Enantioselective alkylation reactions using silylamide as brønsted probase

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**NANYANG
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**ENANTIOSELECTIVE ALKYLATION REACTIONS USING
SILYLAMIDE AS BRØNSTED PROBASE**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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Enantioselective Alkylation Reactions Using Silylamide as Brønsted Probase

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ABSTRACT

In most of the asymmetric phase transfer reactions, Brønsted bases are involved and the inorganic bases used can greatly influence the profile of the reaction. A brief introduction of the recent developments in asymmetric phase transfer catalysis is presented in the first chapter of this thesis. Alkoxide salts are able to activate substrates with high pK_a values but the occurrence of side reactions is unavoidable. On the other hand, carbonate and phosphate salts are milder but their low basicity limits the scope of their reactions. This presents a difficult situation in which sensitive substrates, such as lactone, are easily hydrolyzed in the presence of a strong base, but unreactive when a weaker base is used. In order to circumvent this issue, a Brønsted probase strategy, which involves the *in situ* generation of a strong base from silylamide (probase) through the use of fluoride, is hence devised. In this approach, the strong base produced is a transient species and does not exist in excess, thus, reducing background and side reactions.

Herein, an introduction to the background and recent development in asymmetric phase transfer catalysis and asymmetric catalytic Brønsted base reactions is first presented, which forms the basis for our proposed research design. We demonstrate that when pentanidinium and bisguanidinium are used as catalysts, highly enantioselective phase transfer alkylation of dihydrocoumarin (lactone) can be achieved, and the results are presented in Chapter 2. In the next chapter, this Brønsted probase strategy is further extended to cyclic and linear ketone substrates. Consolidating the results achieved in the preceding chapters, control experiments were conducted to investigate the mechanism of our strategy, with the results presented in Chapter 4. These experiments prove that hypervalent silicates form ion-pair intermediates with pentanidinium and bisguanidinium in the reaction, and it is through these ion-pairs that the selective enantiofacial approach of the electrophiles is determined.

PUBLICATION

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ABBREVIATIONS

Ac	acetate
AIBN	2,2'-azo <i>bisisobutyronitrile</i>
Am	amyl (<i>n</i> -pentyl)
Boc	<i>tert</i> -butyloxycarbonyl
BQ	benzoquinone
Bu	butyl
Bn	benzyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DMA	<i>N, N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Equiv.	equivalent
ESI	electrospray ionization
GC	gas chromatography
HRMS	high-resolution mass spectrometry

HPLC	high performance liquid chromatography
HWE	Horner–Wadsworth–Emmons
IBX	<i>o</i> -iodoxybenzoic acid
IPA	isopropyl alcohol
<i>i</i> Pr	isopropyl
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
Mes	mesityl
MOM	methoxymethyl
Ms	mesyl (methanesulfonyl)
NBS	<i>N</i> -bromosuccinimide
NMO	<i>N</i> -methylmorpholine oxide
OAc	acetate
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
TBAI	tetra- <i>n</i> -butylammonium iodide
TBAB	tetra- <i>n</i> -butylammonium bromide
TBS	<i>tert</i> -butyldimethylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl

α	alpha
β	beta
γ	gamma
μ	micro
π	pi
η	eta
ω	omega
σ	sigma

Chapter 1

Introduction

1.1 New strategies in asymmetric catalytic Brønsted base reactions

Despite the good development of asymmetric catalytic Brønsted base reactions in recent years. Overcoming problems in reactions involving substrates with high pK_a remains a challenge in asymmetric catalytic Brønsted base reactions due to the limited basicity of catalysts, the stability of catalyst under strong basic condition, low enantioselectivity of product, and the sensitivity of substrates under basic condition. In order to circumvent these issues, two main methods are traditionally used. One approach is the modification of substrates through the introduction of electron-withdrawing groups, which serve to decrease the pK_a of substrates. Using the precursor of substrates can also negate the need for an additional deprotonation step. Another approach involves the development of new strategies to overcome the high pK_a issue in the asymmetric catalytic Brønsted base reactions, which is anticipated to be more efficient since the substrate scope can be extended to include the asymmetric catalysis of high pK_a substrates.

Besides asymmetric phase transfer catalysis, new strategies of asymmetric Brønsted base reactions that have been developed in recent years include the use of: chiral organosuperbase; the combination of Lewis acid and Brønsted base; difunctional metal catalyst; and the combination of chiral crown ether and strong non-nucleophilic base.

1.1.1 Chiral organosuperbase strategy

The synthesis of various chiral organo-Brønsted base catalysts and their role in catalytic asymmetric transformations have been reported.¹ However, the substrate scope is limited due to the weak basicity of the chiral organo-Brønsted bases. Recently, Terada and co-workers developed a series of chiral bis(guanidino)iminophosphorane catalysts, which are strongly basic.² This allows the formation of a conjugated structure between two guanidine fragment

and iminophosphorane core. However, it was discovered that the catalyst C₂-symmetric structure is necessary in order for highly enantioselective amination reaction to be achieved (Scheme 1.1).^{2a} It was further observed that the *in situ* formation of organobase catalyst was crucial for this reaction.

Scheme 1.1 Chiral bis(guanidino)iminophosphorane-catalyzed amination.

The Ooi group developed a new type chiral tetraaminophosphonium salt as the precursor of super organobase to carry out different types of chiral transformations.³ Interestingly, due to intermolecular hydrogen bonding interaction, the chiral tetraaminophosphonium cation, two phenols and a phenoxide anion could self-assemble into a 10-membered cyclic supramolecular structure (Scheme 1.2).^{3d} This supramolecular catalyst can deprotonate esters to form chiral enolate intermediates, which react with α,β -unsaturated acylbenzotriazole to give the products with high enantioselectivity.

Scheme 1.2 Self-assembled chiral ion-pair catalyst in 1,4-addition reaction.

The Lambert group also developed a chiral cyclopropenimines as super organobase.⁴ The chiral cyclopropenimines catalyst was used to catalyze Michael addition of glycine imine and methyl acrylate (Scheme 1.3).^{4a} The intramolecular, noncovalent CH-O interaction between hydroxyl group and cyclohexane in the catalyst is crucial for high enantioselectivity.^{4c}

Scheme 1.3 Chiral cyclopropenimine-catalyzed 1,4-addition.

1.1.2 Combination of Lewis acid and Brønsted base

A strategy of combining Lewis acid and Brønsted base has also been used in asymmetric catalytic reactions.⁵ The Kanai group reported a boron-catalyzed Mannich reaction of carboxylic acids (Scheme 1.4).^{5m} In Kanai's method, a catalytic amount of BH_3 could activate the carboxylic acid to give an acyloxyborane intermediate. Compared to the carboxylic acid, the acyloxyborane intermediate has lower $\text{p}K_a$ due to the acidity of the hydrogen in the α -position. The enantioselectivity of the reaction is controlled by the coordination of the chiral BINOL ligand to the boron center.

Scheme 1.4 Boron-catalyzed Mannich reaction.

The Dixon group employed cinchona alkaloids and silver (I) salt as a combination catalytic system to carry out the Aldol reaction of isocyanoacetate and aldehyde (Scheme 1.5).^{5f} In this reaction, the cinchona alkaloid acts as chiral backbone and Brønsted base, while the Ag (I) salt acts as Lewis acid. Coordination of the Ag (I) salt to the phosphine group in cinchona alkaloid forms the bifunctional chiral catalyst.

Scheme 1.5 Alkaloids and Ag (I) salt-catalyzed Aldol reaction.

The combination of copper salts and Brønsted base has also been reported. The Shibasaki group reported a direct Mannich reaction of fluorinated amides (Scheme 1.6).⁵ⁿ The copper (I) salt acts as soft Lewis acid and coordinates to the 7-azaindoline amide to form a cyclic intermediate. The Barton's base then deprotonates the α -proton of amide to produce the enolate intermediate.

Scheme 1.6 Cu (I)-catalyzed Mannich reaction.

1.1.3 Difunctional metal catalyst strategy

The chiral bifunctional Lewis acid and Brønsted base catalyst has also been widely used in asymmetric catalytic Brønsted base reactions.⁶ The Trost group employed the Zn-ProPhenol catalyst to realize a Mannich reaction of alkynyl ketones (Scheme 1.7).^{6m} In the Zn-ProPhenol catalyst, the zinc metal center acts as a Lewis acid and the ethyl group coordinating to the zinc center is the Brønsted base. Strong chelation between substrates and catalyst resulted in the good enantioselectivity of the product.

Scheme 1.7 Zn-ProPhenol catalyzed Mannich reaction.

Metal amides and alkoxides can catalyze many types of proton transfer reactions due to their strong Bronsted basicity and Lewis acidity.⁶ Kobayashi's group reported a chiral calcium complex-catalyzed 1,4-addition and [3+2] cycloaddition of acrylate with glycine ester derivatives (Scheme 1.8)^{6j}. The slight structural variability between acrylates and glycine esters with different substituents resulted in the formation of 1,4-addition and [3+2] cycloaddition products respectively, which may be attributed to the difference in stability of the ester enolates. It was further discovered that the presence of molecular sieves, type of solvent and the method of preparation of the chiral calcium complex have significant influence on the reaction result.

Scheme 1.8 Chiral calcium complex-catalyzed reactions.

Shibasaki and coworkers developed many types of multi-metallic chiral complexes of rare earth metals, alkaline metals.⁶ⁿ They employed a Pd/La/Schiff base complex for an asymmetric Henry reaction (Scheme 1.9). The dinucleating complex of Pd and La was synthesized from the chiral Schiff base ligand and metal salts, in which the special chiral dinucleating complex provided a good chiral environment for the Henry reaction and the phenolate anion is the real Brønsted base in the reaction.

Scheme 1.9 Bimetallic Schiff base complex-catalyzed Henry reaction.

1.1.4 Chiral crown ether and strong non-nucleophilic base strategy

Less acidic carbonyl compounds can be activated by the combination of chiral crown ether and strong non-nucleophilic base.⁷ Kobayashi and coworkers reported an asymmetric 1,4-addition of simple amide (Scheme 1.10).^{7a} In their method, a catalytic amount of KHMDS was employed and the chiral counter ion formed between the amide anion in KHMDS and chiral crown ether acts as the base in the 1,4-addition reaction. This is in contrast to KHMDS, NaHMDS and LiHMDS, which do not have sufficient basicity to activate the amide substrate.

Scheme 1.10 Chiral crown ether-catalyzed 1,4-addition.

Although the aforementioned new strategies in asymmetric catalytic Brønsted base reaction have further extended the applicability of reactions in this field, the substrate scope remains limited due to their intrinsic mechanism involved in these reactions. They mainly involve proton transfers, such as Aldol reaction, Mannich reaction and Michael addition. Hence, the development of new strategies to circumvent these drawbacks remains of paramount importance in asymmetric alkylation reactions.

1.2 Asymmetric Phase Transfer Catalysis (PTC)

In 1971, Starks and coworkers introduced the definition of “phase transfer catalysis” to describe tetraalkylammonium or phosphonium salts acting as catalysts to increase the reactivity of two substrates primarily localised in different immiscible phases.⁸ Thereafter, a variety of chiral phase transfer catalysts have been developed and synthesized, and many of these catalysts have been used in various organic transformations (Scheme 1.11).⁹ Due to the mild reaction conditions and low catalyst loading required, asymmetric phase transfer catalysis possesses great potential to be further extended into industrial applications.¹⁰

Scheme 1.11 Chiral phase transfer catalysts.

A representative example of asymmetric phase transfer catalysis, which features base promoted alkylation, is illustrated in Scheme 1.12. The chiral salt ($^*\text{cat}^+\text{x}^-$) has good solubility in organic solvents but the base salt (Q^+B^-) has poor solubility in organic solvents. After ion-exchange between the chiral catalyst ($^*\text{cat}^+\text{x}^-$) and base salt (Q^+B^-), the actual base in the reaction ($^*\text{cat}^+\text{B}^-$) is formed in the organic phase. Thereafter, $^*\text{cat}^+\text{B}^-$ deprotonates substrate **A** to generate enolate intermediate **I**, which reacts with an electrophile (E-Br) to give the alkylation product **B**, and regenerates the catalyst ($^*\text{cat}^+\text{Br}^-$). In this cycle, the stereoselectivity is controlled by weak electrostatic interactions and van der Waals forces between enolates and the chiral cation. In comparison with the inorganic base salt (Q^+B^-), the real base ($^*\text{cat}^+\text{B}^-$) has higher basicity due to the weaker interactions between cat^+ and B^- .

Therefore, the nearly ‘free anion’ can be used for activating many substrates possessing high pK_a values.

Scheme 1.12 Mechanism of chiral phase transfer catalysis.

1.3 Bases in asymmetric PTC reactions

Although asymmetric oxidation¹¹ and reduction¹² reactions can be realized under PTC conditions, more than 90% of asymmetric PTC reactions involve Brønsted bases.⁹ Out of these, inorganic bases such as alkoxide salts, hydroxide salts, carbonate salts and phosphate salts are the major Brønsted bases used in asymmetric PTC reactions. However, these inorganic bases have their inherent limitations.

Alkoxide salts are able to activate substrates with high pK_a due to their strong basicity. However, suppression of the background reactions is a challenge due to the excellent solubility¹³ and strong nucleophilicity¹⁴ of these alkoxide salts in most organic solvents (Scheme 1.13). Hence, this leads to difficulty in achieving high stereocontrol of the reaction products.

	advantage	disadvantages
alkoxide salts:	strong basicity	good solubility in organic solvents strong nucleophilicity

*** good solubility in organic solvent**

e.g. solubility of tBuOK/100g solvent at 25 °C: hexane 0.27 g, toluene 2.27 g, ether 4.34 g, tBuOH 17.8 g, THF 25.00 g.

*** strong nucleophilicity**

Williamson ether synthesis⁷

Scheme 1.13 Characteristics of alkoxide salts used in asymmetric PTC reactions.

The hydroxide salts used in asymmetric phase transfer reactions are considered “standard bases” as they have the greatest basicity and are the least soluble in most of the organic solvents. However, due to the strong nucleophilicity of the hydroxide anions, many base-

sensitive substrates and reagents are unable to withstand the reaction conditions (Scheme 1.14).¹⁵

	<i>advantages</i>	<i>disadvantage</i>
hydroxide salts:	strong basicity less solubility in organic solvent	strong nucleophilicity

*** strong nucleophilicity**

asymmetric hydrolysis of enol esters catalyzed by PTC⁸

Scheme 1.14 Characteristics of hydroxide salts in asymmetric PTC reactions.

Although other types of bases, such as carbonate, phosphate and acetate salts can be applied in PTC reactions, their applications are limited due to their weak basicity¹⁶ (Scheme 1.15). Hence, the major challenge in asymmetric phase transfer catalysis is to obtain a strong base that is weak in nucleophilicity.

	<i>advantage</i>	<i>disadvantage</i>
carbonate, phosphate and acetate salts:	weak nucleophilicity	weak basicity

*** weak basicity**

H_2CO_3 pKa = 3.6	H_3PO_4 pKa ₁ = 2.14 pKa ₂ = 7.19 pKa ₃ = 12.3	HOAc pKa = 4.76	H_2O pKa = 15.7
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pKa determined at 25 °C in H₂O

Scheme 1.15 Characteristics of other salts in asymmetric PTC reactions.

1.4 Proposed research design

Many alkali metal amides, such as LDA, LiHMDS, LiTMP, are commonly used in organic chemistry as strong non-nucleophilic bases due to their bulkiness (Scheme 1.16). However, due to their great solubility in organic solvents, these alkali metal amides are not suitable for asymmetric phase transfer catalysis.¹⁷

Scheme 1.16 Bulky strong bases in organic chemistry.

Silyl compounds are extensively studied as Lewis acids, protecting groups and nucleophiles.¹⁸ At the same time, the activation of silyl compounds in asymmetric phase transfer catalysis is also well established (Scheme 1.17).¹⁹

Scheme 1.17 Activation of silyl compound under PTC condition.¹⁹

Recently, Kondo and coworkers reported an *in situ* method to produce an onium amide base through fluoride anion activation of aminosilanes (Scheme 1.18).²⁰ In their method, ammonium fluoride was used as a fluoride source to activate trimethylsilyl amine (TMS_3N)

to produce the onium amide *in situ*. The strong base then deprotonates the substrate to give an anion intermediate, which reacts with a ketone to give the product.

Scheme 1.18 Bulky strong base produced *in situ*.

Based on the hypothesis that a larger steric effect could reduce nucleophilicity, and pioneering work on asymmetric PTC reactions and Kondo's work, we have devised a probase strategy, which generates a chiral strong organic Brønsted base with weak nucleophilicity *in situ* through “deprotection” of the silyl compound (probase) under chiral phase transfer conditions (Scheme 1.19).

Scheme 1.19 Proposed probase strategy in asymmetric PTC.

In our hypothesis, anion exchange between the chiral PTC catalyst ($\text{*cat}^+\text{X}^-$) and fluoride salt (Q^+F^-) produces a chiral fluoride ($\text{*cat}^+\text{F}^-$), which activates a silyl compound (B-Si , probase) to generate a bulky strong base ($\text{*cat}^+\text{B}^-$) *in situ*. The chiral bulky strong base then deprotonates substrate **A** to give the chiral catalyst-controlled enolate intermediate **I**, which then reacts with an electrophile (E-Br) to afford product **B** and regenerates the catalyst ($\text{*cat}^+\text{Br}^-$).

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Chapter 2

Enantioselective Alkylation of Dihydrocoumarins

2.1 Introduction

Dihydrocoumarin compounds have attracted extensive research interest due to their biological significance¹ (Scheme 2.1). The direct enantioselective alkylation of dihydrocoumarins is an attractive method to construct chiral dihydrocoumarins. However, the direct enantioselective alkylation has yet been explored due to the high pK_a at the α -position, and the dihydrocoumarin structure is sensitive to basic conditions. Hence, there are only a few examples to construct chiral α -substituted dihydrocoumarins under mild conditions to date.

Scheme 2.1 Selected dihydrocoumarin compounds with biological activity.

Hoshino's group reported a chiral Lewis acid catalyzed enantioselective radical type allylation of dihydrocoumarins (Scheme 2.2).² In their method, α -iododihydrocoumarin was employed as the substrate, allyltributyltin as the electrophile and chiral BINOL as the chiral ligand to give the allylation product in moderate to high enantioselectivity.

catalytic enantioselective radical allylation

Scheme 2.2 Chiral Lewis acid-catalyzed radical allylation of dihydrocoumarin.

List and coworkers reported an excellent asymmetric protonation of ketene dithioacetals to produce α -aryl dihydrocoumarins (Scheme 2.3).³ The key intermediate ketene dithioacetal was synthesized from *rac*- α -aryl dihydrocoumarins. The ketene dithioacetal can then undergo cyclization in the presence of chiral phosphoric acid to give the protected hydroxycoumarin derivatives. After hydrolysis, asymmetric protonation can provide α -aryl dihydrocoumarins with high enantioselectivity.

Scheme 2.3 Catalytic asymmetric protonation of ketene dithioacetals.

Scheidt, in his dual Lewis base activation strategy, reported an example of chiral carbene-catalyzed annulation of acrolein and *o*-quinone methides precursor (Scheme 2.4).⁴ The desired chiral dihydrocoumarin was obtained in high *ee* value.

Scheme 2.4 Carbene-catalyzed enantioselective annulation in the synthesis of chiral dihydrocoumarin.

Hou and co-workers used a palladium complex and chiral ligand to mediate an asymmetric

allylic alkylation reaction by employing the bulky strong base LiHMDS for the deprotonation step (Scheme 2.5).⁵ However, the chiral dihydrocoumarin products were obtained in moderate enantioselectivity.

Scheme 2.5 Palladium catalyzed asymmetric allylic alkylation.

In view of the importance of chiral dihydrocoumarin compounds and the dearth of efficient methods to construct them, we decided to choose dihydrocoumarin as a model compound to test our Brønsted probase strategy.

2.2 Results and discussion

Several silyl compounds were first tested in our Brønsted probase strategy using dihydrocoumarin **1a** as substrate. In our control reaction, we observed the decomposition of dihydrocoumarin **1a** when alkoxides or hydroxides salts were employed as the base, and no reaction was observed when carbonates and phosphates salts were used (Table 2.1, equation 1). On the other hand, many different types of silyl compounds (probase) were examined (Table 1, equation 2). We found that many silylamines (Table 1, entries 2-5) and alkoxide silanes (entry 6) could not be activated in our condition. Silyl urea **pb-2** and **pb-3** resulted in partial hydrolysis of **1a** due to their strong nucleophilicity, resulting in a low yield of desired product (entries 7-8).

Table 2.1 Probase screening

Entry ^a	Probase (equiv.)	Result ^b
1	pb-1 (2)	85% yield
2	TMS ₂ NH (2)	NR
3	TMSNMe ₂ (2)	NR
4	TMSNEt ₂ (2)	NR
5	TMSN(<i>i</i> Pr) ₂ (2)	NR
6	<i>t</i> BuOTMS (2)	NR
7	pb-2 (4)	35% yield
8	pb-3 (4)	24% yield
9	pb-4 (4)	87% yield

^a Reaction was conducted with of **2a** (0.1 mmol, 1.0 equiv.) and BnBr (0.2 mmol, 2.0 equiv.) in 0.4 mL THF in the presence of 10% mol TBAB for 24 h at room temperature. ^b Isolated yield.

Fortunately, it was discovered that bis(trimethylsilyl)-acetamide **pb-4** (BSA) and trimethylsilyl amine **pb-1** (TMS₃N) were able to generate an amide base *in situ*, which is strong enough to activate **1a** and yet mild enough to prevent the hydrolysis of the lactone (entries 1 and 9).

With the suitable probase in hand, we commenced with the screening of our chiral catalyst. In our previous work, our group has successfully developed two types of guanidinium salts for asymmetric phase transfer catalysis.⁶ Thus, these chiral guanidinium salts were chosen in the initial screening (Table 2.2).

Table 2.2 Chiral catalyst screening

Entry ^a	Catalyst (mol%)	Probase (equiv.)	CsF (equiv.)	Yield ^b	ee ^c
1	cat-1 (10)	pb-4 (5)	4	85	55
2	cat-2 (10)	pb-4 (5)	4	83	40
3	cat-3 (10)	pb-4 (5)	4	85	91
4	cat-4 (10)	pb-4 (5)	4	88	97
5	cat-5 (10)	pb-4 (5)	4	84	93
6	cat-4 (5)	pb-4 (3)	2	83	95
7	cat-4 (10)	pb-1 (1.5)	6	trace	--
8 ^d	cat-4 (10)	pb-1 (1.5)	6	82	80

^a Reaction was carried out with **1a** (0.10 mmol), benzyl bromide (0.20 mmol), **pb-4** (0.3 mmol), CsF (0.2 mmol) and catalyst (5 mol%) in 0.4 mL of THF at -40 °C for 24 h. ^b Isolated yield. ^c Determined by HPLC analysis on a chiral stationary phase. ^d Reaction temperature was -20 °C.

Different solvents were tested under chiral condition, and we found the ether type solvents had the higher enantioselectivity than toluene type solvents. The THF had the best result so we choose it as standard solvent for our catalyst screening. Moderate enantioselectivity was achieved in the presence of BSA (**pb-4**) as the probase with pentanidium salts **cat-1** and **cat-2** as chiral PTC catalysts (Table 2.2, entries 1 and 2). The presence of halogenated substituents in the catalyst seems to be vital as all of the tested halogenated pentanidium salts afforded

good yields with high enantioselectivity (entries 3-5). The bromo-substituted catalysts **cat-4** achieved the best results in terms of yield and enantioselectivity (entry 4).

By reducing the catalyst-loading (from 10 mol% to 5 mol%), the amount of **pb-4** and CsF used, the optimized reaction condition for enantioselective alkylation of dihydrocoumarin was found (entry 6). Under the same reaction condition, probase TMS₃N (**pb-1**) cannot activate the substrate (entry 7) unless the reaction temperature was increased to -20 °C. In comparison with **pb-4** probase, **pb-1** requires a higher catalyst loading and relatively lower enantioselectivity was obtained (entry 8).

With the suitable chiral catalyst in hand, we employed **cat-4** in the presence of different inorganic and organic bases. As shown in Table 2.3, different types of carbonate salts were not sufficiently basic to activate dihydrocoumarin **1a** (entries 1-3). Similar to carbonate salts, phosphate and acetate salts also could not deprotonate the substrate (entries 4-6). The nucleophilicity of all hydroxide salts tested was too strong and resulted in the decomposition of dihydrocoumarin **1a** under these conditions (entries 7-10). For alkoxide salts, less sterically hindered salts led to nucleophilic attack of **1a** (entry 11). Although more sterically hindered alkoxide salts have weaker nucleophilicity, the high solubility in organic solvents resulted in side reactions and gave the racemic product (entry 12). Organic base triethyl amine did not react with dihydrocoumarin substrate (entry 13) and LiHMDS also led to a racemic product due to the high solubility in the organic solvent (entry 14).

These experiments proved that our Brønsted probase strategy can generate a strong base with weak nucleophilicity. Probase **pb-4** has stronger basicity than carbonate, phosphate, and acetate salts. In comparison with hydroxide salts, probase **pb-4** has similar basicity but weaker nucleophilicity. As compared to strong bases, such as *t*BuOK and LiHMDS, the *in situ* generation of base in the presence of PTC catalyst can suppress background reaction, hence excellent enantioselectivity can be obtained.

Table 2.3 Control experiments in the presence of chiral catalyst

Entry ^a	Base	Result ^{b,c}
1	Na ₂ CO ₃	NR
2	K ₂ CO ₃	NR
3	Cs ₂ CO ₃	NR
4	K ₃ PO ₄	SM decomposed
5	KOAc	NR
6	PhCO ₂ K	NR
7	LiOH·H ₂ O	SM decomposed
8	NaOH	SM decomposed
9	KOH	SM decomposed
10	CsOH·H ₂ O	SM decomposed
11 ^d	NaOMe	SM decomposed
12 ^d	<i>t</i> BuOK	Low yield, 0% ee
13	Triethylamine	NR
14 ^e	LiHMDS	65% yield, 0% ee

^a Reaction was conducted with of **1a** (0.1 mmol, 1.0 equiv) , **2a** (0.2 mmol, 2.0 equiv) in 0.4 mL THF in the presence of 10 mol% **c4** for 24h at -40 °C. ^b Isolated yields. ^c Determined by HPLC analysis on a chiral stationary phase. ^d3 equiv base was used in reaction. ^e 1.5 equiv. base was used in reaction.

Having demonstrated the advantage of our Brønsted probase strategy, we next turned our attention to investigate the substrate scope of the enantioselective alkylation of dihydrocoumarin. The wide substrate scope of the enantioselective alkylation of dihydrocoumarin using Brønsted probase strategy is apparent from the results shown in Chart 2.1. Various substituents at α -position of dihydrocoumarins such as allylic, propargylic, ester group and benzylic moieties provided the alkylation products in good yield with enantioselectivity (**3b-3i**). Surprisingly, satisfactory results were also obtained with geranyl substituted substrate **3g** (91% yield, 93% *ee*).

Chart 2.1 Substrate scope of the enantioselective alkylation of dihydrocoumarins ^{a,b,c}

^a Reaction was carried out with **1** (0.10 mmol), electrophile (0.20 mmol), **pb-4** (0.3 mmol), CsF (0.2 mmol) and **cat-4** catalyst (5 mol%) in 0.4 mL of THF at -40 °C for 24 h. ^b Unless otherwise noted, yields are isolated total yields, ee was determined by HPLC analysis on a chiral stationary phase. ^c Absolute configuration determined by comparing with ref 2.

Electrophiles with diverse structural variability were also tested in the optimized reaction condition. Allylic bromides seemed suitable electrophiles, with the corresponding products obtained in good yield and enantioselectivity (**3j-3l**). Benzyl bromide containing electron-donating or electron-withdrawing group in *para*-, *meta*-, *ortho*- position did not influence the yield or enantioselectivity (**3m-3r**). Simultaneously changing both R¹ and electrophile also gave a good result (**3j**).

Dihydrocoumarins with different substituents R² in the aromatic ring were also employed in the standard condition. The electronic properties of substituents and the substitution position appear to have limited effect on the stereoselectivity. Substituents in the aromatic ring of dihydrocoumarins bearing electron withdrawing and electron donating groups in *para*-, *meta*-, *ortho*- positions reacted smoothly to give high yield and enantioselectivity (**3s-3w**). The probase strategy was also suitable for benzochromenone-type substrates. Benzochromenones

with different substituents in the phenyl ring were subjected to the standard condition, resulting in high yield and enantioselectivity (**3x-3ab**).

2.3 Summary

In summary, we have found silyl compound bis(trimethylsilyl)-acetamide (BSA, **pb-4**) to be a suitable probase in our Brønsted probase strategy. Dihydrocoumarin, with high pK_a due to the low acidity of the α -proton but easily attacked by nucleophiles, was chosen as a model compound to prove the strong basicity with weak nucleophilicity of the Brønsted probase strategy.

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2.5 Experimental section

2.5.1 General information

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), tt (triplet of triplets), m (multiplets), etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker (400 MHz) (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *e.e.* was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]_D^{25}$ (*c* in g per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

2.5.2 Preparation of starting material

To a dry RBF equipped with a magnetic stir bar was added dihydrocoumarin and dry THF. The solution then was cooled to -78 °C and 1.05 equiv. LiHMDS was slowly added. The reaction was stirred at -78 °C for 45 min. The electrophile (1.05 equiv.) was then added slowly to the yellow solution. The reaction was slowly warmed from -78 °C to room temperature and stirred overnight. NH_4Cl solution was then added to quench the reaction. The organic phase was extracted with EA, dried with Na_2SO_4 , and after concentration of the organic layer, the residue was purified by flash chromatography (EA/Hexane: 1:50-1:20) to obtain the desired product in 35% to 87% yield.

2.5.3 General procedure for enantioselective catalytic reactions

To a dry Schlenk tube equipped with a magnetic stir bar was added 5 mol% catalyst **cat-4**, 3 equiv. **pb-4**, 2 equiv. CsF and 2 equiv. electrophile followed by addition of 0.4 mL THF. The resulting mixture was stirred at -40 °C for 24 h. The reaction mixture was then directly purified *via* silica gel chromatography (EA/Hexane: 1:200- 1:30) to obtain the desired product.

2.4.4 Characterization of catalysts and products

3-cinnamylchroman-2-one (1a)

physical property : White solid.

mp: 105.0 - 106.2 °C;

¹H NMR: (400 MHz, CDCl₃) δ 7.40 – 7.24 (m, 6H), 7.20 – 7.18 (m, 1H), 7.13 – 7.00 (m, 2H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.30 – 6.22 (m, 1H), 3.06 – 3.00 (m, 1H), 2.93 – 2.83 (m, 3H), 2.55 – 2.52 (m, 1H);

¹³C NMR: (100 MHz, CDCl₃) δ 170.4, 151.6, 136.9, 133.4, 128.6, 128.2, 128.1, 127.4, 126.2, 125.8, 124.4, 122.6, 116.6, 39.2, 33.2, 28.7;

HRMS: (ESI) [M+H]⁺ calcd. for C₁₈H₁₇O₂, 265.1229 found, 265.1232;

IR (film): ν_{max} 1764, 1489, 1458, 1232, 1134, 966, 756, 694 cm⁻¹

3-allylchroman-2-one (1b)

physical property : colourless oil.

¹H NMR: (400 MHz, CDCl₃) δ 7.29 – 7.22 (m, 1H), 7.20 – 7.15 (m, 1H), 7.13 – 7.01 (m, 2H), 5.92 – 5.80 (m, 1H), 5.20 – 5.12 (m, 2H), 3.06 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.88 – 2.63 (m, 3H), 2.41 – 2.32 (m, 1H);

¹³C NMR: (100 MHz, CDCl₃) δ 170.4, 151.6, 134.3, 128.2, 128.1, 124.3, 118.2, 116.6, 38.7, 33.9, 28.6;

HRMS: (ESI) [M+H]⁺ calcd. for C₁₂H₁₃O₂, 189.0916 found, 189.0914;

IR (film): ν_{max} 1770, 1489, 1458, 1232, 1145, 918, 756 cm⁻¹

3-(3-methylbut-2-en-1-yl)chroman-2-one (1c)

physical property :colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 7.29 – 7.22 (m, 1H), 7.20 – 7.15 (m, 1H), 7.13 – 7.01 (m, 2H), 5.22 – 5.16 (m, 1H), 5.20 – 5.12 (m, 2H), 3.00 (dd, $J = 16.0, 8.0$ Hz, 1H), 2.81 (dd, $J = 16.0, 8.0$ Hz, 1H), 2.75 – 2.67 (m, 1H), 2.64 – 2.55 (m, 1H), 1.75 (s, 3H), 1.61 (s, 3H);

^{13}C NMR: (100 MHz, CDCl_3) δ 170.8, 151.7, 135.1, 128.2, 128.1, 124.2, 122.7, 119.9, 116.5, 39.5, 28.6, 28.1, 25.8, 17.9;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{17}\text{O}_2$, 217.1229 found, 217.1225;

IR (film): ν_{max} 1768, 1489, 1458, 1234, 918, 756 cm^{-1}

3-(prop-2-yn-1-yl)chroman-2-one (1d)

physical property :colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 7.30 – 7.22 (m, 2H), 7.15 – 7.10 (m, 1H), 7.08 – 7.03 (m, 1H), 3.20 (dd, $J = 16.0, 4.0$ Hz, 1H), 3.05 – 2.95 (m, 1H), 2.93 – 2.81 (m, 2H), 2.66 – 2.55 (m, 1H), 2.12 – 2.09 (m, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 169.2, 151.5, 128.4, 128.1, 124.5, 122.4, 116.6, 80.4, 71.0, 38.2, 28.5, 19.5;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{12}\text{H}_{11}\text{O}_2$, 187.0759 found, 187.0760;

IR (film): ν_{max} 3290, 1766, 1489, 1458, 1232, 1141, 756 cm^{-1}

3-(3-phenylprop-2-yn-1-yl)chroman-2-one (1e)

physical property : White solid.

mp: 54.5 - 56.5 °C;

¹H NMR: (400 MHz, CDCl₃) δ 7.48 – 7.40 (m, 2H), 7.36 – 7.23 (m, 5H), 7.17 – 7.06 (m, 2H), 3.28 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.14 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.12 – 3.03 (m, 1H), 3.02 – 2.91 (m, 1H), 2.84 (dd, *J* = 16.0, 8.0 Hz, 1H);

¹³C NMR: (100 MHz, CDCl₃) δ 169.5, 151.6, 131.7, 128.4, 128.3, 128.4, 128.1, 124.5, 123.1, 122.4, 116.7, 85.8, 83.0, 38.6, 28.8, 20.5;

HRMS: (ESI) [*M*+*H*]⁺ calcd. for C₁₈H₁₅O₂, 263.1072 found, 263.1067;

IR (film): ν_{max} 1768, 1489, 1458, 1232, 1138, 756 cm⁻¹

3-(3-(trimethylsilyl)prop-2-yn-1-yl)chroman-2-one (1f)

physical property : White solid.

mp: 67.5 - 68.7 °C;

¹H NMR: (400 MHz, CDCl₃) δ 7.31 – 7.21 (m, 2H), 7.15 – 7.09 (m, 1H), 7.07 – 7.02 (m, 1H), 3.21 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.04 – 2.83 (m, 2H), 2.61 (dd, *J* = 16.0, 8.0 Hz, 1H), 0.19 (s, 9H);

¹³C NMR: (100 MHz, CDCl₃) δ 169.4, 151.6, 128.4, 128.2, 124.5, 122.5, 116.7, 102.6, 87.6, 38.3, 28.6, 20.9, 0.1;

HRMS: (ESI) [*M*+*H*]⁺ calcd. for C₁₅H₁₉O₂Si, 259.1154 found, 259.1157;

IR (film): ν_{max} 2177, 1768, 1489, 1460, 1249, 1232, 1138, 842, 758 cm⁻¹

(*Z*)-3-(3,7-dimethylocta-2,6-dien-1-yl)chroman-2-one (1g)

physical property :colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 7.30 – 7.22 (m, 1H), 7.20 – 7.15 (m, 1H), 7.12 – 7.02 (m, 2H), 5.22 – 5.15 (m, 1H), 5.13 – 5.06 (m, 1H), 3.00 (dd, $J = 16.0, 8.0$ Hz, 1H), 2.81 (dd, $J = 16.0, 8.0$ Hz, 1H), 2.77 – 2.67 (m, 1H), 2.66 – 2.56 (m, 1H), 2.38 – 2.28 (m, 1H), 2.15 – 2.01 (m, 4H), 1.70 (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H);

^{13}C NMR: (100 MHz, CDCl_3) δ 170.8, 151.7, 138.7, 131.6, 128.2, 128.1, 124.2, 124.1, 122.7, 119.9, 116.5, 39.7, 39.5, 28.5, 28.0, 26.5, 25.7, 17.7, 16.1;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{25}\text{O}_2$, 285.1855 found, 285.1855;

IR (film): ν_{max} 1768, 1489, 1458, 1232, 1130, 756 cm^{-1}

Ethyl 2-(2-oxochroman-3-yl)acetate (1h)

physical property :White solid.

mp: 75.9 - 77.2 $^{\circ}\text{C}$;

^1H NMR: (400 MHz, CDCl_3) δ 7.24 – 7.11 (m, 1H), 7.16 – 7.11 (m, 1H), 7.08 – 7.02 (m, 1H), 7.00 – 6.95 (m, 1H), 4.17 (d, $J = 8.0$ Hz, 1H), 4.13 (d, $J = 8.0$ Hz, 1H), 3.18 – 3.07 (m, 1H), 3.03 – 2.85 (m, 3H), 2.55 (dd, $J = 16.0, 8.0$ Hz, 1H), 1.24 (t, $J = 8.0$ Hz, 3H);

^{13}C NMR: (100 MHz, CDCl_3) δ 171.1, 169.9, 151.5, 128.3, 128.0, 124.4, 122.6, 116.6, 60.8, 36.0, 34.5, 29.3, 14.1;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{13}\text{H}_{15}\text{O}_4$, 235.0969 found, 235.0970;

IR (film): ν_{max} 1766, 1732, 1489, 1458, 1230, 1138, 767 cm^{-1}

3-benzylchroman-2-one (1i)

physical property :White solid.

mp: 104.5 - 105.5 °C;

¹H NMR: (400 MHz, CDCl₃) δ 7.39 – 7.19 (m, 6H), 7.13 – 7.05 (m, 3H), 3.40 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.02 – 2.93 (m, 1H), 2.87 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.80 – 2.70 (m, 2H);

¹³C NMR: (100 MHz, CDCl₃) δ 170.6, 151.6, 138.0, 129.2, 128.7, 128.3, 128.2, 126.8, 124.4, 122.3, 116.6, 40.8, 35.6, 28.2;

HRMS: (ESI) [M+H]⁺ calcd. for C₁₆H₁₅O₂, 239.1072 found, 239.1071;

IR (film): ν_{max} 1762, 1489, 1458, 1230, 1128, 700 cm⁻¹

6,8-dibromo-3-(3-methylbut-2-en-1-yl)chroman-2-one (1j)

physical property :White solid.

mp: 88.0 - 89.1 °C;

¹H NMR: (400 MHz, CDCl₃) δ 7.50 (d, *J* = 4.0 Hz, 1H), 7.20 (d, *J* = 4.0 Hz, 1H), 5.18 – 5.10 (m, 1H), 3.01 – 2.81 (m, 3H), 2.46 – 2.25 (m, 2H), 1.73 (s, 3H), 1.62 (s, 3H);

¹³C NMR: (100 MHz, CDCl₃) δ 181.2, 149.8, 134.8, 133.2, 132.4, 128.8, 120.1, 112.3, 111.2, 45.2, 32.2, 30.6, 25.8, 17.9;

HRMS: (ESI) [M+H]⁺ calcd. for C₁₄H₁₅Br₂O₂, 372.9439 found, 372.9427;

IR (film): ν_{max} 1705, 1460, 1215, 756 cm⁻¹

8-methyl-3-(3-methylbut-2-en-1-yl)chroman-2-one (1k)

physical property :colourless oil.

¹H NMR: (400 MHz, CDCl₃) δ 7.12 – 7.08 (m, 1H), 7.03 – 6.95 (m, 2H), 5.24 – 5.16 (m, 1H), 3.00 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.78 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.74 – 2.54 (m, 2H), 2.36 – 2.31 (m, 1H), 2.31 (s, 3H), 1.76 (s, 3H), 1.62 (s, 3H);

¹³C NMR: (100 MHz, CDCl₃) δ 171.0, 149.9, 135.0, 129.7, 125.8, 125.7, 123.8, 122.5, 120.1, 39.6, 28.8, 28.1, 25.8, 17.9, 15.7;

HRMS: (ESI) [M+H]⁺ calcd. for C₁₅H₁₉O₂, 231.1385 found, 231.1385;

IR (film): ν_{max} 1766, 1469, 1269, 1132, 767 cm⁻¹

3-cinnamyl-6-methylchroman-2-one (1l)

physical property :White solid.

mp: 78.5 - 79.7 °C;

¹H NMR: (400 MHz, CDCl₃) δ 7.42 – 7.21 (m, 5H), 7.20 – 7.18 (m, 1H), 7.08 – 7.04 (m, 1H), 7.00 – 6.94 (m, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.30 – 6.21 (m, 1H), 3.04 – 2.93 (m, 1H), 2.91 – 2.80 (m, 3H), 2.60 – 2.49 (m, 1H), 2.33 (s, 3H);

¹³C NMR: (100 MHz, CDCl₃) δ 170.6, 149.5, 137.0, 133.9, 133.3, 128.7, 128.6, 127.5, 126.2, 125.9, 122.2, 116.3, 39.3, 33.2, 28.7, 20.7;

HRMS: (ESI) [M+H]⁺ calcd. for C₁₉H₁₉O₂, 279.1385 found, 279.1388;

IR (film): ν_{max} 1764, 1494, 1257, 1213, 1136, 742 cm⁻¹

6-methoxy-3-(3-methylbut-2-en-1-yl)chroman-2-one (1m)

physical property :colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 6.94 (d, $J = 8.0$ Hz, 1H), 6.75 (dd, $J = 8.0, 4.0$ Hz, 1H), 6.69 (d, $J = 4.0$ Hz, 1H), 5.20 – 5.12 (m, 1H), 3.77 (s, 3H), 2.93 (dd, $J = 16.0, 4.0$ Hz, 1H), 2.75 (dd, $J = 16.0, 8.0$ Hz, 1H), 2.70 – 2.51 (m, 2H), 2.34 – 2.21 (m, 1H), 1.73 (s, 3H), 1.60 (s, 3H);

^{13}C NMR: (100 MHz, CDCl_3) δ 171.0, 156.0, 145.5, 125.1, 123.6, 120.0, 117.2, 113.3, 113.2, 55.6, 39.4, 28.8, 28.1, 25.8, 17.9;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{19}\text{O}_3$, 247.1334 found, 247.1336;

IR (film): ν_{max} 1759, 1494, 1433, 1205, 1157, 1037, 813 cm^{-1}

3-cinnamyl-7-methoxychroman-2-one (1n)

physical property :White solid.

mp: 56.0 - 57.0 $^{\circ}\text{C}$;

^1H NMR: (400 MHz, CDCl_3) δ 7.43 – 7.19 (m, 4H), 7.07 (d, $J = 8.0$ Hz, 1H), 6.71 – 6.58 (m, 2H), 6.50 (d, $J = 16.0$ Hz, 1H), 6.30 – 6.20 (m, 1H), 3.81 (s, 3H), 3.04 – 2.72 (m, 3H), 2.60 – 2.49 (m, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 170.4, 159.7, 152.3, 137.0, 133.3, 128.6, 127.5, 126.2, 125.9, 114.3, 110.4, 102.3, 55.5, 39.4, 33.3, 28.1;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{19}\text{O}_3$, 295.1334 found, 295.1329;

IR (film): ν_{max} 1762, 1625, 1589, 1508, 1155, 1130, 694 cm^{-1}

2-cinnamyl-1*H*-benzo[*f*]chromen-3(2*H*)-one (1o)

physical property :White solid.

mp: 105.8 - 107.4 °C;

¹H NMR: (400 MHz, CDCl₃) δ 7.93 – 7.75 (m, 3H), 7.63 – 7.53 (m, 1H), 7.52 – 7.44 (m, 1H), 7.43 – 7.30 (m, 4H), 7.29 – 7.22 (m, 2H), 6.53 (d, *J* = 16.0 Hz, 1H), 6.38 – 6.26 (m, 1H), 3.53 (dd, *J* = 24.0, 8.0 Hz, 1H), 3.13 (dd, *J* = 24.0, 8.0 Hz, 1H), 3.05 – 2.89 (m, 2H), 2.71 – 2.61 (m, 1H);

¹³C NMR: (100 MHz, CDCl₃) δ 170.3, 149.2, 136.9, 133.6, 131.2, 130.8, 128.9, 128.8, 128.6, 127.5, 127.1, 126.2, 125.7, 125.1, 122.9, 117.1, 115.4, 38.6, 33.5, 24.9;

HRMS: (ESI) [*M*+*H*]⁺ calcd. for C₂₂H₁₉O₂, 315.1385 found, 315.1382;

IR (film): ν_{max} 1762, 1224, 1138, 810, 746 cm⁻¹

3-(3-methylbut-2-en-1-yl)-3,4-dihydro-2*H*-benzo[*h*]chromen-2-one (1p)

physical property :colourless oil.

¹H NMR: (400 MHz, CDCl₃) δ 8.28 – 8.20 (m, 1H), 7.86 – 7.79 (m, 1H), 7.62 – 7.48 (m, 3H), 7.30 – 7.23 (m, 1H), 5.28 – 5.18 (m, 1H), 3.13 (dd, *J* = 24.0, 8.0 Hz, 1H), 2.93 (dd, *J* = 24.0, 8.0 Hz, 1H), 2.88 – 2.77 (m, 1H), 2.71 – 2.61 (m, 1H), 2.43 – 2.33 (m, 1H), 1.77 (s, 3H), 1.63 (s, 3H);

^{13}C NMR: (100 MHz, CDCl_3) δ 170.8, 146.4, 135.2, 133.4, 127.5, 126.5, 126.4, 125.6, 123.8, 123.5, 121.0, 120.3, 117.1, 39.5, 28.8, 28.2, 25.9, 17.9;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{19}\text{O}_2$, 267.1385 found, 267.1386;

IR (film): ν_{max} 1762, 1379, 1126, 808 cm^{-1}

8-bromo-2-cinnamyl-1H-benzo[f]chromen-3(2H)-one (1q)

physical property : colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 8.02 – 7.96 (m, 1H), 7.77 – 7.56 (m, 3H), 7.42 – 7.30 (m, 4H), 7.29 – 7.22 (m, 2H), 6.52 (d, $J = 16.0$ Hz, 1H), 6.35 – 6.25 (m, 1H), 3.46 (dd, $J = 16.0$, 8.0 Hz, 1H), 3.12 – 3.03 (m, 1H), 3.02 – 2.88 (m, 2H), 2.71 – 2.58 (m, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 169.8, 149.4, 136.8, 133.7, 131.9, 130.6, 130.3, 129.7, 128.6, 128.0, 127.5, 126.2, 125.5, 124.6, 119.0, 118.3, 115.7, 38.4, 33.4, 24.9;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{22}\text{H}_{18}\text{O}_2\text{Br}$, 393.0492 found, 393.0490;

IR (film): ν_{max} 1766, 1224, 1134, 810, 694 cm^{-1}

9-bromo-2-cinnamyl-1H-benzo[f]chromen-3(2H)-one (1r)

physical property : colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 8.06 – 8.00 (m, 1H), 7.78 – 7.67 (m, 2H), 7.57 – 7.51 (m, 1H), 7.42 – 7.30 (m, 4H), 7.29 – 7.21 (m, 2H), 6.53 (d, $J = 16.0$ Hz, 1H), 6.36 – 6.26 (m, 1H), 3.41 (dd, $J = 16.0, 8.0$ Hz, 1H), 3.11 – 2.85 (m, 3H), 2.72 – 2.60 (m, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 169.7, 149.9, 136.9, 133.7, 132.5, 130.3, 129.1, 128.9, 128.6, 128.5, 127.5, 126.2, 125.4, 125.3, 121.7, 117.6, 114.7, 38.4, 33.4, 24.9;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{22}\text{H}_{18}\text{O}_2\text{Br}$, 393.0490 found, 393.0490;

IR (film): ν_{max} 1766, 1620, 1141, 830, 756 cm^{-1}

2-cinnamyl-9-methoxy-1H-benzo[f]chromen-3(2H)-one (1s)

physical property : colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 7.78 – 7.66 (m, 2H), 7.42 – 7.29 (m, 4H), 7.29 – 7.23 (m, 1H), 7.18 – 7.07 (m, 3H), 6.50 (d, $J = 16.0$ Hz, 1H), 6.37 – 6.27 (m, 1H), 3.91 (s, 3H), 3.37 (dd, $J = 16.0, 8.0$ Hz, 1H), 3.10 – 2.84 (m, 3H), 2.70 – 2.59 (m, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 170.2, 158.8, 149.8, 137.0, 133.5, 132.6, 130.3, 128.6, 127.5, 126.2, 126.1, 125.8, 117.2, 114.5, 114.1, 101.9, 55.3, 38.6, 33.4, 25.0;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{21}\text{O}_3$, 345.1496 found, 345.1491;

IR (film): ν_{max} 1766, 1627, 1225, 1134, 833, 746 cm^{-1}

(S)-3-benzyl-3-cinnamylchroman-2-one (3a)

physical property : White solid.

mp: 114.6 - 116.4 $^{\circ}\text{C}$;

Optical rotation: $[\alpha]^{24}_{\text{D}}$ (*c* 1.30, CHCl_3): -2.16

^1H NMR: (400 MHz, CDCl_3) δ 7.38 – 7.21 (m, 9H), 7.21 – 7.10 (m, 4H), 7.09 – 7.03 (m, 1H), 6.42 (d, J = 16.0 Hz, 1H), 6.23 (ddd, J = 4.0, 8.0, 16.0 Hz, 1H), 3.10 (d, J = 16.0 Hz, 1H), 2.98 (d, J = 16.0 Hz, 1H), 2.90 (d, J = 16.0 Hz, 1H), 2.83 – 2.72 (m, 2H), 2.39 (ddd, J = 8.0, 16.0, 24.0 Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 171.2, 151.1, 136.9, 135.6, 134.8, 130.6, 128.6, 128.5, 128.3, 128.2, 127.5, 127.1, 126.4, 124.6, 124.1, 121.8, 116.2, 45.9, 40.9, 38.8, 32.6;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{23}\text{O}_2$, 355.1698 found, 355.1698;

IR (film): ν_{max} 1759, 1489, 1456, 1232, 1143, 754, 700 cm^{-1}

HPLC: 96% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 6.5 min, *tr* = 8.9 min.

(S)-3-allyl-3-benzylchroman-2-one (3b)

physical property : colourless oil.

Optical rotation: $[\alpha]^{24}_{\text{D}}$ (*c* 1.40, CHCl_3): -27.6

^1H NMR: (400 MHz, CDCl_3) δ 7.35 – 7.22 (m, 4H), 7.18 – 7.08 (m, 4H), 7.07 – 7.02 (m, 1H), 5.92 – 5.80 (m, 1H), 5.19 (d, J = 8.0 Hz, 1H), 5.10 (d, J = 8.0 Hz, 1H), 3.06 (d, J = 16.0 Hz, 1H), 2.96 – 2.70 (m, 3H), 2.56 (dd, J = 8.0, 16.0 Hz, 1H), 2.24 (dd, J = 8.0, 16.0 Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 171.1, 151.0, 135.7, 132.6, 130.6, 128.6, 128.2, 128.1, 127.0, 124.5, 121.7, 119.9, 116.1, 45.4, 40.6, 39.3, 32.5;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{19}\text{O}_2$, 279.1385 found, 279.1391;

IR (film): ν_{max} 1759, 1489, 1456, 1232, 1155, 1134, 756, 702 cm^{-1}

HPLC: 85% *ee* determined by HPLC (OJ-H, 95/5 hexanes/i-PrOH, 1.0 ml/min) $tr(R)$ = 9.6 min, $tr(S)$ = 13.9 min.

(S)-3-benzyl-3-(3-methylbut-2-en-1-yl)chroman-2-one (3c)

physical property : colourless oil.

Optical rotation: $[\alpha]^{24}_D$ (*c* 2.07, CHCl₃): +4.3

¹H NMR: (400 MHz, CDCl₃) δ 7.42 – 7.02 (m, 9H), 5.25 – 5.20 (m, 1H), 3.11 (d, *J* = 16.0 Hz, 1H), 2.85 (d, *J* = 16.0 Hz, 1H), 2.80 (d, *J* = 16.0 Hz, 1H), 2.76 (d, *J* = 16.0 Hz, 1H), 2.75 – 2.70 (m, 1H), 2.34 (dd, *J* = 8.0, 16.0 Hz, 1H), 2.32 (dd, *J* = 8.0, 16.0 Hz, 1H), 1.75 (s, 3H), 1.52 (s, 3H);

¹³C NMR: (100 MHz, CDCl₃) δ 171.6, 151.1, 136.2, 136.0, 130.6, 128.6, 128.2, 128.0, 126.9, 124.4, 121.9, 118.0, 116.0, 45.9, 40.7, 33.5, 32.6, 26.0, 18.0;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₁H₂₃O₂, 307.1698 found, 307.1693;

IR (film): $\nu_{\max}$ 1759, 1489, 1456, 1232, 1141, 756, 649 cm⁻¹

HPLC: 93% *ee* determined by HPLC (AD-H, 99/1 hexanes/i-PrOH, 1.0 ml/min) tr = 12.0 min, tr = 15.9 min.

(S)-3-benzyl-3-(prop-2-yn-1-yl)chroman-2-one (3d)

physical property : White solid.

mp: 94.2 - 95.4°C

Optical rotation: $[\alpha]^{24}_D$ (*c* 1.60, CHCl₃): +2.2

¹H NMR: (400 MHz, CDCl₃) δ 7.45 – 7.08 (m, 9H), 3.21 (d, *J* = 16.0 Hz, 1H), 3.05 (d, *J* = 16.0 Hz, 1H), 3.12 – 2.94 (m, 2H), 2.61 – 2.56 (s, 2H), 2.25 – 2.20 (m, 1H);

¹³C NMR: (100 MHz, CDCl₃) δ 170.2, 151.1, 134.9, 130.2, 128.8, 128.5, 128.4, 127.3, 124.7, 121.2, 116.3, 79.7, 72.3, 45.1, 39.2, 33.4, 24.9;

HRMS: (ESI) [M+H]⁺ calcd. for C₁₉H₁₇O₂, 277.1229 found, 277.1228;

IR (film): ν_{max} 3296, 1707, 1456, 1232, 756, 702 cm⁻¹

HPLC: 94% ee determined by HPLC (OD-H, 99/1 hexanes/i-PrOH, 1.0 ml/min) *tr* = 14.4 min, *tr* = 16.3 min.

(*R*)-3-benzyl-3-(3-phenylprop-2-yn-1-yl)chroman-2-one (3e)

physical property : White solid.

mp: 145.0 - 147.0 °C

Optical rotation: [α]²⁴_D (*c* 1.23, CHCl₃): -1.36

¹H NMR: (400 MHz, CDCl₃) δ 7.52 – 7.42 (m, 2H), 7.38 – 7.05 (m, 12H), 3.24 (d, *J* = 16.0 Hz, 1H), 3.08 (d, *J* = 16.0 Hz, 1H), 3.01 (d, *J* = 16.0 Hz, 1H), 3.12 – 2.96 (m, 1H), 2.81 – 2.72 (s, 2H);

¹³C NMR: (100 MHz, CDCl₃) δ 170.4, 151.1, 135.2, 131.7, 130.3, 128.2, 128.4, 128.3, 128.2, 127.3, 124.7, 123.2, 121.3, 116.3, 85.0, 84.4, 45.6, 39.6, 33.7, 25.9;

HRMS: (ESI) [M+H]⁺ calcd. for C₂₅H₂₁O₂, 353.1542 found, 353.1549;

IR (film): ν_{max} 1761, 1489, 1234, 1141, 754 cm⁻¹

HPLC: 90% ee determined by HPLC (OJ-H, 85/15 hexanes/i-PrOH, 1.0 ml/min) *tr* = 15.2 min, *tr* = 21.8 min.

(*S*)-3-benzyl-3-(3-(trimethylsilyl)prop-2-yn-1-yl)chroman-2-one (3f)

physical property :White solid.

mp: 107.7 - 109.1 °C

Optical rotation: $[\alpha]^{24}_D$ (*c* 1.00, CHCl₃): +1.37

¹H NMR: (400 MHz, CDCl₃) δ 7.34 – 7.08 (m, 9H), 3.26 (d, *J* = 16.0 Hz, 1H), 3.23 – 3.02 (m, 3H), 2.54 – 2.40 (m, 2H), 0.31 (s, 9H);

¹³C NMR: (100 MHz, CDCl₃) δ 170.2, 151.1, 135.2, 130.2, 128.8, 128.4, 128.3, 127.2, 124.6, 121.3, 116.2, 101.9, 89.2, 45.2, 39.3, 33.5, 26.4, 0.1;

¹⁹F NMR: (376 MHz, CDCl₃) -114.6 – -114.68 (m, 1F);

HRMS: (ESI) [M+H]⁺ calcd. for C₂₂H₂₅O₂Si, 349.1624 found, 349.1624;

IR (film): $\nu_{\max}$ 1732, 1489, 1456, 1249, 1232, 842, 756, 702 cm⁻¹

HPLC: 94% *ee* determined by HPLC (OD-H, 99/1 hexanes/i-PrOH, 1.0 ml/min) *tr* = 14.4 min, *tr* = 16.3 min.

(S,Z)-3-benzyl-3-(3,7-dimethylocta-2,6-dien-1-yl)chroman-2-one (3g)

physical property :White solid.

mp: 82.5 - 83.0 °C

Optical rotation: $[\alpha]^{24}_D$ (*c* 0.86, CHCl₃): -9.8

¹H NMR: (400 MHz, CDCl₃) δ 7.35 – 6.98 (m, 9H), 5.36 – 5.29 (m, 1H), 5.15 – 5.08 (m, 1H), 3.09 (d, *J* = 16.0 Hz, 1H), 2.93 – 2.72 (m, 3H), 2.44 – 2.33 (m, 2H), 2.32 – 2.23 (m, 2H), 2.15 – 1.97 (m, 4H), 1.67 (s, 3H), 1.61 (s, 3H), 1.51 (s, 3H) ;

^{13}C NMR: (100 MHz, CDCl_3) δ 171.6, 151.1, 139.7, 136.1, 131.6, 130.6, 128.6, 128.2, 128.0, 126.9, 124.4, 124.1, 122.0, 118.1, 116.1, 46.0, 40.1, 39.9, 33.4, 32.6, 26.5, 25.7, 17.7, 16.3;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{31}\text{O}_2$, 375.2324 found, 375.2320;

IR (film): ν_{max} 1761, 1489, 1458, 1234, 1136, 756, 702 cm^{-1}

HPLC: 93% *ee* determined by HPLC (AD-H, 99/1 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 7.3 min, *tr* = 11.0 min.

(S)-ethyl 2-(3-benzyl-2-oxochroman-3-yl)acetate (3h)

physical property : White solid.

mp: 72.6 - 73.1 $^{\circ}\text{C}$

Optical rotation: $[\alpha]^{24}_{\text{D}}$ (*c* 1.00, CHCl_3): -21.7

^1H NMR: (400 MHz, CDCl_3) δ 7.34 – 7.24 (m, 4H), 7.22 – 7.13 (m, 2H), 7.12 – 7.06 (m, 3H), 4.18 (d, *J* = 8.0 Hz, 1H), 4.14 (d, *J* = 8.0 Hz, 1H), 3.48 (d, *J* = 16.0 Hz, 1H), 3.02 (d, *J* = 16.0 Hz, 1H), 2.94 (d, *J* = 16.0 Hz, 1H), 2.89 (d, *J* = 16.0 Hz, 1H), 2.80 (d, *J* = 16.0 Hz, 1H), 2.45 (d, *J* = 16.0 Hz, 1H), 1.28 (t, *J* = 8.0 Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 171.2, 170.7, 151.2, 134.6, 130.5, 128.6, 128.4, 128.3, 127.3, 124.7, 121.3, 116.4, 60.8, 44.0, 40.4, 39.1, 32.4, 14.1;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{21}\text{O}_4$, 325.1444 found, 325.1440;

IR (film): ν_{max} 1759, 1728, 1489, 1458, 1022, 763 cm^{-1}

HPLC: 86% *ee* determined by HPLC (OJ-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 15.1 min, *tr* = 19.3 min.

(S)-3-benzyl-3-(4-chlorobenzyl)chroman-2-one (3i)

physical property : White solid.

mp: 97.5 - 98.4 °C

Optical rotation: $[\alpha]^{24}_{\text{D}}$ (*c* 1.30, CHCl₃): +11.0

¹H NMR: (400 MHz, CDCl₃) δ 7.38 – 7.01 (m, 13H), 3.24 (d, *J* = 16.0 Hz, 1H), 2.20 (d, *J* = 16.0 Hz, 1H), 2.79 – 2.70 (m, 4H);

¹³C NMR: (100 MHz, CDCl₃) δ 170.9, 150.8, 135.4, 134.4, 133.1, 132.1, 130.8, 128.6, 128.4, 128.3, 128.2, 127.2, 124.7, 121.7, 116.2, 47.0, 41.5, 40.7, 31.7;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₃H₂₀ClO₂, 363.1152 found, 363.1157;

IR (film): ν_{max} 1759, 1489, 1457, 1016, 756 cm⁻¹

HPLC: 93% *ee* determined by HPLC (IC, 99/1 hexanes/*i*-PrOH, 0.5 ml/min) *tr* = 29.6 min, *tr* = 32.7 min.

(R)-3-benzyl-3-(2-methylallyl)chroman-2-one (3j)

physical property : colourless oil.

Optical rotation: $[\alpha]^{24}_{\text{D}}$ (*c* 1.40, CHCl₃): -11.4

¹H NMR: (400 MHz, CDCl₃) δ 7.32 – 7.05 (m, 9H), 4.96 – 4.93 (m, 1H), 4.76 – 4.73 (m, 1H), 3.21 (d, *J* = 16.0 Hz, 1H), 2.89 (d, *J* = 24.0 Hz, 1H), 2.83 – 2.71 (m, 2H), 2.66 (d, *J* = 16.0 Hz, 1H), 1.78 (s, 3H);

¹³C NMR: (100 MHz, CDCl₃) δ 171.6, 151.0, 140.9, 135.8, 130.8, 128.6, 128.2, 128.1, 127.0, 124.5, 122.0, 116.5, 116.1, 45.4, 43.1, 42.0, 32.4, 24.3;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{20}H_{21}O_2$, 293.1542 found, 293.1537;

IR (film): $\nu_{\max}$ 1759, 1489, 1456, 1234, 1139, 754, 702 cm^{-1}

HPLC: 90% *ee* determined by HPLC (OD-H, 95/5 hexanes/*i*-PrOH, 0.5 ml/min) $t_r = 9.6$ min, $t_r = 10.4$ min.

(S)-3-cinnamyl-3-(2-methylallyl)chroman-2-one (3k)

physical property : White solid.

mp: 84.5 - 85.8 $^{\circ}\text{C}$

Optical rotation: $[\alpha]^{25}_{\text{D}}$ (*c* 1.19, CHCl_3): -0.6

^1H NMR: (400 MHz, CDCl_3) δ 7.35 – 7.03 (m, 9H), 6.43 (d, $J = 16.0$ Hz, 1H), 6.25 – 6.14 (m, 1H), 4.97 – 4.94 (m, 1H), 4.77 – 4.74 (m, 1H), 3.00 (d, $J = 16.0$ Hz, 1H), 2.89 (d, $J = 16.0$ Hz, 1H), 2.79 – 2.71 (m, 1H), 2.55 (d, $J = 16.0$ Hz, 1H), 2.51 – 2.44 (m, 1H), 2.32 (d, $J = 16.0$ Hz, 1H), 1.78 (s, 3H);

^{13}C NMR: (100 MHz, CDCl_3) δ 172.6, 151.1, 140.7, 137.0, 134.7, 128.6, 128.5, 128.1, 127.5, 126.2, 124.5, 124.2, 121.9, 116.5, 116.1, 44.6, 43.0, 39.6, 33.4, 24.1;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{22}H_{23}O_2$, 319.1698 found, 319.1708;

IR (film): $\nu_{\max}$ 1759, 1489, 1458, 1232, 1141, 756, 694 cm^{-1}

HPLC: 89% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 0.5 ml/min) $t_r = 10.4$ min, $t_r = 11.8$ min.

(S)-3-cinnamyl-3-((E)-2-methyl-3-phenylallyl)chroman-2-one (3l)

physical property :White solid.

mp: 123.0 - 125.0 °C

Optical rotation: $[\alpha]^{25}_D$ (*c* 0.65, CHCl₃): -25.2

¹H NMR: (400 MHz, CDCl₃) δ 7.39 – 7.03 (m, 14H), 6.48 (d, *J* = 16.0 Hz, 1H), 6.33 – 6.19 (m, 2H), 3.12 (d, *J* = 16.0 Hz, 1H), 2.95 – 2.75 (m, 2H), 2.67 (d, *J* = 16.0 Hz, 1H), 2.57 – 2.44 (m, 2H), 1.89 (s, 3H);

¹³C NMR: (100 MHz, CDCl₃) δ 171.7, 151.1, 137.6, 137.0, 134.8, 133.6, 130.9, 129.0, 128.7, 128.6, 128.2, 128.1, 127.5, 126.5, 126.3, 124.6, 124.3, 121.9, 116.2, 46.7, 45.2, 40.0, 33.6, 19.9;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₈H₂₇O₂, 395.2011 found, 395.2013;

IR (film): $\nu_{\max}$ 1755, 1489, 1458, 1234, 1141, 754 cm⁻¹

HPLC: 91% *ee* determined by HPLC (OD-H, 95/5 hexanes/*i*-PrOH, 0.5 ml/min) *tr* = 17.6 min, *tr* = 26.4 min.

(S)-3-cinnamyl-3-(naphthalen-2-ylmethyl)chroman-2-one (3m)

physical property :White solid.

mp: 148.5 - 151.4 °C

Optical rotation: $[\alpha]^{24}_D$ (*c* 0.40, CHCl₃): -6.6

^1H NMR: (400 MHz, CDCl_3) δ 8.02 – 7.03 (m, 16H), 6.42 (d, $J = 16.0$ Hz, 1H), 6.33 – 6.20 (m, 1H), 3.30 (d, $J = 16.0$ Hz, 1H), 3.07 (d, $J = 16.0$ Hz, 1H), 3.01 (d, $J = 16.0$ Hz, 1H), 2.85 – 2.75 (m, 2H), 2.44 (dd, $J = 8.0, 16.0$ Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 171.3, 151.1, 136.9, 134.9, 133.2, 133.1, 132.5, 129.5, 128.7, 128.6, 128.5, 128.2, 127.8, 127.7, 127.6, 127.5, 126.3, 126.2, 125.8, 124.6, 124.1, 121.8, 116.2, 46.0, 41.1, 38.9, 32.6;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{29}\text{H}_{25}\text{O}_2$, 405.1855 found, 405.1842;

IR (film): ν_{max} 1755, 1489, 1458, 1234, 1143, 754 cm^{-1}

HPLC: 91% *ee* determined by HPLC (OD-H, 95/5 hexanes/*i*-PrOH, 1.0 ml/min) $t_r = 11.9$ min, $t_r = 15.1$ min.

(*S*)-3-cinnamyl-3-(3-methoxybenzyl)chroman-2-one (3n)

physical property : colourless oil.

Optical rotation: $[\alpha]_D^{25}$ (*c* 1.40, CHCl_3): -1.6

^1H NMR: (400 MHz, CDCl_3) δ 7.42 – 7.02 (m, 10H), 6.82 (dd, $J = 4.0, 8.0$ Hz, 1H), 6.78 – 6.70 (m, 2H), 6.42 (d, $J = 16.0$ Hz, 1H), 6.27 – 6.16 (m, 1H), 3.81 (s, 3H), 3.09 (d, $J = 16.0$ Hz, 1H), 2.97 (d, $J = 16.0$ Hz, 1H), 2.88 – 2.72 (m, 3H), 2.44 – 2.36 (m, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 171.3, 159.5, 151.1, 137.1, 136.9, 134.8, 129.2, 128.6, 128.5, 128.2, 127.5, 126.2, 124.6, 124.1, 123.9, 121.8, 116.4, 116.2, 112.4, 55.2, 45.8, 40.9, 38.9, 32.6;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{25}\text{O}_3$, 385.1084 found, 385.1083;

IR (film): ν_{max} 1759, 1583, 1489, 1456, 1263, 1232, 1141, 756, 694 cm^{-1}

HPLC: 95% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 8.2 min, *tr* = 10.5 min.

(*R*)-3-(2-bromobenzyl)-3-cinnamylchroman-2-one (3o)

physical property : White solid.

mp: 107.0 - 109.0 °C

Optical rotation: $[\alpha]_D^{25}$ (*c* 1.85, CHCl₃): -1.2

¹H NMR: (400 MHz, CDCl₃) δ 7.55 – 7.51 (m, 1H), 7.40 – 6.95 (m, 12H), 6.44 (d, *J* = 16.0 Hz, 1H), 6.27 – 6.18 (m, 1H), 3.41 (d, *J* = 16.0 Hz, 1H), 3.30 (d, *J* = 16.0 Hz, 1H), 3.13 (d, *J* = 16.0 Hz, 1H), 2.87 (d, *J* = 16.0 Hz, 1H), 2.76 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H), 2.51 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H);

¹³C NMR: (100 MHz, CDCl₃) δ 171.2, 150.8, 136.9, 136.2, 134.9, 133.0, 132.0, 128.7, 128.6, 128.5, 128.1, 127.6, 127.5, 126.3, 124.5, 123.7, 121.7, 116.0, 47.0, 40.0, 39.8, 32.3;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₅H₂₂BrO₂, 433.0803 found, 433.0801;

IR (film): $\nu_{\max}$ 1759, 1489, 1458, 1234, 1143, 754 cm⁻¹

HPLC: 89% *ee* determined by HPLC (OD-H, 95/5 hexanes/*i*-PrOH, 0.5 ml/min) *tr* = 14.9 min, *tr* = 16.7 min.

(*S*)-3-cinnamyl-3-(4-methylbenzyl)chroman-2-one (3p)

physical property :White solid.

mp: 114.8 - 116.8 °C

Optical rotation: $[\alpha]^{26}_D$ (*c* 0.82, CHCl₃): -1.7

¹H NMR: (400 MHz, CDCl₃) δ 7.37 – 7.03 (m, 13H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.28 – 6.18 (m, 1H), 3.04 (d, *J* = 16.0 Hz, 1H), 2.98 (d, *J* = 16.0 Hz, 1H), 2.87 (d, *J* = 16.0 Hz, 1H), 2.83 – 2.73 (m, 2H), 2.41 – 2.29 (m, 1H), 2.38 (s, 3H);

¹³C NMR: (100 MHz, CDCl₃) δ 171.4, 151.1, 137.0, 136.7, 134.7, 132.4, 130.5, 129.0, 128.6, 128.5, 128.1, 127.5, 126.2, 124.6, 14.3, 121.9, 116.2, 45.9, 40.5, 38.7, 32.5, 21.1;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₆H₂₅O₂, 369.1855 found, 369.1854;

IR (film): $\nu_{\max}$ 1759, 1489, 1458, 1232, 1141, 756, 694 cm⁻¹

HPLC: 91% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 6.0 min, *tr*(*R*) = 7.2 min.

(*S*)-3-cinnamyl-3-(4-fluorobenzyl)chroman-2-one (3q)

physical property :White solid.

mp: 106.5 - 118.0 °C

Optical rotation: $[\alpha]^{25}_D$ (*c* 0.52, CHCl₃): -4.5

¹H NMR: (400 MHz, CDCl₃) δ 7.37 – 6.95 (m, 13H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.26 – 6.15 (m, 1H), 3.09 (d, *J* = 16.0 Hz, 1H), 2.98 (d, *J* = 16.0 Hz, 1H), 2.86 (d, *J* = 16.0 Hz, 1H), 2.78 (d, *J* = 16.0 Hz, 1H), 2.43 – 2.35 (m, 1H);

¹³C NMR: (100 MHz, CDCl₃) δ 171.1, 151.0, 136.8, 134.9, 132.0, 131.4, 131.3, 128.6, 128.3, 127.6, 126.2, 124.7, 123.8, 121.6, 116.2, 115.3, 115.1, 45.9, 40.3, 38.9, 32.6;

^{19}F NMR: (376 MHz, CDCl_3) δ -115.6;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{22}\text{FO}_2$, 373.1604 found, 373.1611;

IR (film): ν_{max} 1759, 1508, 1489, 1458, 1232, 1143, 756 cm^{-1}

HPLC: 93% *ee* determined by HPLC (OD-H, 95/5 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 9.1 min, *tr* = 16.6 min.

(S)-3-cinnamyl-3-(4-(trifluoromethyl)benzyl)chroman-2-one (3r)

physical property : White solid.

mp: 99.2 - 101.0 $^{\circ}\text{C}$

Optical rotation: $[\alpha]^{25}_{\text{D}}$ (*c* 0.60, CHCl_3): -5.6

^1H NMR: (400 MHz, CDCl_3) δ 7.59 – 7.52 (m, 2H), 7.38 – 7.10 (m, 10H), 7.07 – 7.02 (m, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.25 – 6.15 (m, 1H), 3.21 (d, *J* = 16.0 Hz, 1H), 2.99 (d, *J* = 16.0 Hz, 1H), 2.93 (d, *J* = 16.0 Hz, 1H), 2.79 (d, *J* = 16.0 Hz, 1H), 2.71 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H), 2.42 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 170.8, 150.9, 139.9, 136.7, 135.1, 130.9, 128.6, 128.5, 128.4, 127.7, 126.3, 125.2, 125.1, 124.7, 123.4, 121.4, 116.2, 45.9, 40.9, 39.0, 32.8;

^{19}F NMR: (376 MHz, CDCl_3) δ -62.5;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{22}\text{F}_3\text{O}_2$, 423.1572 found, 423.1588;

IR (film): ν_{max} 1759, 1489, 1458, 1325, 1234, 1122, 1068, 756 cm^{-1}

HPLC: 91% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 7.9 min, *tr* = 11.0 min.

(S)-3-benzyl-6,8-dibromo-3-(3-methylbut-2-en-1-yl)chroman-2-one (3s)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 1.80, CHCl₃): -63.7

¹H NMR: (400 MHz, CDCl₃) δ 7.62 (d, *J* = 4.0 Hz, 1H), 7.33 – 7.12 (m, 6H), 5.23 – 5.15 (m, 1H), 3.13 (d, *J* = 16.0 Hz, 1H), 2.85 (d, *J* = 16.0 Hz, 1H), 2.84 – 2.80 (m, 2H), 2.36 (dd, *J* = 8.0, 16.0 Hz, 1H), 2.27 (dd, *J* = 8.0, 16.0 Hz, 1H), 1.74 (s, 3H), 1.54 (s, 3H);

¹³C NMR: (100 MHz, CDCl₃) δ 169.7, 147.3, 137.0, 135.5, 134.0, 130.5, 130.4, 128.3, 127.2, 125.5, 117.4, 116.7, 110.7, 45.8, 41.1, 33.9, 33.2, 26.1, 18.0;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₁H₂₁Br₂O₂, 462.9908 found, 462.9906;

IR (film): $\nu_{\max}$ 1772, 1489, 1458, 1134, 756, 702 cm⁻¹

HPLC: 90% *ee* determined by HPLC (IC, 99/1 hexanes/*i*-PrOH, 0.5 ml/min) *tr* = 19.1 min, *tr* = 21.9 min.

(S)-3-benzyl-8-methyl-3-(3-methylbut-2-en-1-yl)chroman-2-one (3t)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 1.51, CHCl₃): +25.5

¹H NMR: (400 MHz, CDCl₃) δ 7.32 – 7.20 (m, 3H), 7.18 – 7.12 (m, 2H), 7.11 – 7.06 (m, 1H), 7.01 – 6.93 (m, 2H), 5.27 – 5.20 (m, 1H), 3.09 (d, *J* = 16.0 Hz, 1H), 2.87 (d, *J* = 16.0 Hz, 1H), 2.82 (d, *J* = 16.0 Hz, 1H), 2.76 (d, *J* = 16.0 Hz, 1H), 2.31 (s, 3H), 2.39 – 2.22 (m, 2H), 1.74 (s, 3H), 1.52 (s, 3H);

^{13}C NMR: (100 MHz, CDCl_3) δ 171.7, 149.3, 136.2, 137.1, 130.6, 129.5, 128.1, 126.8, 126.1, 125.3, 123.9, 121.7, 118.2, 45.9, 40.7, 33.4, 32.9, 26.0, 18.0, 15.7;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{22}\text{H}_{25}\text{O}_2$, 321.1855 found, 321.1857;

IR (film): ν_{max} 1757, 1489, 1458, 1193, 1139, 756, 702 cm^{-1}

HPLC: 95% *ee* determined by HPLC (OJ-H, 99/1 hexanes/*i*-PrOH, 0.5 ml/min) *tr* = 12.6 min, *tr* = 15.4 min.

(S)-3-benzyl-3-cinnamyl-7-methylchroman-2-one (3u)

physical property : White solid.

mp: 154.1 - 155.3°C

Optical rotation: $[\alpha]_D^{26}$ (*c* 1.03, CHCl_3): -3.2

^1H NMR: (400 MHz, CDCl_3) δ 7.37 – 7.20 (m, 8H), 7.20 – 7.15 (m, 2H), 7.08 – 7.03 (m, 1H), 6.98 – 6.92 (m, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.28 – 6.16 (m, 1H), 3.08 (d, *J* = 16.0 Hz, 1H), 2.93 (d, *J* = 16.0 Hz, 1H), 2.89 (d, *J* = 16.0 Hz, 1H), 2.40 – 2.33 (m, 1H), 2.34 (s, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 171.4, 149.0, 137.0, 135.7, 134.7, 134.1, 130.6, 129.0, 128.6, 128.5, 128.3, 127.5, 127.1, 126.2, 124.2, 121.4, 115.9, 45.8, 40.9, 38.7, 32.7, 20.8;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{25}\text{O}_2$, 369.1855 found, 369.1855;

IR (film): ν_{max} 1751, 1489, 1458, 1215, 754, 669 cm^{-1}

HPLC: 90% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 0.5 ml/min) *tr* = 11.7 min, *tr* = 16.1 min.

(S)-3-benzyl-6-methoxy-3-(3-methylbut-2-en-1-yl)chroman-2-one (3v)

physical property :White solid.

mp: 103.2 - 104.7 °C

Optical rotation: $[\alpha]^{26}_D$ (*c* 1.20, CHCl₃): -1.0

¹H NMR: (400 MHz, CDCl₃) δ 7.32 – 7.22 (m, 3H), 7.19 – 7.13 (m, 2H), 7.10 – 7.05 (m, 1H), 6.98 – 6.93 (m, 1H), 6.81 – 6.75 (m, 1H), 6.11 – 6.65 (m, 1H), 5.36 – 6.31 (m, 1H), 3.80 (s, 3H), 3.13 (d, *J* = 16.0 Hz, 1H), 2.87 (d, *J* = 16.0 Hz, 1H), 2.79 (d, *J* = 16.0 Hz, 1H), 2.73 (d, *J* = 16.0 Hz, 1H), 2.36 (dd, *J* = 8.0, 16.0 Hz, 1H), 2.25 (dd, *J* = 8.0, 16.0 Hz, 1H), 1.75 (s, 3H), 1.52 (s, 3H);

¹³C NMR: (100 MHz, CDCl₃) δ 170.6, 149.5, 137.0, 138.0, 133.3, 128.7, 128.6, 127.5, 126.2, 125.9, 122.2, 116.3, 39.3, 33.2, 28.7, 20.7;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₂H₂₅O₃, 337.1804 found, 337.1809;

IR (film): $\nu_{\max}$ 1749, 1489, 1458, 1215, 754, 702 cm⁻¹

HPLC: 96% *ee* determined by HPLC (AD-H, 95/5 hexanes/*i*-PrOH, 0.5 ml/min) *tr* = 22.6 min, *tr* = 26.0 min.

(S)-3-benzyl-3-cinnamyl-7-methoxychroman-2-one (3w)

physical property :White solid.

mp: 74.5 - 76.0 °C

Optical rotation: $[\alpha]^{26}_D$ (*c* 1.63, CHCl₃): -6.9

¹H NMR: (400 MHz, CDCl₃) δ 7.37 – 7.20 (m, 8H), 7.19 – 7.15 (m, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.69 (dd, *J* = 4.0, 8.0 Hz, 1H), 6.63 (d, *J* = 4.0 Hz, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.26 –

6.16 (m, 1H), 3.81 (s, 3H), 3.08 (d, $J = 16.0$ Hz, 1H), 2.90 (d, $J = 16.0$ Hz, 1H), 2.78 – 2.69 (m, 2H), 2.38 (ddd, $J = 8.0, 16.0, 24.0$ Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 171.3, 159.6, 151.7, 137.0, 135.7, 134.6, 130.6, 129.1, 128.5, 128.3, 127.5, 127.1, 126.2, 124.2, 113.5, 110.6, 101.8, 55.5, 46.0, 41.0, 38.8, 31.9;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{25}\text{O}_3$, 385.1804 found, 385.1804;

IR (film): ν_{max} 1759, 1627, 1589, 1508, 1442, 1141, 750, 700 cm^{-1}

HPLC: 94% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) $t_r = 8.0$ min, $t_r = 10.0$ min.

(S)-2-benzyl-2-cinnamyl-1H-benzo[*f*]chromen-3(2*H*)-one (2x)

physical property : colourless oil.

Optical rotation: $[\alpha]_{\text{D}}^{25}$ (c 1.41, CHCl_3): -0.7

^1H NMR: (400 MHz, CDCl_3) δ 7.90 – 7.75 (m, 3H), 7.61 – 7.46 (m, 2H), 7.36 – 7.15 (m, 10H), 7.14 – 7.07 (m, 2H), 6.43 (d, $J = 16.0$ Hz, 1H), 6.34 – 6.24 (m, 1H), 3.27 (d, $J = 16.0$ Hz, 1H), 3.17 (d, $J = 16.0$ Hz, 1H), 3.16 (d, $J = 16.0$ Hz, 1H), 2.96 (d, $J = 16.0$ Hz, 1H), 2.89 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H), 2.46 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 171.4, 148.6, 136.9, 135.4, 134.9, 131.4, 131.0, 128.9, 128.8, 128.5, 128.3, 127.5, 127.2, 127.1, 126.3, 125.1, 124.1, 122.8, 116.8, 114.6, 45.6, 41.5, 39.1, 28.4;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{29}\text{H}_{25}\text{O}_2$, 405.1855 found, 405.1854;

IR (film): ν_{max} 1757, 1489, 1458, 1217, 756, 702 cm^{-1}

HPLC: 90% *ee* determined by HPLC (OD-H, 90/10 hexanes/i-PrOH, 1.0 ml/min) *tr* = 9.0 min, *tr* = 11.6 min.

(S)-3-benzyl-3-(3-methylbut-2-en-1-yl)-3,4-dihydro-2H-benzo[h]chromen-2-one (3y)

physical property :colourless oil.

Optical rotation: $[\alpha]^{24}_{\text{D}}$ (*c* 1.00, CHCl₃): +2.3

¹H NMR: (400 MHz, CDCl₃) δ 8.27 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.48 (m, 3H), 7.33 – 7.15 (m, 6H), 5.31 – 5.23 (m, 1H), 3.15 (d, *J* = 16.0 Hz, 1H), 3.05 – 2.88 (m, 3H), 2.45 (dd, *J* = 8.0, 16.0 Hz, 1H), 2.34 (dd, *J* = 8.0, 16.0 Hz, 1H), 1.73 (s, 3H), 1.52 (s, 3H);

¹³C NMR: (100 MHz, CDCl₃) δ 171.5, 145.7, 136.2, 136.0, 133.4, 130.6, 128.2, 127.6, 126.9, 126.5, 126.3, 125.9, 124.0, 123.2, 121.0, 118.1, 116.4, 46.0, 40.8, 33.5, 32.9, 26.1, 18.1;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₅H₂₅O₂, 357.1855 found, 357.1854;

IR (film): ν_{max} 1761, 1489, 1458, 1377, 1132, 756 cm⁻¹

HPLC: 93% *ee* determined by HPLC (AD-H, 95/5 hexanes/i-PrOH, 0.5 ml/min) *tr* = 12.4 min, *tr* = 15.5 min.

(S)-2-benzyl-8-bromo-2-cinnamyl-1H-benzo[f]chromen-3(2H)-one (3z)

physical property :colourless oil.

Optical rotation: $[\alpha]^{25}_{\text{D}}$ (*c* 0.61, CHCl_3): -1.3.

^1H NMR: (400 MHz, CDCl_3) δ 8.05 – 8.00 (m, 1H), 7.73 – 7.56 (m, 3H), 7.34 – 7.18 (m, 9H), 7.12 – 7.03 (m, 2H), 6.42 (d, $J = 16.0$ Hz, 1H), 6.32 – 6.21 (m, 1H), 3.23 (d, $J = 16.0$ Hz, 1H), 3.15 (d, $J = 16.0$ Hz, 1H), 3.11 (d, $J = 16.0$ Hz, 1H), 2.98 – 2.84 (m, 2H), 2.47 – 2.40 (m, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 171.0, 148.8, 136.7, 135.1, 135.0, 132.1, 130.7, 130.6, 130.3, 129.9, 128.5, 128.3, 127.9, 127.5, 127.2, 126.2, 124.5, 123.9, 119.0, 117.9, 115.0, 45.4, 41.6, 39.2, 28.3;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{29}\text{H}_{24}\text{O}_2\text{Br}$, 483.0958 found, 483.0960;

IR (film): ν_{max} 1759, 1489, 1357, 1149, 810, 649 cm^{-1}

HPLC: 95% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) $t_r = 8.2$ min, $t_r = 13.2$ min.

(S)-2-benzyl-9-bromo-2-cinnamyl-1H-benzo[f]chromen-3(2H)-one (3aa)

physical property : colourless oil.

Optical rotation: $[\alpha]^{25}_{\text{D}}$ (*c* 0.81, CHCl_3): 26.0.

^1H NMR: (400 MHz, MeOD) δ 8.05 – 8.02 (m, 1H), 7.79 – 7.73 (m, 2H), 7.56 – 7.51 (m, 1H), 7.29 – 7.11 (m, 11H), 6.38 (d, $J = 16.0$ Hz, 1H), 6.30 – 6.19 (m, 1H), 3.23 (d, $J = 16.0$ Hz, 1H), 3.118 – 3.10 (m, 2H), 2.92 (d, $J = 16.0$ Hz, 1H), 2.75 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H), 2.49 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H);

^{13}C NMR: (100 MHz, MeOD) δ 171.1, 149.0, 136.9, 135.7, 134.7, 132.6, 130.2, 130.1, 129.4, 128.6, 128.1, 128.0, 127.8, 127.0, 126.7, 125.8, 125.0, 123.5, 121.2, 116.7, 114.3, 45.5, 41.4, 39.3, 28.4;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{29}\text{H}_{24}\text{O}_2\text{Br}$, 483.0951 found, 483.0960;

IR (film): ν_{max} 1759, 1496, 1357, 1149, 833, 640 cm^{-1}

HPLC: 94% *ee* determined by HPLC (OD-H, 95/5 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 10.2 min, *tr* = 12.7 min.

(S)-2-benzyl-2-cinnamyl-9-methoxy-1H-benzo[f]chromen-3(2H)-one (3ab)

physical property : colourless oil.

Optical rotation: $[\alpha]_{\text{D}}^{25}$ (*c* 1.90, CHCl_3): -53.9.

^1H NMR: (400 MHz, CDCl_3) δ 7.81 – 7.67 (m, 2H), 7.35 – 7.20 (m, 8H), 7.18 – 7.07 (m, 4H), 7.06 – 7.02 (m, 1H), 6.43 (d, J = 16.0 Hz, 1H), 6.35 – 6.25 (m, 1H), 3.90 (s, 3H), 3.22 – 2.88 (m, 5H), 2.48 – 2.39 (m, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 171.4, 158.8, 149.3, 136.9, 135.3, 134.9, 132.7, 130.8, 130.3, 128.6, 128.5, 128.2, 127.5, 127.1, 126.3, 126.2, 124.2, 117.3, 114.2, 113.4, 101.7, 55.3, 45.6, 41.5, 39.0, 28.1;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{30}\text{H}_{27}\text{O}_3$, 435.1965 found, 435.1960;

IR (film): ν_{max} 1759, 1627, 1149, 833, 694 cm^{-1}

HPLC: 96% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 8.9 min, *tr* = 12.7 min.

2.6 Appendices

TBO9117-2-H1
AV400 CDCL3

TBO9117-2-C13
AV400 CDCL3

TBO13073-19-H1
AV 400 CDCl₃

7.482
7.479
7.476
7.473
7.466
7.357
7.351
7.348
7.340
7.331
7.323
7.319
7.305
7.292
7.295
7.290
7.284
7.277
7.255
7.237
7.211
7.207
7.191
7.182
7.179
7.163
7.161
7.145
7.142
7.126
7.106

3.259
3.218
3.099
3.065
3.027
2.992
2.804

TBO9107-2-C13
AV400 CDCl₃

170.35

151.12

135.39

130.74

130.28

128.82

128.43

128.31

128.15

127.28

124.69

123.22

122.32

116.26

85.04

84.36

77.36

77.04

76.72

45.55

39.60

33.67

25.89

TB013007-6-H1
AV400 CDCL₃

TB013007-6-C13
AV400 CDCL₃

TBO13073-8-F19
AV 400 CDCl₃

TBO13073-14-H1
AV 400 CDCl₃

TBO9114-2-H1
AV400 CDCL₃

TBO9114-2-C13
AV400 CDCL₃

96% *ee* (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min)

mAU

PDA Ch2 254nm

Peak#	Ret. Time	Area	Height	Area%
1	6.423	3258626	259789	49.957
2	8.578	3264210	169234	50.043
Total		6522836	429023	100.000

Peak Table

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	6.532	8380562	658025	98.231
2	8.906	150879	7984	1.769
Total		8531441	666009	100.000

Peak Table

85% ee (OJ-H, 95/5 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.567	25836173	823233	49.673
2	13.218	26176617	497340	50.327
Total		52012790	1320572	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.692	4152716	140406	7.547
2	13.909	50869833	984102	92.453
Total		55022549	1124508	100.000

93% ee (AD-H, 99/1 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.878	212388	8079	49.903
2	15.919	213211	6524	50.097
Total		425599	14604	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	12.043	83077	2206	3.728
2	15.945	2145588	50363	96.272
Total		2228664	52570	100.000

94% ee (OD-H, 99/1 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.121	658207	23080	49.816
2	15.966	663070	19514	50.184
Total		1321277	42595	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.444	4407	212	2.809
2	16.384	152453	4764	97.191
Total		156860	4976	100.000

90% ee (OJ-H, 85/15 hexanes/i-PrOH, 1.0 ml/min)

mAU

PDA Ch1 254nm

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.961	17537453	222569	50.415
2	21.378	17248500	143683	49.583
Total		34785953	366252	100.000

mAU

PDA Ch1 254nm

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	15.283	423834	4948	4.977
2	21.814	8091306	65194	95.023
Total		8515140	70142	100.000

94% *ee* (OD-H, 99/1 hexanes/*i*-PrOH, 1.0 ml/min)

mAU

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.121	658207	23080	49.816
2	15.966	663070	19514	50.184
Total		1321277	42595	100.000

mAU

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.444	4407	212	2.809
2	16.384	152453	4764	97.191
Total		156860	4976	100.000

93% *ee* (AD-H, 99/1 hexanes/*i*-PrOH, 1.0 ml/min)

86% ee (OJ-H, 90/10 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	15.456	53933392	1094853	49.195
2	20.103	55698766	855941	50.805
Total		109632159	1950795	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	15.066	796866	21267	6.812
2	19.297	10900706	183124	93.188
Total		11697572	204391	100.000

93% ee (IC, 99/1 hexanes/i-PrOH, 0.5 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	28.482	165578	3994	49.865
2	35.669	166476	2830	50.135
Total		332054	6824	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	29.620	64624	1877	3.470
2	32.730	1797995	21430	96.530
Total		1862619	23307	100.000

90% *ee* (OD-H, 95/5 hexanes/*i*-PrOH, 0.5 ml/min)

mAU

Peak Table

Peak#	Ret. Time	Area	Area%	Height	Mark
1	9.909	952870	49.541	65583	
2	10.671	970510	50.459	61767	V
Total		1923380	100.000	127353	

mAU

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.698	18905	1436	4.563
2	10.394	395413	27714	95.437
Total		414318	29150	100.000

89% ee (OD-H, 90/10 hexanes/i-PrOH, 0.5 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.422	12908129	713643	50.047
2	11.710	12883957	651671	49.953
Total		25792087	1365313	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.476	30602514	1564428	94.115
2	11.834	1913542	90359	5.885
Total		32516056	1654787	100.000

91% ee (OD-H, 95/5 hexanes/i-PrOH, 0.5 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	17.711	33355315	903217	49.902
2	26.285	33486973	613860	50.098
Total		66842288	1517077	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	17.686	54428632	1544137	95.668
2	26.437	2464769	44675	4.332
Total		56893401	1588812	100.000

91% *ee* (OD-H, 95/5 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. time	Area	Height	Area%
1	11.861	29110125	958400	50.720
2	14.959	28283277	692830	49.280
Total		57393402	1651229	100.000

Peak Table

Peak#	Ret. time	Area	Height	Area%
1	11.922	10848164	352677	95.507
2	15.174	510390	12235	4.493
Total		11358554	364912	100.000

95% *ee* (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min)

89% *ee* (OD-H, 95/5 hexanes/*i*-PrOH, 0.5 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.897	18411182	693488	50.062
2	16.554	18365418	600177	49.938
Total		36776600	1293664	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.994	46056267	1770040	94.275
2	16.701	2796946	92603	5.725
Total		48853213	1862643	100.000

91% *ee* (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	6.029	11907106	999377	49.505
2	7.191	12144985	770678	50.495
Total		24052091	1770055	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	6.038	45027380	3747855	95.931
2	7.233	1909756	115817	4.069
Total		46937136	3863672	100.000

93% *ee* (OD-H, 95/5 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.213	18387663	871664	50.306
2	16.908	18361877	417486	49.694
Total		36949541	1289150	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.155	61937010	3394709	96.516
2	16.652	2236036	54402	3.484
Total		64173045	3449112	100.000

91% *ee* (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. time	Area	Height	Area%
1	7.979	7832692	413810	50.589
2	11.009	7650165	273368	49.411
Total		15482857	687178	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.939	12503431	676420	95.842
2	11.028	542403	19303	4.158
Total		13045835	695723	100.000

90% *ee* (IC, 99/1 hexanes/*i*-PrOH, 0.5 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	18.918	1216551	36707	50.601
2	21.978	1187649	32964	49.399
Total		2404200	69671	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	19.134	3387672	135807	95.310
2	21.975	166688	5241	4.690
Total		3554360	141048	100.000

95% *ee* (OJ-H, 99/1 hexanes/*i*-PrOH, 0.5 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	13.635	26561226	440136	49.495
2	17.292	27103464	302467	50.505
Total		53664689	742602	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	12.687	51292432	1267280	97.219
2	15.381	1467046	22820	2.781
Total		52759478	1290100	100.000

mAU

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.968	17476940	847525	49.390
2	16.622	17908422	561314	50.610
Total		35385362	1408838	100.000

mAU

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.792	89987376	3661806	95.232
2	16.164	4505759	138029	4.768
Total		94493335	3799834	100.000

96% ee (AD-H, 95/5 hexanes/i-PrOH, 0.5 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	22.900	2809742	49694	50.591
2	26.275	2744098	42732	49.409
Total		5553840	92426	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	22.603	3848234	57124	98.044
2	26.010	76766	1293	1.956
Total		3925000	58417	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.006	3825120	203829	50.867
2	10.068	3694748	148065	49.133
Total		7519868	351893	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.980	26218049	1434545	97.268
2	10.094	736477	30794	2.732
Total		26954526	1465339	100.000

90% *ee* (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.002	30380468	1180416	49.914
2	11.298	30484573	1029591	50.086
Total		60865041	2210007	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.005	56563955	2235675	95.475
2	11.690	2680751	83377	4.525
Total		59244706	2319052	100.000

93% *ee* (AD-H, 95/5 hexanes/*i*-PrOH, 0.5 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	12.726	928663	33109	49.719
2	15.568	939162	22769	50.281
Total		1867824	55877	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	12.417	39041	1259	3.601
2	15.587	1043003	24974	96.399
Total		1084046	26233	100.000

95% ee (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.357	26457454	1200928	49.920
2	13.236	26541862	629137	50.080
Total		52999316	1830065	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.207	48041983	2230496	97.549
2	13.224	1108860	28602	2.451
Total		49148843	2259098	100.000

94% ee (OD-H, 95/5 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.564	19983229	736163	49.564
2	13.142	20334740	522715	50.436
Total		40317969	1258878	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.228	47704811	1883703	97.267
2	12.754	1340164	36694	2.733
Total		49044975	1920398	100.000

96% ee (OD-H, 90/10 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.844	39928689	1809842	49.430
2	12.387	40850327	1124216	50.570
Total		80779016	2934058	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.957	51933842	2358085	98.310
2	12.737	892521	24559	1.690
Total		52826364	2382644	100.000

Chapter 3

Enantioselective Alkylation of Cyclic and Linear Ketones

3.1 Introduction

In the 1980s, chiral alkaloid salts were employed in enantioselective alkylation of cyclic ketones.¹ From then on, there have been many publications involving enantioselective alkylation of cyclic ketones. However, efficient examples of enantioselective alkylation of cyclic ketones are still lacking.

In 1984, Dolling's group reported an alkaloid salt catalyzed enantioselective alkylation of cyclic ketone (Scheme 3.1).¹ The reaction resulted in formation of the desired product with high enantioselectivity but only 2 successful examples were shown in the paper.

Scheme 3.1 Enantioselective synthesis of (+)-indarinoe.

Vandewalle's group reported a similar work using alkaloid salt as catalyst (Scheme 3.2, equation 1).² Shioiri and coworkers reported enantioselective alkylation of fluorotetralone (equation 2)³ while indanone was used as substrate in the chiral PTC reaction, with moderate enantioselectivity of 63% *ee* obtained (equation 3).⁴ Scheidt's group also developed an enantioselective alkylation of isoflavanones (equation 4).⁵ Moderate enantioselectivity and limited substrate scope were achieved in this work. As evident in these examples, the challenge of achieving high enantioselectivity remains.

Scheme 3.2 Enantioselective alkylation of cyclic ketones with moderate enantioselectivity.

There are many publications focusing on enantioselective alkylation of 1,3-dicarbonyl compounds, which can be easily activated in basic condition due to its low pK_a at the α -position (Scheme 3.3).⁶

Scheme 3.3 Enantioselective alkylation of cyclic ketones using 1,3-dicarbonyl compounds.

The most efficient method in enantioselective alkylation of cyclic ketones was reported by Maruoka group (Scheme 3.4).⁷ The *N,N*-diphenylaminomethylene auxiliary group is vital for the high enantioselectivity of alkylation.

Scheme 3.4 Enantioselective alkylation of masked 2-phenylcyclohexanone.

Reviewing the literature on enantioselective alkylation of cyclic ketones using asymmetric PTC, we found that enantioselective alkylation involving indanone and tetralone compounds is still a challenge. Hence, in order to extend the applicability of our Brønsted probase strategy, we chose indanone and tetralone as substrates to commence our investigation.

3.2 Results and discussion

Our optimization commenced with indanone **4a** as the substrate and cinnamyl bromide **2b** as the electrophile (Table 3.1).

Table 3.1 Optimization of reaction conditions for cyclic ketone

Entry ^a	Catalyst (mol %)	Probase (equiv.)	CsF (equiv.)	Yield ^b	ee ^c
1 ^d	cat-4 (10)	pb-4 (3)	2	trace	--
2	cat-4 (10)	pb-4 (2)	5	92	43
3	cat-6 (10)	pb-4 (2)	5	90	80
4	cat-7 (10)	pb-4 (2)	5	88	78
5	cat-8 (10)	pb-4 (2)	5	84	15
6	cat-9 (10)	pb-4 (2)	5	83	13
7	cat-6 (10)	pb-6 (2)	5	94	79
8	cat-6 (10)	pb-7 (2)	5	90	78
9	cat-6 (10)	pb-8 (2)	5	trace	--
10	cat-6 (10)	pb-5 (2)	5	98	95

^a Reaction was carried out with **4a** (0.10 mmol), **2b** (0.20 mmol), probase (0.2 mmol), CsF (0.50 mol) and catalyst (10 mol%) in 0.4 mL of Et₂O at -40 °C for 48 h. ^b Isolated yield. ^c Determined by HPLC analysis on a chiral stationary phase. ^d Main product is silyl enol ether **8b**.

After solvent screening, we found Et₂O could increase the reaction rate and enantioselectivity. For different F source screening, only the CsF gave the high yield and reaction rate for our substrate. The best condition obtained with dihydrocoumarin substrate was used in cyclic ketone alkylation, however, no desired product was obtained and the main product was the silyl enol ether of **4a** (Table 3.1, entry 1). By decreasing the amount of **pb-4** and increasing the amount of CsF, desired alkylation product **5a** was provided in good yield with 43% *ee* (Table 3.1, entry 2). Bisguanidium salt **cat-6** demonstrated to be more efficient than pentanidium salt **cat-4** in this transformation (entry 3). Fluoro-substituted bisguanidium salt **cat-7** gave similar results as **cat-6** (entry 4). Other bisguanidium salts were tested but low enantioselectivity was obtained (entries 5, 6). Changing the structure of the probase did not affect the enantioselectivity (entries 7, 8). Probase **pb-8** was unable to promote the reaction due to the low basicity (entry 9). Finally, it was discovered that bis(*tert*-butyldimethylsilyl)-acetamide (BTBSA, **pb-5**) is a more suitable probase than **pb-4**, and the enantioselectivity increased significantly from 80% *ee* to 95% *ee* (entry **10**). The optimization results indicated that the presence of the silyl group in the probase is of paramount importance for good enantioselectivity.

Having established the optimized reaction condition, we turned our attention to the substrate scope examination. As fluorinated compounds⁸ and heterocyclic rings⁹ are commonly found in medicine chemistry, many fluorinated and heterocyclic substrates were included in our substrate testing (Chart 3.1). The trifluoromethyl group in the *ortho*, *para*, *meta* position on the benzyl ring gave excellent yield and enantioselectivity (**5b-5d**). Other halogen substituents on the benzyl ring also provided good results (**5e**). Indanone with heterocyclic substituents resulted in slightly lower enantioselectivity (**5f**, **5g**). Various different electrophiles, such as allylic bromide, propargylic bromide and methyl bromoacetate, were tested and good yield and enantioselectivity were obtained (**5h-5l**). Substituents on the

indanone phenyl ring were also tested and good results were achieved (**5m**, **5n**).

Chart 3.1 Substrate scope of the enantioselective alkylation of cyclic ketones ^{a,b,c,d}

^a For indanone substrates, reaction was carried out with **4** (0.10 mmol), electrophile (0.20 mmol), **pb-5** (0.20 mmol), CsF (0.50 mol) and **cat-6** catalyst (10 mol%) in 0.4 mL of Et_2O at -40°C for 72 h. ^b For tetralone, the

reaction was carried out the same condition as indanone for 96 h. ^c Unless otherwise indicated, yields are isolated total yields, *ee* was determined by HPLC analysis on a chiral stationary phase. ^d Absolute configuration was determined by comparing with ref 10.

For tetralone substrates, fluoro-substituents on the benzyl ring gave good enantioselectivity (**5o-5q**). Similar to the indanone substrates, allylic bromide and propargylic bromide were also suitable electrophiles and afforded satisfying results (**5r-5t**). However, methyl bromoacetate was less suitable as an electrophile for tetralone as diminished enantioselectivity was observed (**5u**).

After exploring the enantioselective alkylation of cyclic ketones, we turned our attention to linear ketone substrates. It was initially intended that our Brønsted probase strategy would be used for direct enantioselective alkylation of the linear ketones (Table 3.2). However, different hydroxide salts were unable to activate linear ketone due to the *pK_a* issue (Table 3.2, entries 1-4). Probase **pb-4** gave low yield and moderate enantioselectivity (entry 5), while **pb-5** did not react (entry 6).

Table 3.2 Direct enantioselective alkylation of linear ketones

CCC(=O)c1ccccc1 (**9a**) + BrCC(=O)OC (**2c**) $\xrightarrow[\text{-15 } ^\circ\text{C}]{\text{10 mol\% cat-6, base condition, 4-tert-butyltoluene}}$ CCC(=O)c1ccccc1C(C)C(=O)OC (**7a**)

Entry ^a	Base condition	Yield ^c	<i>ee</i> ^d
1	LiOH·H ₂ O (5 equiv.)	trace	--
2	NaOH (5 equiv.)	trace	--
3	KOH (5 equiv.)	trace	--
4	CsOH·H ₂ O (5 equiv.)	trace	--
5 ^b	pb-4 (2 equiv.) and CsF (5 equiv.)	35 ^e	56
6 ^b	pb-5 (2 equiv.) and CsF (5 equiv.)	trace	--

^a Reaction was carried out with **9a** (0.10 mmol), **2c** (0.20 mmol), base (0.50 mmol) and catalyst (10 mol%) in 0.4 mL of 4-*tert*-butyltoluene for 24 h at -15 °C. ^b Reaction was carried out with **9a** (0.10 mmol), **2c** (0.20 mmol), probase (0.20 mmol), CsF (0.50 mmol) and catalyst (10 mol%) in 0.4 mL 4-*tert*-butyltoluene for 24 h at

-15 °C. ^c Isolated yield. ^d Determined by HPLC analysis on a chiral stationary phase. ^e Silyl enol ether byproduct was formed.

Silyl enol ethers, as precursors of ketone enolates, are widely used in many asymmetric reactions.¹¹ Pre-formation of the silyl enol ether from ketone substrates is good method to overcome the high pK_a issue in the substrates. In our previous screening, we found that the Brønsted probase strategy did not have enough basicity to activate linear ketones, hence silyl enol ether derived from linear ketone was chosen as a substrate to carry out the new examination (Table 3.3).

The desired alkylation product was obtained in 50% yield and 46% *ee* in the presence of **cat-6** and CsF as the fluoride source (Table 3.3, entry 1). It was discovered that silver fluoride cannot activate silyl enol ether substrate unless 1 equivalent of CsCl was added as an additive (entry 2). The combination of AgF and CsCl increased reactivity and enantioselectivity significantly (entry 3), while decreasing the amount of AgF had minimal effect on the result (entry 4).

Table 3.3 Optimization of reaction conditions for linear ketone

Reaction scheme: 6a + 2c $\xrightarrow[\text{-15 °C}]{\text{10 mol\% cat-6, fluoro source, additive, probase}}$ 7a

Entry ^a	Probase (equiv.)	Fluoride source (equiv.)	Additive (equiv.)	Yield ^b	<i>ee</i> ^c
1	none	CsF (5)	none	50	46
2	none	AgF (5)	none	trace	--
3	none	AgF (5)	CsCl (1)	47	80
4	none	AgF (2)	CsCl (1)	45	77
5	pb-4 (1)	AgF (2)	CsCl (1)	23	54
6	pb-4 (0.4)	AgF (2)	CsCl (1)	82	86
7	pb-5 (0.4)	AgF (2)	CsCl (1)	80	79

^a Reaction was carried out with **6a** (0.10 mmol), **2c** (0.20 mmol), **pb-4** (0.04 mmol), CsCl (0.10 mmol) and catalyst (10 mol%) in 0.4 mL 4-*tert*-butyltoluene for 24 h at -15 °C. ^b Isolated yield. ^c Determined by HPLC analysis on a chiral stationary phase.

Interestingly, adding 1 equivalent of probase **pb-4** had an inhibitory effect on the reaction (entry 5), but using catalytic amount of **pb-4** increased both yield and enantioselectivity of the desired product (entry 6). Probase **pb-5** was found to be less suitable in the silyl enol ether reaction (entry 7).

The optimized reaction condition was then used in the testing of substrate scope. Substrates with long alkyl chains could provide good yield and enantioselectivity (**7b-7d**). Using a different electrophile, such as ethyl bromoacetate, gave comparable results (**7e**). Although only substrates with *para* substituents in the phenyl ring gave high enantioselectivity, the presence of both electron withdrawing and electron donating groups in *para* position can afford good results (**7f-7i**).

Chart 3.2 Substrate scope of enantioselective alkylation of linear ketones ^{a,b,c,d}

^a Reaction was carried out with **6** (0.10 mmol), 2-bromoacetate (0.20 mmol), **pb-4** (0.04 mmol), CsCl (0.10 mmol) and catalyst (10 mol%) in 0.4 mL of 4-*tert*-butyltoluene for 24 h at -15 °C. ^b Unless otherwise noted, yields are isolated total yields and *ee* was determined by HPLC analysis on a chiral stationary phase. ^c Absolute configuration determined by comparing with ref **11**.

3.3 Summary

In summary, we have demonstrated that our Brønsted probase strategy can be used in enantioselective alkylation of cyclic and linear ketones. In our experiment, we found that different probases (**pb-4** and **pb-5**) have different efficiency in the reactions involving cyclic substrates and catalytic amount of probase is crucial for linear ketones.

3.4 References

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3.5 Experimental section

3.5.1 General information

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker (300 or 400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker (400 MHz) (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *e.r.* was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]_D^{25}$ (*c* in g per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

3.5.2 Preparation of starting material

To a RBF equipped with a magnetic stir bar was added ketone substrate, aldehyde and EtOH. Aqueous NaOH solution was added slowly to the RBF, resulting in the formation of a precipitate. The mixture was stirred at r.t. for 30 min to 6 h and then cooled to 0 °C for 1 h. After filtration and washing with cooled MeOH, the solid product was dissolved in MeOH. 10% Pd/C was added to the solution and the reaction was stirred at 1 atm H₂ for 4-12 h to provide the desired product in 45-90% yield.

3.5.3 General procedures for enantioselective catalytic reactions

To a dry Schlenk tube equipped with a magnetic stir bar, was added 10 mol% catalyst **cat-6**, 2 equiv. **pb-5**, 5 equiv. CsF and 2 equiv. electrophile. The tube was closed after addition of Et_2O (0.4 mL). The resulting mixture was stirred at $-40\text{ }^\circ\text{C}$ for 24-96 h. The reaction mixture was then directly purified *via* silica gel chromatography (EA/Hexane: 1:200- 1:30) to obtain the desired product.

To a dry Schlenk tube equipped with a magnetic stir bar, was added 10 mol% catalyst **cat-6**, **pb-4** (0.4 equiv.), AgF (2 equiv.), CsCl (1 equiv.) and electrophile (2 equiv.). The tube was closed after addition of 4-*tert*-butyltoluene (0.4 mL). The resulting mixture was stirred at -

15 °C for 12-24 h protected from light. The reaction mixture was then purified *via* silica gel chromatography (EA/Hexane: 1:10) to obtain the desired product.

3.5.4 Characterization of catalysts, substrates, and products

2-benzyl-2,3-dihydro-1H-inden-1-one (4a)

physical property :colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 7.80 (d, J = 8.0 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.42 – 7.20 (m, 7H), 3.42 (dd, J = 4.0, 16.0 Hz, 1H), 3.15 (dd, J = 8.0, 16.0 Hz, 1H), 3.03 – 2.94 (m, 1H), 2.85 (dd, J = 8.0, 16.0 Hz, 1H), 2.68 (dd, J = 4.0, 16.0 Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 207.6, 153.6, 139.6, 136.6, 134.8, 128.9, 128.5, 127.4, 126.6, 126.4, 123.9, 48.9, 36.9, 32.2;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{15}\text{O}$, 223.1125 found, 223.1123;

IR (film): ν_{max} 1759, 1627, 1589, 1508, 1442, 1141, 750, 700 cm^{-1}

2-(2-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one (4b)

physical property :colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 7.84 – 7.30 (m, 7H), 3.61 (dd, J = 4.0, 16.0 Hz, 1H), 3.22 (dd, J = 8.0, 16.0 Hz, 1H), 3.14 – 3.04 (m, 1H), 2.94 (dd, J = 8.0, 16.0 Hz, 1H), 2.84 (dd, J = 4.0, 16.0 Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 207.1, 153.2, 138.6, 138.5, 136.3, 134.9, 131.2, 130.8, 129.4, 129.1, 128.8, 128.6, 128.5, 127.5, 126.5, 126.4, 126.3, 126.2, 126.1, 126.1, 125.9, 124.0, 123.2, 120.4, 48.2, 32.9, 32.8, 32.3;

^{19}F NMR: (376 MHz, CDCl_3) δ -62.4;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{20}\text{OF}_3$, 321.1465 found, 321.1466;

IR (film): ν_{max} 1712, 1604, 1465, 1311, 1118, 694 cm^{-1}

2-(3-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one (4c)

physical property : colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 7.78 (d, J = 8.0 Hz, 1H), 7.61 – 7.32 (m, 6H), 3.43 (dd, J = 4.0, 16.0 Hz, 1H), 3.19 (dd, J = 8.0, 16.0 Hz, 1H), 3.04 – 2.95 (m, 1H), 2.83 (dd, J = 4.0, 16.0 Hz, 1H), 2.75 (dd, J = 8.0, 16.0 Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 207.0, 153.2, 140.6, 136.4, 134.9, 132.3, 131.2, 130.9, 130.6, 130.3, 129.0, 128.2, 127.5, 126.6, 125.6, 125.6, 125.5, 125.4, 124.0, 123.3, 123.2, 123.2, 123.2, 122.8, 120.1, 48.5, 36.7, 32.1 ;

^{19}F NMR: (376 MHz, CDCl_3) δ -62.5;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{20}\text{OF}_3$, 321.1465 found, 321.1466;

IR (film): ν_{max} 1712, 1612, 1465, 1327, 1126, 702 cm^{-1}

2-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one (4d)

physical property : colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 7.80 (d, $J = 8.0$ Hz, 1H), 7.63 – 7.54 (m, 3H), 7.45 – 7.34 (m, 4H), 3.45 (dd, $J = 4.0, 16.0$ Hz, 1H), 3.21 (dd, $J = 8.0, 16.0$ Hz, 1H), 3.06 – 2.97 (m, 1H), 2.89–2.74 (m, 2H);

^{13}C NMR: (100 MHz, CDCl_3) δ 207.1, 153.3, 143.9, 143.8, 136.3, 135.0, 129.2, 128.9, 128.6, 127.6, 126.6, 125.6, 125.5, 125.4, 125.3, 124.0, 122.9, 48.5, 36.6, 32.0;

^{19}F NMR: (376 MHz, CDCl_3) δ -58.99;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{20}\text{OF}_3$, 321.1473 found, 321.1466;

IR (film): ν_{max} 1705, 1612, 1327, 1118, 694 cm^{-1}

2-(3-bromobenzyl)-2,3-dihydro-1H-inden-1-one (4e)

physical property : colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 7.84 – 7.14 (m, 8H), 3.38 (dd, $J = 4.0, 16.0$ Hz, 1H), 3.20 (dd, $J = 8.0, 16.0$ Hz, 1H), 3.05 – 2.94 (m, 1H), 2.83 (dd, $J = 4.0, 16.0$ Hz, 1H), 2.63 (dd, $J = 8.0, 16.0$ Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 207.1, 153.3, 142.0, 136.4, 134.9, 131.9, 130.1, 129.5, 127.5, 126.6, 124.0, 122.6, 48.6, 36.5, 32.1;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{22}\text{OBr}$, 345.0853 found, 345.0854;

IR (film): ν_{max} 1705, 1604, 1465, 1288, 694 cm^{-1}

2-(thiophen-3-ylmethyl)-2,3-dihydro-1H-inden-1-one (4f)

physical property : colourless oil.

¹H NMR: (400 MHz, CDCl₃) δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.53 (m, 1H), 7.45 – 7.31 (m, 2H), 7.26 – 7.21 (m, 1H), 7.04 – 6.93 (m, 2H), 6.26 (dd, *J* = 2.0, 2.8 Hz, 1H), 6.07 – 6.03 (m, 1H), 3.33 (dd, *J* = 4.0, 16.0 Hz, 1H), 3.23 (dd, *J* = 8.0, 16.0 Hz, 1H), 3.02 – 2.93 (m, 1H), 2.91 – 2.77 (m, 2H);

¹³C NMR: (100 MHz, CDCl₃) δ 207.6, 153.6, 139.7, 136.5, 134.8, 128.3, 127.4, 126.6, 125.7, 123.9, 121.4, 48.2, 32.3, 31.4;

HRMS: (ESI) [M+H]⁺ calcd. for C₁₄H₁₃OS, 229.1071 found, 229.1078;

IR (film): ν_{max} 1705, 1604, 1465, 694 cm⁻¹

2-(furan-2-ylmethyl)-2,3-dihydro-1H-inden-1-one (4g)

physical property : colourless oil.

¹H NMR: (400 MHz, CDCl₃) δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.59 – 7.51 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.25 (m, 2H), 6.26 (dd, *J* = 2.0, 2.8 Hz, 1H), 6.07 – 6.03 (m, 1H), 3.35 – 3.21 (m, 2H), 3.03 – 2.86 (m, 2H), 2.78 (dd, *J* = 8.0, 16.0 Hz, 1H);

¹³C NMR: (100 MHz, CDCl₃) δ 207.1, 153.6, 153.5, 141.4, 136.4, 134.8, 127.4, 126.6, 123.9, 110.2, 106.3, 46.4, 32.4, 29.3;

HRMS: (ESI) [M+H]⁺ calcd. for C₁₄H₁₃O₂, 213.0911 found, 213.0916;

IR (film): ν_{max} 1712, 1612, 1149, 1010, 694 cm⁻¹

6-methyl-2-(2-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one (4h)

physical property : colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 7.71 – 7.58 (m, 2H), 7.53 – 7.408 (m, 3H), 7.38 – 7.27 (m, 2H), 3.59 (dd, $J = 4.0, 16.0$ Hz, 1H), 3.22 – 3.05 (m, 1H), 2.94 (dd, $J = 8.0, 16.0$ Hz, 1H), 2.79 (dd, $J = 4.0, 16.0$ Hz, 1H), 2.43 (s, 3H);

^{13}C NMR: (100 MHz, CDCl_3) δ 207.2, 138.6, 137.4, 136.4, 136.1, 131.8, 130.8, 129.1, 128.8, 126.4, 126.2, 126.1, 125.8, 123.9, 32.8, 31.9, 21.0;

^{19}F NMR: (376 MHz, CDCl_3) δ -59.0;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{16}\text{OF}_3$, 305.1158 found, 305.1153;

IR (film): ν_{max} 1705, 1311, 1118, 700 cm^{-1}

2-benzyl-5-chloro-2,3-dihydro-1H-inden-1-one (4i)

physical property :colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 7.74 – 7.67 (m, 1H), 7.42 – 7.20 (m, 7H), 3.39 (dd, $J = 4.0, 16.0$ Hz, 1H), 3.16 (dd, $J = 8.0, 16.0$ Hz, 1H), 3.08 – 2.99 (m, 1H), 2.86 (dd, $J = 8.0, 16.0$ Hz, 1H), 2.71 (dd, $J = 4.0, 16.0$ Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 206.2, 155.0, 141.3, 139.2, 135.0, 128.9, 128.6, 128.2, 126.7, 126.4, 125.1, 49.0, 36.9, 31.8;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{14}\text{OCl}$, 257.0730 found, 257.0733;

IR (film): ν_{max} 1705, 1612, 1147, 694 cm^{-1}

2-(4-(trifluoromethyl)benzyl)-3,4-dihydronaphthalen-1(2H)-one (4j)

physical property :colourless oil.

¹H NMR: (400 MHz, CDCl₃) δ 8.12 – 8.06 (m, 1H), 7.63 – 7.54 (m, 2H), 7.52 – 7.46 (m, 1H), 7.42 – 7.30 (m, 3H), 7.28 – 7.22 (m, 1H), 3.61 – 3.49 (m, 1H), 2.98 (dd, *J* = 4.0, 8.0 Hz, 1H), 2.85 – 2.72 (m, 2H), 2.18 – 2.07 (m, 1H), 1.91-1.75 (m, 1H);

¹³C NMR: (100 MHz, CDCl₃) δ 198.7, 144.3, 143.8, 133.4, 132.3, 129.6, 128.8, 128.7, 128.3, 127.5, 126.7, 125.6, 125.4, 125.3, 125.2, 122.9, 49.2, 35.6, 28.7, 27.9;

¹⁹F NMR: (376 MHz, CDCl₃) δ -62.3;

HRMS: (ESI) [M+H]⁺ calcd. for C₂₁H₂₄OF₃, 349.1722 found, 349.1779;

IR (film): ν_{max} 1674, 1465, 1327, 1118, 694 cm⁻¹

2-(3-(trifluoromethyl)benzyl)-3,4-dihydronaphthalen-1(2H)-one (4k)

physical property : colourless oil.

¹H NMR: (400 MHz, CDCl₃) δ 8.13 – 8.06 (m, 1H), 7.56 – 7.39 (m, 5H), 7.52 – 7.46 (m, 1H), 7.36 – 7.28 (m, 1H), 7.27 – 7.21 (m, 1H), 3.62 – 3.50 (m, 1H), 2.97 (dd, *J* = 4.0, 8.0 Hz, 1H), 2.84 – 2.72 (m, 2H), 2.17 – 2.08 (m, 1H), 1.90-1.74 (m, 1H);

¹³C NMR: (100 MHz, CDCl₃) δ 198.7, 144.9, 141.1, 133.4, 132.7, 132.3, 130.8, 130.5, 128.8, 128.7, 127.5, 126.6, 125.9, 125.9, 125.6, 123.1, 123.0, 122.9, 49.2, 35.6, 28.7, 27.9;

¹⁹F NMR: (376 MHz, CDCl₃) δ -62.4;

HRMS: (ESI) [M+H]⁺ calcd. for C₂₁H₂₄OF₃, 349.1722 found, 349.1777;

IR (film): ν_{max} 1705, 1643, 1465, 1327, 1126, 694 cm⁻¹

2-(4-fluorobenzyl)-3,4-dihydronaphthalen-1(2H)-one (4l)

physical property :colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 8.12 – 8.06 (m, 1H), 7.56 – 7.39 (m, 5H), 7.52 – 7.44 (m, 1H), 7.37 – 7.30 (m, 1H), 7.27 – 7.16 (m, 3H), 7.06 – 7.94 (m, 2H), 3.51 – 3.37 (m, 1H), 3.04 – 2.88 (m, 2H), 2.79 – 2.65 (m, 2H), 2.18 – 2.06 (m, 1H), 1.88-1.72 (m, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 198.1, 162.7, 160.2, 143.9, 135.6, 135.5, 133.3, 132.4, 130.6, 130.5, 128.7, 127.5, 126.6, 115.2, 115.0, 49.4, 34.8, 28.6, 27.7;

^{19}F NMR: (376 MHz, CDCl_3) δ -117.2;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{24}\text{OF}$ 299.1815 found, 299.1811;

IR (film): ν_{max} 1681, 1512, 1296, 694 cm^{-1}

2-(4-bromobenzyl)-3,4-dihydronaphthalen-1(2H)-one (4m)

physical property :colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 8.11 – 8.05 (m, 1H), 7.53 – 7.40 (m, 3H), 7.37 – 7.30 (m, 1H), 7.28 – 7.21 (m, 1H), 7.17 – 7.09 (m, 2H), 3.43 (dd, $J = 4.0, 16.0$ Hz, 1H), 3.03 – 2.89 (m, 2H), 2.79 – 2.65 (m, 2H), 2.17 – 2.07 (m, 1H), 1.87-1.73 (m, 1H);

^{13}C NMR: 100 MHz, CDCl_3) δ 198.9, 143.9, 139.0, 133.3, 132.4, 131.4, 131.0, 128.7, 127.5, 126.6, 119.9, 49.2, 35.1, 28.7, 27.8;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{22}\text{OBr}$, 345.0851 found, 345.0854;

IR (film): ν_{max} 1759, 1627, 1589, 1508, 1442, 1141, 750, 700 cm^{-1}

2-(thiophen-3-ylmethyl)-3,4-dihydronaphthalen-1(2H)-one (4n)

physical property :colourless oil.

^1H NMR: (400 MHz, CDCl_3) δ 8.12 – 8.06 (m, 1H), 7.52 – 7.44 (m, 1H), 7.37 – 7.21 (m, 3H), 7.06 – 6.96 (m, 2H), 3.41 (dd, $J = 4.0, 16.0$ Hz, 1H), 3.03 – 2.94 (m, 2H), 2.87 ((dd, $J = 4.0, 16.0$ Hz, 1H), 2.81 – 2.72 (m, 1H), 2.23 – 2.12 (m, 1H), 1.89-1.75 (m, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 199.2, 144.0, 140.0, 133.3, 132.5, 128.7, 128.6, 127.5, 126.6, 125.4, 121.7, 48.7, 30.1, 27.7, 27.9;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{17}\text{H}_{21}\text{OS}$, 273.1315 found, 273.1313;

IR (film): ν_{max} 1681, 1465, 1288, 1010, 694 cm^{-1}

(S)-2-benzyl-2-cinnamyl-2,3-dihydro-1H-inden-1-one (5a)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_{\text{D}}$ (c 1.43, CHCl_3): 2.5;

^1H NMR: (400 MHz, MeOD) δ 7.68 (d, $J = 8.0$ Hz, 1H), 7.67 – 7.61 (m, 1H), 7.38 – 7.05 (m, 12H), 6.45 (d, $J = 16.0$ Hz, 1H), 6.06 – 5.95 (m, 1H), 3.27 – 3.16 (m, 2H), 3.11 (d, $J = 16.0$ Hz, 1H), 2.67 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H), 2.52 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H);

^{13}C NMR: (100 MHz, MeOD) δ 211.5, 153.6, 137.1, 134.9, 133.5, 129.7, 128.0, 127.6, 127.0, 126.8, 126.2, 126.1, 125.6, 124.4, 122.9, 54.3, 42.3, 41.7, 35.1;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{23}\text{O}$, 339.1747 found, 339.1749;

IR (film): ν_{max} 1705, 1604, 1465, 1296, 1010, 694 cm^{-1}

HPLC: 94% *ee* determined by HPLC (OJ-H, 70/30 hexanes/*i*-PrOH, 1.0 ml/min) $t_r = 8.8$ min, $t_r = 15.3$ min.

(R)-2-cinnamyl-2-(2-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one (5b)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 1.57, CHCl_3): 1.57;

^1H NMR: (400 MHz, MeOD) δ 7.74 (d, $J = 8.0$ Hz, 1H), 7.67 – 7.61 (m, 1H), 7.58 – 7.51 (m, 1H), 7.41 – 7.11 (m, 10H), 6.45 (d, $J = 16.0$ Hz, 1H), 6.03 – 5.93 (m, 1H), 3.51 (d, $J = 16.0$ Hz, 1H), 3.30 – 3.23 (m, 1H), 3.11 (d, $J = 16.0$ Hz, 1H), 2.80 (d, $J = 16.0$ Hz, 1H), 2.63 – 2.48 (m, 2H);

^{13}C NMR: (100 MHz, MeOD) δ 211.2, 153.6, 137.1, 136.3, 135.2, 133.8, 131.6, 130.8, 128.0, 127.2, 126.9, 126.6, 126.2, 125.7, 125.6, 124.0, 123.2, 54.4, 42.9, 36.4, 35.0;

^{19}F NMR: (376 MHz, CDCl_3) δ -59.3;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{22}\text{OF}_3$, 407.1627 found, 407.1623;

IR (film): ν_{max} 1705, 1604, 1458, 1311, 1118, 694 cm^{-1}

HPLC: 95% *ee* determined by HPLC (OJ-H, 95/5 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 8.1 min, *tr* = 10.0 min.

(S)-2-cinnamyl-2-(3-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one (5c)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 1.85, CHCl_3): 0.7;

^1H NMR: (400 MHz, MeOD) δ 7.62 (d, $J = 8.0$ Hz, 1H), 7.54 – 7.47 (m, 1H), 7.43 – 7.11 (m, 11H), 6.46 (d, $J = 16.0$ Hz, 1H), 6.07 – 5.97 (m, 1H), 3.25 (d, $J = 16.0$ Hz, 1H), 3.15 (m, 1H),

2.99 (d, $J = 16.0$ Hz, 1H), 2.67 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H), 2.53 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H);

^{13}C NMR: (100 MHz, MeOD) δ 210.8, 153.3, 138.4, 137.1, 136.6, 135.1, 133.7, 133.5, 130.0, 128.3, 128.0, 127.1, 126.9, 126.3, 126.2, 126.1, 125.7, 124.2, 123.0, 122.9, 122.8, 54.1, 42.0, 41.5, 35.1;

^{19}F NMR: (376 MHz, CDCl_3) δ -64.1;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{22}\text{OF}_3$, 407.1622 found, 407.1623;

IR (film): ν_{max} 1705, 1604, 1450, 1327, 1126, 702 cm^{-1}

HPLC: 93% *ee* determined by HPLC (OJ-H, 99/1 hexanes/*i*-PrOH, 1.0 ml/min) $t_r = 8.1$ min, $t_r = 14.8$ min.

(S)-2-cinnamyl-2-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one (5d)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_{\text{D}}$ (c 1.66, CHCl_3): 2.6;

^1H NMR: (400 MHz, MeOD) δ 7.64 (d, $J = 8.0$ Hz, 1H), 7.56 – 7.49 (m, 1H), 7.46 – 7.41 (m, 2H), 7.38 – 7.28 (m, 4H), 7.23 – 7.11 (m, 5H), 6.45 (d, $J = 16.0$ Hz, 1H), 6.05 – 5.95 (m, 1H), 3.25 (d, $J = 16.0$ Hz, 1H), 3.16 (dd, $J = 4.0, 16.0$ Hz, 2H), 2.98 (d, $J = 16.0$ Hz, 1H), 2.66 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H), 2.52 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 209.5, 152.6, 141.5, 137.0, 136.4, 135.0, 133.9, 130.4, 128.4, 127.5, 127.3, 126.3, 126.1, 125.0, 124.9, 124.7, 123.9, 54.2, 42.2, 41.8, 35.6;

^{19}F NMR: (376 MHz, CDCl_3) δ -62.4;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{22}\text{OF}_3$, 407.1622 found, 407.1623;

IR (film): $\nu_{\max}$ 1705, 1612, 1465, 1327, 1118, 694 cm^{-1}

HPLC: 95% *ee* determined by HPLC (OD-H, 99/1 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 34.9 min, *tr* = 41.1 min.

(S)-2-(3-bromobenzyl)-2-cinnamyl-2,3-dihydro-1H-inden-1-one (5e)

physical property : colourless oil.

Optical rotation: $[\alpha]^{26}_{\text{D}}$ (*c* 1.46, CHCl_3): 11.8;

^1H NMR: (400 MHz, MeOD) δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.39 – 7.27 (m, 3H), 7.26 – 7.00 (m, 8H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.05 – 5.93 (m, 1H), 3.21 – 3.08 (m, 3H), 2.87 (d, *J* = 16.0 Hz, 1H), 2.64 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H), 2.50 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H);

^{13}C NMR: (100 MHz, MeOD) δ 210.9, 153.4, 139.8, 137.1, 136.6, 135.1, 133.6, 132.7, 129.3, 129.2, 128.6, 128.0, 127.1, 126.8, 126.1, 125.6, 124.2, 123.0, 121.5, 54.1, 41.8, 41.6, 35.1;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{22}\text{OBr}$, 417.0844 found, 417.0854;

IR (film): $\nu_{\max}$ 1705, 1604, 1465, 1296, 694 cm^{-1}

HPLC: 99% *ee* determined by HPLC (IA, 98/2 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 11.6 min, *tr* = 18.2 min.

(R)-2-cinnamyl-2-(thiophen-3-ylmethyl)-2,3-dihydro-1H-inden-1-one (5f)

physical property : colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 2.31, CHCl₃): 5.17;

¹H NMR: (400 MHz, MeOD) δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.41 – 7.28 (m, 2H), 7.23 – 7.10 (m, 6H), 7.04 – 6.98 (m, 1H), 6.85 – 6.79 (m, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.04 – 5.93 (m, 1H), 3.24 – 3.07 (m, 3H), 2.97 (d, *J* = 16.0 Hz, 1H), 2.62 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H), 2.50 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H);

¹³C NMR: (100 MHz, MeOD) δ 211.5, 153.7, 137.3, 137.1, 136.6, 135.0, 133.4, 128.8, 128.0, 127.0, 126.8, 126.2, 125.6, 124.6, 124.4, 123.0, 122.5, 54.0, 41.5, 36.6, 35.6;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₃H₂₁OS, 345.1313 found, 345.1313;

IR (film): $\nu_{\max}$ 1705, 1604, 1465, 964, 694 cm⁻¹

HPLC: 89% *ee* determined by HPLC (OJ-H, 80/20 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 11.8 min, *tr* = 22.3 min.

(R)-2-cinnamyl-2-(furan-2-ylmethyl)-2,3-dihydro-1H-inden-1-one (5g)

physical property : colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 1.23, CHCl₃): 5.18;

¹H NMR: (400 MHz, MeOD) δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.62 – 7.55 (m, 1H), 7.45 – 7.32 (m, 2H), 7.23 – 7.11 (m, 6H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.20 – 6.17 (m, 1H), 6.06 – 5.92 (m, 2H), 3.24 (d, *J* = 16.0 Hz, 1H), 3.15 (d, *J* = 16.0 Hz, 1H), 3.08 (d, *J* = 16.0 Hz, 1H), 3.00 (d, *J* = 16.0 Hz, 1H), 2.61 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H), 2.49 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H);

¹³C NMR: (100 MHz, MeOD) δ 211.5, 153.4, 151.9, 141.2, 137.1, 136.2, 135.0, 133.6, 128.0, 127.1, 126.8, 126.2, 125.6, 124.2, 123.1, 109.6, 107.4, 53.1, 41.0, 36.0, 34.5;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₃H₂₁O₂, 329.1547 found, 329.1542;

IR (film): $\nu_{\max}$ 1705, 1604, 1465, 1296, 1010, 694 cm⁻¹

HPLC: 85% *ee* determined by HPLC (OD-H, 98/2 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 10.5 min, *tr* = 13.0 min.

(S)-2-(3-bromobenzyl)-2-(3-methylbut-2-en-1-yl)-2,3-dihydro-1H-inden-1-one (5h)

physical property : colourless oil.

Optical rotation: $[\alpha]_D^{26}$ (*c* 2.39, CHCl₃): 1.58;

¹H NMR: (400 MHz, CDCl₃) δ 7.74 – 7.66 (m, 1H), 7.54 – 7.46 (m, 1H), 7.34 – 7.21 (m, 4H), 7.05 – 6.96 (m, 2H), 5.06 – 4.99 (m, 1H), 3.10 (d, *J* = 16.0 Hz, 1H), 3.04 (d, *J* = 16.0 Hz, 1H), 2.94 (d, *J* = 16.0 Hz, 1H), 2.80 (d, *J* = 16.0 Hz, 1H), 2.44 – 2.29 (m, 2H), 1.63 (s, 3H), 1.61 (s, 3H);

¹³C NMR: (100 MHz, CDCl₃) δ 210.1, 152.9, 139.9, 136.7, 135.2, 134.7, 133.0, 129.5, 129.4, 128.7, 127.2, 126.2, 123.8, 122.0, 118.7, 54.3, 41.8, 36.3, 35.6, 25.9, 18.0;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₁H₂₂OBr, 369.0856 found, 369.0854;

IR (film): $\nu_{\max}$ 1705, 1604, 1465, 1296, 1010, 694 cm⁻¹

HPLC: 91% *ee* determined by HPLC (OJ-H, 99/1 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 7.9 min, *tr* = 8.9 min.

(R)-2-(but-2-yn-1-yl)-2-(thiophen-3-ylmethyl)-2,3-dihydro-1H-inden-1-one (5i)

physical property : colourless oil.

Optical rotation: $[\alpha]_D^{26}$ (*c* 1.07, CHCl₃): -16.9;

^1H NMR: (400 MHz, MeOD) δ 7.68 – 7.54 (m, 2H), 7.45 – 7.38 (m, 1H), 7.37 – 7.31 (m, 1H), 7.17 – 7.12 (m, 1H), 7.02 – 6.97 (m, 1H), 6.82 – 6.76 (m, 1H), 3.05 (d, J = 16.0 Hz, 1H), 2.98 (d, J = 16.0 Hz, 1H), 2.54 – 2.36 (m, 2H), 1.58 (t, J = 2.4 Hz, 3H);

^{13}C NMR: (100 MHz, MeOD) δ 210.5, 153.8, 137.0, 136.4, 134.9, 128.7, 126.9, 126.1, 124.6, 123.1, 122.6, 77.3, 74.3, 53.0, 36.2, 27.0, 1.4;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{17}\text{OS}$, 281.0998 found, 281.1000;

IR (film): ν_{max} 1705, 1604, 1465, 1296, 1010, 694 cm^{-1}

HPLC: 95% *ee* determined by HPLC (OD-H, 99/1 hexanes/*i*-PrOH, 1.0 ml/min) t_r = 10.7 min, t_r = 11.7 min.

(R)-2-(but-2-yn-1-yl)-2-(furan-2-ylmethyl)-2,3-dihydro-1H-inden-1-one (5j)

physical property : colourless oil.

Optical rotation: $[\alpha]^{26}_{\text{D}}$ (c 1.29, CHCl_3): -2.9;

^1H NMR: (400 MHz, MeOD) δ 7.69 – 7.56 (m, 2H), 7.48 – 7.43 (m, 1H), 7.40 – 7.34 (m, 1H), 7.19 – 7.17 (m, 1H), 6.17 – 6.15 (m, 1H), 6.01 – 5.99 (m, 1H), 3.23 (m, 1H), 2.99 (m, 1H), 2.52 – 2.35 (m, 2H), 1.56 (t, J = 2.4 Hz, 3H);

^{13}C NMR: (100 MHz, MeOD) δ 209.6, 153.7, 151.6, 141.3, 135.9, 135.0, 127.0, 126.1, 123.2, 109.6, 107.5, 77.3, 74.1, 36.4, 34.2, 26.6, 1.4;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{17}\text{O}_2$, 265.1226 found, 265.1229;

IR (film): ν_{max} 1705, 1604, 1465, 1296, 1010, 694 cm^{-1}

HPLC: 96% *ee* determined by HPLC (OD-H, 99/1 hexanes/*i*-PrOH, 1.0 ml/min) t_r = 9.1 min, t_r = 9.9 min.

(S)-methyl 2-(1-oxo-2-(3-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-2-yl)acetate (5k)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 1.31, CHCl₃): 0.4;

¹H NMR: (400 MHz, CDCl₃) δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.41 – 7.25 (m, 6H), 3.59 (s, 3H), 3.25 – 3.12 (m, 2H), 3.06 (d, *J* = 16.0 Hz, 1H), 2.93 (d, *J* = 16.0 Hz, 1H), 2.92 (d, *J* = 16.0 Hz, 1H), 2.71 (d, *J* = 16.0 Hz, 1H);

¹³C NMR: (100 MHz, CDCl₃) δ 208.2, 171.4, 152.1, 137.1, 136.2, 134.9, 133.5, 128.4, 127.5, 126.7, 126.1, 124.0, 123.6, 123.5, 51.6, 51.1, 42.9, 40.6, 36.6;

¹⁹F NMR: (376 MHz, CDCl₃) δ -62.7;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₀H₁₈O₃F₃, 363.1207 found, 363.1208;

IR (film): $\nu_{\max}$ 1712, 1705, 1604, 1465, 1311, 1118, 1010, 694 cm⁻¹

HPLC: 90% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 6.7 min, *tr* = 8.0 min.

(S)-methyl 2-(1-oxo-2-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-2-yl)acetate (5l)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 1.48, CHCl₃): 1.2;

¹H NMR: (400 MHz, CDCl₃) δ 7.77 – 7.72 (m, 1H), 7.56 – 7.50 (m, 1H), 7.47 – 7.39 (m, 2H), 7.37 – 7.31 (m, 2H), 7.25 – 7.18 (m, 2H), 3.58 (s, 3H), 3.19 (m, 2H), 3.05 (d, *J* = 16.0 Hz, 1H), 2.93 (d, *J* = 16.0 Hz, 1H), 2.91 (d, *J* = 16.0 Hz, 1H), 2.69 (d, *J* = 16.0 Hz, 1H);

^{13}C NMR: (100 MHz, CDCl_3) δ 208.1, 171.3, 152.1, 140.4, 136.0, 134.9, 130.5, 127.5, 126.2, 125.0, 124.9, 124.0, 51.6, 51.1, 42.7, 40.6, 36.6;

^{19}F NMR: (376 MHz, CDCl_3) δ -62.6;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{18}\text{O}_3\text{F}_3$, 363.1205 found, 363.1208;

IR (film): ν_{max} 1712, 1705, 1604, 1465, 1327, 1296, 1118, 1010, 694 cm^{-1}

HPLC: 87% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) t_r = 6.9 min, t_r = 8.4 min.

(R)-2-cinnamyl-6-methyl-2-(2-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one (5m)

physical property : colourless oil.

Optical rotation: $[\alpha]_D^{26}$ (*c* 2.28, CHCl_3): -59.4;

^1H NMR: (400 MHz, MeOD) δ 7.66 – 7.60 (m, 1H), 7.56 – 7.51 (m, 1H), 7.41 – 7.36 (m, 1H), 7.31 – 7.10 (m, 9H), 6.44 (d, J = 16.0 Hz, 1H), 6.04 – 5.92 (m, 1H), 3.49 (d, J = 16.0 Hz, 1H), 3.29 – 3.21 (m, 1H), 3.05 (d, J = 16.0 Hz, 1H), 2.73 (d, J = 16.0 Hz, 1H), 2.58 (ddd, J = 4.0, 8.0, 16.0 Hz, 1H), 2.50 (ddd, J = 4.0, 8.0, 16.0 Hz, 1H), 2.37 (s, 3H);

^{13}C NMR: (100 MHz, MeOD) δ 211.3, 151.0, 137.5, 137.1, 137.0, 136.5, 137.4, 133.7, 131.5, 130.7, 128.7, 128.0, 126.8, 126.5, 125.9, 125.7, 125.6, 124.1, 123.0, 54.7, 43.0, 36.5, 34.6, 19.6;

^{19}F NMR: (376 MHz, MeOD) δ -59.3;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{27}\text{H}_{24}\text{OF}_3$, 421.1774 found, 421.1779;

IR (film): ν_{max} 1705, 1604, 1465, 1311, 1118, 694 cm^{-1}

HPLC: 98% *ee* determined by HPLC (OJ-H, 99/1 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 11.6 min, *tr* = 13.6 min.

(S)-2-benzyl-5-chloro-2-cinnamyl-2,3-dihydro-1H-inden-1-one (5n)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 1.92, CHCl₃): -12.4;

¹H NMR: (400 MHz, MeOD) δ 7.60 – 7.55 (m, 1H), 7.37 – 7.33 (m, 1H), 7.31 – 7.26 (m, 1H), 7.23 – 7.06 (m, 10H), 6.44 (d, *J* = 16.0 Hz, 1H), 6.05 – 5.93 (m, 1H), 3.23 – 3.14 (m, 2H), 3.09 (d, *J* = 16.0 Hz, 1H), 2.87 (d, *J* = 16.0 Hz, 1H), 2.65 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H), 2.51 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H);

¹³C NMR: (100 MHz, MeOD) δ 209.8, 155.1, 141.2, 137.1, 136.9, 135.3, 133.7, 129.7, 128.0, 127.8, 127.7, 126.9, 126.3, 126.2, 125.6, 124.3, 124.2, 54.6, 42.4, 41.6, 34.9;

¹⁹F NMR: (376 MHz, MeOD) δ -59.3;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₅H₂₂OCl, 373.1353 found, 373.1359;

IR (film): $\nu_{\max}$ 1705, 1597, 1496, 694 cm⁻¹

HPLC: 92% *ee* determined by HPLC (OJ-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 8.8 min, *tr* = 12.3 min.

(S)-2-cinnamyl-2-(4-(trifluoromethyl)benzyl)-3,4-dihydronaphthalen-1(2H)-one (5o)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_{\text{D}}$ (*c* 1.85, CHCl_3): 26.6;

^1H NMR: (400 MHz, MeOD) δ 8.05 – 7.99 (m, 1H), 7.57 – 7.47 (m, 3H), 7.38 – 7.23 (m, 8H), 7.22 – 7.16 (m, 1H), 6.46 (d, $J = 16.0$ Hz, 1H), 6.28 – 6.16 (m, 1H), 3.38 (d, $J = 16.0$ Hz, 1H), 3.19 – 2.97 (m, 2H), 2.93 (d, $J = 16.0$ Hz, 1H), 2.66 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H), 2.41 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H), 2.17 – 2.07 (m, 1H), 2.01 – 1.92 (m, 1H);

^{13}C NMR: (100 MHz, MeOD) δ 200.9, 143.4, 142.4, 137.2, 133.7, 133.3, 131.7, 130.9, 128.6, 128.2, 128.1, 127.3, 126.8, 126.4, 126.1, 125.7, 124.6, 124.4, 124.3, 49.7, 40.2, 38.6, 30.4, 24.6;

^{19}F NMR: (376 MHz, CDCl_3) δ -63.8;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{27}\text{H}_{24}\text{OF}_3$, 421.1780 found, 421.1779;

IR (film): ν_{max} 1681, 1604, 1450, 1327, 1118, 694 cm^{-1}

HPLC: 90% *ee* determined by HPLC (OD-H, 98/2 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 14.2 min, *tr* = 15.8 min.

(S)-2-cinnamyl-2-(3-(trifluoromethyl)benzyl)-3,4-dihydronaphthalen-1(2H)-one (5p)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_{\text{D}}$ (*c* 1.82, CHCl_3): 57.3;

^1H NMR: (400 MHz, MeOD) δ 8.03 – 7.97 (m, 1H), 7.54 – 7.14 (m, 12H), 6.44 (d, $J = 16.0$ Hz, 1H), 6.28 – 6.17 (m, 1H), 3.35 (d, $J = 16.0$ Hz, 1H), 3.17 – 2.94 (m, 2H), 2.91 (d, $J = 16.0$ Hz, 1H), 2.62 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H), 2.40 (ddd, $J = 4.0, 8.0, 16.0$ Hz, 1H), 2.14 – 2.03 (m, 1H), 2.00 – 1.89 (m, 1H);

^{13}C NMR: (100 MHz, MeOD) δ 200.9, 143.4, 139.0, 137.2, 134.1, 133.7, 133.3, 131.7, 130.0, 129.7, 128.6, 128.3, 128.1, 127.2, 126.9, 126.4, 125.7, 124.6, 122.8, 122.7, 49.6, 40.2, 38.5, 30.4, 24.5;

^{19}F NMR: (376 MHz, CDCl_3) δ -64.0;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{27}\text{H}_{24}\text{OF}_3$, 421.1780 found, 421.1779;

IR (film): ν_{max} 1681, 1604, 1450, 1327, 1126, 694 cm^{-1}

HPLC: 91% *ee* determined by HPLC (OJ-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 7.9 min, *tr* = 9.9 min.

(S)-2-cinnamyl-2-(4-fluorobenzyl)-3,4-dihydronaphthalen-1(2H)-one (5q)

physical property : colourless oil.

Optical rotation: $[\alpha]_D^{26}$ (*c* 1.82, CHCl_3): 3.9;

^1H NMR: (400 MHz, MeOD) δ 8.03 – 7.97 (m, 1H), 7.53 – 7.47 (m, 1H), 7.36 – 7.10 (m, 9H), 6.98 – 6.90 (m, 2H), 6.42 (d, J = 16.0 Hz, 1H), 6.26 – 6.16 (m, 1H), 3.25 (d, J = 16.0 Hz, 1H), 3.14 – 2.91 (m, 2H), 2.81 (d, J = 16.0 Hz, 1H), 2.64 (ddd, J = 4.0, 8.0, 16.0 Hz, 1H), 2.35 (ddd, J = 4.0, 8.0, 16.0 Hz, 1H), 2.13 – 2.02 (m, 1H), 2.00 – 1.91 (m, 1H);

^{13}C NMR: (100 MHz, MeOD) δ 201.3, 143.5, 137.3, 133.5, 133.4, 133.3, 132.0, 131.9, 131.8, 128.6, 128.1, 127.2, 126.8, 126.4, 125.7, 124.8, 114.2, 114.0, 49.6, 39.7, 38.7, 30.3, 24.6;

^{19}F NMR: (376 MHz, CDCl_3) δ -118.9;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{24}\text{OF}$, 371.1809 found, 371.1811;

IR (film): ν_{max} 1674, 1604, 1450, 1226, 694 cm^{-1}

HPLC: 90% *ee* determined by HPLC (IA, 98/2 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 10.8 min, *tr* = 12.5 min.

(S)-2-(3-methylbut-2-en-1-yl)-2-(4-(trifluoromethyl)benzyl)-3,4-dihydronaphthalen-1(2H)-one (5r)

physical property : colourless oil.

Optical rotation: $[\alpha]_D^{26}$ (*c* 1.89, CHCl₃): 1.8;

¹H NMR: (400 MHz, MeOD) δ 8.02 – 7.94 (m, 1H), 7.56 – 7.46 (m, 3H), 7.37 – 7.22 (m, 4H), 5.25 – 5.18 (m, 1H), 3.32 (d, *J* = 16.0 Hz, 1H), 3.15 – 2.92 (m, 2H), 2.85 (d, *J* = 16.0 Hz, 1H), 2.37 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H), 2.28 (ddd, *J* = 4.0, 8.0, 16.0 Hz, 1H), 2.11 – 2.01 (m, 1H), 1.95 – 1.86 (m, 1H), 1.73 (s, 3H), 1.57 (s, 3H);

¹³C NMR: (100 MHz, MeOD) δ 201.2, 143.3, 142.6, 134.6, 133.2, 131.8, 130.9, 128.5, 127.2, 126.3, 124.3, 124.2, 118.6, 49.8, 39.9, 33.2, 30.2, 24.7, 24.6, 16.7;

¹⁹F NMR: (376 MHz, CDCl₃) δ -63.8;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₃H₂₄OF₃, 373.1777 found, 373.1779;

IR (film): $\nu_{\max}$ 1681, 1604, 1450, 1327, 1165, 1118, 694 cm⁻¹

HPLC: 92% *ee* determined by HPLC (OJ-H, 85/15 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 11.5 min, *tr* = 22.3 min.

(R)-2-(4-bromobenzyl)-2-(but-2-yn-1-yl)-3,4-dihydronaphthalen-1(2H)-one (5s)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 1.21, CHCl₃): -6.1;

¹H NMR: (400 MHz, MeOD) δ 7.97 – 7.92 (m, 1H), 7.56 – 7.49 (m, 1H), 7.40 – 7.29 (m, 4H), 7.04 – 6.98 (m, 2H), 3.19 – 2.98 (m, 3H), 2.95 (d, *J* = 16.0 Hz, 1H), 2.43 – 2.28 (m, 2H), 2.26 – 2.09 (m, 2H), 1.79 (t, *J* = 2.4 Hz, 3H);

¹³C NMR: (100 MHz, MeOD) δ 200.4, 143.3, 136.3, 133.3, 131.9, 131.6, 130.6, 128.7, 127.1, 126.4, 120.0, 78.6, 74.5, 48.8, 38.5, 30.8, 24.7, 24.5, 1.6;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₁H₂₀OBr, 367.0699 found, 367.0698;

IR (film): $\nu_{\max}$ 1681, 1604, 1450, 1288, 1010, 694 cm⁻¹

HPLC: 87% *ee* determined by HPLC (OJ-H, 98/2 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 9.2 min, *tr* = 12.4 min.

(S)-2-(but-2-yn-1-yl)-2-(thiophen-3-ylmethyl)-3,4-dihydronaphthalen-1(2H)-one (5t)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 1.37, CHCl₃): 5.2;

¹H NMR: (400 MHz, MeOD) δ 7.67 – 7.61 (m, 1H), 7.60 – 7.54 (m, 1H), 7.44 – 7.39 (m, 1H), 7.37 – 7.31 (m, 1H), 7.17 – 7.12 (m, 2H), 7.02 – 6.96 (m, 1H), 6.81 – 6.76 (m, 1H), 3.20 (m, 2H), 3.05 (d, *J* = 16.0 Hz, 1H), 2.98 (d, *J* = 16.0 Hz, 1H), 2.53 – 2.37 (m, 2H), 1.58 (t, *J* = 2.4 Hz, 3H);

¹³C NMR: (100 MHz, MeOD) δ 210.5, 153.8, 137.0, 136.4, 134.9, 128.7, 126.9, 126.1, 124.6, 123.1, 122.6, 77.3, 74.3, 53.0, 36.2, 27.0, 1.4;

HRMS: (ESI) $[M+H]^+$ calcd. for C₁₉H₁₉OS, 295.1157 found, 295.1157;

IR (film): $\nu_{\max}$ 1674, 1604, 1450, 1288, 1010, 694 cm⁻¹

HPLC: 92% *ee* determined by HPLC (OJ-H, 99/1 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 14.5 min, *tr* = 28.3 min.

(R)-methyl 2-(1-oxo-2-(4-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (5u)

physical property :colourless oil.

Optical rotation: $[\alpha]_D^{26}$ (*c* 1.72, CHCl₃):18.7;

¹H NMR: (400 MHz, MeOD) δ 8.04 – 7.97 (m, 1H), 7.61 – 7.53 (m, 3H), 7.42 – 7.31 (m, 4H), 3.62 (s, 3H), 3.32 – 3.23 (m, 1H), 3.20 (d, *J* = 16.0 Hz, 1H), 3.10 – 2.99 (m, 2H), 2.88 (d, *J* = 16.0 Hz, 1H), 2.51 – 2.43 (m, 1H), 2.40 (d, *J* = 16.0 Hz, 1H), 2.07 – 1.98 (m, 1H);

¹³C NMR: (100 MHz, MeOD) δ 200.1, 171.9, 143.1, 133.4, 131.4, 130.9, 128.7, 127.3, 126.5, 124.5, 124.4, 50.5, 39.2, 39.1, 30.3, 24.5;

¹⁹F NMR: (376 MHz, CDCl₃) δ -62.4;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₁H₂₀O₃F₃, 376.1412 found, 376.1418;

IR (film): $\nu_{\max}$ 1705, 1604, 1465, 1296, 1010, 694 cm⁻¹

HPLC: 77% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 11.3 min, *tr* = 13.7 min.

(S)-methyl 3-methyl-4-oxo-4-phenylbutanoate¹ (7a)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 1.09, THF): -6.6;

HPLC: 85% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 6.1 min, *tr* = 8.0 min.

(S)-methyl 3-benzoylheptanoate (7b)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 0.64, CHCl₃):3.6;

¹H NMR: (300 MHz, CDCl₃) δ 8.04 – 7.98 (m, 2H), 7.62 – 7.55 (m, 1H), 7.53 – 7.45 (m, 2H), 4.00 – 3.85 (m, 1H), 3.84 (s, 3H), 2.97 (dd, *J* = 9.0, 15.0 Hz, 1H), 2.53 (dd, *J* = 9.0, 15.0 Hz, 1H), 1.78 – 1.59 (m, 2H), 1.55 – 1.40 (m, 1H), 1.39 – 1.25 (m, 3H), 0.89 (t, *J* = 6.0 Hz, 3H);

¹³C NMR: (75 MHz, CDCl₃) δ 202.9, 173.0, 136.7, 128.6, 128.3, 51.7, 42.0, 35.5, 34.6, 20.2, 14.0;

HRMS: (ESI) $[M+H]^+$ calcd. for C₁₅H₂₁O₃, 249.1492 found, 249.1491;

IR (film): $\nu_{\max}$ 1643, 1604, 694 cm⁻¹

HPLC: 89% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 5.1 min, *tr* = 7.6 min.

(S)-methyl 3-benzoylnonanoate (7c)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 0.66, CHCl₃):3.1;

¹H NMR: (400 MHz, CDCl₃) δ 8.03 – 7.97 (m, 2H), 7.61 – 7.56 (m, 1H), 7.53 – 7.46 (m, 2H), 3.96 – 3.88 (m, 1H), 3.64 (s, 3H), 2.97 (dd, *J* = 8.0, 16.0 Hz, 1H), 2.53 (dd, *J* = 8.0, 16.0 Hz, 1H), 1.78 – 1.66 (m, 1H), 1.55 – 1.43 (m, 1H), 1.35 – 1.16 (m, 8H), 0.86 (t, *J* = 8.0 Hz, 3H);

¹³C NMR: (100 MHz, CDCl₃) δ 202.9, 173.0, 136.7, 132.9, 128.6, 128.3, 51.6, 42.2, 35.5, 32.4, 31.5, 29.9, 26.9, 22.4, 13.9;

HRMS: (ESI) $[M+H]^+$ calcd. for C₁₇H₂₅O₃, 277.1805 found, 277.1804;

IR (film): $\nu_{\max}$ 1705, 1604, 694 cm⁻¹

HPLC: 89% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 4.6 min, *tr* = 5.4 min.

(S)-methyl 3-benzoyltridecanoate (7d)

physical property :colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 3.13, CHCl₃):1.2;

¹H NMR: (300 MHz, CDCl₃) δ 8.04 – 7.96 (m, 2H), 7.61 – 7.56 (m, 1H), 7.63 – 7.43 (m, 3H), 3.98 – 3.85 (m, 1H), 3.64 (s, 3H), 2.97 (dd, *J* = 9.0, 15.0 Hz, 1H), 2.53 (dd, *J* = 9.0, 15.0 Hz, 1H), 1.80 – 1.57 (m, 1H), 1.55 – 1.41 (m, 1H), 1.37 – 1.10 (m, 16H), 0.89 (t, *J* = 6.0 Hz, 3H);

¹³C NMR: (75 MHz, CDCl₃) δ 202.9, 173.0, 136.7, 132.9, 128.6, 128.3, 51.6, 42.2, 35.5, 32.4, 31.8, 29.5, 29.4, 29.3, 29.2, 26.9, 22.6, 14.0;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{21}H_{33}O_3$, 333.2448 found, 333.2450;

IR (film): $\nu_{\max}$ 1643, 1604, 1211, 694 cm^{-1}

HPLC: 91% *ee* determined by HPLC (IB, 98/2 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 4.2 min, *tr* = 4.8 min.

(S)-ethyl 3-methyl-4-oxo-4-phenylbutanoate² (7e)

physical property : colourless oil.

Optical rotation: $[\alpha]_D^{26}$ (*c* 0.70, CHCl_3):3.8;

HPLC: 85% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 5.2 min, *tr* = 6.8 min.

(S)-methyl 4-(4-bromophenyl)-3-methyl-4-oxobutanoate (7f)

physical property : colourless oil.

Optical rotation: $[\alpha]_D^{26}$ (*c* 0.78, CHCl_3):6.1;

¹H NMR: (400 MHz, CDCl_3) δ 7.89 – 7.83 (m, 2H), 7.66 – 7.61 (m, 2H), 3.95 – 3.82 (m, 1H), 3.66 (s, 3H), 2.97 (dd, *J* = 8.0, 16.0 Hz, 1H), 2.47 (dd, *J* = 8.0, 16.0 Hz, 1H), 1.22 (d, *J* = 8.0 Hz, 3H);

¹³C NMR: (100 MHz, CDCl_3) δ 201.7, 172.6, 134.6, 132.0, 129.9, 128.2, 51.7, 37.1, 17.7;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{26}H_{25}O_3$, 385.1804 found, 385.1804;

IR (film): $\nu_{\max}$ 1759, 1627, 1589, 1508, 1442, 1141, 750, 700 cm^{-1}

HPLC: 85% *ee* determined by HPLC (OD-H, 90/10 hexanes/i-PrOH, 1.0 ml/min) *tr* = 6.1 min, *tr* = 12.2 min.

(S)-methyl 4-(4-chlorophenyl)-3-methyl-4-oxobutanoate (7g)

physical property : colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 0.73, CHCl₃): 8.1;

¹H NMR: (300 MHz, CDCl₃) δ 7.98 – 7.90 (m, 2H), 7.50 – 7.42 (m, 2H), 3.98 – 3.81 (m, 1H), 3.66 (s, 3H), 2.98 (dd, *J* = 6.0, 15.0 Hz, 1H), 2.47 (dd, *J* = 6.0, 15.0 Hz, 1H), 1.22 (d, *J* = 6.0 Hz, 3H);

¹³C NMR: (75 MHz, CDCl₃) δ 201.5, 172.7, 139.5, 134.2, 129.8, 129.0, 51.7, 37.2, 17.7;

HRMS: (ESI) $[M+H]^+$ calcd. for C₂₆H₂₅O₃, 385.1804 found, 385.1804;

IR (film): $\nu_{\max}$ 1759, 1627, 1589, 1508, 1442, 1141, 750, 700 cm⁻¹

HPLC: 86% *ee* determined by HPLC (OD-H, 90/10 hexanes/i-PrOH, 1.0 ml/min) *tr* = 5.2 min, *tr* = 8.1 min.

(S)-methyl 3-methyl-4-oxo-4-(p-tolyl)butanoate (7h)

physical property : colourless oil.

Optical rotation: $[\alpha]^{26}_D$ (*c* 0.75, CHCl₃): 1.1;

¹H NMR: (300 MHz, CDCl₃) δ 7.97 – 7.84 (m, 2H), 7.34 – 7.24 (m, 2H), 4.02 – 3.86 (m, 1H), 3.66 (s, 3H), 2.96 (dd, *J* = 6.0, 15.0 Hz, 1H), 2.46 (dd, *J* = 6.0, 15.0 Hz, 1H), 2.43 (s, 3H), 1.23 (d, *J* = 6.0 Hz, 3H);

^{13}C NMR: (75 MHz, CDCl_3) δ 201.5, 172.7, 139.5, 134.2, 129.8, 129.0, 51.7, 37.2, 17.7;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{25}\text{O}_3$, 385.1804 found, 385.1804;

IR (film): ν_{max} 1759, 1627, 1589, 1508, 1442, 1141, 750, 700 cm^{-1}

HPLC: 90% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 5.8 min, *tr* = 8.7 min.

(S)-methyl 4-(4-methoxyphenyl)-3-methyl-4-oxobutanoate (7i)

physical property : colourless oil.

Optical rotation: $[\alpha]_{\text{D}}^{26}$ (*c* 0.95, CHCl_3): 17.8;

^1H NMR: (400 MHz, CDCl_3) δ 7.99 – 7.92 (m, 2H), 6.96 – 6.90 (m, 2H), 3.94 – 3.81 (m, 1H), 3.84 (s, 3H), 3.62 (s, 3H), 2.92 (dd, *J* = 8.0, 16.0 Hz, 1H), 2.42 (dd, *J* = 8.0, 16.0 Hz, 1H), 1.20 (d, *J* = 8.0 Hz, 3H);

^{13}C NMR: (100 MHz, CDCl_3) δ 201.1, 172.8, 163.5, 130.6, 128.7, 113.8, 55.4, 51.5, 37.2, 36.8, 18.0;

HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{25}\text{O}_3$, 385.1804 found, 385.1804;

IR (film): ν_{max} 1759, 1627, 1589, 1508, 1442, 1141, 750, 700 cm^{-1}

HPLC: 83% *ee* determined by HPLC (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min) *tr* = 9.2 min, *tr* = 15.3 min.

3.6 Appendices

TBO13075-1-F19

-62.50

TBO13075-5-H1' '
AV 400 MEOD

TBO13075-2-F19

TBO13075-20-H1
AV400 MeOD

TB013075-14-F19
av400 CDCl₃

—62.50

TB013081-1-H1
av300 CDCl₃

95% ee (OJ-H, 70/30 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.745	19906421	610897	50.054
2	15.321	19863375	208077	49.946
Total		39769796	818973	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.851	14723603	408887	98.223
2	15.374	266357	2769	1.777
Total		14989960	411656	100.000

95% *ee* (OJ-H, 95/5 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.161	13126761	393959	50.993
2	10.026	12615614	263192	49.007
Total		25742375	657151	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.167	22879916	693334	97.579
2	10.074	610039	12033	2.421
Total		23490055	714368	100.000

93% ee (OJ-H, 99/1 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.382	2388796	83907	49.811
2	15.286	2406909	29047	50.189
Total		4795705	112954	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.169	19612605	665184	96.817
2	14.880	644757	8920	3.183
Total		20257361	674103	100.000

95% *ee* (OD-H, 99/1 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	34.411	15453165	213394	44.885
2	42.182	18973903	164791	55.115
Total		34426067	378085	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	34.964	533211	7707	2.291
2	41.150	22739090	221963	97.709
Total		23272301	229670	100.000

99% ee (IA, 98/2 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.200	3879847	270497	50.279
2	18.865	3836828	80394	49.721
Total		7716675	350891	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.636	14338270	1123294	99.985
2	18.277	2117	155	0.015
Total		14340387	1123449	100.000

89% ee (OJ-H, 80/20 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	12.063	2246390	74658	50.197
2	22.503	2228794	27292	49.803
Total		4475184	96950	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.860	23514430	802423	94.425
2	22.312	1388338	17928	5.575
Total		24902768	820351	100.000

85% ee (OD-H, 98/2 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.385	10434433	504971	50.833
2	12.932	10092414	384734	49.167
Total		20526846	889705	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.520	718808	34973	7.355
2	13.069	9053823	341814	92.645
Total		9772631	376787	100.000

91% ee (OJ-H, 99/1 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.831	1746538	67169	49.694
2	9.829	1768019	41279	50.306
Total		3514557	108448	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.963	162635	5191	4.451
2	9.960	3491507	80124	95.549
Total		3654142	85315	100.000

95% ee (OD-H, 99/1 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.822	1819117	78512	48.562
2	11.837	1926814	70199	51.438
Total		3745931	148711	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.728	78225	4844	2.412
2	11.773	3165021	142969	97.588
Total		3243246	147813	100.000

96% ee (OD-H, 99/1 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.948	1436451	76993	49.202
2	9.833	1483035	71293	50.798
Total		2919486	148286	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.124	223450	11785	1.804
2	9.970	12160394	598837	98.196
Total		12383844	610622	100.000

90% ee (OD-H, 90/10 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	6.664	912845	77046	50.360
2	7.958	899794	60847	49.640
Total		1812638	137892	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	6.751	3256652	268581	95.333
2	8.070	139445	13134	4.667
Total		3416095	281735	100.000

87% *ee* (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	6.990	2937474	225852	50.625
2	8.601	2864964	170857	49.375
Total		5802439	396709	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	6.914	2796030	215724	93.429
2	8.483	196642	11565	6.571
Total		2992671	227290	100.000

98% *ee* (OJ-H, 99/1 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.372	1292399	37300	49.798
2	13.470	1302876	27240	50.202
Total		2595275	64540	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.657	25294	749	0.833
2	13.668	3012948	61922	99.167
Total		3038242	62670	100.000

92% *ee* (OJ-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.020	6569032	246462	50.563
2	12.540	6422681	148819	49.437
Total		12991713	395281	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.874	28326290	1100570	96.472
2	12.363	1035925	24292	3.528
Total		29362215	1124862	100.000

90% *ee* (OD-H, 98/2 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.491	4169537	183989	50.735
2	17.014	4048692	151726	49.265
Total		8218229	335715	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.210	9577658	350271	95.323
2	15.864	469928	18783	4.677
Total		10047586	369054	100.000

91% ee (OJ-H, 90/10 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.831	1746538	67169	49.847
2	9.829	1757255	40993	50.153
Total		3503794	108162	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.963	162635	5191	4.451
2	9.960	3491507	80124	95.549
Total		3654142	85315	100.000

90% ee (IA, 98/2 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.719	4876391	361876	50.978
2	12.355	4689204	332496	49.022
Total		9565596	694372	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.818	3983313	305030	95.202
2	12.580	200742	13161	4.798
Total		4184056	318191	100.000

92% *ee* (OJ-H, 85/15 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.636	4491260	100505	59.809
2	22.358	3018140	26447	40.191
Total		7509399	126952	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.543	11094447	252315	96.174
2	22.370	441365	4011	3.826
Total		11535812	256326	100.000

87% ee (OD-H, 98/2 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.920	4887840	138635	50.444
2	11.530	4801807	78820	49.556
Total		9689647	217455	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.277	153636	4869	6.515
2	12.426	2204485	29523	93.485
Total		2358122	34393	100.000

92% ee (OJ-H, 99/1 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.970	2514018	81406	50.431
2	28.716	2471010	18510	49.569
Total		4985027	99917	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.516	109858	3719	3.664
2	28.361	2888749	64925	96.336
Total		2998607	68644	100.000

77% *ee* (OD-H, 90/10 hexanes/*i*-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.757	3284446	89159	50.895
2	14.093	3168953	73055	49.105
Total		6453399	162214	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.376	270188	8402	11.922
2	13.792	1996067	46814	88.078
Total		2266255	55215	100.000

85% ee (OD-H, 90/10 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	6.091	14753454	892734	49.744
2	8.015	14905278	862885	50.256
Total		29658733	1755619	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	6.151	7963068	808759	92.591
2	8.054	637196	52596	7.409
Total		8600264	861355	100.000

89% ee (OD-H, 90/10 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	5.201	3194122	353827	48.593
2	7.743	3379038	252015	51.407
Total		6573160	605841	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	5.123	5130407	579193	94.071
2	7.687	323372	20644	5.929
Total		5453779	599837	100.000

89% ee (OD-H, 90/10 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	4.710	2519122	317667	50.552
2	5.508	2464096	267201	49.448
Total		4983218	584867	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	4.617	9365597	653955	94.481
2	5.402	547097	36275	5.519
Total		9912694	690231	100.000

91% ee (IB, 98/2 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	4.187	1865096	252679	51.578
2	4.737	1751005	224553	48.422
Total		3616101	477232	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	4.238	2184050	307602	95.763
2	4.836	96626	10590	4.237
Total		2280676	318192	100.000

85% ee (OD-H, 90/10 hexanes/i-PrOH, 1.0 ml/min)

PDA Ch2 254nm

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	5.261	5355127	635824	50.226
2	6.897	5306969	491150	49.774
Total		10662096	1126975	100.000

PDA Ch2 254nm

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	5.224	13723461	1625239	92.633
2	6.845	1091398	101637	7.367
Total		14814858	1726876	100.000

85% ee (OD-H, 90/10 hexanes/i-PrOH, 1.0 ml/min)

PDA Ch2 254nm

Peak#	Ret. Time	Area	Height	Area%
1	6.116	13385378	1403074	50.369
2	12.084	13189138	656541	49.631
Total		26574516	2059616	100.000

Peak Table

PDA Ch2 254nm

Peak#	Ret. Time	Area	Height	Area%
1	6.102	31076538	3116209	92.714
2	12.269	2442183	137352	7.286
Total		33518721	3253561	100.000

Peak Table

86% ee (OD-H, 90/10 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	5.329	3913436	486074	50.716
2	8.217	3802997	286159	49.284
Total		7716433	772233	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	5.282	19093129	2136944	93.095
2	8.126	1416110	109387	6.905
Total		20509239	2246330	100.000

90% ee (OD-H, 90/10 hexanes/i-PrOH, 1.0 ml/min)

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	5.837	5887179	618564	50.908
2	8.708	5677094	409386	49.092
Total		11564274	1027950	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	5.816	11048681	1190938	95.084
2	8.656	571238	42062	4.916
Total		11619919	1233000	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.251	6228921	387904	50.436
2	15.230	6121154	222038	49.564
Total		12350075	609942	100.000

Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.259	9703841	597332	91.578
2	15.346	892454	35348	8.422
Total		10596295	632680	100.000

Chapter 4

Mechanistic Studies

4.1 Introduction

After demonstrating the wide application of the Brønsted probase strategy, the mechanism was investigated in detail. The initial proposed mechanism is shown in Scheme 4.1. After ion exchange between chiral guanidinium salt ($^*\text{cat}^+\text{Br}^-$) and fluoride source (CsF), the chiral guanidinium fluoride ($^*\text{cat}^+\text{F}^-$) formed activates the probase to give chiral bulky strong base **A**. The base **A** then deprotonates substrate **B** to afford chiral enolate intermediate **I**. The enolate **I** then acts as a nucleophile to react with electrophile **D** to give the product and regenerate the chiral catalyst.

Scheme 4.1 Initial proposed mechanism.

However, the experimental results and observations during the optimization led us to consider the existence of other mechanisms involving the Brønsted probase strategy. Probase

BSA (**pb-4**) was used as highly efficient silylation reagent for many functional groups and there are some interesting publications using BSA to form silyl compounds. The first work using BSA as a silylation reagent was reported by White's group in 1966.¹ Amides, ureas, amino acids, phenols and carboxylic acids were successfully silylated in the presence of BSA. The most interesting example is shown in Scheme 4.2. The β -keto acid reacts with BSA in an ether solvent at room temperature to provide the silyl enol ether product in quantitative yield.

Scheme 4.2 *In situ* formation of silyl enol ether I.

In 2001, Mioskowski reported a new method for the synthesis of silyl enol ether involving BSA and TBAB ionic liquid (Scheme 4.3).² Various ketone and aldehyde substrates can be transformed into a silyl enol ether using BSA as silylation reagent.

Scheme 4.3 Synthesis of silyl enol ether.

Craig's group reported a decarboxylative Claisen rearrangement of tosylacetate esters (Scheme 4.4).³ In their reaction, BSA was used as both a base and silylation reagent. They believe that the combination of BSA and KOAc resulted in a base generated *in situ* to activate

tosylacetate ester and form a silyl ketene acetal intermediate. The intermediate then proceeded to rearrange and underwent decarboxylation to give the sulfone product.

Scheme 4.4 [3,3]-Sigmatropic rearrangement of tosylacetate esters.

Recently, Levacher's group reported an enantioselective desymmetrization reaction (Scheme 4.5).⁴ Cinchona alkaloid salt (5 mol%) was used as a Lewis base to activate BSA and generate a base *in situ*, which deprotonates the ketone to give an enolate. In this reaction, BSA also acted as silylation reagent to trap the enolate intermediate and form the silyl enol ether. The cinchona alkaloid salt was used to provide a chiral environment for the enantioselective desymmetrization reaction. These references indicated that BSA not only acts as a base but also as a silylation reagent to trap the enolate intermediate to form the silyl enolate.

Scheme 4.5 Enantioselective desymmetrization reaction.

4.2 Results and discussion

In our dihydrocoumarin substrate screening, we found that using BSA (**pb-4**) condition, a new compound, besides the desired product, was also formed in the reaction. Through analyzing the crude ^1H -NMR, the new compound was identified as silyl ketene acetal **8a**. In comparison with the BSA condition (95% *ee*), the other probase condition using TMS_3N (**pb-1**) gave a lower enantioselectivity (80% *ee*), but no formation of silyl ketene acetal was observed in reaction (Scheme 4.6, equation 1). Hence, we propose that the *in situ* formation of silyl ketene acetal is the main reason for the BSA condition achieving a higher enantioselectivity than the TMS_3N condition.

In order to verify our hypothesis, control experiments were conducted. Dihydrocoumarin **1a** was subjected to standard BSA condition without addition of electrophile. After 36 h, silyl ketene acetal **8a** was formed in high yield (Scheme 4.6, equation 2). Similar to the observation in standard probase condition, TMS_3N condition was used without adding electrophile, but silyl ketene acetal **8a** was not formed (Scheme 4.6, equation 3). Silyl ketene acetal **8a** was also synthesized from dihydrocoumarin **1a**. Thereafter, **8a** was subjected to the standard condition without addition of probase (Scheme 4.6, equation 4), which resulted in the formation of alkylation product **3a** with high enantioselectivity (91% *ee*). These experiments proved our hypothesis that *in situ* formation of silyl ketene acetal in our Brønsted probase strategy is crucial for high enantioselectivity.

Scheme 4.6 Control experiments involving dihydrocoumarin.

In cyclic ketones, we also found some interesting results. As the ketone substrate is stable in hydroxide salt condition, hydroxide salts were used in our optimized catalytic system for cyclic ketones. In the presence of **cat-6**, addition of 5 equiv. of hydroxide salts gave alkylation product **5a** with 35% to 58% enantioselectivity (Scheme 4.7, equation 5) which is much lower than our probase condition (Scheme 4.7, equation 6). Meanwhile, we also found that in our probase strategy, the BSA condition resulted in lower enantioselectivity than BTBSA condition. We believe that *in situ* formation of silyl enol ether is the reason for probase strategy achieving higher enantioselectivity than the normal inorganic base condition, and *in situ* formation of different silyl enol ether is responsible for BTBSA condition possessing higher enantioselectivity than BSA condition.⁵

In other experiments conducted to probe the mechanism, silyl enol ethers **8b** and **8c** were first synthesized from cyclic ketone **4a**. Thereafter, **8b** and **8c** were subjected to the standard reaction conditions without addition of probase (Scheme 4.7, equation 7, 8). TMS silyl enol ether **8b** resulted in the desired product with 80% *ee* while TBS silyl enol ether **8c** led to a higher enantioselectivity of 94% *ee*, which matches the results of BSA and BTBSA condition exactly. These control experiments involving cyclic ketone substrates further proved that *in situ* formation of the silyl enolate is very important for high enantioselectivity and that formation of different silyl enol ethers could affect enantioselectivity.

Scheme 4.7 Control experiments involving cyclic ketone.

In the screening of linear ketone substrates, we also found that addition of catalytic amount of BSA can increase yield and enantioselectivity significantly (Table 4.1, entry 1 vs entry 3).

Without BSA, a larger amount of hydrolysis product **9a** was observed. However, stoichiometric amount of BSA was detrimental to the reaction, and low yield was obtained (entry 2).

Table 4.1 The importance of BSA in reactions involving linear ketones

Entry	Probase (equiv.)	Fluoride source (equiv.)	Additive (equiv.)	Yield ^b	ee ^c
1	none	AgF (2)	CsCl (1)	45	77
2	BSA (1)	AgF (2)	CsCl (1)	23	54
3	BSA (0.4)	AgF (2)	CsCl (1)	82	86

In our direct alkylation of linear ketone experiments, we found that the low yield of desired product **7a** was due to the formation of silyl enol ether **6a** as the main product (Scheme 4.8, equation 9). Hence, in reactions involving linear ketones, BSA acts as both the base and silylation reagent (equation 10). Without BSA, the silyl enol ether **6a** was easily hydrolyzed into linear ketone **9a**. When 0.4 equivalent BSA was added, deprotonation and silylation of the hydrolysis product **9a** can occur to form silyl enol ether **6a** again. However, stoichiometric amount of BSA would result in the consumption of fluoride, which hinders the activation of silyl enol ether.

Scheme 4.8 Additional control experiments involving linear ketones.

With reference to the above control experiments, a new catalytic cycle of the Brønsted probase strategy is proposed (Scheme 4.9). Chiral guanidinium salt ($\text{*cat}^+\text{Br}^-$) undergoes anion-exchange with the fluoride source to form a new chiral guanidinium fluoride ($\text{*cat}^+\text{F}^-$), which activate probase to generate a chiral organic base **A**. The chiral organic base, which has strong basicity but weak nucleophilicity so that it can be used for many compounds and reagents prone to nucleophilic attack, then deprotonates substrate **B** to give enolate intermediate **I**. The enolate intermediate **I** can directly react with electrophile **D** to give the product, but our mechanism study demonstrates that enolate **I** reacts with the probase to form silyl enolate intermediate **C** *in situ*, which plays an important role in the good enantioselectivity of our reactions.

The chiral guanidinium fluoride ($\text{*cat}^+\text{F}^-$) subsequently activates the silyl enolate **C** to generate hypervalent silicon intermediate **II** or **III**. The formation of both pentacoordinated and hexacoordinated silicon is possible in this step.⁶ This anionic hypervalent silicon intermediate would interact with chiral guanidinium cation to form a chiral ion-pair, in which different ligands coordinating to the hypervalent silicon can affect the enantioselectivity of

the product, as evident in the experimental results of the BTBSA and BSA conditions.

The chiral ion-pair then reacts with electrophile **D** to give the alkylation product and regenerate the chiral catalyst ($^*\text{cat}^+\text{Br}^-$). In comparison with our previous proposed catalytic cycle (Scheme 4.1), further mechanistic studies clearly demonstrated the *in situ* formation of silyl enolate as the key step in our Brønsted probase strategy, and chiral hypervalent silicon ion-pairs are the real reactive intermediates in our enantioselective alkylation.

Scheme 4.9 Amended catalytic cycle of Brønsted probase strategy.

4.3 Summary

In summary, we have demonstrated that our Brønsted probase strategy involves *in situ* generation of silyl enolate intermediate, as demonstrated in various mechanistic studies. The *in situ* generation of silyl enolate intermediate is crucial for high enantioselectivity and high yield of the alkylation reactions. Chiral ionic complex, which is formed from hypervalent silicon anion and chiral guanidinium cation is the active intermediate, which controls the enantioselectivity of alkylation.

4.4 References

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4.5 Experimental section

4.5.1 General information

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), tt (triplet of triplets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker (400 MHz) (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *e.e.* was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]_{\text{D}}^{\text{rt}}$ (*c* in g per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

4.5.2 Experimental procedure for mechanism study

To a dry Schlenk tube equipped with a magnetic stir bar was added **1a**. The solid was dissolved in dry THF and the solution was cooled to 0 °C. 1.1 equiv. LiHMDS was added slowly to the solution. After stirring at 0 °C for 30 min, 1.4 equiv. TMSCl was added slowly to the reaction. After stirring at r.t. for 3 h, the solvent was removed under reduced pressure and the residue was washed with hexane. Thereafter, the product was added into a dry Schlenk tube with 2 equiv. bromide, 5% mol **cat-4** and 3 equiv. CsF. The resulting mixture was stirred at -40 °C for 20 h. The reaction mixture was then purified *via* silica gel chromatography (EA/Hexane: 1:200- 1:30) to obtain the product.

To a dry Schlenk tube equipped with a magnetic stir bar was added **4a**. The solid was dissolved in dry THF and the solution was cooled to -78 °C. 1.1 equiv. LiHMDS/KHMDS was added slowly to the solution. After stirring at -78 °C for 30 min, 1.4 equiv.

TMSCl/TBSCl was added slowly to the reaction. After stirring at r.t. for 12 h, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (EA:Hex = 1:40). The product **8b/8c** was added into a dry Schlenk tube with 2 equiv. bromide, 10 mol % **cat-6** and 5 equiv. CsF. The resulting mixture was stirred at -40 °C for 24 h. The reaction mixture was then purified *via* silica gel chromatography (EA/Hexane: 1:200-1:30) to obtain the product.

4.5.4 Characterization of catalysts and products

((2-benzyl-1H-inden-3-yl)oxy)trimethylsilane (8b)

¹H NMR: (400 MHz, CDCl₃) δ 7.45 – 7.20 (m, 9H), 3.85 (s, 2H), 3.19 (s, 3H), 0.42 (s, 9H);

¹³C NMR: (100 MHz, CDCl₃) δ 148.2, 142.4, 141.3, 140.8, 128.7, 128.4, 126.1, 126.0, 124.5, 123.6, 123.0, 117.8, 36.1, 33.1, 0.96;

((2-benzyl-1H-inden-3-yl)oxy)(tert-butyl)dimethylsilane (8c)

¹H NMR: (400 MHz, CDCl₃) δ 7.42 – 7.15 (m, 9H), 3.85 (s, 2H), 3.16 (s, 2H), 1.18 (s, 9H), 0.32 (s, 6H);

¹³C NMR: (100 MHz, CDCl₃) δ 148.1, 142.4, 141.4, 140.8, 128.7, 128.4, 126.0, 124.4, 123.6, 122.7, 118.0, 36.1, 33.2, 25.9, 18.4, -3.5;

4.6 Appendices