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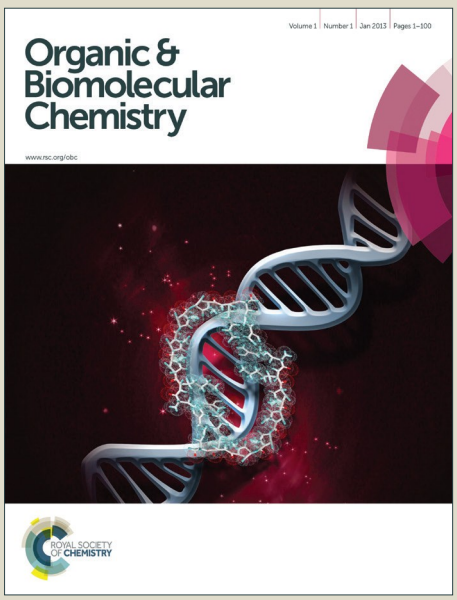

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ARTICLE

An Effective and novel enantioselective preparation of pyranopyrazoles and pyranocoumarins that is catalyzed by a qunine-derived primary amine †

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In this study, we executed an effective and novel enantioselective Michael/cyclodehydration sequential reaction between Pyrozolin-5-one (or 4-hydroxy-2-pyrone) and chalcones that is catalyzed by a quinine-derived primary amine L7 in the presence of Boc-D-Phg-OH. Chiral pyranopyrazoles and pyranocoumarins were obtained in excellent enantioselectivities (up to 93%) with moderate yields and moderate enantioselectivities with high yields (up to 84%).

Introduction

4*H*-pyran, a biologically attractive structure, has been associated with a wide range of pharmacological properties, possessing antibacterial, antioxidant, anticancer, anti-inflammatory, and anticholinesterase activities.[1,2] Among different 4*H*-pyran derivatives, pyranocoumarins and pyranopyrazoles are both of significance importance in terms of their bioactivities (Fig. 1).[2]

Figure 1 shows several representative compounds containing the 4*H*-pyran motif. Among these compounds, pyranopyrazole **6** is a potential antiviral agent,[2d] pyranocoumarin **2** has shown cytotoxic activity on MCF-7 human breast cancer cells,[2b] and the chiral pyranocoumarin **1** has been reported to significantly inhibit CYP2C9 isozyme and lung tumour cell proliferation.[2c] Even though the effect of 4*H*-pyran's chirality on biological functions is currently unknown, the difference in bioactivity between compounds **1** and **2** suggest that chiral structures are highly promising chemical targets.[2b-c,3] Herein, we focus on constructing chiral 4*H*-pyran building blocks using a "green", organocatalyst.

In the past few decades, chemists have demonstrated the principle of "green chemistry" using organocatalysts, which are low molecular weight organic compounds that play an important function in chiral induction (even at minute quantities). Among various organocatalysts, bifunctional thiourea[4] and bifunctional squaramide catalysts,[5] as well as cinchona alkaloid-derived primary amines[6] have been widely used in asymmetric synthesis.

Recently, most pyranopyrazole and pyranocoumarin derivates, which contain the 2-amino-4*H*-pyran motif, have been synthesized via organocatalyst-catalyzed Michael addition and Thorpe-Ziegler type cyclisation (*i.e.*, cyclization via nucleophilic addition to the nitrile group) reactions.[7] However, few other strategies for the synthesis of new pyranopyrazole have been reported. Nonetheless, Enders *et al.* have previously reported the synthesis of novel pyranopyrazole compounds via Michael addition and hydroalkoxylation using a combination of squaramide and silver catalysts.[8a]

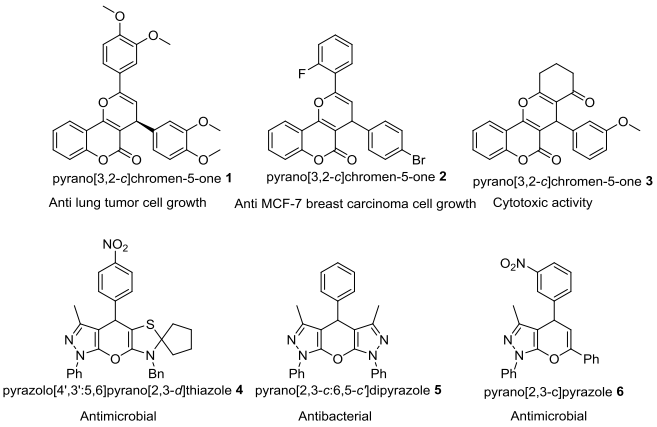

Fig. 1 Biologically important molecules of pyranocoumarins and pyranopyrazoles.

Herein, we used a cinchona alkaloid (quinine)-derived primary amine catalyst (**L7**) for a Michael addition/cyclodehydration sequential reaction. Several pyrazolone compounds, 4-hydroxy-2-pyrones, and chalcones were selected as the starting materials for the synthesis of our target chiral pyranopyrazoles and pyranocoumarins. Using the **L7** catalyst, enantioselective pyranopyrazoles were obtained in moderate conversion yields but high enantiomeric excess (up to 93% ee), whereas enantioselective pyranocoumarins were obtained in high conversion yields, with

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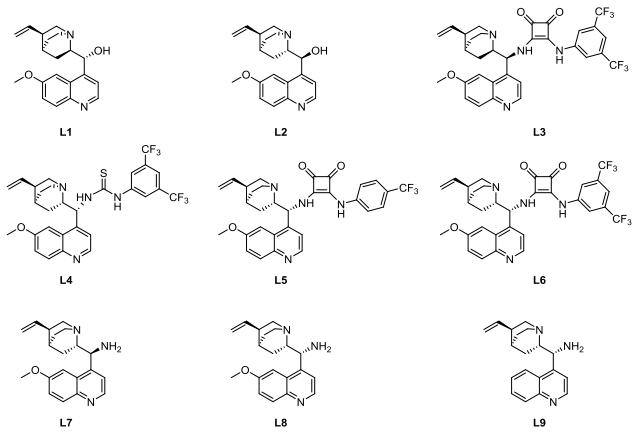


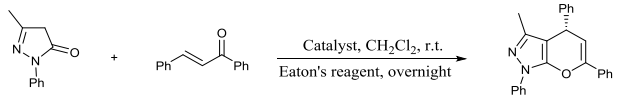
Fig. 2 The organocatalysts tested in this study.

moderate enantioselectivity. Therefore, we discovered a new synthetic method to access chiral pyranocoumarins and pyranopyrazoles using a quinine-derived primary amine catalyst (**L7**). Currently, it remains unknown if these new chiral compounds are biologically active. However, ongoing research aims to elucidate their potential bioactivities, in addition to using these newly synthesized compounds as the fundamental scaffolds to create other 4H-pyran-based compounds.

Results and discussion

Firstly, we attempted an Michael addition/dehydration reaction using 3-methyl-1-phenyl-2-pyrazolin-5-one (**1**), *trans*-chalcone (**2a**), and the organo catalysts shown in Fig. 2. Based on NMR and IR spectroscopy analysis, the Michael addition intermediate compound were rapidly converted to their corresponding imidic acid and amide compounds, and when treated with Eaton's reagent,[8b] formed the pyranopyrazole compound. The enantiomer **3a** was obtained after cyclisation. Table 1 shows the isolated yields of **3a** using different catalysts.

Table 1 Screening of organocatalysts.[a]



Entry	Catalyst	Additive	Loading[mol%]	Time[h]	Yield[b] (%)	ee[c] (%)
1	**L1**	-	10	72	74	0
2	**L2**	-	10	72	41	0
3[e]	**L3**	-	10	168	27	45
4	**L4**	-	10	168	24	12
5	**L5**	-	10	168	19	23
6	**L6**	-	10	168	16	17
7	**L7**	-	20	168	45	11
8	**L7**	TFA[d]	20	168	73	83
9[e]	**L8**	TFA[d]	20	168	30	65
10[e]	**L9**	TFA[d]	20	168	30	66

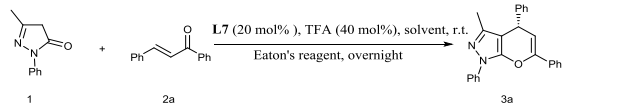
[a] Reaction conditions: 3-methyl-1-phenyl-2-pyrazolin-5-one **1** (0.1 mmol) and *trans*-chalcone **2a** (0.1 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. [b] Yield of isolated product. [c] Determined by HPLC using a Daicel Chiralpak IA column with *n*-hexane/*i*-propanol (90:10 v/v) as the eluent. [d] Acid additive (40 mol%).[e] The opposite enantiomer.

According to the literature,[4,5,6] catalysts **L1**-**L6** play an excellent bifunctional hydrogen-bonding role in the Michael addition reaction. However, in our study, poor enantioselectivity was observed using catalysts **L1**-**L6**. Squaric amide and thiourea catalysts showed better enantiomeric excess (Table 1, entries 3-6) compared to cinchona alkaloids (Table 1, entries 1 & 2), owing to their ability to induce a stronger hydrogen-bond effect between *trans*-chalcone compounds. The primary amine turned out to be not a good catalyst for this reaction (Table 1, entry 7).Further attempts to improve the enantioselectivity are shown in Table 1 (entries 9-10). We also tested primary amine/TFA systems because of their stronger hydrogen-bond donor and stable iminium ion effects during the formation of a transition state between the chalcone compounds and the catalysts. We found that the enantioselectivity was increased using the primary amine/TFA systems (Table 1, entries 8-10). When primary amine derived from quinidine and cinchonine were used, the opposite enantiomer of **3a** was obtained in low yields, with moderate enantioselectivity values (Table 1, entries 9 & 10). Nonetheless, the enantiomer **3a** was obtained in good yield (73 %) with high enantioselectivity (83% ee) using the quinine-derived catalyst **L7** (Table 1, entry 8). Therefore, **L7** was chosen as the catalyst for further reaction optimization.

The effect of different solvents on the reaction is listed in Table 2. Evidently, ether-based solvents were detrimental to the reaction enantioselectivity (Table 2, entries 4 & 5). Other polar and nonpolar solvents gave no discernible improvement of the enantioselectivity (Table 2, entries 6-9). Hence, considering both reaction yield and enantioselectivity, dichloromethane was the best solvent for this particular transformation.

Next, the effect of acid additives on the reaction was investigated. The results are shown in Table 3. The model reaction showed the importance of using a 1:2 ratio of **L7** to a co-catalyst (acid additive) (Table 3, entries 1 & 2). The reaction enantioselectivity did not improve when different sulfonic and benzoic acid derivatives were utilized (Table 3, entries 3-8). Based on asymmetric counterion-directed catalysis (ACDC),[9] which is known as an efficient strategy for enantioselective transformation, chiral acids were subsequently tested (Table 3, entries 9-13). Gratifyingly, **3a** was formed in moderate yield (70%) with the

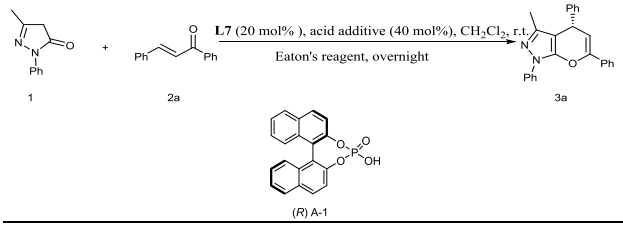
Table 2 Screening of solvents.[a]



Entry	Solvent	Time(h)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	168	73	83
2	$CHCl_3$	168	56	70
3	$C_2H_4Cl_2$	168	60	83
4	THF	168	58	21
5	Et_2O	168	80	15
6	Toluene	168	78	23
7	Xylene	168	60	68
8	MeCN	168	65	54
9	EtOH	168	63	67

[a] Reaction conditions: 3-methyl-1-phenyl-2-pyrazolin-5-one **1** (0.1 mmol), *trans*-chalcone **2a** (0.1 mmol), catalyst **L7** (20 mol%), and TFA (40 mol%) in test solvent (1.0 mL) at room temperature.[b] Yield of isolated product. [c] Determined by HPLC using a Daicel Chiralpak IA column with *n*-hexane/*i*-propanol (90:10 v/v) as the eluent.

Table 3 Screening of acid additives.[a]



Entry	Additive	Time(h)	Yield[b] (%)	ee[c] (%)
1	TFA	168	73	83
2[d]	TFA	168	60	61
3	*p*-Toluenesulfonic acid	168	42	70
4	Triflic acid	168	30	36
5	Benzoic acid	72	44	72
6	3-nitrobenzoic acid	72	45	84
7	4-nitrobenzoic acid	72	33	80
8	3,5-dinitrobenzoic acid	72	44	83
9	(*S*)-A-1	168	35	84
10	(*R*)-A-1	168	21	74
11	Boc-D-Phg-OH	72	70	93
12	Boc-L-Phg-OH	72	66	69
13	Boc-L-proline	96	50	50
14[e]	Boc-D-Phg-OH	60	75	93
15[e] [f]	Boc-D-Phg-OH	180	68	93

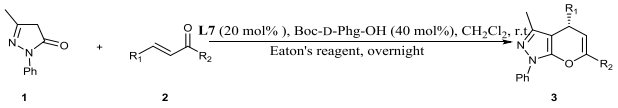
[a] Reaction conditions: 3-methyl-1-phenyl-2-pyrazolin-5-one **1** (0.1 mmol), *trans*-chalcone **2a** (0.1 mmol), catalyst **L7** (20 mol%), and acid additive (40 mol%) in CH_2Cl_2 (1.0 mL) at room temperature. [b] Yield of isolated product. [c] Determined by HPLC using a Daicel Chiralpak IA column with *n*-hexane/*i*-propanol (90:10 v/v) as the eluent. [d] 20 mol% of TFA loading [e] amounts of **1** (0.1 mmol) and **2a** (0.2 mmol). [f] The reaction temperature is 0 °C.

highest enantiomeric excess of 93% (Table 3, entry 11) by using *N*-Boc-D- phenylglycine (40 mol%) and **L7** (20 mol%). This organocatalyst system was previously reported by Melchiorre *et al*. for the Michael addition reaction.[10]

When two equivalents of the *trans*-chalcone **2a** were added, the product yield was increased to 75% in the shortest reaction time (60 h). Then we tried to run this reaction at 0℃, the chemical yield was decreased to 70% with the same enantioselectivity in a long reaction time (180 h). As such, the optimal reaction conditions were 2:1 equiv of **2a** to **1**, 20 mol% of **L7** catalyst loading with 40 mol% of *N*-Boc-D-phenylglycine as additive, and DCM as the reaction solvent at 25 °C for 60 h.

Having established the optimum conditions, the scope of the Michael addition/cyclodehydration sequential reaction was explored using various chalcones. As shown in Table 4, most products were obtained in moderate yields with good to high enantioselectivity values (up to 93% ee). Notably, the R1 group on the aromatic ring of the Michael acceptor has a crucial effect on reaction enantioselectivity. With a strongly electron-withdrawing group (*i.e.*, R1 = CF_3 or NO_2), the product yields and enantioselectivity values decreased, but they were subsequently improved by lowering the reaction temperature (Table 4, entries 5 & 6). Interestingly, we found that the electronic nature of the R2 group on the aromatic ring of the Michael acceptor has little effect on the reaction enantioselectivity (Table 4, entries 7-13).

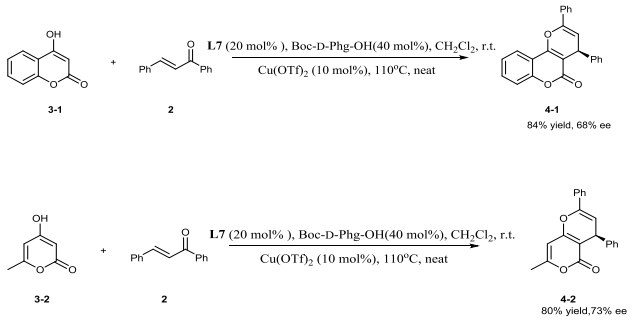
Table 4 Synthesis of pyranopyrazole derivates.[a]



Entry	R1	R2	Product	Yield[b] (%)	ee[c] (%)
1	Ph	Ph	**3a**	75	93
2	4-FC_6H_4	Ph	**3b**	59	91
3	4-ClC_6H_4	Ph	**3c**	81	91
4	4-BrC_6H_4	Ph	**3d**	73	92
5	4-$NO_2C_6H_4$	Ph	**3e**	44(45)[d]	83(90)[d]
6	4-$CF_3C_6H_4$	Ph	**3f**	50(52)[d]	87(91)[d]
7	Ph	4-FC_6H_4	**3g**	64	88
8	Ph	4-ClC_6H_4	**3h**	50	88
9	Ph	3-ClC_6H_4	**3i**	68	90
10	Ph	4-BrC_6H_4	**3j**	61	87
11	Ph	3-BrC_6H_4	**3k**	63	89
12	Ph	4-$NO_2C_6H_4$	**3l**	65	88
13	Ph	4-MeC_6H_4	**3m**	47	90
14	2-naphthalene	Ph	**3n**	56	88

[a] Reaction conditions: 3-methyl-1-phenyl-2-pyrazolin-5-one **1** (0.1 mmol), *trans*-chalcone **2** (0.2 mmol), catalyst **L7** (20 mol%), and Boc-L-Phg-OH (40 mol%) in DCM (1.0 mL) at room temperature. [b] Yield of isolated product. [c] Determined by HPLC using a Daicel Chiralpak IA column with *n*-hexane/*i*-propanol as the eluent. [d] The reaction temperature is 0 °C for 96h.

Nonetheless, a chalcone with an electron-donating R2 group gave a decreased product yield (Table 4, entry 13).



Scheme 1 Synthesis of pyranocoumarins.

The synthetic utility of this new method was demonstrated via the enantioselective preparation of chiral pyranopyran and pyranocoumarin compounds. As shown in Scheme 1, the chiral compounds were obtained in moderate yields with decent enantioselectivity (up to 73% ee). In addition, this is the first known synthesis of chiral 2,4-diphenyl-4*H*-pyranocoumarin and 2,4-diphenyl-7-methylpyrano-4*H*-[4,3-b]pyran-5-one.

Based on the previously proposed mechanism of iminium ion-catalyzed *α,β*-unsaturated ketones activation,[11] Figure 3 depicts the suggested reaction mechanism for the asymmetric Michael addition reaction, which is catalyzed by a chiral primary amine co-catalyst. Initially, 1 equiv of the quinine based primary amine catalyst **L7** interacts with 2 equiv of *N*-Boc-D-phenylglycine to form the co-catalyst. Next, the co-catalyst activates the enone via the formation of the iminium ion intermediate **A**. Based on formal computational

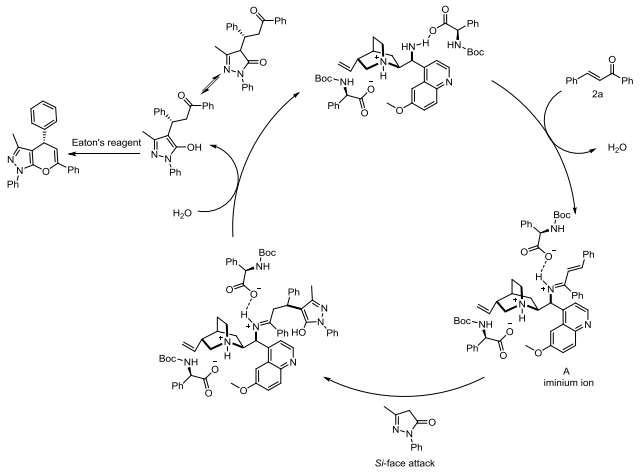


Fig. 3 Proposed mechanism for the **L7**-catalyzed, asymmetric Michael addition reaction.

studies of an intermediate similar to A,[11] the acid anion adduct has an electrostatic interaction with the protonated tertiary amine moiety of the chiral quinine catalyst, effectively shielding the *Re*-face attack. This inevitably leads to a *Si*-face addition. After dehydration of the Michael addition adduct, we obtain the *S*-enantiomer of **3a** with a 4*S* configured stereocentre. The absolute configuration of **3c** was determined by X-ray crystallographic analysis (Supporting information).[13] As X-ray crystallographic analysis result shows, it has no influence to identify the C-4 chiral centre has *S*-form configuration, Although C-2 substituted phenyl group shows a little disorder on X-ray crystallographic spectrum. (flack parameter=0.14(5) supporting information table 1) [14]
We also estimated other products as *S*-form in accordance with the X-ray analysis result of **3c**. This was due to the fact that all compound were treated with the same catalyst, same additives and same conditions exclusive to compound **3c**.

Conclusion

In conclusion, we have successfully demonstrated a new method for synthesising chiral pyranopyrazoles and pyranocoumarins efficiently. The target compounds were obtained via a Michael addition/dehydration sequential reaction between chalcones and pyrazolones or 4-hydro-2-pyrones, catalyzed by a quinine-derived primary amine (a primary amine/*N*-Boc-D-phenylglycine system). The pyranopyrazoles and pyranocoumarins were obtained in moderate yields with high enantioselectivity, and good yields with moderate enantioselectivity, respectively. Moving forward, we aim to improve the efficiency of this catalytic system (focussing on high enantioselectivity) for the synthesis of pyranocoumarins that possess powerful bioactivity.

Experimental Section

General methods

Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. "Concentrated" refers to the removal of volatile solvents via distillation using a rotary evaporator. "Dried" refers to drying over anhydrous magnesium sulfate, followed by gravity filtration to remove the drying agent. Flash chromatography was performed using silica gel (230–400 mesh) with hexane and ethyl acetate as eluents. Reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) and visualised with UV light. ^{1}H and ^{13}C NMR spectra were recorded using a 400 MHz NMR spectrometer and resonance signals were described as chemical shifts (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz), and the number of protons. IR spectra were recorded using an FT-IR spectrometer via the diamond-attenuated total reflectance technique and absorption peaks were described as wavenumbers (cm^{-1}). HR-MS analysis was performed using the electrospray ionisation (ESI) technique and the mass spectrometer was coupled to a quadrupole time-of-flight (Q-TOF) mass analyser. The enantiomeric excess of the products was determined using chiral HPLC analysis on an Agilent 1200 LC instrument with a Daicel Chiralpak IA column. Optical rotations were measured with a Jasco DIP-1020 digital polarimeter at the indicated concentration (g per 100 mL).

Materials

The organocatalysts were prepared according to established procedures.[12a-12d] The racemic product of **3a** was obtained using CH_3ONa as the catalyst. Meanwhile, the racemic products of **3** and **4** were obtained using quinidine as the catalyst. The *α,β*-unsaturated ketones were synthesized according to literature procedures.[12e,12f]

General procedure for preparing compound 3

The catalyst **L7** (20 mol%) was added to a mixture of pyrazolin-5-one (**1**) (0.1 mmol, 1.0 equiv), chalcone **2** (0.2 mmol, 2.0 equiv), and *N*-Boc-D-phenylglycine (40 mol%) in DCM (1 mL) at r.t. The progress of reaction was monitored by TLC (eluent: 5:1:2 of *n*-hexane/ethyl acetate/dichloromethane). Upon completion (48 h), the solvent was evaporated. Eaton's reagent (1 mL) was added into the concentrate and the reaction mixture was stirred overnight (12 h). Thereafter, the reaction mixture was poured into ice water and extracted with diethyl ether (three times). The organic solvent was concentrated under reduced pressure. The residue was purified via column chromatography on silica gel (eluent: 50:1 of *n*-hexane/ethyl acetate) and the combined fractions were concentrated to yield the desired product **3**.

(*S*)-3-Methyl-1,4,6-triphenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3a**)
Compound **3a** was obtained as a yellow solid (27.3 mg, 75% yield); m.p. 150-151 °C. **HPLC** (Daicel Chiralpak IA column, n-hexane/*i*-propanol (90:10 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 11.2 min, major enantiomer t_R = 15.9 min, 93% ee; $[\alpha]_D^{25}$ = -13.0 (c = 1, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* [ppm] 7.86 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 6.8 Hz, 2H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.42-7.26 (m, 9H), 5.62 (d, *J* = 4.0 Hz, 1H), 4.80 (d, *J* = 3.6 Hz, 1H), 1.95 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* [ppm] 147.5, 147.0, 146.6, 144.3, 138.5, 133.2, 129.1, 128.9, 128.7, 128.5, 128.1, 126.9, 125.8, 124.8, 120.6, 103.4, 98.1, 37.8, 13.1. **IR** (ATR, cm^{-1}): *ν* = 3065, 3027, 2921, 2852, 1663, 1598, 1443, 1393, 1302, 1277, 1243, 1179, 1123, 1075, 1031, 906, 849, 810, 747, 692, 661. **HR-MS** (ESI-Q-TOF): $[M + H]^+$ *m/z* = 365.1647 (calcd for $C_{25}H_{21}N_2O$ 365.1648)

(*S*)-4-(4-Fluorophenyl)-3-methyl-1,6-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3b**)
Compound **3b** was obtained as a white solid (22.5 mg, 59% yield); m.p. 110-111 °C. **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-

propanol (90:10 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 8.9 min, major enantiomer t_R = 10.5 min, 91% ee; $[\alpha]_D^{25}$ = -15.0 (c = 1.5, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.85 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 6.8 Hz, 2H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.43-7.34 (m, 3H), 7.32-7.24 (m, 3H), 7.03 (t, *J* = 8.4 Hz, 2H), 5.58 (d, *J* = 3 Hz, 1H), 4.79 (d, *J* = 3.6 Hz, 1H), 1.95 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] 163.0, 160.5, 147.6, 147.0, 146.5, 140.2(d), 138.4, 133.1, 129.6, 129.5, 129.2, 129.0, 128.5, 125.9, 124.8, 120.6, 115.6, 115.4, 103.2, 98.0, 37.1, 13.1. **IR** (ATR, cm^{-1}): *v* = 3046, 3025, 2924, 2845, 1655, 1601, 1439, 1396, 1314, 1274, 1220, 1161, 1122, 1076, 1037, 980, 932, 906, 840, 749, 685. **HR-MS** (ESI-Q-TOF): $[M + H]^+$ *m/z* = 383.1557 (calcd for $C_{25}H_{20}FN_2O$ 383.1554)

(*S*)-4-(4-Chlorophenyl)-3-methyl-1,6-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3c**)

Compound **3c** was obtained as a yellow solid (32.3 mg, 81% yield); m.p. 131-132 °C. **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-propanol (95:5 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 10.1 min, major enantiomer t_R = 13.1 min, 91% ee; $[\alpha]_D^{25}$ = -5.0 (c = 1.2, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.85 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 6.4 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.42-7.35 (m, 3H), 7.30 (t, *J* = 8.4 Hz, 3H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.55 (d, *J* = 3.6 Hz, 1H), 4.77 (d, *J* = 3.6 Hz, 1H), 1.95 (s, 3H). **^{13}C NMR** (100 MHz, CDCl3): δ [ppm] 147.8, 147.0, 146.4, 142.9, 138.4, 133.1, 132.7, 129.4, 129.2, 129.0, 128.8, 128.6, 125.9, 124.8, 120.6, 102.9, 97.7, 37.3, 13.1. **IR** (ATR, cm^{-1}): *v* = 3041, 2956, 2921, 2851, 1654, 1601, 1513, 1439, 1396, 1313, 1274, 1249, 1180, 1123, 1077, 1040, 1013, 981, 936, 907, 847, 830, 802, 749, 686, 668. **HR-MS** (ESI-Q-TOF): $[M + Na]^+$ m/z = 421.1085 (calcd for $C_{25}H_{19}ClN_2NaO$ 421.1078)

(*S*)-4-(4-Bromophenyl)-3-methyl-1,6-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3d**)

Compound **3d** was obtained as a yellow solid (32.3 mg, 73% yield); m.p. 133-134 °C. **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-propanol (90:10 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 9.1 min, major enantiomer t_R = 9.8 min, 92% ee; $[\alpha]_D^{25}$ = +4.3 (c = 1, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.84 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 6.8 Hz, 2H), 7.52-7.44 (m, 4H), 7.42-7.34 (m, 3H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 5.56 (d, *J* = 4 Hz, 1H), 4.77 (d, *J* = 4 Hz, 1H), 1.95 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] 147.8, 147.0, 146.4, 143.4, 138.4, 133.0, 131.8, 129.8, 129.2, 129.0, 128.6, 125.9, 124.8, 120.8, 120.6, 102.8, 97.6, 37.4, 13.1. **IR** (ATR, cm^{-1}): *v* = 3066, 3028, 2922, 2852, 1656, 1599, 1443, 1393, 1298, 1275, 1240, 1176, 1123, 1102, 1075, 1033, 1009, 981, 935, 905, 848, 820, 753, 688, 665.**HR-MS** (ESI-Q-TOF): $[M + Na]^+$ *m/z* = 465.0569 (calcd for $C_{25}H_{19}BrN_2NaO$ 465.0573)

(*S*)-3-Methyl-4-(4-nitrophenyl)-1,6-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3e**)

Compound **3e** was obtained as a yellow solid (18.4 mg, 45% yield); m.p. 123-124 °C. **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-propanol (90:10 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 16.6 min, major enantiomer t_R = 21.4 min, 90% ee; $[\alpha]_D^{25}$ = +12.5 (c = 0.7, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 8.22 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.60-7.59 (m, 2H), 7.54-7.46 (m, 4H), 7.44-7.37 (m, 3H), 7.31 (t, *J* = 7.6 Hz, 1H), 5.56 (d, *J* = 4 Hz, 1H), 4.94 (d, *J* = 3.6 Hz, 1H), 1.95 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] 151.50, 148.5, 147.0, 146.1, 138.2, 132.7, 129.3, 129.2, 129.0, 128.6, 126.2, 125.0, 124.1, 120.7, 101.6, 96.9, 37.8, 13.1. **IR** (ATR, cm^{-1}): *v* = 3060, 2981, 2992, 2857, 1660, 1595, 1511, 1442, 1394, 1345, 1278, 1242, 1181, 1124, 1103, 1076, 1034, 1013, 981, 937, 906, 839, 804, 754, 686, 662. **HR-MS** (ESI-Q-TOF): $[M + Na]^+$ *m/z* = 432.1325 (calcd for $C_{26}H_{19}N_3NaO_3$ 432.1319)

(*S*)-3-Methyl-1,6-diphenyl-4-(4-(trifluoromethyl)phenyl)-1,4-dihydropyrano[2,3-c]pyrazole (**3f**)

Compound **3f** was obtained as a yellow solid (22.5 mg, 52% yield); m.p. 125-126 °C. **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-propanol (95:5 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 9.3 min, major enantiomer t_R = 12.0 min, 91% ee; $[\alpha]_D^{25}$ = -5.5 (c = 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.85 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 8.0 Hz, 4H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.46-7.35 (m, 5H), 7.30 (t, *J* = 7.6 Hz, 1H), 5.58 (d, *J* = 3.6 Hz, 1H), 4.88 (d, *J* = 4 Hz, 1H), 1.95 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] 148.2, 148.1, 147.0, 146.3, 138.3, 132.9, 129.2, 129.1, 128.6, 128.4, 126.0, 125.8 (q), 124.9, 120.6, 102.3, 97.3, 37.7, 13.1. **IR** (ATR, cm^{-1}): *v* = 3045, 2921, 2852, 1656, 1600, 1443, 1396, 1324, 1276, 1245, 1163, 1120, 1106, 1067, 1038, 1017, 982, 937, 902, 844, 749, 680, 662. **HR-MS** (ESI-Q-TOF): $[M + Na]^+$ *m/z* = 455.1339 (calcd for $C_{26}H_{19}F_3N_2NaO$ 455.1342)

(*S*)-6-(4-Fluorophenyl)-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3g**)

Compound **3g** was obtained as a yellow solid (24.5 mg, 64% yield); m.p. 160-161 °C. **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-propanol (95:5 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 9.9 min, major enantiomer t_R = 12.4 min, 88% ee; $[\alpha]_D^{25}$ = +4.8 (c = 0.8, $CHCl_3$). **^{1}H NMR** (400 MHz, CDCl3): δ [ppm] 7.83 (d, *J* = 8.0 Hz, 2H), 7.62 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.38-7.24 (m, 6H), 7.07 (t, *J* = 8.4 Hz, 2H), 5.55 (d, *J* = 3.6 Hz, 1H), 4.78 (d, *J* = 4 Hz, 1H), 1.95 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] 164.2, 161.8, 146.9, 146.7, 146.6, 144.1, 138.3, 129.4 (d), 129.2, 128.7, 128.0, 127.0, 126.7, 126.6, 125.9, 120.6, 115.6, 115.4, 103.2 (d), 98.0, 37.8, 13.1. **IR** (ATR, cm^{-1}): *v* = 3062, 2927, 2856, 1661, 1599, 1440, 1397, 1300, 1275, 1230, 1167, 1122, 1076, 1042, 983, 937, 903, 835, 808, 746, 688, 670. **HR-MS** (ESI-Q-TOF): $[M + Na]^+$ *m/z* = 405.1377 (calcd for $C_{25}H_{19}FN_2NaO$ 405.1374)

(*S*)-6-(4-Chlorophenyl)-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3h**)

Compound **3h** was obtained as a yellow solid (19.9 mg, 50% yield); m.p. 140-141 °C. **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-propanol (95:5 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 10.2 min, major enantiomer t_R = 13.0 min, 88% ee; $[\alpha]_D^{25}$ = -12 (c = 0.9, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.82 (d, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.48 (t, *J* = 8 Hz, 2H), 7.38-7.23 (m, 8H), 5.59 (d, *J* = 3.6 Hz, 1H), 4.78 (d, *J* = 3.6 Hz, 1H), 1.94 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] 146.7, 146.6 (d), 144.0, 138.3, 134.7, 131.7, 129.2, 128.7 (d) 128.1, 127.0, 126.1, 126.0, 120.6, 103.9, 98.0, 37.8, 13.1. **IR** (ATR, cm^{-1}): *v* = 3066, 3027, 2921, 2852, 1655, 1596, 1439, 1395, 1293, 1269, 1176, 1123, 1094, 1072, 1041, 1011, 979, 935, 902, 830, 749, 685, 665. **HR-MS** (ESI-Q-TOF): $[M + H]^+$ *m/z* 399.1254 (calcd for $C_{25}H_{20}ClN_2O$ 399.1259)

(*S*)-6-(3-Chlorophenyl)-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3i**)

Compound **3i** was obtained as a yellow oil (27.1 mg, 68% yield); **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-propanol (90:10 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 8.7 min, major enantiomer t_R = 9.3 min, 90% ee; $[\alpha]_D^{25}$ = +44 (c = 1, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.83 (d, *J* = 8 Hz, 2H), 7.78 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.53-7.45 (m, 3H), 7.39-7.27 (m, 7H), 5.63 (d, *J* = 4 Hz, 1H), 4.80 (d, *J* = 4 Hz, 1H), 1.94 (s, 3H). **^{13}C NMR** (100 MHz, CDCl3): δ [ppm] 146.7, 146.6, 146.1, 143.9, 138.3, 135.2, 131.8, 130.0, 129.2, 128.7, 127.9, 127.0, 126.0, 123.3, 122.7, 120.6, 104.6, 97.9, 37.8, 13.1. **IR** (ATR, cm^{-1}): *v* = 3062, 2923, 2850, 1655, 1596, 1493, 1396, 1288, 1239, 1211, 1123, 1075, 1026, 997, 904, 844, 752, 688 **HR-MS** (ESI-Q-TOF): $[M + H]^+$ *m/z* = 399.1260 (calcd for $C_{25}H_{20}ClN_2O$ 399.1259)

(*S*)-6-(4-Bromophenyl)-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3j**)

Compound **3j** was obtained as a yellow solid (27.0 mg, 61% yield); m.p. 130-131 °C. **HPLC** (Daicel Chiralpak IA column, n-hexane/*i*-propanol (90:10 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 9.5 min, major enantiomer t_R = 11.8 min, 87% ee; $[\alpha]_D^{25}$ = -7 (c = 0.9, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.82 (d, *J* = 8.4 Hz, 2H), 7.53-7.44 (m, 6H), 7.38-7.26 (m, 6H), 5.60 (d, *J* = 3.6 Hz, 1H), 4.77 (d, *J* = 3.6 Hz, 1H), 1.94 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] 146.8, 146.6 (d), 144.0, 138.3, 132.2, 131.7, 129.2, 128.7 128.1, 127.0, 126.4, 126.0, 122.9, 120.6, 103.9, 98.0, 37.8, 13.1. **IR** (ATR, cm^{-1}): *v* = 3062, 3025, 2922, 2853, 1655, 1597, 1452, 1394, 1292, 1269, 1242, 1177, 1123, 1101, 1072, 1041, 1007, 980, 936, 902, 826, 749, 686, 664. **HR-MS** (ESI-Q-TOF): [M + H]$^+$ *m/z* = 443.0759 (calcd for $C_{25}H_{20}BrN_2O$ 443.0754)

(*S*)-6-(3-Bromophenyl)-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2, 3-c]pyrazole (**3k**)

Compound **3k** was obtained as a yellow oil (27.9 mg, 63% yield); **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-propanol (90:10 v/v), flow rate 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 8.6 min, major enantiomer t_R = 9.2 min, 89% ee; $[\alpha]_D^{25}$ = +43 (c = 1.1, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.83 (d, *J* = 8 Hz, 2H), 7.60 (s, 1H), 7.50 (t, *J* = 7.6 Hz, 3H), 7.37-7.26 (m, 8H), 5.64 (d, *J* = 4 Hz, 1H), 4.79 (d, *J* = 3.6 Hz, 1H), 1.94 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] 146.7, 146.6, 146.3, 143.9, 138.3, 135.0, 134.6, 129.8, 129.2, 128.9, 128.8, 128.0 (d), 127.0, 126.0, 125.0, 122.9, 120.7, 104.6, 98.0, 37.8, 13.1. **IR** (ATR, cm^{-1}): *v* = 3061, 2923, 2852, 1655, 1597, 1453, 1393, 1290, 1240, 1213, 1176, 1124, 1076, 1027, 998, 940, 905, 846, 750, 690. **HR-MS** (ESI-Q-TOF): [M + H]$^+$ m/z = 443.0755 (calcd for $C_{25}H_{20}BrN_2O$ 443.0754)

(*S*)-3-Methyl-6-(4-nitrophenyl)-1,4-diphenyl-1,4-dihydropyrano[2, 3-c]pyrazole (**3l**)

Compound **3l** was obtained as a yellow solid (26.6 mg, 65% yield); m.p. 159-160 °C. **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-propanol (90:10 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 15.7 min, major enantiomer t_R = 20.9 min, 88% ee; $[\alpha]_D^{25}$ = +9 (c = 1, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 8.24 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.39-7.28 (m, 6H), 5.83 (d, *J* = 3.6 Hz, 1H), 4.85 (d, *J* = 4 Hz, 1H), 1.95 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] 147.7, 146.6, 146.4, 145.7, 143.4, 139.1, 138.2, 129.3, 128.9, 128.1, 127.3, 126.2, 125.4, 123.9, 120.7, 107.4, 97.7, 38.0, 13.1. **IR** (ATR, cm^{-1}): *v* = 3066, 3027, 2919, 2851, 1650, 1595, 1438, 1395, 1345, 1310, 1282, 1250, 1176, 1154, 1124, 1074, 1041, 1011, 982, 939, 904, 844, 803, 781, 751, 687, 664. **HR-MS** (ESI-Q-TOF): [M + Na]$^+$ *m/z* = 432.1323 (calcd for $C_{25}H_{19}N_3NaO_3$ 432.1319)

(*S*)-3-Methyl-1,4-diphenyl-6-(*p*-tolyl)-1,4-dihydropyrano[2,3-c]pyr-azole (**3m**)

Compound **3m** was obtained as a yellow solid (17.8 mg, 47% yield); m.p. 105-106 °C. **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-propanol (95:5 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 9.4 min, major enantiomer t_R = 11.5 min, 90% ee; $[\alpha]_D^{25}$ = + 2.1 (c = 0.8, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.85 (d, *J* = 8 Hz, 2H), 7.52 (d, *J* = 8 Hz, 2H), 7.48 (t, *J* = 8.4 Hz, 2H), 7.37-7.26 (m, 6H), 7.19 (d, *J* = 8 Hz, 2H), 5.56 (d, *J* = 4 Hz, 1H), 4.78 (d, *J* = 3.6 Hz, 1H), 2.37 (s, 3H), 1.95 (s, 3H). **^{13}C NMR** (100 MHz, CDCl3): δ [ppm] 147.6, 147.1, 146.6, 144.4, 138.9, 138.5, 130.5, 129.2, 129.1, 128.6, 128.1, 126.9, 125.8, 124.8, 120.5, 102.6, 98.1, 37.8, 21.2, 13.1. **IR** (ATR, cm^{-1}): *v* = 3026, 2922, 2854, 1656, 1597, 1439, 1396, 1296, 1272, 1241, 1176, 1123, 1073, 1039, 979, 936, 902, 838, 821, 748, 686. **HR-MS** (ESI-Q-TOF): [M + H]$^+$ *m/z* = 379.1808 (calcd for $C_{26}H_{23}N_2O$ 379.1805)

(*S*)-3-Methyl-4-(naphthalen-2-yl)-1,6-diphenyl-1,4-dihydropyrano [2,3-c]pyrazole (**3n**)

Compound **3n** was obtained as a yellow solid (23.2 mg, 56% yield); m.p. 160-161 °C. **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-propanol (95:5 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 10.7 min, major enantiomer t_R = 14.7 min, 88% ee; $[\alpha]_D^{25}$ = +12.8 (c = 1, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.88 (d, *J* = 8 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 3H), 7.75 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.53-7.42 (m, 5H), 7.42-7.34 (m, 3H), 7.29 (t, *J* = 7.6 Hz, 1H), 5.67 (d, *J* = 4 Hz, 1H), 4.97 (d, *J* = 4 Hz, 1H), 1.94 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] 147.6, 147.1, 146.8, 141.6, 138.5, 133.5, 133.2, 132.6, 129.2, 128.9, 128.6, 128.5, 127.8, 127.7, 126.4, 126.3, 126.2, 125.9, 125.7, 124.9, 120.6, 103.3, 97.9, 38.0, 13.1. **IR** (ATR, cm^{-1}): *v* = 3052, 2920, 2851, 1659, 1598, 1443, 1396, 1296, 1276, 1235, 1184, 1158, 1121, 1075, 1041, 980, 961, 904, 865, 817, 749, 687. **HR-MS** (ESI-Q-TOF): [M + H]$^+$ m/z = 415.1807 (calcd for $C_{29}H_{23}N_2O$ 415.1805)

General procedure for preparing compound 4

The catalyst **L7** (20 mol%) was added to a mixture of 4-hydroxycoumarin **3-1** or 4-hydroxy-6-methyl-2-pyrone **3-2** (0.1 mmol, 1.0 equiv), *trans*-chalcone **2a** (0.2 mmol, 2.0 equiv), and *N*-Boc-D-phenylglycine (40 mol%) in DCM (1 mL) at r.t. The progress of reaction was monitored by TLC (eluent: 5:1:2 of hexane/ethyl acetate/dichloromethane). Upon completion, the solvent was evaporated. Copper(II) trifluoromethanesulfonate (10 mol%) was added to the concentrate and the reaction mixture was heated at 110 °C (6 h). Thereafter, the reaction mixture was extracted with ethyl acetate (three times). The organic solvent was concentrated under reduced pressure. The residue was purified via column chromatography on silica gel (eluent: 50:1 of *n*-hexane/ethyl acetate) and the combined fractions were concentrated to yield the desired products **4-1** and **4-2**.

(*S*)-2,4-Diphenyl-4H,5H-pyrano[3,2-c]chromen-5-one (4-1)

Compound **4-1** was obtained as a white solid (29.6 mg, 84% yield); m.p. 162-163 °C. **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-propanol (90:10 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 26.5 min, major enantiomer t_R = 21.7 min, 68% ee; $[\alpha]_D^{25}$ = +47.8 (c = 1.1, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 8.02 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.48-7.29 (m, 9H), 7.23 (t, *J* = 7.2 Hz, 1H), 5.85 (d, *J* = 5.2 Hz, 1H), 4.71 (d, *J* = 4.8 Hz, 1H). **^{13}C NMR** (100 MHz, CDCl3): δ [ppm] 161.4, 155.7, 152.7, 146.9, 143.5, 132.6, 132.0, 129.2, 128.6 (d, *J* = 4 Hz), 128.4, 127.2, 124.6, 124.1, 122.7, 116.8, 114.5, 103.7, 103.6, 36.6. **IR** (ATR, cm^{-1}): *v* = 3064, 3027, 1720, 1630, 1609, 1285, 1269, 1241, 1202, 1168, 1148, 1111, 1079, 1059, 1031, 1010, 964, 889, 856, 760, 691. **HR-MS** (ESI-Q-TOF): [M + H]$^+$ *m/z* = 353.1175 (calcd for $C_{24}H_{17}O_3$ 353.1172)(

S)-7-Methyl-2,4-diphenyl-4H,5H-pyrano[4,3-b]pyran-5-one (4-2)

Compound **4-2** was obtained as a yellow solid (25.3 mg, 80% yield); 165-166 °C. **HPLC** (Daicel Chiralpak IA column, *n*-hexane/*i*-propanol (90:10 v/v), 0.5 mLmin^{-1}, UV detection at 254 nm): Minor enantiomer t_R = 29.8 min, major enantiomer t_R = 36.2 min, 73% ee; $[\alpha]_D^{25}$ = +8 (c = 1, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.61 (d, *J* = 6.8 Hz, 2H), 7.43-7.34 (m, 5H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 1H), 6.02 (s, 1H), 5.74 (d, *J* = 4.8 Hz, 1H), 4.56 (d, *J* = 4.8 Hz, 1H), 2.23 (s, 3H). **^{13}C NMR** (100 MHz, CDCl3): δ [ppm] 163.3, 161.4, 160.4, 146.8, 143.8, 132.5, 129.0, 128.5 (d, *J* = 2 Hz), 128.3, 127.0, 124.5, 103.7, 100.8, 99.1, 36.0, 19.9. **IR** (ATR, cm^{-1}): *v* = 3071, 2886, 1721, 1648, 1593, 1491, 1436, 1275, 1242, 1194, 1146, 1075, 1037, 1010, 979, 937, 854, 824, 809, 758, 741, 687. **HR-MS** (ESI-Q-TOF): [M + H]$^+$ *m/z* = 317.1176 (calcd for $C_{21}H_{17}O_3$ 317.1172)

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13. Crystallographic data for compound **3c** (CCDC 1422503) has been provided as CIF file in the ESI.†
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