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Enantioselective synthesis of 3,4-dihydropyran-2-ones *via* PTC addition-cyclisation of acetylacetone to cinnamic thioesters

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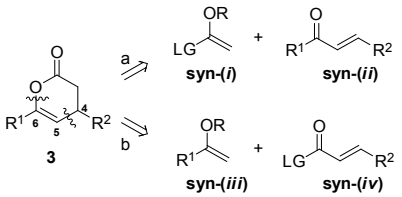
KEYWORDS: Phase Transfer Catalysis, Desymmetrisation, Michael Initiated Cyclisation Reactions

ABSTRACT: Herein we present the first example of synthesis of 3,4-dihydropyran-2-ones from cinnamic thioesters *via* a stereoselective phase-transfer catalysed domino Michael-cyclisation reaction with acetylacetone. The reaction proceeded under the catalysis of *Cinchona*-derived quaternary ammonium phenoxide that in combination with inorganic bases provided 3,4-dihydropyran-2-ones in yields of up to 93% and enantioselectivities of up to 88% ee.

INTRODUCTION

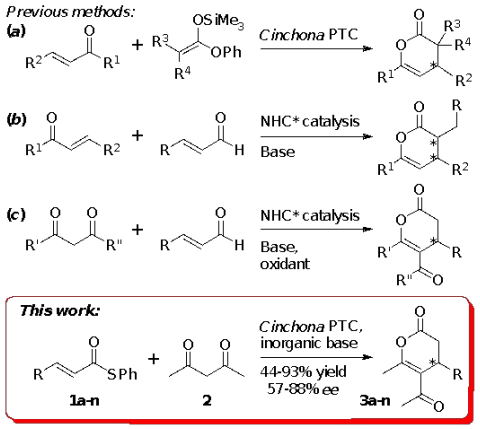
3,4-Dihydropyran-2-ones **3** (Scheme 1) are widely recognised as useful building blocks for the synthesis of valuable classes of organic compounds, such as 2-pyrones,[1–3] γ-lactones,[3] cyclic enamines,[4] functionalised enones.[5] The preparation of heterocycles **3** has been a subject of study for more than two decades.[6] The majority of the reported methods revolved around disconnecting the C_4–C_5 and C_6–O_1 (Scheme 1). This approach identified synthons **syn-(*i-iv*)** as the required building blocks to form 3,4-dihydropyran-2-ones **3**. For example, the reaction of an ester enolate equivalent **syn-(*i*)** with an α,β-unsaturated carbonyl compound **syn-(*ii*)** has been the most frequently reported method (Scheme 1, path a); the presence of a good leaving group (LG) on the nucleophilic component was found to be essential for the cyclisation to take place. A complementary route is represented by the reaction of a carbonyl enolate **syn-(*iii*)** and a cinnamate equivalent **syn-(*iv*)** (Scheme 1, path b), where LG- represents an imidazole.[7,8]

Scheme 1: Frequent disconnections adopted for the assembly of 3,4-dihydropyran-2-ones **3**.



Organocatalytic methodologies have been optimised to provide **3** via disconnecting C_4–C_5 and C_6–O_1.[7–13] In this context, Mukaiyama reported a domino Michael–cyclisation procedure that was catalysed by *Cinchona*-derived quaternary ammonium phenoxides. In this transformation, the phenoxide nucleophile was used to unleash an enolate nucleophile from ketene silyl acetal precursors (Scheme 2a).[9] The ammonium enolates, so obtained, reacted with chalcones to provide, after cyclisation, 3,4-dihydropyran-2-ones with high enantioselectivity.

Scheme 2: Stereoselective syntheses of chiral substituted 3,4-dihydropyran-2-ones **3**.



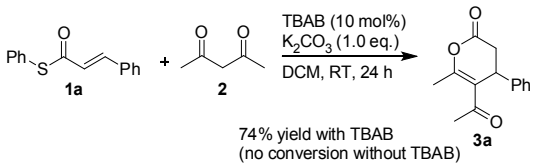
Arylacetyl phosphonates reacted with α,β-unsaturated-γ-keto esters under the catalysis of a bifunctional aminothiourea providing *syn*-3,4-dihydropyran-2-ones in moderate yields, high enantio- and diastereoselectivity.[10] Preparation of **3** via NHC catalysis has been reported (Scheme 2, **b-c**).[11,12] The reaction of α,β-unsaturated aldehydes and α,β-unsaturated ketones offered an alternative route to assembling the 3,4-dihydropran-2-one core **3** based upon disconnecting the C_3–C_4 and the C_6–O_1 bonds. This reaction proceeded in the presence of a *N*-heterocyclic carbenes (NHC) and an organic base;[14] α,β-unsaturated aldehydes reacted 1,3-dicarbonyls under NHC-catalysis and in the presence of an additional oxidant (Scheme 2, **b**–**c**).[15] NHC catalysts have displayed

exceptional activity for a large number of substrates and under various reaction conditions; most notably in their applications in biphasic aqueous/organic systems.[11,12,15] However, in spite of the high ees which have been reported, it should be noted that the preparation of chiral NHCs involve several steps and therefore are less expeditious when compared to other types of organocatalytic systems, for example phase transfer catalysis using *Cinchona*-based quaternary ammonium species. Moreover, very reactive starting materials[11,16] and the use of stoichiometric oxidants[15] constitute an important limitation, which has restricted the scope of NHC-catalysed methodologies. In this context, the development of a new and mild catalytic approach for the formation of 3,4-dihydropyran-2-ones fills a gap in the state of the art, providing an easy-to-execute procedure to access important compounds. Herein we report the first stereoselective synthesis of 3,4-dihydropyran-2-ones **3** from cinnamic thioesters **1** which proceeds *via* a phase-transfer catalysed domino Michael–lactonisation reaction with acetylacetone **2**; where the phase-transfer catalysts (PTC) are *Cinchona*-derived quaternary ammonium salts (Scheme 2).

RESULTS AND DISCUSSION

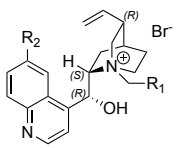
We initially attempted the cyclisation of cinnamic thioester **1a** and acetylacetone (**2**) in the presence of an ammonium phase transfer catalyst—tetrabutylammonium bromide (TBAB)—with potassium carbonate as the base and dichloromethane as the solvent. We found those conditions to furnish the desired 3,4-dihydropyran-2-one **3a** in 74% isolated yield. The dependence of the reaction on PTC was supported by the control reaction which showed no conversion to **3a** in the absence of TBAB (Scheme 3).

Scheme 3: Michael addition of acetylacetone **2** to cinnamic thioester **1a** promoted by ammonium phase transfer catalyst.

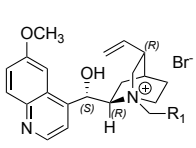


We then considered using chiral phase-transfer catalysis to impart an enantioselective outcome to this reaction. Our research group has recently described some highly enantioselective Michael Initiated Cyclisation Reactions (MICR), which proceed in the presence of chiral *Cinchona*-derived quaternary ammonium salts.[17–24] Salts of *Quininium/Cinchonidinium* **4**, *Quinidinium* **5** and *Dihydroquinidinium* **6** can be easily prepared in a single step by quaternisation of cheap, commercially available *Cinchona* alkaloids with a variety of alkylating agents.[17–24] *Cinchona* alkaloids are convenient materials for organocatalysis, and have been preferred to other classes of chiral ammonium salts, which require longer syntheses.[25] With this in mind, we screened a range of *Cinchona*-derived PTCs **4a**–**g**, **5a**–**b** and **6** (Table 1) in the model reaction of cinnamic thioester **1a** and acetylacetone **2**. This study demonstrated that compound **3a** could be obtained in good isolated yields, however enantioselectivity was limited to 38% ee. Since this initial set of experiments it was noted that the reaction time should be prolonged to 48h to achieve maximal yield in compound **3a**. This additional time was required to aloow lactonisation to occur.

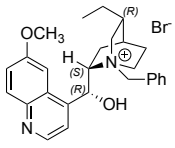
Table 1 Screening of *Cinchona*-derived quaternary ammonium salts [a]



4a: $R_1 = C_6H_5$; R_2 = H
4b: $R_1 = C_6H_5$; $R_2 = OCH_3$
4c: R_1 = 9-anthracenyl; $R_2 = OCH_3$
4d: $R_1 = 3,5\text{-}(^tBu)_2C_6H_3$; $R_2 = OCH_3$
4e: $R_1 = 4\text{-}(CF_3)C_6H_4$; $R_2 = OCH_3$
4f: $R_1 = 3,5\text{-}(CF_3)_2C_6H_4$; $R_2 = OCH_3$
4g: $R_1 = 2\text{-}(OCH_3)C_6H_4$; $R_2 = OCH_3$



5a: $R_1 = C_6H_5$
5b: $R_1 = C_6F_5$



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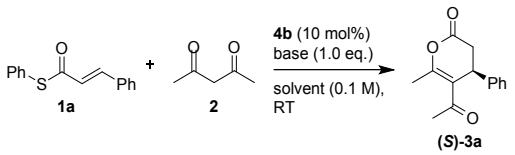
Entry	Catalyst	*t* (h)	Yield (%)[b]	ee (%)[c]
1	**4a**	72	50	27 (*S*)
2	**5a**	48	53	18 (*R*)
3	**4b**	48	63	38 (*S*)
4	**5b**	24	65	20 (*R*)
5	**4c**	48	-	-
6	**4d**	48	60	28 (*S*)
7	**4e**	48	50	35 (*S*)
8	**4f**	48	20	35 (*S*)
9	**4g**	48	64	33 (*S*)
10	**6**	44	61	37 (*S*)

[a] Reaction conditions: **1a** (0.10 mmol), acetylacetone **2** (0.12 mmol), K_2CO_3 (0.10 mmol), catalyst **4a–g**, **5** or **6** (0.01 mmol), solvent (1 mL), 48h. [b] Isolated yield after column chromatography. [c] Determined by HPLC (Chiralpak AD).

This study identified ammonium salt **4b** as the catalyst providing **3a** in highest ees. In a following optimisation step, we reacted **1a** and **2** to provide **3a** under the catalysis of **4b** in the presence of various bases and solvent systems. (Table 2). When the reaction was carried out using cesium fluoride as the base (Table 2, entry 1), the yield of the model reaction was poor with **3a** obtained in just 10% yield and 21% ee. Potassium phosphate gave a significant improvement, providing **3a** in 61% yield and 41% ee (Table 2, entry 2). Potassium hydroxide produced similar enantioselectivity (46% ee) but reduced yield (33%). When lithium hydroxide was tested as the base, there was no conversion towards **3a** (Table 2, entry 4). Tetrahydrofuran, toluene, diethyl ether, 1,4-dioxane and DCM were tested as solvents—with potassium carbonate as a base and 48 h of reaction time—however, none of those solvents produced results superior to that achieved with dichloromethane,

which provided **3a** in 63% yield and 38% ee (Table 2, entries 5–9).

Table 2 Screening of bases and solvents [a]

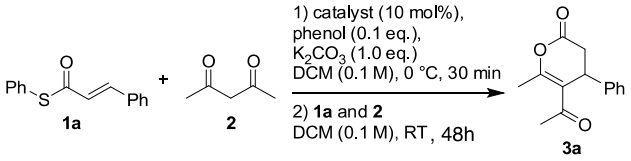


Entry	Base	Solvent	*t* (h)	Yield (%)[b]	ee (*S*, %)[c]
1	CsF	DCM	44	10	21
2	K_3PO_4	DCM	45	61	41
3	KOH	DCM	46	33	46
4	LiOH	DCM	48	-	-
5	K_2CO_3	toluene	48	25	37
6	K_2CO_3	THF	48	53	28
7	K_2CO_3	Et_2O	48	11	16
8	K_2CO_3	1,4-dioxane	48	58	17
9	K_2CO_3	DCM	48	63	38

[a] Reaction conditions: **1a** (0.10 mmol), acetylacetone (0.12 mmol), base (0.10 mmol), **4b** (10 mol%), solvent (1 mL). [b] Isolated yield after column chromatography. [c] Determined by HPLC (Chiralpak AD).

At this point, we considered the addition of a phenolate additive. Lygo and co-workers have reported the use of phenolates to impart improved stereoselectivity to certain types of *Cinchona*-derived PTC-catalysed Michael additions that, using strongly activated electrophilic alkenes, progressed *via* a base catalysed (hence unselective) background pathway.

Table 3 Screening of catalysts in presence of phenol co-catalyst [a]

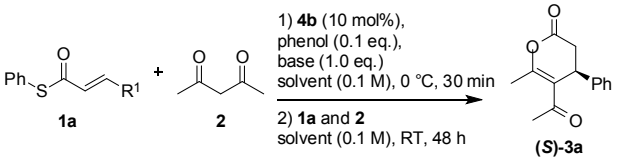


Entry	Catalyst	*t* (h)	Yield (%)[b]	ee (%)[c]
1[d]	**4a**	40	41	23 (*S*)
2	**4a**	40	30	45 (*S*)
3	**4b**	36	62	80 (*S*)
4	**4c**	44	0	-
5	**4d**	44	52	80 (*S*)
6	**4e**	44	30	82 (*S*)
7	**5a**	36	60	78 (*R*)
8	**5b**	44	0	-
9	**6**	44	64	79 (*S*)

[a] Reaction conditions: **1a** (0.10 mmol), acetylacetone (0.12 mmol), base (0.10 mmol), catalyst (0.01 mmol), phenol (0.01 mmol), DCM (1 mL). [b] Isolated yield after column chromatography. [c] Determined by HPLC (Chiralpak AD). [d] No phenol added.

Hence, the Michael addition of glycine imides to methyl acrylate were significantly influenced by addition of a softer base relay such as a phenolate, which suppressed the undesired uncatalysed background reaction.[26] Adapting the procedure reported by Lygo and co-workers, *Cinchona*-derived quaternary ammonium phenoxides (10 mol%) were generated *in situ* by stirring a mixture of the ammonium bromide salts with co-catalytic amounts of phenol and a stoichiometric amount of K_2CO_3 at 0 °C for 30 min, before warming to room temperature and completing the addition of the cinnamic thioester **1a** and acetylacetone **2**. This protocol was applied to the model reaction using a suite of PTCs (Table 3). Significantly, when compounds **1a** and **2** were reacted in the presence of catalyst **4a** the addition of phenolate provoked a significant improvement of the observed enantioselectivity for **3a**, which increased from 23% ee to 45% ee (Table 3, entries 1 and 2). Phenolate addition to catalysts **4b**, **4d** and **4e** (Table 3, entries 3, 5 and 6) improved their performed equally well, providing desired **3a** in significantly higher ees when compared to data obtained without the phenolate (Table 1). We reasoned that the anthracenyl-substituted catalyst **4c** may have been too sterically encumbered to allow the reaction to proceed.

Table 4 Screening of bases and solvents in the presence of phenol co-catalyst [a]

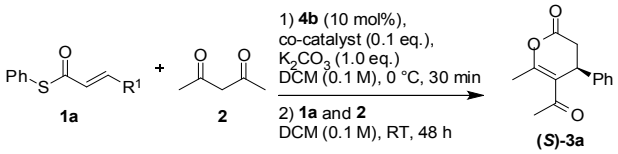


Entry	Base	Solvent	*t* (h)	Yield (%)[b]	ee (*S*, %)[c]
1	K_2CO_3	DCM	36	60	80
2	KOH	DCM	48	73	74
3	Cs_2CO_3	DCM	48	71	78
4	K_2CO_3	toluene	44	20	70
5	K_2CO_3	THF	44	41	49
6	K_2CO_3	CPME[d]	44	16	59
7[e]	K_2CO_3	DCM	47	66	81
8	K_2CO_3	$CHCl_3$	50	35	86

[a] Reaction conditions: **1a** (0.10 mmol), acetylacetone (0.12 mmol), base (0.10 mmol), **4b** (0.01 mmol), solvent (1 mL). [b] Isolated yield after column chromatography. [c] Determined by HPLC (Chiralpak AD). [d] CPME = cyclopentyl methyl ether. [e] anhydrous and anaerobic conditions.

Considering that the presence of phenolate impacted on the catalyst active concentration and basicity of the reaction media, a further base/solvent screening was run to ascertain if higher level of enantioselectivity could be obtained (Table 4). In this study a small selection of bases, such as K_2CO_3, Cs_2CO_3 and KOH, were selected and were tested in a suitably wide range of solvent. This study identified K_2CO_3 as the best base promoting formation of desired compound **3a** in up to 80% ees (Table 4, entries 1, 7 and 8). When the reaction was run in chloroform compound **3a** was obtained in highest 86% ees, but in a reduced 35% yield (Table 4, entry 8). Running the reaction under inert N_2 atmosphere did not have an impact on both yield and enantioselectivity (Table 4, compare entries 1 and 7). Hence, DCM and K_2CO_3 were finally selected as the optimal solvent / base system for the preparation of **3a**.

Table 5 Co-catalyst screening under optimised conditions [a]



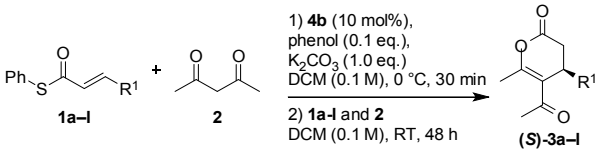
Entry	co-catalyst	pK_a	*t* (h)	Yield (%)[b]	ee (*S*, %)[c]
1	phenol	9.95	36	60	80
2	thiophenol	7.00	48	40	40
3	4-OCH_3-phenol	10.20	48	50	73
4	2,4,6-trimethylphenol	11.10	40	75	67
5	4-bromophenol	9.32	44	45	77
6	4-nitrophenol	7.14	46	30	56
7	2-naphthol	9.50	44	54	77

[a] Reaction conditions: **1a** (0.10 mmol), acetylacetone (0.12 mmol), base (0.10 mmol), **4b** (0.01 mmol), additive (0.01 mmol), DCM (1 mL); Nitrogen atmosphere and dry DCM were used. [b] Isolated yield after column chromatography; apart from the desired product, only unreacted starting material was isolated. [c] Determined by HPLC (Chiralpak AD).

A screening of phenolic co-catalysts was also performed using the optimised reaction conditions identified in Table 4 for the benchmark reaction of cinnamic thioester **1a** and acetylacetone **2** (Table 5). When thiophenol was used as the additive compound (*S*)-**3a** was obtained in 40% yield and in a reduced 40% ee (Table 5, entry 2). Anisole, 4-bromophenol, 4-nitrophenol, and β-naphthol, each provided compound (*S*)-**3a** in 30–50% yield and 56–77% ee; i.e. also inferior to phenol (Table 5; entries 3, 5–7). In the case of 2,4,6-trimethylphenol, however, (*S*)-**3a** was obtained in slightly higher yield of 75%, but reduced enantioselectivity of 67% ee. We have reported (Table 5) the pKa values of the additives.[27] A comparison of the pKa of the additive used and the observed ees for **3a** indicated a link between these figures. Hence additives more acidic than phenol, i.e. thiophenol and 4-NO_2-phenol (Table 5; entries 2 and 6), provided compound **3a** in a significantly reduced enantioselectivity. In contrast, when additives with similar acidity to phenol were employed, i.e. 4-Br-phenol and 2-naphthol (Table 5; entries 5 and 7), **3a** was obtained in similarly high ees. Ultimately, unsubstituted phenol was identified as the optimal additive for this reaction. A control experiment in which only 0.1 equiv of inorganic base was used, which provided the desired compound **3a** in only 17%, but in increased 88% ee; meanwhile, reacting **3a** and **1** in the presence of **4b** and one equivalent of potassium phenoxide provided no conversion. These experiment proved that there is, albeit minimal, a contribution from an uncatalysed background reaction under the optimised conditions.

In order to demonstrate scope of the reaction, an array of cinnamic thioesters **1a–l** were reacted with **2** under the optimised reaction conditions (Table 6). Cinnamic thioesters with electron withdrawing groups reacted equally well, providing their target compounds in nominally high isolated yields and good enantioselectivities (Table 6; entries 2–4, 6–7, 10–12). Conversely, cinnamic thioester **1e** bearing electron-donating methoxy reacted sluggishly, providing the resulting product with moderate yield and as essentially a racemic mixture (Table 6, entry 5). A naphthyl substituent proved to be too sterically encumbering for the reaction to proceed (Table 6, entry 9). Reaction of aliphatic α,β-unsaturated thioesters **1m** and **1n** and **2** under optimised conditions provided correspondent **3m** and **3n** in good yields and enantioselectivity, demonstrating the applicability of the methodology reported herein to the preparation of aromatic and aliphatic title compounds.

Table 6 Substrate scope under optimised conditions [a]



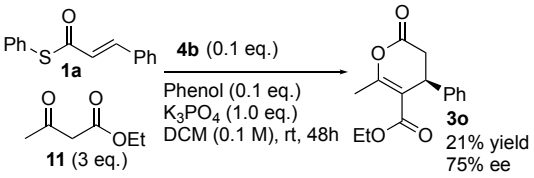
Entry	Product	R^1	Yield (%)[b]	ee (*S*, %)[c]
1	**3a**	Ph	82	77
2	**3b**	2-ClC_6H_4	78	88
3	**3c**	3-ClC_6H_4	72	57
4	**3d**	4-ClC_6H_4	72	82
5	**3e**	4-(OMe)C_6H_4	44	5
6	**3f**	4-FC_6H_4	93	80
7	**3g**	4-$CF_3C_6H_4$	93	83
8	**3h**	4-MeC_6H_4	75	76
9	**3i**	1-naphthyl	-	-
10	**3j**	2-furyl	75	76
11	**3k**	5-methylfur-2-yl	55	77
12	**3l**	Thiophenyl	80	88
13	**3m**	$CH_3(CH_2)_2$	72	78
14	**3n**	CH_3	74	77

[a] Reaction conditions: **1a–l** (0.10 mmol), **2** (0.12 mmol), base (0.10 mmol), **4b** (10 mol%), phenol (0.01 mmol),

DCM (1 mL), 48 h under nitrogen atmosphere. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC (Chiralpak AD).

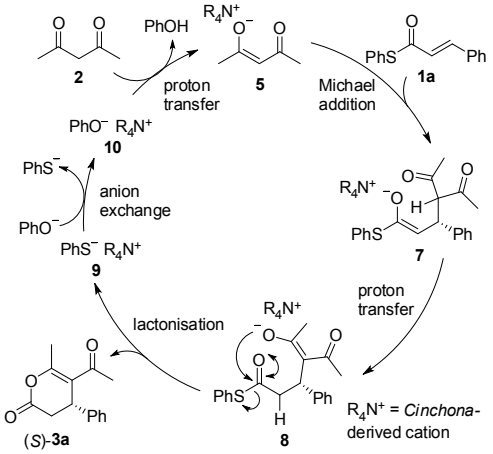
Use of ethyl acetoacetate **11** as the Michael donor, with potassium phosphate as the base, provided the corresponding 3,4-dihydropyran-2-one (*S*)-**3m** (Scheme 4) in 21% yield and 75% ee, where the absolute stereochemistry was confirmed by previously reported literature.[28]

Scheme 4: Preparation of *(S)*-**3m**



The proposed catalytic cycle for the domino Michael–lactonisation process (Scheme 5) is proposed to start *via* deprotonation of acetylacetone **2** by a basic phenoxide anion of chiral quaternary ammonium phenoxide salt **10**. The resulting chiral ammonium–enolate complex **5** then performs a stereoselective Michael addition to the electrophilic olefin moeity of cinnamic thioester **1a**, where the enantiofacial selectivity is directed by the interaction of the enolate **5** with the chiral *Cinchona*-derived cation. The resulting intermediate **7** proceeds *via* an intramolecular proton transfer to form intermediate **8**, which finally undergoes enantioselective lactonisation to give 3,4-dihydropyran-2-one (**3a)**. The resulting chiral ammonium thiophenolate **9** may then undergo an ion exchange to reform **10**, thus completing the catalytic cycle.

Scheme 5: Proposed catalytic cycle for the stereoselective formation of **3**



In conclusion, a new synthesis of 3,4-dihydropyran-2-ones starting from cinnamic thioesters **3** and acetylacetone was uncovered and optimised, where the reaction proceeds exclusively in the presence of quaternary ammonium PTCs and a stoichiometric base. Cinnamic esters are known to be poor Michael acceptors, for which reason a number of cinnamic ester synthetic equivalents, including 4-nitro-5-styrylisoxazoles,[17] have been developed.

Cinnamic thioesters have been scarcely investigated, with only one report in the literature describing their use in the preparation of amino acid derivatives.[29] Therefore the chemistry described herein proposes thioesters as an efficient synthetic handle to impart improved reactivity with cinnamates in Michael reactions. Furthermore, introduction of a phenolate anion to the reaction manifold dramatically improved reaction performance, which indicated that the basic anion facilitates formation of the enolate complex **5**. The use of *Cinchona*-derived ammonium phenolate PTCs permitted access to a range of chiral 3,4-dihydropyran-2-ones **3** in up to 93% yield and 88% ee. The substrate scope of this new transformation was found to tolerate a range of electron rich and electron poor functional groups, providing **3** in generally good yield and enantioselectivity for the range of cinnamic thioesters tested.

EXPERIMENTAL SECTION

Materials and Methods: NMR experiments were performed on a Bruker Avance 400 instrument and samples were obtained in $CDCl_3$ (referenced to 7.26 ppm for ^1H and 77.0 for ^{13}C) and in DMSO-d_6 (referenced to 2.52 and 3.35 ppm for ^1H and 40.0 for ^{13}C). Coupling constants (*J*) are in Hz. Multiplicities are reported as follows: s, singlet; d, doublet; dd, doublets of doublets; t, triplet, q; quartet, m, multiplet; c, complex; and br, broad. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD, Chiralcel OD), using a UV detector operating at 254 nm. Tetrahydrofuran was freshly distilled over sodium benzophenone prior to use according to standard procedure. All other reagents and solvents were used as purchased from Aldrich. Reactions were monitored for completion by TLC (EM Science, silica gel 60 F254). Flash chromatography was performed using silica gel 60 (0.040–0.063 mm, 230–400 mesh). Retention factors (R_f) are reported to ± 0.05. Mass spectra and HRMS were recorded using a MALDI ToF mass spectrometer. Catalysts **4a**–**e**, **5a**–**b**, and **6** were prepared according to the procedures reported by Lygo[30] and Corey.[31]

General procedure A: for the stereoselective synthesis of 3,4-dihydropyran-2-ones (**3a**–**n**).

In a 10 mL test tube *N*-benzylquininium bromide (0.02 mmol), K_2CO_3 (0.20 mmol) and phenol (0.02 mmol) were dissolved in dry DCM (1.8 mL) and the resulting purple reaction mixture was stirred for 30 min at 0 °C. Cinnamic thioester **1a** (0.20 mmol) and acetylacetone (41 μL, 0.40 mmol) were added and the reaction was allowed to warm to room temperature and stirred for 48 h under nitrogen. The solvent was evaporated *in vacuo* and the crude was purified by silica flash chromatography (AcOEt : petroleum ether, 1 : 5). Pure 3,4-dihydropyran-2-ones **3a–l** were obtained as solid materials.

General procedure B: for the racemic synthesis of 3,4-dihydropyran-2-ones (**3a**–**n**).

In a 10 mL test tube cinnamic thioester **3a–l** (0.20 mmol), TBAB (0.02 mmol), K_2CO_3 (0.20 mmol) and phenol (0.02 mmol) were dissolved in dry DCM (1.8 mL). Acetylacetone (0.40 mmol) was added and the reaction mixture was stirred for 24 h under nitrogen. After evaporation of the solvent, crude mixture was purified by silica flash chromatography (AcOEt : petroleum ether, 1 : 5).

(*S*)-5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyran-2-one (**3a**).

White solid, m.p. 69-71 °C, 38 mg, 82% yield (general procedure A), 20 mg, 44% yield (general procedure B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 3H), 7.18 – 7.12 (m, 2H), 4.18 – 4.13 (m, 1H), 2.98 (dd, *J* = 15.7, 7.2 Hz, 1H), 2.84 (dd, *J* = 15.7, 2.6 Hz, 1H), 2.43 (s, 3H), 2.13 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 198.1, 165.7, 160.4, 129.5, 127.6, 126.7, 117.3, 38.9, 38.8, 37.2, 29.6, 19.1 ppm. FTIR (cm^{-1}): 3024, 2924, 1774, 1689, 1627, 1489, 1442, 1357, 1026, 948, 864. HRMS *m/z*: $[M+H]^+$ calcd for $C_{14}H_{15}O_3$ 231.1021; found 231.1018. Chiral HPLC (Chiralpak AD, *n*-hexane/ethanol 95 : 5, 1 mL/min, 76% ee); retention time = 15.96 min, 17.22 min. Physical and spectral data agreed with the literature values.[32]

(*R*)-5-Acetyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyran-2-one (**3b**).

Yellow wax, 41 mg, 78% yield (general procedure A), 39 mg, 72% yield (general procedure B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.43 (m, 1H), 7.26 – 7.21 (m, *J* = 6.4, 2.5 Hz, 2H), 7.06 – 7.02 (m, 1H), 4.64 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.96 (dd, *J* = 15.8, 6.7 Hz, 1H), 2.90 (dd, *J* = 15.8, 2.0 Hz, 1H), 2.47 (s, 3H), 2.07 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.6, 165.3, 161.6, 136.3, 133.1, 130.6, 129.5, 127.9, 127.4, 116.0, 35.6, 34.9, 29.3, 19.1 ppm. HRMS *m/z*: $[M+H]^+$ calcd for $C_{14}H_{14}ClO_3$ 265.0631; found 265.0635. Chiral HPLC (Chiralpak AD, *n*-hexane/ethanol 95 : 5, 1 mL/min 88% ee); retention time = 21.31 min, 22.96 min. Physical and spectral data agreed with the literature values.[33]

(*S*)-5-Acetyl-4-(3-chlorophenyl)-6-methyl-3,4-dihydropyran-2-one (**3c**).

Orange wax, 38 mg, 72% yield (general procedure A), 26 mg, 50% yield (general procedure B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 2H), 7.14 (s, 1H), 7.06 – 7.01 (m, 1H), 4.18 – 4.13 (m, 1H), 2.97 (dd, *J* = 15.7, 7.3 Hz, 1H), 2.83 (dd, *J* = 15.7, 2.5 Hz, 1H), 2.45 (s, 3H), 2.16 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.3, 165.2, 160.9, 141.8, 135.3, 130.8, 128.3, 127.0, 124.8, 116.9, 38.4, 36.9, 30.0, 19.3 ppm. HRMS *m/z*: $[M+H]^+$ calcd for $C_{14}H_{14}ClO_3$ 265.0631; found 265.0633. Chiral HPLC (Chiralpak AD, *n*-hexane/ethanol 95 : 5, 1 mL/min, 57% ee); retention time = 13.21 min, 14.43 min. Physical and spectral data agreed with the literature values.[16]

(*S*)-5-Acetyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyran-2-one (**3d**).

Yellow wax, 38 mg, 72% yield (general procedure A), 35 mg, 67% yield (general procedure B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.12 – 7.06 (m, 2H), 4.17 – 4.12 (m, 1H), 2.96 (dd, *J* = 15.7, 7.2 Hz, 1H), 2.81 (dd, *J* = 15.7, 2.5 Hz, 1H), 2.43 (s, 3H), 2.14 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.5, 165.3, 160.7, 138.3, 133.9, 129.6, 128.1, 117.2, 38.2, 37.0, 31.6, 29.9, 29.7, 22.7, 19.2, 14.1 ppm. HRMS *m/z*: $[M+H]^+$ calcd for $C_{14}H_{14}ClO_3$ 265.0631; found 265.0636. Chiral HPLC (Chiralpak OD, *n*-hexane/ethanol 95 : 5, 1 mL/min 82% ee); retention time = 17.74 min, 22.51 min. Physical and spectral data agreed with the literature values.[33]

(*S*)-5-Acetyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyran-2-one (**3e**)

Yellow wax, 23 mg, 44% yield (general procedure A), 9 mg, 17% yield (general procedure B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 – 6.96 (m, 2H), 6.82 – 6.76 (m, 2H), 4.05 – 4.01 (m, 1H), 3.71 (s, 3H), 2.87 (dd, *J* = 15.6, 7.1 Hz, 1H), 2.74 (dd, *J* = 15.6, 2.6 Hz, 1H), 2.35 (s, 3H), 2.05 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 202.8, 175.6, 158.8, 131.3, 129.1, 127.8, 114.8, 114.2, 55.2, 40.5, 38.9, 29.9, 19.1. HRMS *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}O_4$ 261.1127; found 261.1130. Chiral HPLC (Chiralpak AD, *n*-hexane/ethanol 95 : 5, 1 mL/min, 5% ee); retention time = 20.75 min, 32.00 min. Physical and spectral data agreed with the literature values.[34]

(*S*)-5-Acetyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyran-2-one (**3f**).

Yellow solid, 46 mg, 93% yield (general procedure A), 33 mg, 66% yield (general procedure B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.08 (m, 2H), 7.07 – 6.97 (m, 2H), 4.19 – 4. 14 (m, 1H), 2.96 (dd, *J* = 15.7, 7.2 Hz, 1H), 2.81 (dd, *J* = 15.7, 2.5 Hz, 1H), 2.43 (s, 3H), 2.14 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.6, 165.5, 163.5, 162.3 (d, *J* = 247.0 Hz), 135.5, 135.4, 128.4 (d, *J* = 8.2 Hz), 117.4, 116.4 (d, *J* = 21.6 Hz), 38.1, 37.2, 37.2, 29.9, 19.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –114.37 ppm. HRMS *m/z*: $[M+H]^+$ calcd for $C_{14}H_{14}FO_3$ 249.0927; found 249.0929. Chiral HPLC (Chiralpak AD, *n*-hexane/ethanol 95 : 5, 1 mL/min, 80% ee); retention time = 14.92 min, 19.55 min. Physical and spectral data agreed with the literature values.[33]

(*S*)-5-Acetyl-6-methyl-4-(4-(trifluoromethyl)phenyl)-3,4-dihydropyran-2-one (**3g**).

Orange solid, 55 mg, 93% yield (general procedure A), 45 mg, 75% yield (general procedure B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.28 – 4.24 (m, 1H), 3.00 (dd, *J* = 15.8, 7.3 Hz, 1H), 2.84 (dd, *J* = 15.8, 2.3 Hz, 1H), 2.46 (s, 3H), 2.17 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.1, 165.1, 161.0, 143.9, 130.3 (q, *J* = 32.6 Hz), 127.9, 127.2, 126.5 (q, *J* = 3.7

Hz), 124.5 (q, J = 273.7 Hz), 117.1, 125.2, 122.5, 119.8, 38.5, 36.7, 30.0, 19.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ – 62.66 ppm. FTIR (cm^{-1}): 2922, 2853, 1323, 1108, 1067, 838. HRMS *m/z*: $[M+H]^+$ calcd for $C_{15}H_{14}F_3O_3$ 299.0895; found 299.0891. Chiral HPLC (Chiralpak AD, *n*-hexane/ethanol 95 : 5, 1 mL/min, 83% ee); retention time = 12.48 min, 19.02 min. Physical and spectral data agreed with the literature values.[35]

(*S*)-5-Acetyl-6-methyl-4-(4-tolyl)-3,4-dihydropyran-2-one (**3h**).

Orange wax, 37 mg, 75% yield (general procedure A), 24 mg, 50% yield (general procedure B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.11 (m, 2H), 7.06 – 6.99 (m, 2H), 4.12 – 4.08 (m, 1H), 2.95 (dd, J = 15.6, 7.1 Hz, 1H), 2.81 (dd, J = 15.6, 2.7 Hz, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 2.12 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 198.1, 165.8, 160.2, 137.7, 136.6, 130.1, 126.6, 117.4, 38.5, 37.3, 29.7, 21.0, 19.1 ppm. FTIR (cm^{-1}): 2923, 1772, 1694, 1662, 1597, 1417, 1109, 1018, 819. HRMS *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}O_3$ 245.1178; found 245.1181. Chiral HPLC (Chiralpak AD, *n*-hexane/ethanol 95 : 5, 1 mL/min, 78% ee); retention time = 10.86 min, 14.05 min. Physical and spectral data agreed with the literature values.[35]

(*R*)-5-Acetyl-4-(furan-2-yl)-6-methyl-3,4-dihydropyran-2-one (**3j**)

Orange solid, 33 mg, 75% yield (general procedure A), 26 mg, 60% yield (general procedure B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 1H), 6.29 – 6.25 (m, 1H), 6.08 (d, J = 3.3 Hz, 1H), 4.27 – 4.25 (m, 1H), 3.04 (dd, J = 15.9, 2.1 Hz, 1H), 2.84 (dd, J = 15.9, 6.8 Hz, 1H), 2.36 (s, 3H), 2.30 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.1, 165.5, 161.0, 152.5, 142.8, 115.7, 110.4, 106.6, 33.8, 32.3, 29.8, 19.4 ppm. FTIR (cm^{-1}): 2922, 1782, 1689, 1606, 1145, 1114, 1012, 942, 740. HRMS *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}O_4$ 221.0814; found 221.0809. Chiral HPLC (Chiralpak OD, *n*-hexane/ethanol 95 : 5, 1 mL/min, 76% ee); retention time = 15.76 min, 19.45 min. Physical and spectral data agreed with literature values.[36]

(*R*)-5-Acetyl-6-methyl-4-(5-methylfuran-2-yl)-3,4-dihydropyran-2-one (**3k**)

Orange wax, 26 mg, 55% yield (general procedure A), 7 mg, 15% yield (general procedure B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (d, J = 3.0 Hz, 1H), 5.84 (d, J = 3.0 Hz, 1H), 4.18 (d, J = 6.4 Hz, 1H), 3.04 (dd, J = 15.8, 2.1 Hz, 1H), 2.82 (dd, J = 15.8, 6.4 Hz, 1H), 2.36 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.1, 165.5, 161.0, 152.5, 142.8, 115.7, 110.4, 106.6, 33.8, 32.3, 29.8, 19.4 ppm. FTIR (cm^{-1}): 2922, 1782, 1689, 1606, 1145, 1114, 1012, 942, 740. HRMS *m/z*: $[M+H]^+$ calcd for $C_{13}H_{15}O_4$ 235.0970; found 235.0972. Chiral HPLC (Chiralpak OD, *n*-hexane/ethanol 95 : 5, 1 mL/min, 77% ee); retention time = 11.82 min, 15.12 min.

(*R*)-5-Acetyl-6-methyl-4-(thiophen-2-yl)-3,4-dihydropyran-2-one (**3l**)

Yellow solid, 38 mg, 80% yield (general procedure A), 17 mg, 35% yield (general procedure B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, J = 5.1, 1.1 Hz, 1H), 6.93 (dd, J = 5.1, 3.6 Hz, 1H), 6.84 (d, J = 3.6 Hz, 1H), 4.45 (dd, J = 6.1, 2.9 Hz, 1H), 3.00 (dd, J = 15.8, 2.9 Hz, 1H), 2.95 (dd, J = 15.8, 6.1 Hz, 1H), 2.41 (s, 3H), 2.27 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.2, 165.4, 160.8, 143.1, 127.5, 125.2, 124.8, 118.1, 37.4, 33.8, 29.8, 19.4 ppm. HRMS *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}O_3S$ 237.0585; found 237.0588.

Chiral HPLC (Chiralpak AD, *n*-hexane/ethanol 95 : 5, 1 mL/min, 88% ee); retention time = 17.72 min, 28.45 min. Physical and spectral data agreed with literature values.[37]

(*R*)-5-acetyl-6-methyl-4-propyl-3,4-dihydro-2H-pyran-2-one (**3m**)

Pale yellow oil, 30 mg, 72% yield (general procedure A), 24 mg, 19% yield (general procedure B).^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94 (dd, J = 11.4, 5.8 Hz, 1H), 2.74 (dd, J = 15.9, 1.7 Hz, 1H), 2.59 (dd, J = 15.9, 6.4 Hz, 1H), 2.36 (s, 3H), 2.28 (s, 3H), 1.50 – 1.31 (m, 4H), 0.91 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.81, 167.13, 158.87, 120.37, 35.58, 33.05, 32.03, 30.27, 19.81, 19.35, 13.87. HRMS *m/z*: $[M+H]^+$ calcd for $C_{11}H_{17}O_3$ 197.1178; found 197.1179. Chiral HPLC (Chiralpak AD, *n*-hexane/ethanol 95 : 5, 1 mL/min, 78% ee); retention time = 9.14 min, 14.71 min. Physical and spectral data agreed with the literature values.[38]

(*R*)-5-acetyl-4,6-dimethyl-3,4-dihydro-2H-pyran-2-one (**3n**)

Pale yellow oil, 24 mg, 72% yield (general procedure A), 24 mg, 6 mg, 19% yield (general procedure B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 – 2.99 (m, 1H), 2.67 (dd, $_J$ = 15.7, 6.1 Hz, 1H), 2.58 (dd, J = 15.7, 2.1 Hz, 1H), 2.35 (s, 3H), 2.28 (s, 3H), 1.14 (d, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl3) δ 197.55, 166.93, 159.10, 120.64, 35.81, 30.06, 27.48, 19.38, 19.34. HRMS *m/z*: $[M+H]^+$ calcd for $C_9H_{13}O_3$ 169.0865; found 169.0861. Chiral HPLC (Chiralpak AD, *n*-hexane/ethanol 95 : 5, 1 mL/min, 77% ee); retention time = 13.39 min, 20.99 min. Physical and spectral data agreed with the literature values.[34]

Ethyl 6-methyl-4-phenyl-3,4-dihydropyran-2-one-5-carboxylate (**3o**).

In a 10 mL test tube *N*-benzylquininium bromide (10 mg, 0.02 mmol), K_3PO_4 (47 mg, 0.22 mmol) and phenol (2 mg 0.02 mmol) were dissolved in dry DCM (2.0 mL). The resulting purple reaction mixture was stirred for 30 min at 0 °C. Cinnamic thioester **1a** (48 mg, 0.20 mmol) and ethyl acetoacetate (53 µL, 0.60 mmol) were added and the reaction was allowed to warm up to room temperature and stirred for 48 h under nitrogen. The solvent was evaporated *in vacuo* and the crude was purified by silica flash chromatography (Et_2O : petroleum ether, 1 : 15) to afford 11 mg of **3o** as a white solid material (21% yield). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.35 – 7.20 (m, 3H), 7.19 – 7.10 (m, 2H), 4.29 – 4.22 (m, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.95 (dd, *J* = 15.9, 7.6 Hz, 1H), 2.83 (dd, *J* = 15.9, 2.3 Hz, 1H), 2.48 (d, *J* = 0.9 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1, 166.0, 161.3, 140.7, 129.0, 127.5, 126.6, 110.0, 60.9, 37.9, 36.4, 18.9, 14.1 ppm. HRMS *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}O_4$ 260.1049; found 260.1047. Chiral HPLC (Chiralcel OD, *n*-hexane/*i*-propanol 90 : 10, 1 mL/min, 75% ee (*S*)-enantiomer); retention time = 7.83 min, 14.69 min. $[\alpha]_D$ = +91° (c = 0.6, $CHCl_3$). Physical and spectral data agreed with literature values.[39]

(2*E*)-3-phenyl-1-(phenylsulfanyl)prop-2-en-1-one (**1a**).

To a solution of cinnamoyl chloride (4.00 g, 24.0 mmol) in 30 mL of dry DCM, was added triethylamine (2.02 mL, 14.4 mmol) under nitrogen. A solution of thiophenol (1.32 g, 12.0 mmol) in 10 mL of dry DCM was added dropwise to the reaction mixture over twenty minutes. The reaction was stirred for 22 h than was diluted with 30 mL of DCM and extracted with 1M HCl (2 x 25 mL). The organic phase was than extracted with 25 mL of 5% $NaHCO_3$ with 20 mL of water. The organic layer was dried over sodium sulfate and was evaporated under vacuum. The crude was purified by silica flash chromatography (AcOEt : petroleum ether, 1:25) than crystallized in 40 mL of refluxing hexane. Product **1a** was obtained as a white solid (2.34 g, 82%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 16 Hz, 2H), 7.61 – 7.53 (m, 2H), 7.53 – 7.47 (m, 2H), 7.47 – 7.36 (m, 5H), 6.80 (d, *J* = 16 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 188.0, 141.5, 134.6, 134.0, 130.7, 129.4, 129.2, 129.0, 128.5, 127.6, 124.1. Spectral data agreed with literature values.[40]

(2*E*)-3-(2-chlorophenyl)-1-(phenylsulfanyl)prop-2-en-1-one (**1b**).

S-phenyl 2-(triphenylphosphoranylidene)ethanethioate was added to a solution of 2-chlorobenzaldehyde (1.0 g, 2.4 mmol) in 15 mL of dry toluene, at room temperature. The resulting mixture was stirred under N_2 atmosphere for 48 h at 60 °C. Crude was concentrated, purified via silica flash chromatography (AcOEt : petroleum ether 1 : 200) and crystallized with Et_2O/n-Hexane to obtain **1b** (131 mg, 30% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 16 Hz, 1H), 7.66 (dd, *J* = 7, 2 Hz, 1H), 7.53 – 7.41 (m, 6H), 7.38 – 7.27 (m, 2H), 6.78 (d, *J* = 16 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 187.9, 137.4, 135.6, 134.6, 132.4, 131.5, 130.3, 129.6, 129.3, 127.7, 127.4, 127.2, 126.6. Spectral data agreed with literature values.[40]

(*2E*)-3-(3-chlorophenyl)-1-(phenylsulfanyl)prop-2-en-1-one (**1c**).

S-phenyl 2-(triphenylphosphoranylidene)ethanethioate was added to a solution of 3-chlorobenzaldehyde (1.0 g, 2.4 mmol) in 15 mL of dry toluene, at room temperature. The resulting pink reaction mixture was stirred under N_2 atmosphere for 48 h at room temperature. Crude was concentrated, purified via silica flash chromatography (AcOEt : petroleum ether, 1 : 100) and crystallized with Et2O from n-hexane yielding **1c** as white needles (407 mg, 94% yield, m.p.128-131 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 16 Hz, 1H), 7.55 (s, 1H), 7.53 – 7.41 (m, 6H), 7.41 – 7.31 (m, 2H), 6.78 (d, *J* = 16 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 187.8, 139.8, 135.9, 135.07, 134.6, 130.6, 130.3, 129.6, 129.3, 128.1, 127.3, 126.7, 125.4. FTIR (cm^{-1}): 1608, 1673, 1019, 806, 785, 749, 689. HRMS *m/z*: $[M+H]^+$ calcd for $C_{15}H_{12}OClS$ 275.0297; found 275.0301.

(*2E*)-3-(4-chlorophenyl)-1-(phenylsulfanyl)prop-2-en-1-one *(***1d**).

4-Chlorocinnamic acid (554 mg, 3.0 mmol) was refluxed with thionyl chloride (3.0 mL, 42.5 mmol) in 17 mL of DCM overnight. The reaction mixture was cooled down to room temperature and concentrated to give a yellow oily solution. The concentrated oil was dissolved in 15 mL of dry DCM, and thiophenol (0.4 mL, 4.0 mmol) and triethylamine (5.7 mL, 41.0 mmol) were slowly added. The resulting solution was stirred at room temperature overnight, washed with 2% HCl until acidic pH was reached and extracted with DCM. The combined organic layer was washed with saturated $NaHCO_3$, saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Crude was purified *via* silica flash chromatography (petroleum ether) yielding **1d** as a brown powder (205 mg, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 16 Hz, 1H), 7.52 – 7.47 (m, 4H), 7.47 – 7.42 (m, 3H), 7.41 – 7.35 (m, 2H), 6.76 (d, *J* = 16 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 187.8, 140.0, 136.7, 134.6, 132.5, 129.6, 129.6, 129.3, 129.3, 127.4, 124.6. Spectral data agreed with literature values.[41]

(*2E*)-3-(4-methoxyphenyl)-1-(phenylsulfanyl)prop-2-en-1-one (**1e**).

(*E*)-4-Methoxycinnamic acid (1.0 g, 5.6 mmol) was refluxed with thionyl chloride (4.5 mL, 62.0 mmol) in 28 mL of DCM overnight. The reaction solution was cooled down to room temperature and concentrated to give a yellow oily solution. The concentrated oil was dissolved in 15 mL of DCM, and thiophenol (0.6 mL, 5.6 mmol) and triethylamine (8.3 mL, 60.0 mmol) were slowly added. The resulting solution was stirred at room temperature overnight, washed with 2% HCl until acidic pH was reached and extracted with DCM. The combined organic layer was washed with saturated $NaHCO_3$, saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated. Crude was purified *via* silica flash chromatography (AcOEt : petroleum ether, 1 : 20) yielding **1e** as a white powder (353 mg, 23% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 16 Hz, 1H), 7.55 – 7.46 (m, 4H), 7.46 – 7.42 (m, 3H), 6.95 – 6.89 (m, 2H), 6.68 (d, *J* = 16 Hz, 1H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 187.9, 161.9, 141.3, 134.7, 130.3, 129.3, 129.2, 127.9, 126.7, 121.8, 114.5, 55.4. Spectral data agreed with literature values.[41]

(*2E*)-3-(4-fluorophenyl)-1-(phenylsulfanyl)prop-2-en-1-one (**1f**).

N,N'-Dicyclohexylcarbodiimide (3.0 g, 14.0 mmol) was added to a stirring solution of (*E*)-4-fluorocinnamic acid (2.0 g, 12.0 mmol), thiophenol (1.1 mL, 11.0 mmol) and DMAP (29.0 mg, 0.24 mmol) in 5 mL of dry DCM at 0 °C. After stirring for 1 h at 0 °C, the solution was stirred at room temperature overnight. The precipitated solid was filtered on celite and the filtrate was concentrated under vacuum. Crude was purified by silica flash chromatography (Et_2O : petroleum ether, 1 : 30) and then crystallized with Et_2O, obtaining compound **1f** as white needles (275 mg, 9% yield, m.p: 98-118 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 16 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.52 – 7.41 (m, 5H), 7.15 – 7.06 (m, 2H), 6.72 (d, *J* = 16 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 187.8, 164.2 (d, *J* = 252.4 Hz), 140.2, 134.6, 130.4 (d, *J* = 8.6 Hz), 130.3 (d, *J* = 3.4 Hz), 129.5, 129.3, 127.5, 123.9, 116.2 (d, *J* = 22.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.56. FTIR (cm^{-1}): 1679, 1595, 1507, 1031, 1022, 816. HRMS *m/z*: $[M+H]^+$ calcd for $C_{15}H_{12}FOS$ 259.0593; found 259.0581.

(*2E*)-1-(phenylsulfanyl)-3-[4-(trifluoromethyl)phenyl]prop-2-en-1-one (**1g**).

N,N' Dicyclohexylcarbodiimide (1.0 g, 5.0 mmol) was added to a stirring solution of (E)-4-trifluoromethylcinnamic acid (850 mg, 4.0 mmol), thiophenol (0.4 mL, 3.6 mmol) and DMAP (8.0 mg, 0.08 mmol) in 2 mL of dry DCM at 0 °C. After stirring for 1 h at 0 °C, the solution was stirred at room temperature overnight. The precipitated solid was filtered on celite and the filtrate was concentrated under vacuum. Crude was purified via silica flash chromatography (Et_2O : petroleum ether, 1 : 30) and then crystallized with Et_2O obtaining **1g** as colourless needles (170 mg, 14% yield, m.p.: 101-106 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 5H), 7.53 – 7.43 (m, 5H), 6.85 (d, J = 16 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 187.7, 139.4, 137.4, 134.6, 131.1 (q, *J* = 32.7 Hz), 129.7, 129.3, 128.6, 127.2, 126.4, 126.0 (q, *J* = 3.8 Hz), 123.8 (q, J = 272.3 Hz). ^{19}F NMR (376 MHz, CDCl3) δ -62.89. FTIR (cm^{-1}): 1677, 1617, 1318, 1109, 1021, 990, 821, 755, 741, 691. HRMS *m/z*: $[M+H]^+$ calcd for $C_{16}H_{12}OF_3S$ 309.0561; found 309.0560.

(*2E*)-3-(4-methylphenyl)-1-(phenylsulfanyl)prop-2-en-1-one (**1h**).

N,N'-Dicyclohexylcarbodiimide (3.0 g, 14.0 mmol) was added to a stirring solution of (*E*)-4-methylcinnamic acid (2.0 g, 12.0 mmol), thiophenol (1.1 mL, 11.0 mmol) and DMAP (27.0 mg, 0.22 mmol) in 5 mL of dry DCM at 0 °C. After stirring for 1 h at 0 °C, the solution was stirred at room temperature overnight. The precipitated solid was filtered on celite and the filtrate was concentrated under vacuum. Crude was purified by silica flash chromatography (Et_2O : petroleum ether, 1 : 30) yielding **1h** as a white/yellow powder (303 mg, 10% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 16 Hz, 1H), 7.53 – 7.40 (m, 7H), 7.21 (d, *J* = 8 Hz, 2H), 6.75 (d, *J* = 16 Hz, 1H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 188.0, 141.6, 141.4, 134.7, 131.3, 129.9, 129.4, 129.2, 128.5, 127.8, 123.1, 21.6. Spectral data agreed with literature values.[42]

(*2E*)-3-(naphthalen-2-yl)-1-(phenylsulfanyl)prop-2-en-1-one (**1i**).

(*E*)-3-(1-Naphthyl)prop-2-enoic acid (916 mg, 4.7 mmol) was refluxed with thionyl chloride (4.0 mL, 52.0 mmol) in 23 mL of DCM overnight. The reaction solution was cooled down to room temperature and concentrated to give a yellow oily solution. The concentrated oil was dissolved in 17 mL of dry DCM, then thiophenol (0.5 mL, 5.0 mmol) and triethylamine (7.0 mL, 49.0 mmol) were slowly added. The resulting solution was stirred at room temperature overnight, washed with 2% HCl until acidic pH was reached and extracted with DCM. The combined organic layer was washed with saturated NaHCO3, saturated NaCl, dried over anhydrous Na2SO4 and concentrated under vacuum. Crude was purified via silica flash chromatography (AcOEt : petroleum ether, 1 : 50) obtaining **1i** as an orange powder (253 mg, 19% yield, m.p. 100-102 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 15 Hz, 1H), 8.19 (d, *J* = 8 Hz, 1H), 7.92 (dd, *J* = 15, 8 Hz, 2H), 7.82 (d, *J* = 7 Hz, 1H), 7.65 – 7.43 (m, 8H), 6.89 (d, *J* = 15 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 188.0, 138.5, 134.7, 133.7, 131.7, 131.3, 131.1, 129.5, 129.3, 129.1, 128.9, 127.1, 126.6, 126.4, 125.5, 125.3, 123.3. FTIR (cm^{-1}): 2924, 1476, 1438, 796, 685.83. HRMS *m/z*: $[M+H]^+$ calcd for $C_{19}H_{15}OS$ 291.0844; found 291.0845.

(*2E*)-3-(furan-2-yl)-1-(phenylsulfanyl)prop-2-en-1-one (**1j**).

(*E*)-3-(2-Furyl)prop-2-enoic acid (940 mg, 7.0 mmol) was refluxed with thionyl chloride (5.5 mL, 76.0 mmol) in 34 mL of DCM overnight. The reaction solution was cooled down to room temperature and concentrated to give a yellow oily solution. The concentrated oil was dissolved in 17 mL of dry DCM, then thiophenol (0.5 mL, 5.0 mmol) and triethylamine (7.0 mL, 49.0 mmol) were slowly added. The resulting solution was stirred at room temperature overnight, washed with 2% HCl until acidic pH was reached and extracted with DCM. The combined organic layer was washed with saturated $NaHCO_3$, saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Crude was purified *via* silica flash chromatography (petroleum ether) yielding **1j** as an orange powder (143 mg, 9% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.45 (m, 3H), 7.45 – 7.35 (m, 4H), 6.73 – 6.63 (m, 2H), 6.52 – 6.46 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 187.6, 150.6, 145.3, 134.6, 129.4, 129.2, 127.7, 127.5, 121.5, 116.6, 112.7. Spectral data agreed with literature values.[40]

(*2E*)-3-(5-methylfuran-2-yl)-1-(phenylsulfanyl)prop-2-en-1-one (**1k**).

N,N' Dicyclohexylcarbodiimide (2.0 g, 10.0 mmol) was added to a stirring solution of (E)-3-(5-methylfuran-2-

yl)prop-2-enoic acid (1.3 g, 8.5 mmol), thiophenol (0.7 mL, 7.6 mmol) and DMAP (21.0 mg, 0.17 mmol) in 3.5 mL of dry DCM at 0 °C. After stirring for 1 h at 0 °C, the solution stirred at room temperature overnight. The precipitated solid was filtered on celite and the filtrate was concentrated. Crude was purified via silica gel chromatography (Et_2O : petroleum ether, 1 : 30) and then crystallized with Et_2O obtaining **1k** as orange needles (1.25 g, 60% yield, m.p.: 76 80 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 2H), 7.45 – 7.38 (m, 3H), 7.34 (d, *J* = 15 Hz, 1H), 6.61 (d, *J* = 3 Hz, 1H), 6.60 (d, *J* = 15 Hz, 1H), 6.11 (d, *J* = 3 Hz, 1H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 187.5, 156.3, 149.3, 134.6, 129.3, 129.1, 128.0, 127.5, 119.8, 118.5, 109.4, 14.0. FTIR (cm^{-1}): 2954, 2922, 2853, 1460, 1017, 964, 824, 786, 742, 709, 688, 623. HRMS *m/z*: $[M+H]^+$ calcd for $C_{14}H_{13}O_2S$ 245.0636; found 245.0641.

(*2E*)-1-(phenylsulfanyl)-3-(thiophen-2-yl)prop-2-en-1-one (**1l**).

N,N'-Dicyclohexylcarbodiimide (2.7 g, 13.0 mmol) was added to a stirring solution of (*E*)-3-(thiophen-2-yl)prop-2-enoic acid (1.7 g, 11.0 mmol), thiophenol (1.0 mL, 10.0 mmol) and DMAP (27.0 mg, 0.22 mmol) in 5 mL of dry DCM at 0 °C. After stirring for 1 h at 0 °C, the solution was stirred overnight at room temperature. The precipitated solid was filtered on celite and the filtrate was concentrated under vacuum. The crude was purified *via* silica gel chromatography (AcOEt : petroleum ether, 1 : 30) and then crystallized with Et_2O yielding **1l** as yellow crystals (801 mg, 30% yield, m.p: 86-91 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 15 Hz, 1H), 7.53 – 7.40 (m, 6H), 7.33 (d, *J* = 4 Hz, 1H), 7.09 (d, *J* = 4 Hz, 1H), 6.59 (d, *J* = 15 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 187.5, 139.3, 134.6, 133.9, 132.3, 129.5, 129.3, 129.2, 128.4, 127.6, 122.8. FTIR (cm^{-1}): 1661, 1597, 1277, 1203, 1018, 865, 834, 823, 746, 714. HRMS *m/z*: $[M+H]^+$ calcd for $C_{13}H_{11}OS_2$ 247.0251; found 247.0254.

S-phenyl (*E*)-hex-2-enethioate (**1m**)

Compound **1m** was obtained according to the procedure reported by Tingoli and coworkers as an oil, (713 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 6.97 – 6.86 (m, 1H), 6.12 (d, *J* = 15.5 Hz, 1H), 2.15 (q, *J* = 7.2 Hz, 2H), 1.51 – 1.39 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 187.1, 145.7, 133.7, 128.3, 128.1, 126.9, 126.6, 33.3, 20.2, 12.7. Spectral data agreed with literature values.[43]

S-phenyl (*E*)-but-2-enethioate (**1n**)

Compound **1n** was obtained according to the procedure reported by Tabarelli and coworkers as an oil, (498 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.36 (m, 5H), 6.99 (dq, *J* = 13.8, 6.9 Hz, 1H), 6.21 (dd, *J* = 15.4, 1.5 Hz, 1H), 1.91 (dd, *J* = 6.9, 1.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 188.0, 142.2, 134.8, 129.4, 129.2, 129.1, 127.7, 18.2. Spectral data agreed with literature values.[44]

ASSOCIATED CONTENT

Supporting Information: copies of the ^{1}H- and ^{13}C- NMR of compounds **1a-o and 3a-o**. Copies of chiral HPLC traces for experiments listed in Table 6. HPLC obtained for compound **3a** by using 0.1 equiv of base only. The Supporting Information is available free of charge on the ACS Publications website.

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SYNOPSIS TOC