 3.51 (dtt, J = 16.3, 5.4, 1.8 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 168.6, 168.1, 154.4, 135.9, 134.9, 134.8, 129.2, 129.1, 126.9, 126.6, 121.7, 120.8, 119.1, 118.8, 118.0, 116.5, 115.5, 114.7, 111.1, 58.4, 40.89, 40.86, 35.2. IR (neat, selected peaks): 3695, 2947, 1737, 1610 cm^{-1}. Exact mass calculated for $C_{24}H_{25}N_3NaO_3^+$ $[M + Na]^+$, 426.1794; found, 426.1792

*2-((4-(Dimethylamino)-2-methoxyphenyl)(2-hydroxyphenyl)-methyl)-N^1,N^3-bis(4-methoxyphenyl)malonamide (**12**).* Prepared from **5** (1.0 equiv, 0.14 mmol, 51 mg), *p*-anisidine (3.0 equiv, 0.43 mmol, 54 mg), lanthanum triflate (0.010 equiv, 0.014 mmol, 8.2 mg), and CH_2Cl_2 (0.15 mL). After 24 h, the reaction mixture was purified via flash column chromatography (gradient of 10% to 75% EtOAc/CH_2Cl_2 with 0.1% triethylamine) to yield **12** a colorless chalky solid, mp = 165−167 °C (40 mg, 49% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.67 (s, 1H), 9.63 (s, 1H), 9.18 (s, 1H), 7.39 (d, 2H), 7.36 (dd, J = 8.0, 1.4 Hz, 1H), 7.33 (d, J = 9.0 Hz, 2H), 7.31 (d, J = 3.8 Hz, 1H), 6.88 (ddd, J = 7.8, 1.5 Hz, 1H), 6.86−6.78 (m, 4H), 6.68−6.62 (m, 2H), 6.18 (dd, J = 8.6, 2.3 Hz, 1H), 6.15 (s, 1H), 5.25 (d, J = 12.3 Hz, 1H), 4.75 (d, J = 12.3 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.67 (s, 3H), 2.80 (s, 6H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.5, 166.3, 157.8, 155.4, 155.3, 155.0, 150.2, 150.1, 132.0, 131.8, 129.6, 129.4, 129.3, 128.3, 126.6, 121.0, 120.7, 120.6, 118.3, 117.8, 115.3, 113.9, 113.82, 113.80, 104.1, 96.6, 58.1, 55.3, 55.2, 40.3, 39.0. IR (neat, selected peaks): 3298, 3240, 1677, 1646 cm^{-1}. Exact mass calculated for $C_{33}H_{36}N_3O_6^+$ $[M + H]^+$, 570.2599; found, 570.2597.

General Procedure for the La(OTf)$_3$-Catalyzed 3CR Synthesis of Indolylmalonamides. Coumarin-3-carboxylate **1** (1.0 equiv, 0.20 mmol), indole **2** (3.0 equiv, 0.60 mmol), amine (3.0 equiv, 0.60 mmol), and CH_2Cl_2 (0.2 mL) were added to a flame-dried 4 mL vial, followed by the addition of lanthanum triflate (0.10 equiv, 0.020 mmol). The vial was then purged with Ar, and the mixture was stirred at room temperature until the coumarin-3-carboxylate was consumed by TLC (1% EtOAc/CH_2Cl_2). The solids were collected via vacuum filtration on grade 1 Whatman filter paper and washed with 3 × 2 mL of CH_2Cl_2 to isolate the indolylmalonamide **7** as a colorless solid; no further purification was typically required.

*2-((2-Hydroxyphenyl)(1H-indol-3-yl)methyl)-N^1,N^3-bis(4-methoxyphenyl)malonamide (**7a**).* Prepared from methyl coumarin-3-carboxylate (41 mg), indole (74 mg), *p*-anisidine (75 mg), lanthanum triflate (12 mg), and 0.2 mL CH_2Cl_2. After 63 h the product was isolated as a colorless solid, mp = 184−191 °C with decomposition (65 mg, 61% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.74 (s, 1H), 10.06 (s, 1H), 9.52 (s, 1H), 9.35 (s, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 2.2 Hz, 1H), 7.39 (ddd, J = 9.8, 2.6 Hz, 2H), 7.32−7.28 (m, 3H), 7.22 (d, J = 8.1 Hz, 1H), 6.97 (dd, J = 7.5 Hz, 1H), 6.90−6.83 (m, 2H), 6.81 (d, J = 5.5 Hz, 2H), 6.79 (d, J = 5.5 Hz, 2H), 6.68 (d, J = 7.6 Hz, 1H), 6.64 (dd, J = 7.4 Hz, 1H), 5.45 (d, J = 12.3 Hz, 1H), 4.62 (d, J = 12.3 Hz, 1H), 3.67 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.9, 166.1, 155.5, 155.4, 154.6, 135.9, 131.9, 131.6, 129.4, 128.6, 128.9, 126.9, 121.7, 121.3, 120.9, 120.8, 119.0, 118.9, 118.2, 116.2, 115.5, 113.83, 113.79, 111.2, 59.9, 55.19, 55.17, 36.1. IR (neat, selected peaks): 3404, 3359, 2952, 1542 cm^{-1}. Exact mass calculated for $C_{32}H_{29}N_3NaO_5^+$ $[M + Na]^+$, 558.2005; found, 558.1996.

*2-((2-Hydroxyphenyl)(2-methyl-1H-indol-3-yl)methyl)-N^1,N^3-bis-(4-methoxyphenyl)malonamide (**7b**).* Prepared from methyl coumarin-3-carboxylate (41 mg), 2-methylindole (79 mg), *p*-anisidine (75 mg), lanthanum triflate (12 mg), and 0.2 mL CH_2Cl_2. After 63 h, the product was isolated as a pink solid, mp = 170−172 °C with decomposition (0.10 g, 90% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.61 (s, 1H), 10.11 (s, 1H), 9.38 (s, 1H), 9.33 (s, 1H), 7.79 (d, J = 6.7 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.2 Hz, 1H), 6.96−6.84 (m, 5H), 6.80 (d, J = 8.9 Hz, 2H), 6.75 (dd, J = 7.5 Hz, 1H), 6.69 (d, J = 7.9 Hz, 1H), 5.38 (d, J = 12.5 Hz, 1H), 4.91 (d, J = 12.5 Hz, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.6, 166.0, 155.4, 155.3, 155.0, 135.2, 133.1, 131.9, 131.6, 128.7, 127.1, 126.4, 120.9, 120.7, 119.2, 118.8, 118.2, 117.7, 115.1, 113.9, 113.8, 113.7, 110.4, 109.5, 57.7, 55.2, 55.1, 55.1, 35.8, 12.1. IR (neat, selected peaks): 3326, 3392, 1656, 1628 cm^{-1}. Exact mass calculated for $C_{33}H_{32}N_3O_5$ $[M + H]^+$, 550.2336; found, 550.2362.

*2-((2-Hydroxyphenyl)(2-methyl-1H-indol-3-yl)methyl)-N^1,N^3-diphenylmalonamide (**7c**).* Prepared from methyl coumarin-3-carboxylate (41 mg), 2-methylindole (79 mg), aniline (56 mL), lanthanum triflate (12 mg), and 0.2 mL of CH_2Cl_2. After 48 h, the product was isolated as a colorless solid, mp = 188−190 °C with decomposition (61 mg, 80% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.59 (s, 1H), 10.21 (s, 1H), 9.50 (s, 1H), 9.33 (s, 1H), 7.82−7.72 (m, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.29 (dd, J = 7.8 Hz, 2H), 7.21 (dd, J = 7.8 Hz, 2H), 7.16−7.10 (m, 1H), 7.04 (dd, J = 7.4 Hz, 1H), 6.98 (dd, J = 7.3 Hz, 1H), 6.94−6.80 (m, 3H), 6.72 (dd, J = 7.4 Hz, 1H), 6.66 (d, J = 7.9 Hz, 1H), 5.38 (d, J = 12.4 Hz, 1H), 4.98 (d, J = 12.4 Hz, 1H), 2.52 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.8, 166.2, 155.0, 138.7, 138.4, 135.2, 133.2, 128.8, 128.69, 128.67, 127.1, 126.4, 123.6, 123.5, 119.4, 119.24, 119.19, 118.8, 118.3, 117.8, 115.2, 113.9, 110.4, 109.4, 57.9, 35.7, 12.2. IR (neat, selected peaks): 3412, 3369, 1667, 1637 cm^{-1}. Exact mass calculated for $C_{31}H_{28}N_3O_3$ $[M + H]^+$, 490.2125; found, 490.2160.

*2-((1,2-Dimethyl-1H-indol-3-yl)(2-hydroxyphenyl)methyl)-N^1,N^3-bis(4-methoxyphenyl)malonamide (**7d**).* Prepared from methyl coumarin-3-carboxylate (1.0 equiv, 0.30 mmol, 63 mg), 1,2-dimethylindole (6.0 equiv, 0.90 mmol, 0.13 g), *p*-anisidine (3.0 equiv, 0.90 mmol, 0.12 g), lanthanum triflate (22 mg), and 0.3 mL of CH_2Cl_2. After 45 h, the product was isolated as a colorless solid, mp = 169−170 °C with decomposition (0.13 g, 75% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.09 (s, 1H), 9.38 (s, 1H), 9.30 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 9.0 Hz, 2H), 7.24 (d, J = 8.1 Hz, 1H), 6.96 (dd, J = 7.5 Hz, 1H), 6.92 (dd, J = 7.5 Hz, 1H), 6.88−6.83 (m, 3H), 6.78 (d, J = 9.0 Hz, 2H), 6.70 (dd, J = 7.5 Hz, 1H), 6.63 (d, J = 7.9 Hz, 1H), 5.38 (d, J = 12.5 Hz, 1H), 4.89 (d, J = 12.5 Hz, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.54 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.0, 166.3, 155.9, 155.7, 155.4, 136.7, 135.1, 132.3, 132.0, 129.1, 127.5, 126.9, 121.4, 121.2, 121.1, 119.8, 119.5, 118.6, 118.4, 115.6, 114.4, 114.2, 110.0, 109.4, 58.2, 55.6, 55.5, 36.5, 29.7, 11.1. IR (neat, selected peaks): 3312, 3268, 2950, 1672 cm^{-1}. Exact mass calculated for $C_{34}H_{34}N_3O_5$ $[M + H]^+$, 564.2493; found, 564.2511.

*2-((5-Fluoro-2-hydroxyphenyl)(1H-indol-3-yl)methyl)-N^1,N^3-bis(4-methoxyphenyl)malonamide (**7e**).* Prepared from methyl 6-fluoro coumarin-3-carboxylate (44 mg), indole (70 mg), *p*-anisidine (74 mg), lanthanum triflate (11 mg), and 0.2 mL of CH_2Cl_2. After 42 h, the product was isolated as a colorless solid, mp = 185−188 °C (69 mg, 63% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.80 (s, 1H), 10.09 (s, 1H), 9.57 (s, 1H), 9.48 (s, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 2.1 Hz, 1H), 7.43 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 8.9 Hz, 2H), 7.28 (d, J = 8.1 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.02 (dd, J = 7.5 Hz, 1H), 6.95 (dd, J = 7.5 Hz, 1H), 6.85 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 6.76−6.68 (m, 2H), 5.50 (d, J = 12.2 Hz, 1H), 4.65 (d, J = 12.2 Hz, 1H), 3.69 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.6, 165.9, 155.6, 155.5, 155.3 (d, J^1_{CF} = 233.5 Hz), 151.0, 135.9, 131.9, 131.5, 130.3 (d, J^3_{CF} = 6.3 Hz), 126.8, 121.9, 121.4, 121.0, 120.9, 118.9, 118.3, 116.2 (d, J^3_{CF} = 8.0 Hz), 115.4 (d, J^2_{CF} = 20.5 Hz), 114.6, 113.81, 113.80, 113.2 (d, J^2_{CF} = 22.4 Hz), 111.3, 59.6, 55.20, 55.18, 36.1. IR (neat, selected peaks): 3346, 3194, 1670, 1644 cm^{-1}. Exact mass calculated for $C_{32}H_{29}FN_3O_5$ $[M + H]^+$, 554.2086; found, 554.2097.

*2-((5-Fluoro-2-hydroxyphenyl)(2-methyl-1H-indol-3-yl)methyl)-N^1,N^3-bis(4-methoxyphenyl)malonamide (**7f**).* Prepared from methyl 6-fluoro coumarin-3-carboxylate **1** (1.0 equiv, 0.5 mmol, 0.11 g), 2-methylindole (3.0 equiv, 1.5 mmol, 0.20 g), *p*-anisidine (3.0 equiv, 1.5 mmol, 0.19 g), lanthanum triflate (0.1 equiv, 0.050 mmol, 29 mg), and

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0.5 mL CH_2Cl_2. After 46 h, the product was isolated as a colorless solid, mp = 192−198 °C with decomposition (0.24 g, 85% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.66 (s, 1H), 10.16 (s, 1H), 9.38 (s, 2H), 7.77 (d, J = 5.5 Hz, 1H), 7.50 (d, J = 10.2 Hz, 1H), 7.44 (dd, J = 9.1, 2.4 Hz, 2H), 7.28 (dd, J = 9.0, 2.2 Hz, 2H), 7.17 (dd, J = 5.0, 2.3 Hz, 1H), 6.93 (dd, J = 6.2, 2.6 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 6.73 (ddd, J = 8.7, 5.6, 2.5 Hz, 1H), 6.64 (ddd, J = 7.9, 5.0, 2.8 Hz, 1H), 5.36 (d, J = 12.4 Hz, 1H), 4.84 (d, J = 12.4 Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.5, 165.7, 155.6, 155.4, 155.0 (d, J^1_{CF} = 232.9 Hz), 151.3 (d, J^4_{CF} = 1.3 Hz), 135.2, 133.5 (d, J^3_{CF} = 6.4 Hz), 131.8, 131.6, 130.4, 127.0, 121.1, 120.9, 119.4, 118.6, 117.9, 115.6 (d, J^3_{CF} = 8.1 Hz), 114.0, 113.8 (d, J^2_{CF} = 23.3 Hz), 112.4 (d, J^2_{CF} = 22.3 Hz), 110.5, 108.8, 57.6, 55.2, 55.1, 36.2, 12.1. IR (neat, selected peaks): 3435, 3324, 3305, 1659, 1627 cm^{-1}. Exact mass calculated for $C_{33}H_{31}FN_3O_5$ $[M + H]^+$, 568.2242; found, 568.2251.

*2-((5-Fluoro-2-hydroxyphenyl)(5-methoxy-1H-indol-3-yl)methyl)-N^1,N^3-bis(4-methoxyphenyl)malonamide (**7g**).* Prepared from methyl 6-fluoro-coumarin-3-carboxylate (1.0 equiv, 0.30 mmol, 66 mg), 5-methoxyindole (3.0 equiv, 0.90 mmol, 0.14 g), *p*-anisidine (3.0 equiv, 0.9 mmol, 0.12 g), lanthanum triflate (0.1 equiv, 0.030 mmol, 20 mg), and 0.3 mL CH_2Cl_2. After 48 h, the product was isolated as a colorless solid, mp = 174−176 °C (0.11 g, 63% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.63 (s, 1H), 10.04 (s, 1H), 9.57 (s, 1H), 9.42 (s, 1H), 7.42−7.36 (m, 3H), 7.31 (d, J = 8.9 Hz, 2H), 7.18 (d, J = 2.5 Hz, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.08 (d, J = 9.4 Hz, 1H), 6.81 (m, 4H), 6.73−6.61 (m, 3H), 5.41 (d, J = 12.3 Hz, 1H), 4.54 (d, J = 12.3 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.5, 165.9, 155.6, 155.4, 155.3 (d, J^1_{CF} = 233.6 Hz), 152.8, 150.9 (d, J^4_{CF} = 1.4 Hz), 131.8, 131.4, 131.0, 130.3 (d, J^3_{CF} = 6.3 Hz), 127.2, 122.4, 121.4, 120.9, 116.1 (d, J^3_{CF} = 7.9 Hz), 115.5, 115.3 (d, J^2_{CF} = 23.2 Hz), 115.0, 114.5, 113.8, 113.1 (d, J^2_{CF} = 22.4 Hz), 111.8, 110.8, 101.2, 59.6, 55.3, 55.18, 55.16. IR (neat, selected peaks): 3368, 3318, 1667, 1603 cm^{-1}. Exact mass calculated for $C_{33}H_{30}FN_3NaO_6$ $[M + Na]^+$, 606.2016, Found 606.2036.

*2-((1,2-Dimethyl-1H-indol-3-yl)(5-fluoro-2-hydroxyphenyl)-methyl)-N^1,N^3-diphenylmalonamide (**7h**).* Prepared from methyl 6-fluoro-coumarin-3-carboxylate (1.0 equiv, 0.18 mmol, 40 mg), 1,2-dimethylindole (3.0 equiv, 0.54 mmol, 78 mg), aniline (3.0 equiv, 0.54 mmol, 50 mg), lanthanum triflate (0.10 equiv, 0.018 mmol, 11 mg), and 0.2 mL of dry CH_2Cl_2. After 72 h, the product was isolated as a colorless solid, mp = 163−165 °C (68 mg, 72% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.28 (s, 1H), 9.56 (s, 1H), 9.40 (s, 1H), 7.82 (d, J = 6.8 Hz, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.46 (dd, J = 10.1, 2.6 Hz, 1H), 7.38 (d, J = 8.3 Hz, 2H), 7.30 (dd, J = 7.7 Hz, 2H), 7.26 (d, J = 7.3 Hz, 1H), 7.21 (dd, J = 7.7 Hz, 2H), 7.06 (dd, J = 7.4 Hz, 1H), 7.02−6.95 (m, 3H), 6.71 (ddd, J = 8.4, 2.9 Hz, 1H), 6.63 (dd, J = 8.7, 5.1 Hz, 1H), 5.42 (d, J = 12.5 Hz, 1H), 4.94 (d, J = 12.5 Hz, 1H), 3.54 (s, 3H), 2.53 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.6, 165.8, 155.0 (d, J^1_{CF} = 233.0 Hz), 151.2 (d, J^4_{CF} = 1.3 Hz), 138.6, 138.4, 136.3, 135.0, 130.2 (d, J^3_{CF} = 6.2 Hz), 128.9, 128.6, 125.9, 123.8, 123.6, 119.54, 119.51, 119.3, 118.7, 118.2, 115.6 (d, J^3_{CF} = 8.1 Hz), 113.7 (d, J^2_{CF} = 23.3 Hz), 112.5 (d, J^2_{CF} = 22.3 Hz), 109.1, 108.7, 57.9, 36.2, 29.3, 10.7. IR (neat, selected peaks): 3298, 3240, 1677, 1646 cm^{-1}. Exact mass calculated for $C_{32}H_{29}FN_3O_3$ $[M + H]^+$, 522.2187; found, 522.2193

*2-((2-Hydroxy-3-methoxyphenyl)(2-methyl-1H-indol-3-yl)-methyl)-N^1,N^3-bis(4-methoxyphenyl)malonamide (**7i**).* Prepared from methyl-8-methoxy-coumarin-3-carboxylate (1.0 equiv, 0.30 mmol, 70 mg), 2-methylindole (3.0 equiv, 0.90 mmol, 0.12 g), *p*-anisidine (3.0 equiv, 0.90 mmol, 0.11 g), lanthanum triflate (0.10 equiv, 0.030 mmol, 18 mg), and 0.3 mL CH_2Cl_2. After 46 h, the product was isolated as a colorless solid, mp = 191−192 °C (80 mg, 47% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.58 (s, 1H), 10.09 (s, 1H), 9.37 (s, 1H), 8.45 (s, 1H), 7.77 (d, J = 7.0 Hz, 1H), 7.43 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 7.4 Hz, 1H), 7.27 (d, J = 9.0 Hz, 2H), 7.13 (dd, J = 6.6, 1.5 Hz, 1H), 6.93−6.83 (m, 4H), 6.78 (d, J = 9.0 Hz, 2H), 6.73−6.64 (m, 2H), 5.38 (d, J = 12.5 Hz, 1H), 4.88 (d, J = 12.5 Hz, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.6, 166.0, 155.5, 155.4, 147.3, 143.9, 135.2, 133.2, 132.0, 131.7, 129.2, 127.2, 121.0, 120.8, 119.4, 119.2, 118.9, 117.9, 117.7, 114.0, 113.8, 110.4, 109.6, 109.1, 57.8, 55.6, 55.22, 55.16, 35.8, 12.2. IR (neat, selected peaks): 3286, 3267, 1669, 1510 cm^{-1}. Exact mass calculated for $C_{34}H_{33}N_3NaO_6$ $[M + Na]^+$, 602.2267; found, 602.2258.

*2-((2-Hydroxyphenyl)(2-methyl-1H-indol-3-yl)methyl)-1,3-di-(pyrrolidin-1-yl)propane-1,3-dione (**7j**).* Prepared from methyl coumarin-3-carboxylate (1.0 equiv, 0.20 mmol, 43 mg), 2-methylindole (3.0 equiv, 0.60 mmol, 76 mg), pyrrolidine (3.0 equiv, 0.60 mmol, 50 μL), lanthanum triflate (0.10 equiv, 0.020 mmol, 12 mg), and 0.2 mL of PhMe. The reaction was stirred at 50 °C for 48 h. The reaction mixture was then passed through a plug of silica gel and eluted with 10% MeOH in CH_2Cl_2. The eluent was concentrated in vacuo. The resulting residue was purified via flash column chromatography using neutral alumina (gradient of 0% to 15% MeOH/CH_2Cl_2) to yield the product as an orange powder, mp = 182−185 °C (37 mg, 40% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.55 (s, 1H), 9.01 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 6.88 (dd, J = 7.4 Hz, 1H), 6.84 (dd, J = 7.4 Hz, 1H), 6.75 (dd, J = 7.5 Hz, 1H), 6.71 (dd, J = 7.4 Hz, 1H), 6.61 (d, J = 7.9 Hz, 1H), 5.20 (d, J = 11.8 Hz, 1H), 4.78 (d, J = 11.8 Hz, 1H), 3.23−3.09 (m, 5H), 3.04 (ddd, J = 12.2, 7.7, 5.4 Hz, 1H), 2.82−2.74 (m, 2H), 2.34 (s, 3H), 1.89−1.82 (m, 2H), 1.75−1.65 (m, 2H), 1.50−1.41 (m, 1H), 1.36 (dp, J = 11.2, 5.8 Hz, 1H), 1.26−1.19 (m, 1H), 0.68−0.58 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.7, 165.8, 154.8, 135.0, 133.0, 129.9, 127.7, 127.3, 125.9, 119.1, 118.5, 118.0, 117.6, 115.0, 110.1, 109.3, 51.1, 46.0, 45.9, 45.4, 45.3, 36.4, 25.8, 25.0, 23.6, 23.4, 11.9. IR (neat, selected peaks): 3316, 3248, 1676, 1630 cm^{-1}. Exact mass calculated for $C_{27}H_{32}N_3O_3^+$ $[M + H]^+$, 446.2438; found, 446.2453.

*2-((2-Hydroxyphenyl)(2-methyl-1H-indol-3-yl)methyl)-1,3-dimorpholinopropane-1,3-dione (**7k**).* Prepared from methyl coumarin-3-carboxylate (1.0 equiv, 0.30 mmol, 67 mg), 2-methylindole (3.0 equiv, 0.90 mmol, 0.12 g), morpholine (3.0 equiv, 0.90 mmol, 76 μL), lanthanum triflate (0.10 equiv, 0.030 mmol, 19 mg), and 0.3 mL PhMe. The reaction was stirred at 50 °C for 48 h. The reaction mixture was then passed through a plug of silica gel and eluted with 10% MeOH in CH_2Cl_2. The eluent was concentrated in vacuo. The resulting residue was purified via flash column chromatography using neutral alumina (gradient of 0% to 15% MeOH/CH_2Cl_2) to yield the product as a colorless powder, mp = 178−181 °C (55 mg, 35% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.63 (s, 1H), 9.01 (s, 1H), 7.50 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 6.87 (q, J = 7.6 Hz, 2H), 6.75 (t, J = 7.4 Hz, 1H), 6.71 (t, J = 7.4 Hz, 1H), 6.60 (d, J = 7.9 Hz, 1H), 5.22 (d, J = 11.7 Hz, 1H), 5.19 (d, J = 11.9 Hz, 1H), 3.69−3.36 (m, 9H), 3.28−3.10 (m, 3H), 3.01 (d, J = 11.7 Hz, 1H), 2.89−2.75 (m, 2H), 2.70−2.58 (m, 1H), 2.32 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.6, 166.9, 155.2, 135.5, 133.5, 130.4, 127.6, 126.3, 119.6, 119.2, 118.4, 118.1, 115.3, 110.6, 66.6, 66.3, 65.3, 46.4, 45.7, 42.7, 42.0, 12.2. IR (neat, selected peaks): 3292, 3047, 1678, 1622 cm^{-1}. Exact mass calculated for $C_{27}H_{32}N_3O_5^+$ $[M + H]^+$ 478.2336; found, 478. 2328.

*N^1,N^3-Dibenzyl-2-((2-hydroxyphenyl)(2-methyl-1H-indol-3-yl)-methyl)malonamide (**7l**).* Prepared from methyl coumarin-3-carboxylate (1.0 equiv, 0.20 mmol, 43 mg), 2-methylindole (3.0 equiv, 0.60 mmol, 96 mg), benzylamine (3.0 equiv, 0.60 mmol, 66 μL), lanthanum triflate (0.10 equiv, 0.020 mmol, 16 mg), and 0.2 mL CH_2Cl_2. The reaction was stirred at rt for 48 h. The reaction mixture was then passed through a plug of silica gel and eluted with 10% MeOH in CH_2Cl_2. The eluent was concentrated in vacuo. The resulting residue was purified via flash column chromatography (gradient of 0% to 10% MeOH/CH_2Cl_2) to yield the product as a colorless solid, mp = 164−166 °C (29 mg, 27% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.62 (s, 1H), 9.20 (s, 1H), 8.37 (dd, J = 6.0 Hz, 1H), 7.87 (dd, J = 5.8 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 7.3 Hz, 1H), 7.35−7.16 (m, 9H), 7.07 (d, J = 7.4 Hz, 3H), 7.02−6.96 (m, 2H), 6.93 (ddd, J = 8.7, 7.8, 1.2 Hz, 2H), 6.88 (dd, J = 7.5 Hz, 1H), 6.82 (dd, J = 7.4 Hz, 1H), 6.73 (dd, J = 7.3 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 6.5 Hz, 2H), 5.27 (d, J = 12.7 Hz, 1H), 4.74 (d, J = 12.7 Hz, 1H), 4.28−4.13 (m, 3H), 3.94 (dd, J = 15.6, 4.9 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 168.4, 168.1, 166.8, 154.9, 139.2, 139.1, 138.9, 129.1, 128.2, 128.1, 127.9, 127.2, 126.8, 126.8, 126.5, 126.2, 126.2, 118.9, 118.1, 117.7, 115.1, 110.2, 56.3, 43.5, 42.2, 41.8, 35.3. IR (neat, selected peaks): 3304, 3107, 1685, 1630 cm^{-1}.

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Exact mass calculated for $C_{33}H_{32}N_3O_3^+$ $[M + H]^+$ 518.2438; found, 518.2328.

*Synthesis of N-(4-Methoxyphenyl)-2-oxo-2H-chromene-3-carboxamide (**13**).* Methyl coumarin-3-carboxylate (1.0 equiv, 0.50 mmol, 0.10 g), *p*-anisidine (3.0 equiv, 1.5 mmol, 0.19 g), and CH_2Cl_2 (0.5 mL) were added to a flame-dried 4 mL vial, followed by lanthanum triflate (0.050 equiv, 0.025 mmol, 15 mg). The vial was then purged with Ar, and the mixture was stirred at room temperature until the coumarin-3-carboxylate was consumed by TLC (100% CH_2Cl_2). Upon completion, the reaction mixture was passed through a plug of silica gel. The eluent was then concentrated in vacuo. The resulting residue was purified via flash column chromatography (gradient of 50% 100% hexanes/CH_2Cl_2 to 100% CH_2Cl_2) to yield the amide **13** as a bright yellow solid (88 mg, 60% yield). Spectral data matched literature values.[55] ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.71 (s, 1H), 9.00 (s, 1H), 7.72 (dd, J = 7.8, 1.5 Hz, 1H), 7.69 (ddd, J = 8.7, 7.3, 1.6 Hz, 1H), 7.65 (d, J = 8.9 Hz, 2H), 7.44 (d, J = 8.4 Hz, 1H), 7.40 (td, J = 7.6, 1.1 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H). LRMS (ESI) calculated for $C_{17}H_{14}NO_4^+$ $[M + H]^+$, 296.1; found, 296.3.

*(E)-2-(((4-Methoxyphenyl)imino)methyl)phenol (**14**).* During the synthesis of *N*-(4-methoxyphenyl)-2-oxo-2*H*-chromene-3-carboxamide (**13**), imine **14** was also isolated as a light yellow solid (37 mg, 33% yield). Spectral data matched literature values.[56] ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.43 (s, 1H), 8.55 (s, 1H), 7.33 (d, J = 7.5 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.3 Hz, 1H), 6.95−6.87 (m, 3H), 3.80 (s, 3H). LRMS (ESI) calculated for $C_{14}H_{14}NO_2^+$ $[M + H]^+$, 228.1; found, 228.3.

*N-Benzyl-2-oxo-2H-chromene-3-carboxamide (**15**).* During the synthesis of 2-((2-hydroxyphenyl)(2-methyl-1*H*-indol-3-yl)methyl)-1,3-dimorpholinopropane-1,3-dione (**7l**), carboxamide **15** was also isolated as a bright yellow solid (16 mg, 27% yield). Spectral data matched literature values.[55] ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.96 (s, 1H), 7.70 (d, J = 7.4 Hz, 1H), 7.67 (dd, J = 7.8 Hz, 1H), 7.44−7.32 (m, 5H), 7.28 (dd, J = 6.6 Hz, 1H), 4.67 (d, J = 5.8 Hz, 2H). LRMS (ESI) calculated for $C_{17}H_{14}NO_3^+$ $[M + H]^+$, 280.10; found, 280.16.

*(E)-2-((Benzylimino)methyl)phenol (**16**).* During the synthesis of 2-((2-hydroxyphenyl)(2-methyl-1*H*-indol-3-yl)methyl)-1,3-dimorpholinopropane-1,3-dione (**7l**), imine **16** was also isolated as a light yellow solid (15 mg, 34% yield). Spectral data matched literature values.[57] ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.41 (s, 1H), 8.43 (s, 1H), 7.35 (dd, J = 7.5 Hz, 2H), 7.33−7.25 (m, 5H), 6.96 (d, J = 8.3 Hz, 1H), 6.88 (dd, J = 7.5 Hz, 1H), 4.80 (s, 2H). LRMS (ESI) calculated for $C_{14}H_{14}NO^+$ $[M + H]^+$, 212.11; found, 212.13.

*N^1,N^3-Bis(4-methoxyphenyl)malonamide (**18**).* Synthesized according to literature procedure.[58] Dimethyl malonate (1.0 equiv, 0.50 mmol, 0.63 mL) and *p*-anisidine (2.0 equiv, 1.0 mmol, 0.12 g) were heated to 150 °C for 2 h in a 10 mL flask fitted with a septa and needle to allow methanol to escape. The mixture was allowed to cool to room temperature, and then 50:50 CH_2Cl_2/hexanes was added. The solids were collected by vacuum filtration and washed with additional 50:50 CH_2Cl_2/hexanes to give a white solid (46 mg, 30% yield). Spectral data matched literature values.[58] ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.01 (s, 2H), 7.51 (d, J = 9.1 Hz, 4H), 6.89 (d, J = 9.1 Hz, 4H), 3.72 (s, 6H), 3.39 (s, 2H). LRMS (ESI) calculated for $C_{17}H_{19}N_2O_4^+$ $[M + H]^+$, 315.3; found, 315.2.

3CR Lewis Acid Screen and NMR Studies. The 3CR Lewis acid screen was conducted using general procedure for the La(OTf)$_3$-catalyzed 3CR synthesis of indolylmalonamides methyl coumarin-3-carboxylate (1.0 equiv, 0.10 mmol, 20 mg), 2-methylindole (3.0 equiv, 0.030 mmol, 39 mg), *p*-anisidine (3.0 equiv, 0.30 mmol, 37 mg), lanthanum triflate (0.10 equiv, 0.010 mmol, 6.0 mg), and 0.1 mL of solvent. After 24 h, the reaction mixture was diluted with 3 mL of acetone and passed through a plug of silica gel to remove the catalyst and stop the reaction. The eluent was concentrated in vacuo, and phenyltrimethylsilane (0.30 equiv, 0.030 mmol, 16 μL) was then added to the unpurified reaction mixture as an external standard. The unpurified sample was diluted in 0.5 mL of DMSO-d_6, and yields were determined using ^{1}H NMR spectroscopy with 8 scans.

Determination of NMR Yields for Table 1. Reactions were performed according to the general procedure for the Sc(III)-catalyzed synthesis of indolylchromanones using 0.1 mmol of methyl coumarin-3-carboxylate, 0.3 mmol of indole, and 0.1 mL of PhMe unless otherwise indicated. After 12 or 24 h, the reaction mixture was passed through a plug of silica gel and the eluent was concentrated in vacuo. The crude reaction mixture was taken up in 1.0 mL of $CDCl_3$ containing 10.1 mg/mL hexamethylcyclotrisiloxane. ^{1}H NMR spectra were obtained using a 400 MHz instrument with 16 scans. The peaks at 0.18, 4.11, 4.22, and 8.56 were integrated, corresponding to the standard, minor diastereomer, major diastereomer, and starting material, respectively.

Competition experiment (eq 5). Indolylchromanone **3a** (1.0 equiv, 0.05 mmol, 16 mg), coumarin-3-carboxylate **1a** (1.0 equiv, 0.05 mmol, 10 mg), and CH_2Cl_2 (0.05 mL) were added to a flame-dried 4 mL vial, followed by the addition of lanthanum triflate (0.10 equiv, 0.005 mmol, 4.6 mg). *p*-Anisidine (2.0 equiv, 0.10 mmol, 16.9 mg) was added last. The vial was then purged with Ar and wrapped in parafilm. The mixture stirred at room temperature for 20 h. The reaction mixture was passed through a plug of silica gel, and the eluent was concentrated in vacuo. The crude reaction mixture was taken up in 1.0 mL of $CDCl_3$, and 6.7 mg of phenyltrimethylsilane were added as an internal standard. ^{1}H NMR spectra were obtained using a 600 MHz instrument with 8 scans. The peaks at 0.24 (phenylTMS), 5.48 (**7a**), 8.92 (**13**), and 8.94 (**14**) were integrated and used to calculate the reported yields.

Fluorescence. Solutions for UV/vis spectroscopic studies were prepared by dissolving compounds in anhydrous DMSO or methanol, diluting to a final concentration of 1.0×10^{-5} M. Argon was bubbled through the samples to remove any dissolved oxygen. Absorption spectra were recorded with a UV−vis spectrophotometer in UV-cuvette cells in 2 mL of solution. Emission spectra were recorded with a fluorescence spectrophotometer in UV-cuvette cells in 2 mL of solution with a slit width of 5 nm and a scan rate of 30 nm/min. Quantum yields were determined relative to tryptophan in water[49] using eq 9 and following a protocol reported by Würth et al.[49]

$$\Phi_{f,x} = \Phi_{f,st} \cdot \frac{F_x}{F_{st}} \cdot \frac{f_{st}}{f_x} \cdot \frac{N_x^2(\lambda_{em})}{N_{st}^2(\lambda_{em})} \quad (9)$$

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00541.

^{1}H and ^{13}NMR spectra for all pure products (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Stuart L. Schreiber on the occasion of his 60th birthday.

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(46) We do not attribute the fluorescence of chromanones **3** and malonamides **7** to lanthanide fluorescence. The presence of lanthanum salts or lanthanum-malonamide complexes were not observed using ESI-MS. Initial NMR binding studies of lanthanide salts with malonamides have been conducted to observe lanthanide−malonamide complexes. Such complexes were not observed in malonamide samples after purification, further confirming the absence of such complexes in samples used for fluorescence analysis. Additionally, N^1,N^3-bis(4-methoxyphenyl)malonamide exhibits fluorescence and was syntheized without the use of metals.
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