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Lewis Base Catalyzed [4+2] Annulation of Electron-Deficient Chromone-Derived Heterodienes and Acetylenes

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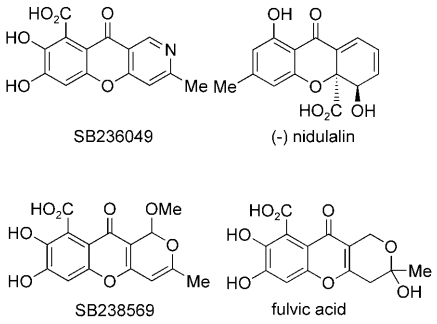
Abstract: Lewis base catalyzed [4+2] annulation reactions between electron-deficient chromone oxa- and azadienes and acetylene carboxylates provide tricyclic benzopyrones inspired by natural products. An asymmetric synthesis of the tricyclic benzopyrones was developed by using modified cinchona alkaloids as enantiodifferentiating Lewis base catalysts.

Keywords: annulation · benzopyrones · Lewis bases · natural products · organocatalysis

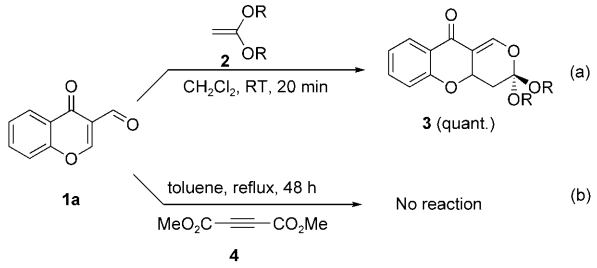
Introduction

Small molecules embodying molecular scaffolds that exist in natural product structures are rich sources of inspiration for drug discovery and probes for chemical biology investigations.[1] While the syntheses of highly complex natural products, as well as analogues thereof, remain challenging, alternative strategies aimed at the synthesis of compounds inspired by natural products are gaining attention.[2] In a related research program, we targeted tricyclic benzopyrone scaffolds, which occur in numerous natural products displaying pronounced biological activities (Scheme 1).[3] For instance, (−)-nidulalin, a dihydroxanthone, isolated from *Emericella nidulans*,[3c] is a DNA topoisomerase II inhibitor and shows immunomodulatory activity.[3e,f] The fungal metabolites SB238569 and SB236049 from *C. funicola* TCF 6040 are inhibitors of several bacterial metallo-β-lactamases,[4] which makes them potential guiding structures for antibiotic research aimed at multidrug-resistant bacteria.[5] Among other benzopyrones, the commonly occurring fulvic acid has been widely studied.[6]



Scheme 1. Natural products embodying the tricyclic benzopyrone scaffold.

Tricyclic benzopyrones have been synthesized by employing 3-formylchromones as oxadienes in the hetero-Diels–Alder reaction with electron-rich olefins (Scheme 2a).[7]



Scheme 2. Reaction of 3-formylchromone with an electron-rich olefin and a failed attempt to annulate 1 with dimethylacetylenedicarboxylate (DMAD).

However, 3-formylchromones, which are electron-deficient heterodienes, should not entertain classical uncatalyzed cycloadditions with electron-poor dienophiles.[8] Accordingly, our attempts to realize the annulation reaction of 3-formylchromone and DMAD under harsh conditions met with failure (Scheme 2b).

The electronic compatibility required for a [4+2] cycloaddition reaction between electron-poor substrates **1** and **4** is the major obstacle for this electron-deficient version of a hetero Diels–Alder reaction. To find a solution to this synthetic challenge, we turned to Lewis base catalysis by using tertiary phosphines and amines as catalysts.[9] The underlying idea herein is to catalytically transform the electron-

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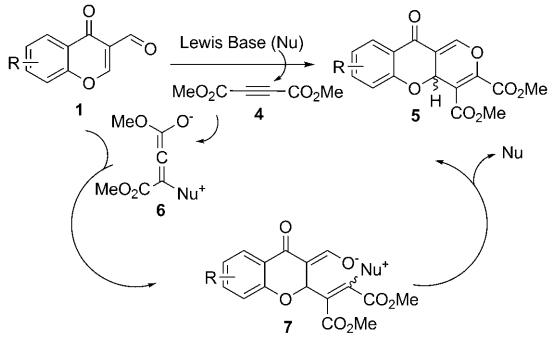
poor acetylene into a nucleophilic zwitterion,[10] which could add in a 1,4-addition to the chromone moiety to yield a stabilized oxanion (**7**, Scheme 3) that further undergoes a 1,4-addition to an activated olefin and liberates the catalyst to yield the desired cycloadduct (**5**, Scheme 3).



Scheme 3. Lewis base catalyzed [4+2] annulation of 3-formylchromones (**1**) and an alkyne (**4**).

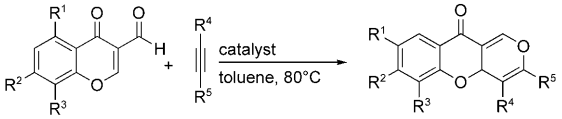
Indeed, the reaction of the zwitterions **6** (generated by the addition of triphenylphosphine to DMAD) with 3-formylchromone yielded the desired annulation product **5**. After optimizing the reaction conditions, a variety of substituted 3-formylchromones and acetylenecarboxylates were successfully employed in this annulation reaction and a small collection of novel tricyclic benzopyrones was generated.[11] Herein, we present a full account of this work and a deeper exploration of this novel annulation reaction[12] using diverse chromone-based heterodienes and electron-poor acetylenes to generate different tricyclic benzopyrones. We also propose a mechanistic model for the asymmetric annulation reaction catalyzed by cinchona alkaloid derived organocatalysts.

Results and Discussion

[4+2] Annulation of 3-formylchromones and electron-poor acetylenes: Natural products often embody electron-rich benzopyrone rings, that is, polyhydroxy benzenes originating from polyketide biosynthetic pathways.[13] To induce this characteristic feature of natural products in our collection of tricyclic benzopyrones, 3-formyl-5-hydroxychromone (**1c**) and the methyl derivative (**1b**) were synthesized by the Vilsmeier–Haack reaction of the corresponding hydroxyacetophenones, according to literature procedures (see the Supporting Information).[14] In addition, 3-formylbenzo[*h*]chromone with a bulky naphthalene ring (**1d**) was employed in the annulation reactions with acetylenes.

3-Formyl-5-methoxychromone (**1c**) reacted well with three acetylene dicarboxylates under optimized reaction conditions when using either triphenyl- or tributylphosphine (up to 30 mol%) catalysts in toluene at 80°C. The reactions were completed in 3 h to provide the tricyclic benzopyrones **5a–c** in high yields. The bulky di-*tert*-butylacetylene diester performed equally well (Table 1, entry 3) to provide **5c** in 74% yield. While the reaction of **1c** with methyl propiolate using triphenylphosphine as the catalyst provided only moderate yields of tricyclic benzopyrone **5d** (Table 1, entry 4), phenylpropargyl aldehyde yielded the corresponding aldehyde-substituted tricyclic benzopyrone **5e** in 58% yield (Table 1, entry 5). Unexpectedly, the use of more nucleophilic tributylphosphine reduced the yield to 17% (Table 1, entry 6).

Table 1. Results of the phosphine-catalyzed [4+2] annulations.



Entry	5	R^1	R^2	R^3	R^4	R^5	Yield [%][a]
1	**5a**	OMe	H	H	CO_2Me	CO_2Me	82[b]
2	**5b**	OMe	H	H	CO_2Et	CO_2Et	78[c]
3	**5c**	OMe	H	H	CO_2tBu	CO_2tBu	74[c]
4	**5d**	OMe	H	H	CO_2Me	H	42[d]
5	**5e**	OMe	H	H	CHO	Ph	58[e,g]
6	**5e**	OMe	H	H	CHO	Ph	17[f]
7	**5f**	OH	H	H	CO_2Me	CO_2Me	25[b]
8	**5g**	OH	H	H	CO_2Et	CO_2Et	25[b]
9	**5h**	H	−Ph−		CO_2Me	CO_2Me	60[b]
10	**5i**	H	H	H	CO_2tBu	CO_2tBu	67[f]
11	**5j**	H	H	H	CHO	Ph	78[e]
12	**5k**	H	H	H	CN	Ph	28[f,h]
13	**5l**	H	H	H	CHO	n-C_5H_{11}	–[f]

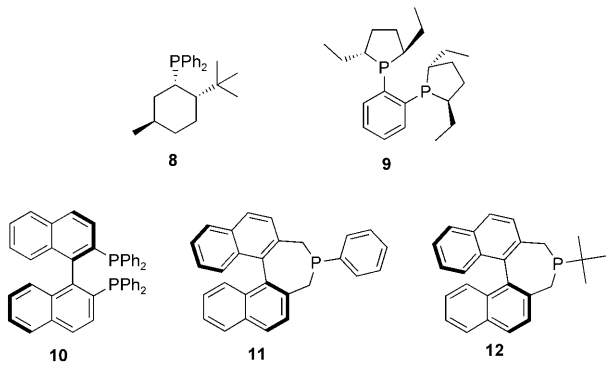
[a] Isolated yields. [b] PPh_3 (60 mol%) was used as the catalyst. [c] PBu_3 (60 mol%) was used as the catalyst. [d] PPh_3 (30 mol%) was used as the catalyst. [e] PPh_3 (50 mol%) was used as the catalyst. [f] PBu_3 (30 mol%) was used as the catalyst. [g] 31% of **1c** was recovered. [h] 37% of **1c** was recovered.

The zwitterion **6**, generated by the addition of phosphine to acetylenecarboxylates, could abstract acidic protons, for instance, from the hydroxyl group.[15] Therefore, we were pleased to find that 3-formyl-5-hydroxychromone (**1c**) gave the desired product in a yield of 25% by using triphenylphosphine catalyst (60 mol%; Table 1, entries 7 and 8). 3-Formylbenzo[*h*]chromone (**1d**) reacted well with DMAD to provide the corresponding tricyclic benzopyrone **5h** in good yield.

[4+2] Annulation of **1a** with bulky di-*tert*-butylacetylenedicarboxylate led to the isolation of adduct **5i** in 67% yield (Table 1, entry 10). Phenylpropargyl aldehyde and chromone **1a** provided adduct **5j** in comparatively better yields than chromone **1b** (Table 1, entries 11 and 5). Interestingly, 3-phenyl-2-propyne-nitrile also undergoes the [4+2] annulation reaction with 3-formylchromone to provide adduct **5k**, albeit in low yields with much of the chromone recovered unreacted (Table 1, entry 12). To the best of our knowledge, this is the first report of employing an acetylenic nitrile in an organocatalyzed zwitterionic annulation reaction. 2-Octynal did not yield any desired product and most of the 3-formylchromone was recovered (Table 1, entry 13).

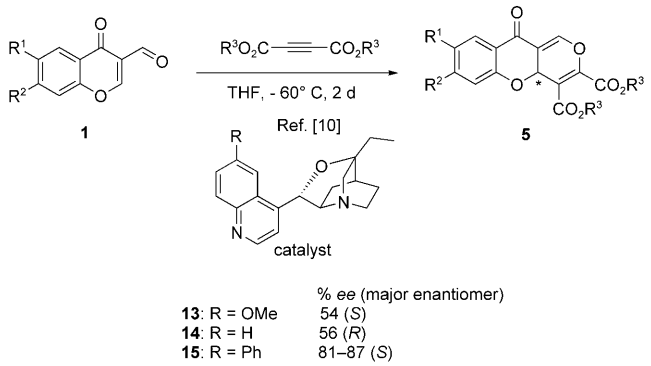
These results demonstrate the wide scope of the phosphine-catalyzed [4+2] annulation reaction, which tolerates a variety of electron-rich 3-formylchromones and different electron-poor acetylenes to yield diversely functionalized tricyclic benzopyrones.

Asymmetric [4+2] annulation reaction of 3-formylchromones and acetylenedicarboxylates: The organocatalyzed [4+2] annulation reaction of 3-formylchromones and acetylenecarboxylates generates tricyclic benzopyrones with one stereocenter. To develop an enantioselective version of this annulation reaction, we investigated the suitability of chiral phosphine catalysts. Chiral phosphines **8**–**12** were tested in a [4+2] annulation reaction between 3-formylchromone and DMAD in toluene under varying reaction conditions, that is, from room temperature to 70 °C, with varying equivalents of DMAD and reaction times. However, these phosphines proved ineffective and mostly did not catalyze the reaction. Only in the case of **11** could we observe product formation (<5%) with an enantiomeric excess of about 36%.



We observed that diazabicyclo[2.2.0]octane (DABCO) was as efficient a catalyst as triphenylphosphine in this annulation reaction. This finding suggested it would be worthwhile to explore chiral tertiary amines in the development of an enantioselective version of this annulation reaction. To this end, we investigated several Cinchona alkaloids and derivatives thereof as chiral catalysts. The naturally occurring alkaloids cinchonidine, cinchonine, and *O*-methylhydroquinidine did not catalyze the above reaction. Gratifyingly, in the presence of β-isoquinidine **13**[16] (20 mol%), which embodies a cyclic ether between the isoquinuclidine system and the quinoline-substituted side chain, the transformation proceeded at −50 °C in THF to yield the tricyclic benzopyrone **5m** ($R^1=R^2=H$, $R^3=Me$) with around 50% enantiomeric excess (*ee*) and preferred the formation of the *S* enantiomer (Scheme 4).[11]

The demethoxy analogue **14**, however, yielded an excess of the opposite *R* enantiomer (Scheme 4). Since cinchona alkaloids are not generally available in both enantiomeric forms, this finding is highly advantageous. Catalyst **15**, with a phenyl ring at C-6 of the quinoline moiety, provided excellent yields and enantioselectivity. In the presence of catalyst

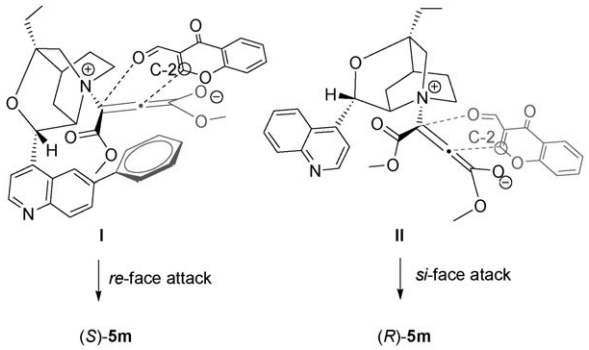


Scheme 4. Enantioselective [4+2] annulation reaction catalyzed by cinchona alkaloid based catalysts.

15, differently substituted formylchromones reacted with acetylene carboxylates at −60 to −70 °C to provide the desired tricyclic benzopyrones **5** with appreciable to good yields (up to 91%) and with *ee* values consistently above 80% and up to 87% (Scheme 4).[11]

These findings indicate that the quinidine ring embedded in the catalyst and the substituents are important for the steric steering of the annulation reactions. In addition, the tricyclic catalysts are sufficiently nucleophilic for catalysis even at low temperatures (analogues lacking an oxa ring were only sluggish catalysts; data not shown).

To rationalize the observed direction of the stereoselection, we propose that in the case of the isocupreidines with a substituent at C-6 of the quinoline moiety, the catalyst adopts a conformation in which steric interactions between the C-6 substituent and the bicyclic system are minimized (for catalyst **15**, see **I** in Scheme 5). Upon formation of the intermediate zwitterion **I**, the additional undesirable interactions between the phenyl ring of the chromone and the ester of the allenoate, as well as between the chromone and the quinuclidine ring, are minimized. In the ensuing arrangement **I** shown in Scheme 5, the *si* face of the allenoate is shielded by the phenyl substituent at C-6 of the quinoline, which facilitates the *re*-face attack at the C-2 position of the formylchromone and thus preferred formation of the *S* enantiomer.

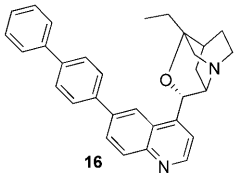


Scheme 5. Possible transition states in the enantioselective annulation reaction.

In the absence of a C-6 substituent, conformation **II** may be preferred in which the *si* face of the allenoate is open for the approach by the chromone. In this arrangement again undesirable interactions between the phenyl ring of the chromone, the ester of the allenoate, the quinoline ring of the catalyst, and the isoquinuclidine system are minimized by favoring the allenoate addition on the *si* face of the C-2 position of the formylchromone, thus leading to the *R* enantiomer as the major product.

The proposed selectivity was further supported by experiments performed with catalyst **16** (Table 2) prepared by the Suzuki coupling of 4-biphenylboronic acid and β-isocinchonine-6′-trifluoromethanesulfonate (see the Supporting Information). With a *p*-biphenyl group in the 6′-position of the catalyst, the same stereoselectivity as that observed for catalyst **15** should be recorded. Indeed, in all of the reactions performed with catalyst **16** with different 3-formylchromones and acetylenedicarboxylates, the *S* enantiomers were formed in preference to the *R* enantiomers (Table 2), clearly supporting the proposed transition-state model (Scheme 5). Also, it was observed that diethylacetylenedicarboxylate was less reactive than DMAD in these asymmetric reactions. This again might be due to the proximity of the generated allenoate and the quinuclidine ring, which would further avoid the incoming 3-formylchromone for the ensuing reaction.

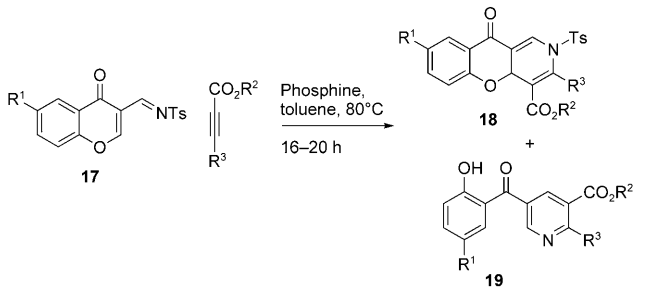
Table 2. Results of the enantioselective [4+2] annulation reaction with catalyst **16** (20 mol%).



Entry	R^1	R^2	R^3	**5**	Yield [%][a]	*ee*[b] [%]
1	H	H	Me	**5m**	48	84
2	*i*Pr	H	Me	**5n**	32	77
3	Cl	H	Me	**5o**	67	81
4	Br	H	Me	**5p**	64	81
5	Cl	Me	Me	**5q**	53	80
6	H	H	Et	**5r**	15	84
7	*i*Pr	H	Et	**5s**	42	77
8	Cl	H	Et	**5t**	31	79
9	Br	H	Et	**5u**	27	81
10	Cl	Me	Et	**5v**	18	82

[a] Isolated yields. [b] The enantiomeric excesses were determined on an Agilent 1100 series HPLC machine using a Daicel IC column with 25% ethanol/isohexane at 0.5 mL min^{-1}.

[4+2] Annulation reaction between chromone azadienes and acetylene carboxylates: To capitalize on this novel annulation reaction for accessing further benzopyrones with a fused azaheterocycle, 3-formylchromone-derived N-tosylimines were employed in the [4+2] annulation reaction. Due to their very low solubility in toluene at room temperature, the reactions of imines **17** were performed at 80°C (Scheme 6). Gratifyingly these transformations also proceeded smoothly with PBu_3 as the catalyst. Compared with the 3-formylchromones, imines **17** displayed significantly lower reactivity even at elevated temperatures. After chromatographic separation, the tricyclic reaction products **18**, which can also be regarded as highly substituted dihydropyridines, were obtained in acceptable yields. However, along with the desired adduct, pyridines **19** were isolated in varying yields (Table 3). Product formation did not occur in the absence of the catalyst when the reactions were performed for longer times. Moreover, the alternative formation of α,β-unsaturated five-membered lactams[17] was not observed.



Scheme 6. [4+2] Annulation reaction of N-tosylimines of 3-formylchromones and acetylene carboxylates.

Table 3. Results of the [4+2] annulation reaction of N-tosylimines of 3-formylchromones and acetylene carboxylates with PBu_3 (30 mol%) as the catalyst.

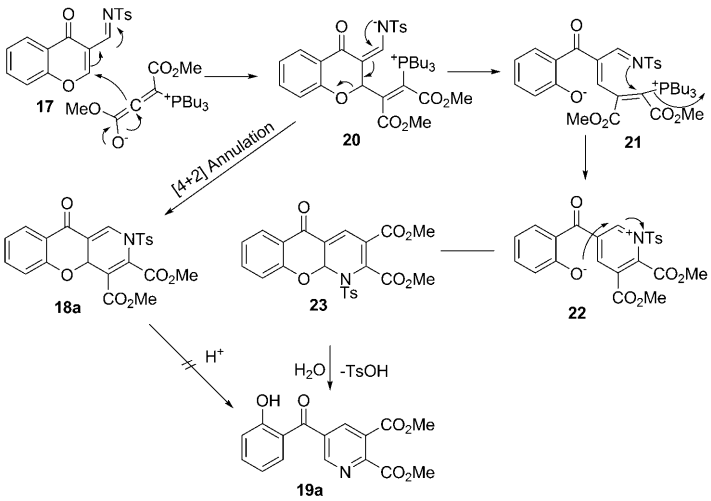
Entry	R^1	R^2	R^3	**18**	Yield [%][a]	**19**	Yield [%][a]
1	H	Me	CO_2Me	**18a**	50	**19a**	41
2	H	Et	CO_2Et	**18b**	57	**19b**	30
3	Me	Me	CO_2Me	**18c**	54	**19c**	32
4	Me	Et	CO_2Et	**18d**	61	**19d**	35
5	*i*Pr	Me	CO_2Me	**18e**	58	**19e**	31
6	*i*Pr	Et	CO_2Et	**18f**	62	**19f**	15
7	Br	Me	CO_2Me	**18g**	41	**19g**	25
8	Br	Et	CO_2Et	**18h**	40	**19h**	22
9	H	Me	H	**18i**	–	**19i**	60[b]

[a] Isolated yields. [b] PPh_3 (30 mol%) was used as the catalyst.

Tricyclic dihydropyridines **18** were obtained in moderate yields in the reactions with DMAD or diethylacetylenedicarboxylate along with pyridines **19** (Table 3, entries 1–8). However, in the triphenylphosphine-catalyzed reaction of methylpropiolate with 3-formylchromone, the pyridine **19i** was obtained as the major product. The diyhdropyridine **18i** was observed in trace amounts and could not be isolated (Table 3, entry 9).

In a separate experiment, we could not convert the tricyclic dihydropyridine **18a** into pyridine **19a**, which suggested different reaction mechanisms for the formation of these two products. Moreover, unlike the tricyclic benzopyrones **5**, which are very sensitive to acidic conditions and undergo rearrangements,[18] the dihydropyridines **18** were stable. This could be due to the electron-withdrawing N-tosyl functionality, which reduces the push–pull character unlike benzopyrone **5**. Thus, the chromone ring in **18** does not tend to open up as in the case of **5**.

Mechanistically, we assume that the initial attack of the zwitterion formed by addition of the phosphine catalyst to the acetylene carboxylates occurs at the C-2 position of the chromone and generates the intermediate **20** (Scheme 7).



Scheme 7. Proposed mechanism for the formation of tricyclic dihydropyridines **18** and pyridines **19**. Ts = tosyl.

This should be a relatively stable zwitterion due to the electronegative N-tosyl moiety. A direct 1,4-addition of the tosylamide to the phospha-substituted olefin would yield the dihydropyridine **18** after releasing the catalyst. Alternatively, the phosphine catalyst could also leave **21** to generate a different dipole system, **22**, wherein phenoxide would add to the pyridinium ring to generate tricyclic aminal **23**. Water can easily cleave the tosyl group with concomitant chromone ring opening to provide the pyridines **19**. The aromatization of the pyridine ring would also encourage such nucleophilic removal of the tosyl moiety.

Conclusion

In our endeavors to synthesize compound collections inspired by natural products for chemical biology and medicinal chemistry research,[19] we have developed a hitherto unprecedented [4+2] annulation reaction between electron-deficient chromone oxa- and azadienes and acetylenes. The strategy provided novel tricyclic benzopyrone ring systems inspired by natural products with either a substituted dihydropyran or a dihydropyridine ring fused to the benzopyrone scaffold. An enantioselective route to tricyclic benzopyrones was established successfully by using modified cinchona alkaloids as chiral Lewis base catalysts. Mechanistic insights suggest that the substitution pattern on the quinoline ring of the cinchona alkaloid controls the stereoselectivity of the annulation reaction.

Experimental Section

General: Unless otherwise noted, chemicals were obtained from Aldrich, Acros, or Alfa and were used without further purification. Reactions were carried out in standard glassware or in a Radleys Carousel 12 parallel reactor. ^{1}H and ^{13}C NMR spectroscopic data were recorded on Varian Mercury VX 400 or Varian 500-inova500 spectrometers at RT. NMR spectra were calibrated to the solvent signals of $CDCl_3$ ($\delta = 7.26$ and 77.00 ppm). The *ee* values were determined on an Agilent 1100 series HPLC using a Daicel IC column with 25% ethanol/isohexane at 0.5 mL min^{-1}. Fast atom bombardment (FAB) MS measurements were recorded on a Finnigan MAT MS 70 spectrometer and electrospray ionization (ESI) MS were measured by using an Agilent 1100 series binary pump together with a reversed-phase HPLC column (Macherey–Nagel). TLC was performed on Merck silica gel 60 F254 aluminum sheets. For flash chromatography, Baker silica gel (40–70 μm) was used. Medium-pressure liquid chromatography (MPLC) purifications were carried out on an ISCO sq16 instrument using silica gel (30 μm) columns by interchim. Melting points were recorded on Büchi Melting points B-540 apparatus and are uncorrected.

Representative example of [4+2] annulation of the substituted 3-formylchromones: Compound 5a: A solution of **1c** (204 mg; 1.00 mmol; 1.0 equiv) and DMAD (284 mg; 2.00 mmol; 2.0 equiv) in toluene (10 mL) was heated to 80 °C and degassed by flushing with argon. Triphenylphosphine (157 mg; 0.6 mmol; 0.6 equiv) was added to this solution and the solution was stirred until **1c** was consumed (as determined by TLC). The reaction mixture was directly subjected to MPLC (12 g silica gel, cyclohexane (CH)/EtOAc 0:1 to 1:0). The product was isolated as an off-white solid (284 mg; 0.82 mmol; 82%). $R_f = 0.22$ (CH/EtOAc 2:3); m.p. 154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.53$ (s, 1H), 7.43 (t, $J = 8.4$ Hz, 1H), 6.59 (t, $J = 7.8$ Hz, 2H), 5.83 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.90 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 179.7$, 164.8, 161.4, 161.0, 160.1, 147.1, 144.6, 136.8, 114.0, 113.2, 110.6, 110.5, 105.2, 66.9, 56.4, 53.6, 53.0 ppm; HRMS: *m/z* calcd for $C_{17}H_{15}O_8$ $[M+H]^+$: 347.07614; found: 347.07619.

Compound 5b: Brown amorphous solid; $R_f = 0.31$ (CH/EtOAc 3:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.51$ (d, $J = 1.2$ Hz, 1H), 7.40 (t, $J = 8.4$ Hz, 1H), 6.58 (d, $J = 8.4$ Hz, 1H), 6.55 (dd, $J = 8.3$, 0.9 Hz, 1H), 5.81 (d, $J = 1.2$ Hz, 1H), 4.38–4.32 (m, 4H), 3.93 (s, 3H), 1.40–1.31 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 179.8$, 164.2, 161.4, 160.9, 160.6, 147.4, 144.7, 136.8, 114.0, 113.3, 110.5, 110.4, 105.2, 67.1, 63.0, 62.0, 56.4, 14.1, 14.0 ppm; HRMS: *m/z* calcd for $C_{19}H_{19}O_8$ $[M+H]^+$: 375.10744; found: 375.10741.

Compound 5c: Yellow amorphous solid; $R_f = 0.46$ (CH/EtOAc 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.50$ (d, $J = 1.2$ Hz, 1H), 7.39 (t, $J = 8.3$ Hz, 1H), 6.57 (d, $J = 8.4$ Hz, 1H), 6.52 (d, $J = 8.3$ Hz, 1H), 5.75 (d, $J = 1.2$ Hz, 1H), 3.92 (s, 3H), 1.55 (s, 9H), 1.55 ppm (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 180.1$, 163.3, 161.4, 161.1, 159.6, 147.3, 145.0, 136.7, 113.9, 113.3, 111.1, 110.4, 105.1, 84.6, 82.9, 67.8, 56.4, 28.2, 27.9 ppm; HRMS: *m/z* calcd for $C_{23}H_{27}O_8$ $[M+H]^+$: 431.17004; found: 431.16978.

Compound 5d: Off-white solid; $R_f = 0.28$ (CH/EtOAc 1:2); m.p. 155 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.73$ (s, 1H), 7.49–7.46 (m, 1H), 7.40 (t, $J = 8.4$ Hz, 1H), 6.59 (dd, $J = 8.3$, 0.9 Hz, 1H), 6.56 (dd, $J = 8.4$, 0.6 Hz, 1H), 5.73 (d, $J = 0.4$ Hz, 1H), 3.93 (s, 3H), 3.85 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 180.7$, 165.1, 161.4, 161.1, 152.1, 144.9, 136.8,

115.3, 113.2, 110.7, 108.4, 104.9, 65.5, 56.4, 52.2 ppm; HRMS: *m/z* calcd for $C_{15}H_{13}O_6$ $[M+H]^+$: 289.07066; found: 289.07070.

Compound 5e: Brown amorphous solid; $R_f=0.30$ (CH/EtOAc 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.76$ (s, $J=0.5$ Hz, 1H), 7.62 (d, $J=$ 0.9 Hz, 1H), 7.61–7.57 (m, 3H), 7.55–7.50 (m, 2H), 7.43 (t, $J=8.4$ Hz, 1H), 6.64 (dd, $J=8.3$, 0.9 Hz, 1H), 6.59 (dd, $J=8.4$, 0.6 Hz, 1H), 5.96–5.87 (m, 1H), 3.95 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=190.2$, 180.7, 167.6, 161.4, 144.6, 136.9, 132.1, 130.1, 129.7, 128.9, 115.9, 113.3, 113.0, 110.9, 104.9, 65.2, 56.4 ppm; HRMS: *m/z* calcd for $C_{20}H_{15}O_5$ $[M+H]^+$: 335.09140; found: 335.09147.

Compound 5f: Yield: 82 mg, 0.25 mmol, 25%; yellow amorphous solid; $R_f=0.66$ (CH/EtOAc 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.72$ (s, 1H), 7.55 (d, $J=1.3$ Hz, 1H), 7.37 (t, $J=8.3$ Hz, 1H), 6.55 (dd, $J=8.4$, 0.9 Hz, 1H), 6.41 (dd, $J=8.2$, 0.9 Hz, 1H), 5.86 (d, $J=1.3$ Hz, 1H), 3.91 (s, 3H), 3.89 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=186.3$, 164.5, 162.9, 160.7, 158.7, 146.3, 145.3, 139.2, 112.1, 111.4, 110.8, 109.6, 108.1, 66.9, 53.7, 53.1 ppm.

Compound 5g: Yield: 90 mg, 0.25 mmol, 25%; yellow amorphous solid; $R_f=0.77$ (CH/EtOAc 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.73$ (s, 1H), 7.55 (d, $J=1.3$ Hz, 1H), 7.37 (t, $J=8.3$ Hz, 1H), 6.55 (dd, $J=8.4$, 0.9 Hz, 1H), 6.39 (dd, $J=8.2$, 1.0 Hz, 1H), 5.86 (d, $J=1.2$ Hz, 1H), 4.42–4.28 (m, 4H), 1.39–1.32 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=$ 186.4, 164.0, 162.8, 160.3, 158.8, 146.4, 145.4, 139.1, 112.0, 111.2, 110.7, 109.5, 108.0, 67.0, 63.2, 62.3, 14.1, 14.0 ppm.

Compound 5h: Light-yellow solid; $R_f=0.61$ (CH/EtOAc 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.13$ (dd, $J=8.4$, 1.2 Hz, 1H), 7.89 (d, $J=8.7$ Hz, 1H), 7.78 (d, $J=8.2$ Hz, 1H), 7.62 (ddd, $J=8.2$, 6.9, 1.3 Hz, 1H), 7.59 (d, $J=1.4$ Hz, 1H), 7.51 (ddd, $J=8.2$, 7.0, 1.2 Hz, 1H), 7.46 (d, $J=8.7$ Hz, 1H), 6.06 (d, $J=1.4$ Hz, 1H), 3.97 (s, 3H), 3.94 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=180.7$, 164.7, 161.1, 157.3, 147.4, 144.7, 138.0, 130.2, 128.1, 126.8, 125.0, 123.7, 122.4, 122.0, 117.5, 113.0, 110.5, 68.1, 53.7, 53.1 ppm; HRMS: *m/z* calcd for $C_{20}H_{15}O_7$ $[M+H]^+$: 367.08123; found: 367.08136.

Compound 5i: Light-brown solid; $R_f=0{,}74$ (CH/EtOAc 6:4); m.p. 145°C ; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.95$ (dd, $J=7.9$, 1.8 Hz, 1H), 7.53 (d, $J=1.3$ Hz, 1H), 7.53–7.47 (m, 1H), 7.08 (ddd, $J=8.2$, 7.2, 1.1 Hz, 1H), 6.95–6.88 (m, 1H), 5.86 (d, $J=1.3$ Hz, 1H), 1.57 (s, 9H), 1.56 ppm (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=181.4$, 163.2, 159.5, 159.4, 146.9, 145.2, 136.7, 127.6, 122.9, 122.4, 118.4, 113.0, 111.7, 84.7, 83.1, 68.1, 28.2, 28.0 ppm; HRMS: *m/z* calcd for $C_{22}H_{25}O_7$ $[M+H]^+$: 401.15948; found: 401.15939.

Compound 5j: Light-brown solid; $R_f=0.64$ (CH/EtOAc 6:4); m.p. 146°C ; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=9.79$ (s, 1H), 8.27 (s, 1H), 8.20 (d, $J=$ 7.8 Hz, 1H), 7.94–7.80 (m, 3H), 7.67 (t, $J=7.6$ Hz, 1H), 7.56 (t, $J=$ 7.3 Hz, 1H), 7.49–7.34 ppm (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=$ 195.3, 191.2, 175.1, 157.3, 156.0, 141.5, 140.5, 135.7, 134.7, 134.5, 129.4, 129.1, 126.4, 126.3, 123.6, 118.8, 118.4 ppm; HRMS: *m/z* calcd for $C_{19}H_{13}O_4$ $[M+H]^+$:305.08084; found: 305.08087.

Compound 5k: Yellow amorphous solid; $R_f=0.67$ (CH/EtOAc 6:4); m.p. 107°C ; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.96$ (dt, $J=4.0$, 2.0 Hz, 1H), 7.89–7.85 (m, 2H), 7.64 (dd, $J=2.7$, 1.2 Hz, 1H), 7.60–7.46 (m, 5H), 7.15–7.07 (m, 1H), 5.76 ppm (d, $J=1.3$ Hz, 1H);^{13}C NMR (101 MHz, $CDCl_3$): $\delta=181.0$, 162.6, 159.0, 145.3, 137.2, 132.6, 129.9, 129.1, 128.3, 127.6, 123.0, 122.8, 118.8, 116.4, 112.2, 87.2, 68.0 ppm; HRMS: *m/z* calcd for $C_{19}H_{12}O_3N$ $[M+H]^+$: 302.08117; found: 302.08132.

General procedure for asymmetric and enantioselective [4+2] annulation reaction: A solution of the 3-formylchromone derivative (0.10 mmol; 1.0 equiv) and 6′-(4-biphenyl)-β-isocinchonine (8.9 mg; 20 μmol; 0.2 equiv) in dry THF (4 mL) was cooled to −70°C. Then, dialkylacetylenedicarboxylate (0.2 mmol; 2.0 equiv) was added. The solution was stirred at −70°C for 3 d. A saturated aqueous solution of NH_4Cl (10 μL) was added to the solution and it was allowed to warm to RT. The mixture was filtered, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (5 g silica gel, CH/EtOAc 87:13) to yield the pure products.[11] For HPLC data, see the Supporting Information.

Representative example of [4+2] annulation of tosylimines derived from 3-formylchromones and acetylenecarboxylates: nBu$_3$P (9.1 mg, 0.045 mmol,0.3 equiv) was added to a solution containing 3-(tosyliminomethyl)-4-chromen-4-one (50 mg, 0.15 mmol, 1.0 equiv) and dimethylacetylenedicarboxylate (43 mg, 0.30 mmol, 2 equiv) at 80°C in degassed toluene (5 mL) and the reaction mixture was stirred for 4 h (other imines take up to 20 h for full conversion, as monitored by TLC). After evaporation of the solvent, the crude product was purified by column chromatography (silica gel, CH/EtOAc 9:1) to yield dihydropyridine **18a** and pyridine **19a**.

Compound 18a: Off-white solid; $R_f=0.17$ (CH/EtOAc 7:3); m.p. 172°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.07$ (s, 1H), 7.74–7.72 (dd, $J=8.0$, 1.6 Hz, 1H), 7.68–7.64 (ddd, $J=8.4$, 7.2, 1.6 Hz, 1H), 7.63–7.61 (m, 2H), 7.46–7.44 (dd, $J=8.0$, 1.0 Hz, 1H), 7.33–7.29 (ddd, $J=8.0$, 7.2, 0.8 Hz, 1H), 6.88–6.86 (dd, $J=8.4$, 0.8 Hz, 1H), 5.48 (s, 1H), 4.33 (s, 3H), 3.69 (s, 3H), 2.16 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.1$, 162.8, 162.0, 156.9, 155.6, 152.9, 144.9, 134.9, 133.7, 129.2, 127.8, 125.3, 125.1, 124.1, 118.0, 116.1, 115.4, 60.0, 56.9, 51.9, 21.4 ppm; HRMS (FAB): *m/z* calcd for $C_{23}H_{19}NO_8S$ $[M+H]^+$: 470.0910; found: 470.0891.

Compound 19a: Yellow oil; $R_f=0.52$ (CH/EtOAc 3:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.66$ (s, 1H), 9.01 (d, $J=2.1$ Hz, 1H), 8.47 (d, $J=$ 2.1 Hz, 1H), 7.63–7.56 (m, 1H), 7.48–7.42 (m, 1H), 7.15–7.09 (m, 1H), 6.94 (ddd, $J=8.1$, 7.2, 1.1 Hz, 1H), 4.05 (s, 3H), 3.97 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=197.4$, 166.1, 164.8, 163.6, 153.0, 151.5, 138.3, 137.8, 134.7, 132.9, 126.1, 119.6, 119.2, 118.8, 53.5, 53.4 ppm; HRMS: *m/z* calcd for $C_{16}H_{14}O_6N$ $[M+H]^+$: 316.08156; found: 316.08157.

Compound 18b: White solid; $R_f=0.28$ (CH/EtOAc 7:3); m.p. 176°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.05$ (s, 1H), 7.78–7.75 (dd, $J=8.0$, 1.6 Hz, 1H), 7.68–7.65 (ddd, $J=8.4$, 7.2, 1.6 Hz, 1H), 7.64–7.63 (m, 2H), 7.46–7.44 (dd, $J=8.4$, 0.4 Hz, 1H), 7.34–7.30 (ddd, $J=8.0$, 6.8, 1.0 Hz,1H), 6.91–6.89 (dd, $J=8.0$, 1H), 5.52 (s, 1H), 4.79–4.65 (m, 2H), 4.20–4.06 (m, 2H), 2.17 (s, 3H), 1.40 (t, $J=7.2$, 3H), 1.20 ppm (t, $J=7.2$, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.0$, 163.1, 156.7, 155.6, 152.7, 144.9, 135.0, 133.7, 129.2, 127.9, 125.4, 125.1, 124.1, 118.0, 117.1, 115.8, 68.6, 60.9, 56.8, 21.4, 15.6, 13.9 ppm; HRMS (FAB): *m/z* calcd for $C_{25}H_{23}NO_8S$ $[M+H]^+$: 498.12172; found: 498.12097.

Compound 19b: Yellow oil; $R_f=0.66$ (CH/EtOAc 3:2); NMR ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.73$ (brs, 1H), 9.00 (d, $J=2.1$ Hz, 1H), 8.48 (d, $J=2.1$ Hz, 1H), 7.61–7.55 (m, 1H), 7.50–7.41 (m, 1H), 7.15–7.10 (m, 1H), 6.94 (ddd, $J=8.2$, 5.4, 1.8 Hz, 1H), 4.51 (q, $J=7.2$ Hz, 2H), 4.43 (q, $J=7.1$ Hz, 2H), 1.45 (t, $J=7.2$ Hz, 3H), 1.40 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=197.6$, 164.4, 163.6, 153.5, 151.4, 138.3, 137.8, 134.5, 132.9, 126.2, 119.6, 119.1, 77.5, 77.2, 76.8, 62.8, 62.7, 14.2 ppm; HRMS: *m/z* calcd for $C_{18}H_{18}O_6N$ $[M+H]^+$: 344.11286; found: 344.11285.

Compound 18c: White solid; $R_f=0.19$ (CH/EtOAc 7:3); m.p. 231–232°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.04$ (s, 1H), 7.64–7.61 (dt, $J=8.4$, 2.0 Hz, 2H), 7.52 (d, $J=0.8$ Hz, 1H), 7.48–7.45 (dd, $J=8.4$, 2.0 Hz, 1H), 7.36–7.34 (d, $J=8.4$ Hz, 1H), 6.89–6.87 (d, $J=8.4$ Hz, 2H), 5.48 (s, 1H), 4.33 (s, 3H), 3.69 (s, 3H), 2.38 (s, 3H), 2.17 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.2$, 162.9, 162.1, 156.9, 153.9, 152.9, 144.9, 135.3, 135.0, 134.9, 129.2, 127.8, 124.7, 123.8, 117.7, 116.2, 115.1, 60.0, 56.9, 51.9, 21.3, 20.8 ppm; HRMS (ESI): *m/z* calcd for $C_{24}H_{21}NO_8S$ $[M+H]^+$: 484.10607; found: 484.10526.

Compound 19c: Yellow oil; $R_f=0.50$(CH/EtOAc 60:40); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.49$ (s, 1H), 8.98 (d, $J=2.0$ Hz, 1H), 8.47 (d, $J=$ 2.0 Hz, 1H), 7.40 (dd, $J=8.5$, 1.8 Hz, 1H), 7.19 (d, $J=1.0$ Hz, 1H), 7.02 (d, $J=8.5$ Hz, 1H), 4.05 (s, 3H), 3.97 (s, 3H), 2.26 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=197.3$, 166.2, 164.9, 161.6, 152.9, 151.4, 139.0, 138.2, 134.9, 132.4, 128.9, 126.2, 118.9, 118.5, 53.5, 53.4, 20.6 ppm; HRMS: *m/z* calcd for $C_{17}H_{16}O_7N$ $[M+H]^+$: 330.09721; found: 330.09717.

Compound 18d: White solid; $R_f=0.32$ (CH/EtOAc 7:3); m.p. 151–152°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.01$ (s, 1H), 7.65–7.62 (td, $J=$ 8.4, 2.0 Hz, 2H), 7.55–7.54 (dd, $J=1.2$, 0.4 Hz, 1H), 7.48–7.45 (ddd, $J=$ 8.4, 2.4, 0.4 Hz, 1H), 7.35–7.33 (d, $J=8.4$ Hz, 1H), 6.91–6.89 (dd, $J=8.4$, 0.8 Hz, 2H) 5.51 (s, 1H), 4.79–4.65 (m, 2H), 4.20–4.05 (m, 2H), 2.39 (s, 3H), 2.18 (s, 3H), 1.40 (t, $J=7.0$ Hz, 3H), 1.20 ppm (t, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.1$, 163.1, 161.6, 156.6, 153.9, 152.7,

144.8, 135.2, 135.0, 134.9, 129.2, 127.8, 124.7, 123.8, 117.7, 117.2, 115.5, 68.6, 60.9, 56.8, 21.3, 20.8, 15.6, 13.9 ppm; HRMS (ESI): *m/z* calcd for $C_{26}H_{25}NO_8S$ $[M+H]^+$: 512.13737; found: 512.13656.

Compound 19d: Yellow oil; $R_f=0.63$ (CH/EtOAc 60:40); NMR (400 MHz, $CDCl_3$): $\delta=11.51$ (s, 1H), 8.98 (d, $J=2.0$ Hz, 1H), 8.48 (d, $J=2.0$ Hz, 1H), 7.39 (dd, $J=8.5$, 2.1 Hz, 1H), 7.21 (d, $J=1.5$ Hz, 1H), 7.02 (d, $J=8.5$ Hz, 1H), 4.52 (q, $J=7.2$ Hz, 2H), 4.43 (q, $J=7.1$ Hz, 2H), 2.26 (s, 3H), 1.45 (t, $J=7.2$ Hz, 3H), 1.40 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (101 MHz,): $\delta=197.5$, 165.9, 164.4, 161.6, 153.3, 151.3, 139.0, 138.3, 134.7, 132.4, 128.9, 126.2, 118.9, 118.5, 62.8, 62.7, 29.9, 20.6, 14.2 ppm; HRMS: *m/z* calcd for $C_{19}H_{20}O_6N$ $[M+H]^+$: 358.12851; found: 358.12853.

Compound 18e: Off-white solid; $R_f=0.31$ (CH/EtOAc 7:3); m.p. 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.06$ (s, 1H), 7.65–7.64 (m, 1H), 7.62–7.60 (m, 2H), 7.55–7.52 (dd, $J=8.4$, 2.4 Hz, 1H), 7.40–7.38 (d, $J=8.8$ Hz, 1H), 6.91–6.89 (d, $J=8.4$ Hz, 2H), 5.49 (s, 1H), 4.33 (s, 3H), 3.69 (s, 3H), 2.95 (m, 1H), 2.17 (s, 3H), 1.25–1.23 ppm (dd, $J=7.2$, 1.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.4$, 162.8, 162.0, 156.9, 154.1, 152.9, 146.4, 144.8, 134.9, 132.8, 129.2, 127.8, 123.8, 121.9, 117.8, 116.1, 115.1, 60.0, 57.0, 51.9, 33.7, 23.9, 23.8, 21.4 ppm; HRMS (ESI): *m/z* calcd for $C_{26}H_{25}NO_8S$ $[M+H]^+$: 512.13737; found: 512.13692.

Compound 19e: Yellow oil; $R_f=0.62$ (CH/EtOAc 3:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.50$ (s, 1H), 9.02 (d, $J=2.0$ Hz, 1H), 8.53–8.47 (m, 1H), 7.48 (dd, $J=8.7$, 2.2 Hz, 1H), 7.28–7.24 (m, 1H), 7.07 (d, $J=8.6$ Hz, 1H), 4.06 (s, 3H), 3.98 (s, 3H), 2.82 (dd, $J=13.9$, 6.9 Hz, 1H), 1.19 ppm (d, $J=6.9$ Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=197.3$, 161.9, 153.0, 151.6, 140.2, 138.6, 136.5, 134.9, 133.1, 130.0, 128.4, 126.3, 119.1, 118.4, 53.6, 53.5, 33.4, 24.1 ppm; HRMS (ESI): *m/z* calcd for $C_{19}H_{20}O_6N$ $[M+H]^+$: 358.12851; found: 358.12832.

Compound 18f: White solid; $R_f=0.43$ (CH/EtOAc 7:3); m.p. 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.04$ (s, 1H), 7.65–7.64 (m, 1H), 7.63–7.62 (m, 2H), 7.64–7.63 (m, 2H), 7.54–7.51 (dd, $J=8.8$, 2.4 Hz, 1H), 7.39–7.37 (d, $J=8.8$ Hz, 1H), 6.92–6.90 (d, $J=8.0$ Hz, 2H), 5.51 (s, 1H), 4.76–4.67 (m, 2H), 4.17–4.06 (m, 2H), 2.95 (m, 1H), 2.18 (s, 3H), 1.39 (t, $J=7.0$ Hz, 3H), 1.24–1.23 (d, $J=6.8$ Hz, 6H), 1.19 ppm (t, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.3$, 163.0, 161.6, 156.7, 154.0, 152.7, 146.3, 144.7, 134.9, 132.7, 129.1, 127.8, 123.8, 122.0, 117.8, 117.1, 115.8, 68.6, 60.8, 56.9, 33.6, 23.9, 23.8, 21.4, 15.6, 13.9 ppm; HRMS (ESI): *m/z* calcd for $C_{28}H_{29}NO_8S$ $[M+H]^+$: 540.16867; found: 540.16776.

Compound 19f: Brown oil; $R_f=0.72$ (CH/EtOAc 3:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.52$ (s, 1H), 9.02 (d, $J=2.1$ Hz, 1H), 8.51 (d, $J=2.1$ Hz, 1H), 7.48 (dd, $J=8.6$, 2.3 Hz, 1H), 7.27 (d, $J=2.3$ Hz, 1H), 7.06 (d, $J=8.6$ Hz, 1H), 4.52 (dt, $J=7.1$, 6.2 Hz, 2H), 4.44 (dt, $J=13.5$, 3.9 Hz, 2H), 2.90–2.78 (m, 1H), 1.46 (t, $J=7.2$ Hz, 3H), 1.39 (t, $J=7.2$ Hz, 3H), 1.19 ppm (d, $J=6.9$ Hz, 9H); ^{13}C NMR (101 MHz,): $\delta=197.2$, 165.7, 164.2, 161.7, 153.3, 151.3, 138.4, 136.2, 134.5, 129.8, 128.9, 126.0, 118.8, 118.3, 62.7, 62.5, 33.2, 23.9, 23.9, 14.1 ppm; HRMS: *m/z* calcd for $C_{21}H_{24}O_6N$ $[M+H]^+$: 386.15981; found: 386.15948.

Compound 18g: Yellow solid; $R_f=0.23$ (CH/EtOAc 7:3); m.p. 219–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.07$ (s, 1H), 7.83 (d, $J=2.4$, 1H), 7.75–7.72 (dd, $J=8.8$, 2.4 Hz, 1H), 7.63–7.60 (td, $J=8.4$, 2.0 Hz, 2H), 7.36–7.34 (d, $J=8.8$ Hz, 1H), 6.91–6.89 (d, $J=8.4$ Hz, 1H), 5.46 (s, 1H), 4.33 (s, 3H), 3.69 (s, 3H), 2.23 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=173.8$, 162.7, 162.0, 157.0, 154.3, 152.9, 145.3, 136.7, 134.9, 129.2, 128.0, 127.7, 125.3, 119.9, 118.7, 115.8, 115.7, 60.0, 56.7, 52.0, 21.4 ppm; HRMS (ESI): *m/z* calcd for $C_{23}H_{18}{}^{79}BrNO_8{}^{32}S$ $[M+H]^+$: 548.00093; found: 548.00026.

Compound 19g: Brown oil; $R_f=0.53$ (CH/EtOAc 3:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.56$ (s, 1H), 9.00 (d, $J=2.1$ Hz, 1H), 8.48 (d, $J=2.1$ Hz, 1H), 7.66 (dd, $J=8.8$, 2.3 Hz, 1H), 7.55 (d, $J=2.4$ Hz, 1H), 7.03 (d, $J=8.9$ Hz, 1H), 4.05 (s, 3H), 3.98 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=196.4$, 165.8, 164.5, 162.3, 153.3, 151.1, 140.4, 138.1, 134.4, 133.9, 126.1, 121.0, 119.8, 111.1, 53.4, 53.3 ppm; HRMS: *m/z* calcd for $C_{16}H_{13}O_6N^{79}Br$ $[M+H]^+$: 393.99208; found: 395.99003.

Compound 18h: White solid; $R_f=0.43$ (CH/EtOAc 7:3); m.p. 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.04$ (s, 1H), 7.85 (d, $J=2.4$ Hz, 1H), 7.74–7.72 (dd, $J=8.8$, 2.4 Hz, 1H), 7.64–7.60 (td, $J=8.4$, 2.0 Hz, 2H), 7.36–7.34 (d, $J=8.8$ Hz, 1H), 6.92–6.90 (d, $J=8.0$ Hz, 1H), 5.48 (s, 1H), 4.80–4.64 (m, 2H), 4.20–4.05 (m, 2H), 2.23 (s, 3H), 1.39 (t, $J=7.0$ Hz, 3H), 1.20 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=173.7$, 163.0, 161.5, 156.8, 154.3, 152.8, 145.2, 135.0, 134.4, 129.2, 128.0, 127.7, 125.3, 119.9, 118.6, 116.8, 116.0, 68.7, 60.9, 56.6, 21.4, 15.6, 13.9 ppm; HRMS (ESI): *m/z* calcd for $C_{25}H_{22}{}^{79}BrNO_8{}^{32}S$ $[M+H]^+$: 576.03223; found: 576.03195.

Compound 19h: Brown oil; $R_f=0.61$ (CH/EtOAc 3:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.59$ (s, 1H), 8.99 (d, $J=2.1$ Hz, 1H), 8.49 (d, $J=2.1$ Hz, 1H), 7.66 (dd, $J=8.9$, 2.4 Hz, 1H), 7.57 (d, $J=2.4$ Hz, 1H), 7.04 (d, $J=8.9$ Hz, 1H), 4.52 (q, $J=7.2$ Hz, 2H), 4.44 (q, $J=7.2$ Hz, 2H), 1.46 (t, $J=7.2$ Hz, 3H), 1.43–1.38 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=196.7$, 165.7, 164.2, 162.5, 153.9, 151.2, 140.5, 138.4, 134.6, 133.9, 126.3, 121.2, 120.0, 111.2, 62.9, 62.8, 14.2 ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}O_6N^{79}Br$ $[M+H]^+$: 422.02338; found: 422.02310.

Compound 19i: Off-white solid; $R_f=0.55$ (CH/EtOAc 3:2); m.p. 90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.75$ (d, $J=3.9$ Hz, 1H), 9.40 (d, $J=1.9$ Hz, 1H), 9.06 (d, $J=2.0$ Hz, 1H), 8.58 (t, $J=2.1$ Hz, 1H), 7.60–7.55 (m, 1H), 7.48 (dd, $J=8.0$, 1.6 Hz, 1H), 7.11 (dd, $J=8.5$, 0.8 Hz, 1H), 6.93 (ddd, $J=8.2$, 7.2, 1.1 Hz, 1H), 4.00 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=198.3$, 164.8, 163.4, 153.2, 153.0, 137.37, 137.35, 132.8, 119.3, 118.9, 77.3, 77.0, 76.7, 52.8 ppm; HRMS: *m/z* calcd for $C_{13}H_{12}O_4N$ $[M+H]^+$: 258.07608; found: 258.07583.

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