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Yb(OTf)$_3$-Catalyzed Reactions of 5-Alkylidene Meldrum's Acids with Phenols: One-Pot Assembly of 3,4-Dihydrocoumarins, 4-Chromanones, Coumarins, and Chromones

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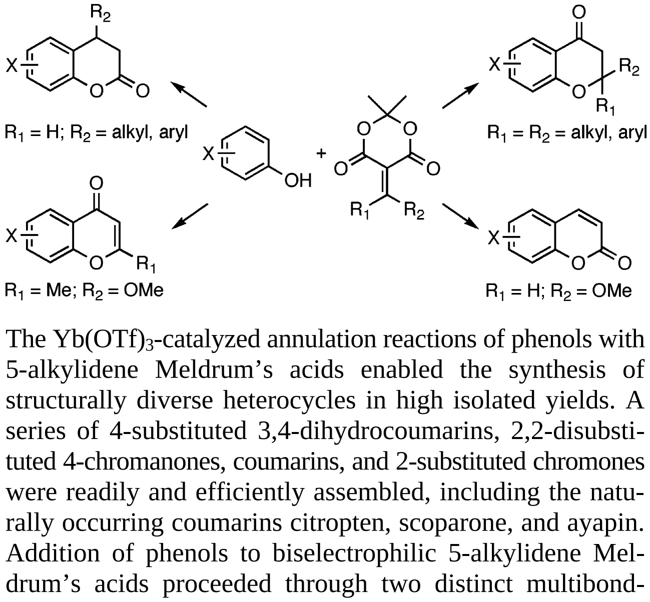

The Yb(OTf)$_3$-catalyzed annulation reactions of phenols with 5-alkylidene Meldrum's acids enabled the synthesis of structurally diverse heterocycles in high isolated yields. A series of 4-substituted 3,4-dihydrocoumarins, 2,2-disubstituted 4-chromanones, coumarins, and 2-substituted chromones were readily and efficiently assembled, including the naturally occurring coumarins citropten, scoparone, and ayapin. Addition of phenols to biselectrophilic 5-alkylidene Meldrum's acids proceeded through two distinct multibond-forming modes: Friedel−Crafts *C*-alkylation/*O*-acylation and Friedel−Crafts *C*-acylation/*O*-alkylation. The regioselectivity of the catalytic annulation reaction was controlled by the degree of substitution on the alkylidene moiety.

The Friedel−Crafts acylation and alkylation reactions are the most powerful processes for direct functionalization of aromatics through C−H bond conversion into a C−C bond.[1] A multitude of inter- and intramolecular variants are available to effect this synthetically significant transformation.[2] Of particular importance are acylative and alkylative Friedel−Crafts cyclizations from which a variety of carbo- and heterocycles have been fashioned.[3]

5-Alkylidene Meldrum's acids are biselectrophilic species and useful precursors in a variety of transformations.[4] However, examples of electrophilic aromatic substitution of arenes with Meldrum's acid derivatives are scarce. Benzylidene Meldrum's acids have been shown to participate in intramolecular Friedel−Crafts acylations when treated with concentrated H_2SO_4 or TFA.[5] The biselectrophilic nature of 5-alkylidene Meldrum's acids in the design of multiple bond-forming synthetic strategies with phenols was exploited in only one instance; Nair described the preparation of 3,4-dihydrocoumarins from the reaction of Meldrum's acid with aldehydes and phloroglucinol.[6] This reaction seemed, however, limited to the highly nucleophilic phloroglucinol, and the synthetic scope of this multicomponent reaction was not subsequently defined.[7]

Our group has previously established that Meldrum's acid derivatives are powerful acylating agents in metal triflate-catalyzed intramolecular Friedel−Crafts reactions,[8] and this approach was applied to the synthesis of benzocyclic ketones. Herein, we describe the Yb(OTf)$_3$-catalyzed reactions of 5-alkylidene Meldrum's acids with phenols for the one-pot assembly of 3,4-dihydrocoumarins, 4-chromanones, coumarins, and

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(1) For reviews, see: (a) Yonezawa, N.; Hino, T.; Ikeda, T. *Recent Res. Devel. Synth. Org. Chem.* **1998**, *1*, 213−223. (b) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon Press: Oxford, UK, 1991; Vol. 2, pp 733−752. (c) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon Press: Oxford, UK, 1991; Vol. 3, pp 293−339. (d) Roberts, R. M.; Khalaf, A. A. *Friedel−Crafts Alkylation Chemistry*: *A Century of Discovery*; Marcel Dekker: New York, 1984. (e) Olah, G. A. *Friedel−Crafts Chemistry*; John Wiley and Sons: New York, 1973. (f) Popp, F. D.; McEwen, W. E. *Chem. Rev.* **1958**, *58*, 321−401.

(2) Larock, R. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999; pp 129−133 and 1422−1433.

(3) (a) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 2, pp 753−768. For recent examples, see: (b) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942−8943. (c) Tran, Y. S.; Kwon, O. *Org. Lett.* **2005**, *7*, 4289−4291. (d) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204−10205. (e) Cui, D.-M.; Zhang, C.; Kawamura, M.; Shimada, S. *Tetrahedron Lett.* **2004**, *45*, 1741−1745. (f) Ishikawa, T.; Manabe, S.; Aikawa, T.; Kudo, T.; Saito, S. *Org. Lett.* **2004**, *6*, 2361−2364. (g) Fillion, E.; Beingessner, R. L. *J. Org. Chem.* **2003**, *68*, 9485−9488. (h) Hanessian, S.; Papeo, G.; Angiolini, M.; Fettis, K.; Beretta, M.; Munro, A. *J. Org. Chem.* **2003**, *68*, 7204−7218. (i) Cui, D.-M.; Kawamura, M.; Shimada, S.; Hayashi, T.; Tanaka, M. *Tetrahedron Lett.* **2003**, *44*, 4007−4010.

(4) For reviews on Meldrum's acid, see: (a) Gaber, A. E.-A. O.; McNab, H. *Synthesis* **2001**, 2059−2074. (b) Chen, B.-C. *Heterocycles* **1991**, *32*, 529−597. (c) Strozhev, M. F.; Lielbriedis, I. É.; Neiland, O. Ya. *Khim. Geterotsikl. Soedin.* **1991**, 579−599. (d) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345−358.

(5) (a) Campaigne, E.; Frierson, M. R. *J. Heterocycl. Chem.* **1979**, *16*, 235−237. (b) Van Allan, J. A.; Reynolds, G. A. *J. Heterocycl. Chem.* **1972**, *9*, 669−673. (c) Synthesis of 3-carboxycoumarins from the cyclization of *o*-methoxybenzylidene Meldrum's acid derivatives: Armstrong, V.; Soto, O.; Valderrama, J. A.; Tapia, R. *Synth. Commun.* **1988**, *18*, 717−725.

(6) Nair, V. *Synth. Commun.* **1987**, *17*, 723−727.

(7) (a) For an application of Nair's protocol see: Kumar, A.; Singh, B. K.; Tyagi, R.; Jain, S. K.; Sharma, S. K.; Prasad, A. K.; Raj, H. G.; Rastogi, R. C.; Watterson, A. C.; Parmar, V. S. *Bioorg. Med. Chem.* **2005**, *13*, 4300−4305. The synthesis of benzo[*f*]quinoline derivatives via the reaction of 2-aminonaphthalene with various benzylidene Meldrum's acids has been reported, see: (b) Wang, X.-S.; Zhang, M.-M.; Zeng, Z.-S.; Shi, D.-Q.; Tu, S.-J.; Wei, X.-Y.; Zong, Z.-M. *Tetrahedron Lett.* **2005**, *46*, 7169−7173. (c) Kozlov, S. N.; Basalaeva, L. I.; Ol'khovik, V. K.; Kalechits, G. V.; Matveenko, Yu. V. *Russ. J. Gen. Chem.* **2003**, *73*, 1434−1440. (d) Kozlov, N. G.; Basalaeva, L. I.; Tychinskaya, L. Yu. *Russ. J. Org. Chem.* **2002**, *38*, 1166−1170. (e) Strods, Ya. A.; Tsiekure, V. P.; Kampars, V. É.; Lielbriedis, I. É.; Neiland, O. Ya. *Khim. Geterotsikl. Soedin.* **1978**, 1369−1372. (f) Strods, Ya. A.; Lielbriedis, I. É.; Neiland, O. Ya. *Izv. Akad. Nauk Latv. SSR, Ser. Khim.* **1978**, 225−228. (g) Strods, Ya. A.; Lielbriedis, I. É.; Neiland, O. Ya. *Khim. Geterotsikl. Soedin.* **1977**, 977−979. (h) Strods, Ya. A.; Kampare, R. B.; Lielbriedis, I. É.; Neiland, O. Ya. *Khim. Geterotsikl. Soedin.* **1977**, 973−976.

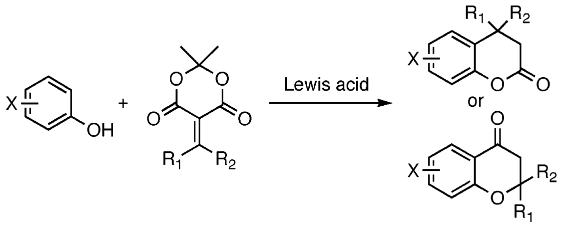
(8) (a) Fillion, E.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144−13145. (b) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316−1327. (c) Fillion, E.; Fishlock, D. *Org. Lett.* **2003**, *5*, 4653−4656.

10.1021/jo052000t CCC: \$33.50

chromones. These heterocycles are important pharmacophores present in diverse bioactive compounds.[9]

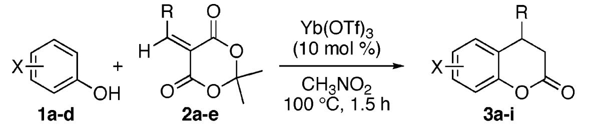
As depicted in Scheme 1, we initially studied the reaction of 5-alkylidene Meldrum's acids with phenols under Lewis acid catalysis. 3,4-Dihydrocoumarins and 4-chromanones could potentially be accessed by this strategy.

SCHEME 1. Synthetic Strategy for the Preparation of 3,4-Dihydrocoumarins and 4-Chromanones

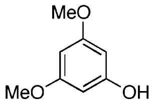
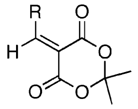
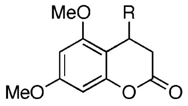
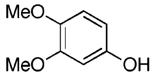
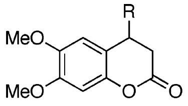
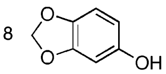
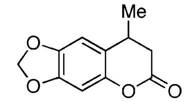
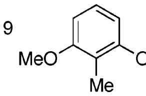
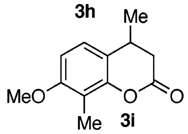


We began our study by reacting 3,5-dimethoxyphenol (**1a**) with 5-ethylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (**2a**) in the presence of Yb(OTf)$_3$ (10 mol %) in refluxing CH$_3$NO$_2$. After 1.5 h, the reaction was complete and 5,7-dimethoxy-4-methyl-3,4-dihydrocoumarin (**3a**) was isolated in 80% yield (Table 1, entry 1).[10] Under the same reaction conditions, Sc(OTf)$_3$ provided **3a** in 55% yield, and decomposition of the Meldrum's acid reagent was observed with Mg(OTf)$_2$. Alternatively, excess TFA promoted the reaction, albeit in lower yield. In the absence of a catalyst, the starting materials were recovered. From these results, Yb(OTf)$_3$ was the optimal catalyst for this transformation and was used throughout the study. As shown in Table 1, **1a** reacted with a number of 5-alkylidene Meldrum's acids to afford 3,4-dihydrocoumarins in good yields (entries 2−5). 3,4-Dimethoxyphenol (**1b**) and sesamol (**1c**) were also potent nucleophiles in this Lewis acid-catalyzed domino transformation, regioselectively forming dihydrocoumarins **3f−h** (Table 1, entries 6−8). Of note, 3-methoxyphenol was unreactive toward **2a**,[11] but **3i** was generated from 3-methoxy-2-methylphenol (**1d**) in 61% yield (Table 1, entry 9).

TABLE 1. Synthesis of 4-Substituted 3,4-Dihydrocoumarins



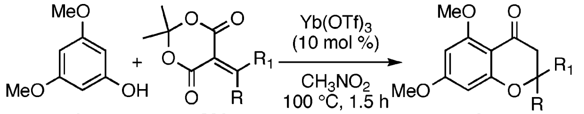
1a-d **2a-e** **3a-i**

entry	phenol	Meldrum's acid derivative	3,4-dihydrocoumarin	Yield (%)
				
1	**1a**	R = Me (**2a**)	R = Me (**3a**)	80[a]
2	**1a**	R = Ph (**2b**)	R = Ph (**3b**)	84
3	**1a**	R = 4-MeOPh (**2c**)	R = 4-MeOPh (**3c**)	82
4	**1a**	R = 4-NO$_2$Ph (**2d**)	R = 4-NO$_2$Ph (**3d**)	91
5	**1a**	R = 3,5-MeOPh (**2e**)	R = 3,5-MeOPh (**3e**)	70
				
6	**1b**	**2a**	R = Me (**3f**)	75[b]
7	**1b**	**2d**	R = 4-NO$_2$Ph (**3g**)	82[c]
8	 **1c**	**2a**	 **3h**	76[b]
9	 **1d**	**2a**	 **3i**	61

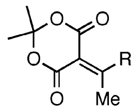
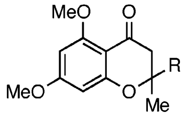
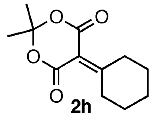
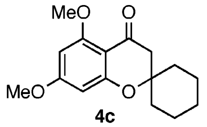
[a] Dihydrocoumarin **3a** was formed in 70% yield when the reaction of **1a** with **2a** was promoted by TFA (5 equiv) in CH$_3$NO$_2$ at 100 °C for 1.5 h. [b] The reaction was run over 2 h. [c] The reaction was run over 2.5 h.

The synthesis of 4,4-dimethyl-3,4-dihydrocoumarins was then explored. These compounds have been previously prepared via the one-pot protic acid-promoted reaction of 3,3-dimethylacrylic acid or methyl 3,3-dimethyl acrylate with phenols.[10e,f] However, treatment of phenol **1a** with 5-(1-methylethylidene) Meldrum's acid (**2f**) did not provide the expected dihydrocoumarin. Instead, 5,7-dimethoxy-2,2-dimethyl-4-chromanone (**4a**) was formed in 83% yield (Table 2, entry 1). This unprecedented chromanone synthesis was extended to other substituted alkylidenes (Table 2, entries 2 and 3). Unfortunately, this protocol was limited to electron-rich phenol **1a**, and all attempts to react 3-methoxyphenol, 3,5-dimethylphenol, and phenols **1b−d** with **2f** failed.

TABLE 2. 2,2-Disubstituted 5,7-Dimethoxy-4-chromanone Synthesis



1a **2f-h** **4a-c**

entry	electrophile	4-chromanone	Yield (%)
			
1	R = Me (**2f**)	R = Me (**4a**)	83[a]
2	R = Ph (**2g**)	R = Ph (**4b**)	77
3	 **2h**	 **4c**	71

[a] Chromanone **4a** was formed in 83% yield when the reaction of **1a** with **2f** was promoted by TFA (5 equiv) in CH$_3$NO$_2$ at 100 °C for 1.5 h.

The synthesis of coumarins and chromones by the reaction of phenols with 5-(1-methoxyalkylidene) Meldrum's acids was

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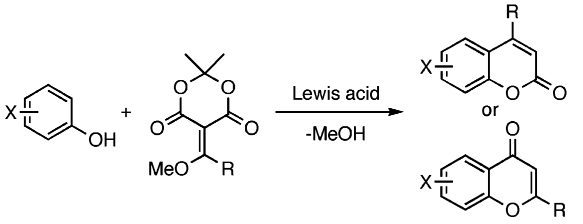
(9) For a review on chromanones and chromones, see: (a) Saengchantara, S. T.; Wallace, T. W. *Nat. Prod. Rep.* **1986**, *3*, 465−475. For reviews on coumarins, see: (b) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*, 887−916. (c) Murray, R. D. H. *Nat. Prod. Rep.* **1995**, *12*, 477−505. (d) Murray, R. D. H. *Nat. Prod. Rep.* **1989**, *6*, 591−624.

(10) One-pot synthesis of 3,4-dihydrocoumarins from cinnamic acids and phenols, see: (a) Aoki, S.; Amamoto, C.; Oyamada, J.; Kitamura, T. *Tetrahedron* **2005**, *61*, 9291−9297 and references therein. (b) Li, K.; Foresee, L. N.; Tunge, J. A. *J. Org. Chem.* **2005**, *70*, 2881−2883. (c) Singh, I.; Prasad, A. K.; Sharma, A. K.; Saxena, R. K.; Olsen, C. E.; Cholli, A. L.; Samuelson, L. A.; Kumar, J.; Watterson, A. C.; Parmar, V. S. *Bioorg. Med. Chem.* **2003**, *11*, 529−538. (d) Shukla, M. R.; Patil, P. N.; Wadgaonkar, P. P.; Joshi, P. N.; Salunkhe, M. M. *Synth. Commun.* **2000**, *30*, 39−42. From methyl 3,3-dimethyl acrylate and 3,5-dimethoxyphenol: (e) Song, X.; Siahaan, T. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3439−3442. From 3,3-dimethylacrylic acid and phenols: (f) Amsberry, K. L.; Borchardt, R. T. *J. Org. Chem.* **1990**, *55*, 5867−5877.

(11) Meldrum's acid **2** decomposed in the course of the reaction, but the phenol remained unreacted.

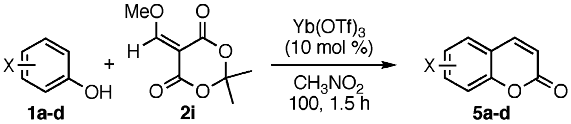
then pursued (Scheme 2). It was postulated that the Lewis acid catalyst, in addition to promoting the acylation/alkylation, would further induce methanol elimination to produce unsaturated heterocycles.

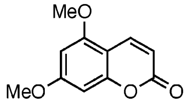
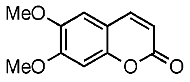
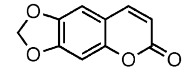
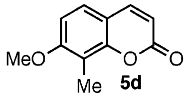
SCHEME 2. Synthetic Strategy for the Preparation of Coumarins and Chromones



The addition of **1a** to 5-(methoxymethylene) Meldrum's acid (**2i**) catalyzed by Yb(OTf)$_3$ proceeded smoothly and yielded 5,7-dimethoxycoumarin (**5a**) in 88% yield (Table 3, entry 1).[12] Phenols **1b** and **1c** reacted cleanly with **2i** (Table 2, entries 2 and 3). Citropten (**5a**), scoparone (**5b**), and ayapin (**5c**) are naturally occurring coumarins isolated from a number of sources.[13]

TABLE 3. Yb(OTf)$_3$-Catalyzed Coumarin Synthesis



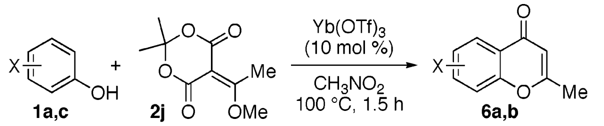
entry	phenol	coumarin	Yield (%)
1	**1a**	 **5a**	88[a]
2	**1b**	 **5b**	84
3	**1c**	 **5c**	72
4	**1d**	 **5d**	31

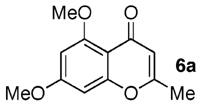
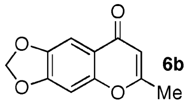
[a] Coumarin **5a** was formed in 64% yield when the reaction of **1a** with **2i** was promoted by TFA (5 equiv) in CH$_3$NO$_2$ at 100 °C for 1.5 h.

Reacting phenol **1a** with 5-(1-methoxyethylidene) Meldrum's acid **2j** furnished chromone **6a** in 77% yield (Table 4, entry 1). A similar result was obtained with **1c**. The application of this method to the synthesis of flavones was unsuccessful.

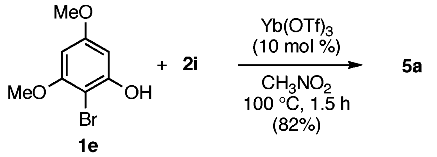
Finally, the compatibility of this methodology with bromide and amino substituted phenols was investigated. As depicted in eq 1, the reaction of 2-bromo-3,5-dimethoxyphenol **1e** with **2i** gave solely debrominated coumarin **5a** in 82% yield. This result may be rationalized by the known reversible electrophilic substitution of electron-rich arenes by metal triflates.[14] It was theorized that CH$_3$NO$_2$ was acting as bromonium scavenger (via its aci form) and that a non-nucleophilic solvent would decrease the debromination rate. Indeed, carrying out the reaction in 1,2-dichloroethane gave bromocoumarin **5e** in 67% yield, accompanied by a minor amount of **5a** (eq 2). Interestingly, **1e** and **2i** engaged in an unprecedented atom-transfer reaction in the presence of TfOH in 1,2-dichloroethane and 3-bromocoumarin **5f** was isolated in 38% yield, in addition to 41% of coumarin **5a** (eq 3).

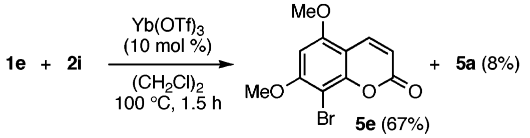
TABLE 4. Synthesis of Chromones

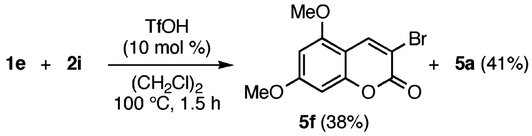


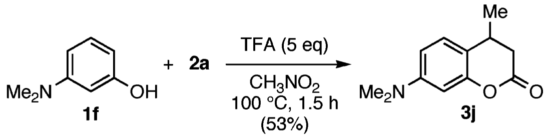
entry	phenol	chromone	Yield (%)
1	**1a**		77[a]
2	**1c**		76

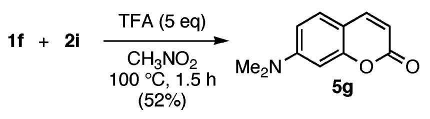
[a] Chromone **6a** was formed in 72% yield when the reaction of **1a** with **2j** was promoted by TFA (5 equiv) in CH$_3$NO$_2$ at reflux for 1.5 h.

(1) 

(2) 

(3) 

(4) 

(5) 

The compatibility of anilines was demonstrated by the synthesis of **3j** and **5g** from 3-(dimethylamino)phenol (**1f**). Lewis basic phenol **1f** inhibited Yb(OTf)$_3$ and the reaction did not proceed. However, the domino process was successful when promoted by excess TFA (eqs 4 and 5).

In conclusion, we have disclosed a mild and catalytic procedure for the reaction of phenols with alkylidene Meldrum's acids. Excess TFA was demonstrated to be a complementary alternative to Yb(OTf)$_3$. The present protocol is operationally simple and versatile in terms of the precursors and resulting heterocycles. 3,4-Dihydrocoumarins, 4-chromanones, coumarins, and chromones are assembled in a single synthetic operation in good yields. Further research is ongoing to establish the reaction mechanism and apply this methodology to other systems.

Experimental Section

General Procedure for Yb(OTf)$_3$-Catalyzed Reaction of Phenols with 5-Alkylidene Meldrum's Acids. All reactions were performed with 100 mg of phenol. To a resealable, oven-dried Schlenk tube cooled under nitrogen was added Yb(OTf)$_3$ (10 mol %) in a glovebox. Outside of the box, phenol (1.0 equiv) and 5-alkylidene Meldrum's acid (1.5 equiv) were added to the Schlenk tube under N_2, and the residue was washed into the flask with $MeNO_2$; sufficient solvent was used such that the reaction was 0.4 M in phenol. The flask was placed in an oil bath at 100 °C and allowed to stir until the reaction was complete as monitored by TLC. The tube was removed from the bath and allowed to cool; the contents were rinsed into a separatory funnel with EtOAc. The organic layer was washed twice with water and once with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The products were purified by silica gel chromatography, using EtOAc:petroleum ether (35−60 °C).

General Procedure for Trifluoroacetic Acid-Promoted Reaction of Phenols with 5-Alkylidene Meldrum's Acid. An oven-dried Schlenk tube cooled under nitrogen was charged with phenol (1.0 equiv) and 5-alkylidene Meldrum's acid (1.5 equiv). TFA (5 equiv) was then added, and immediately washed into the flask with $MeNO_2$; sufficient solvent was used such that the total volume made the reaction 0.4 M in phenol. The remainder of the procedure is identical to the previous procedure, with the addition of a saturated $NaHCO_3$ wash of the organic phase before using water and brine.

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Supporting Information Available: Experimental procedures and NMR spectra for **3a**−**j**, **4a**−**c**, **5a**−**g**, and **6a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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