Ni-catalyzed enantio- stereoselective synthesis of chiral chromans with quaternary allylic siloxanes and their antitumor activity

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Nickel-catalyzed efficient asymmetric synthesis of chiral chromans with quaternary allylic siloxanes and their antitumor activity is reported for the first time. A *P*-chiral monophosphine ligand **(*R*)-AntPhos** was found to be the ideal ligand to form a series of tertiary allylic siloxanes bearing chroman structures with excellent yields, enantioselectivities and *E*/*Z* selectivity using triethylsilane as the reductant. This reaction has a broad substrate scope and provides a practical way to synthesize useful chroman derivatives with chiral tertiary allylic alcohols. Up to 69 examples were successfully established with this method. A series of 3-hydroxychroman derivatives were obtained and tested for anti-tumor activity. Number of compounds showed good anti-tumor activity, less toxicity to reference cell, and specificity to different cancer cells, which could be new anticancer leading compounds. The configuration and substituent of the 3-hydroxychromans has big effects for their anti-tumor activity. Further study on structure-activity relationships of these 3-hydroxychromans is under investigation to discover new anti-cancer drugs.

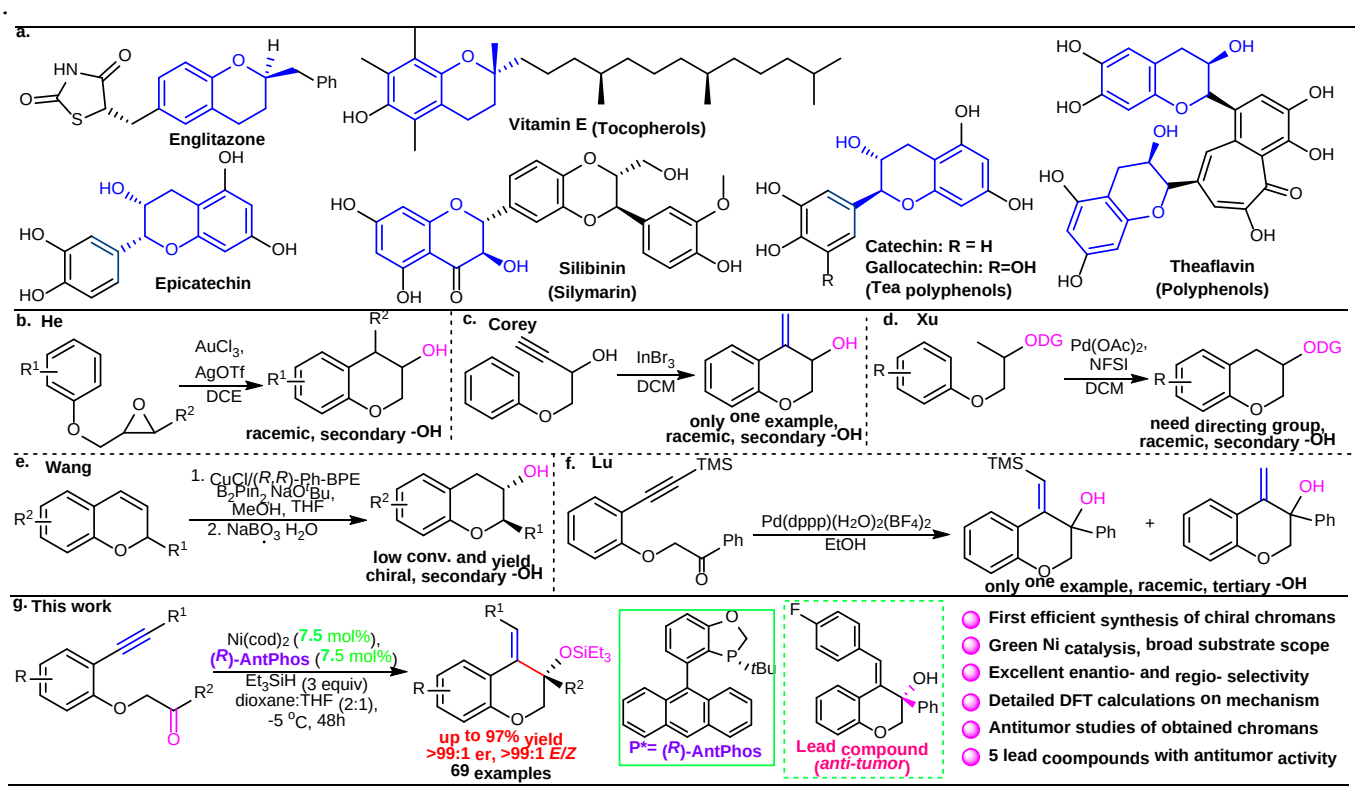

Fig. 1 | a. Several therapeutic agents and bio-active molecules bearing a multi-substituted chiral chromans moiety. b-f. Previous work of constructing functionalized multi-substituted 3-Hydroxychroman via metal-catalyzed cyclizations. g. This work: an efficient nickel-catalyzed asymmetric synthesize chromans with chiral tertiary alcohol sillyl ether.

Chiral chromans widely exist in a large number of bioactive natural products and pharmaceuticals (Fig 1a). Englitazone[1] is a drug used to treat type II diabetes. Epicatechin[2-3] could reduce blood lipid and glucose and protect nerves. Silymarin[4-5] is a natural flavonoid lignan extracted from the dried fruit of the Compositae plant, milk thistle, which can be used to treat liver diseases and inhibit tumor cell growth. Vitamin E[6-8] is the most important member of the tocopherols family and has anti-inflammatory, immune boosting, and antioxidant effects.

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3-hydroxychromans were key kind of chiral chromans with important biological activities. Theaflavins[9-10], polyphenols extracted from black tea, one kind of chiral 3-hydroxychroman, prevented cancer, reduced blood lipids, and resisted cardiovascular diseases. Tea polyphenols[11-12], one chiral 3-hydroxychromans, played an important role in anti-cancer, hypoglycemic, and anti-oxidation. Thus, development of efficient methods to synthesize these structures, especially 3-hydroxychromans in an enantiomerically enriched form has important research significance in biology and medicine. However, the current methods are limited.

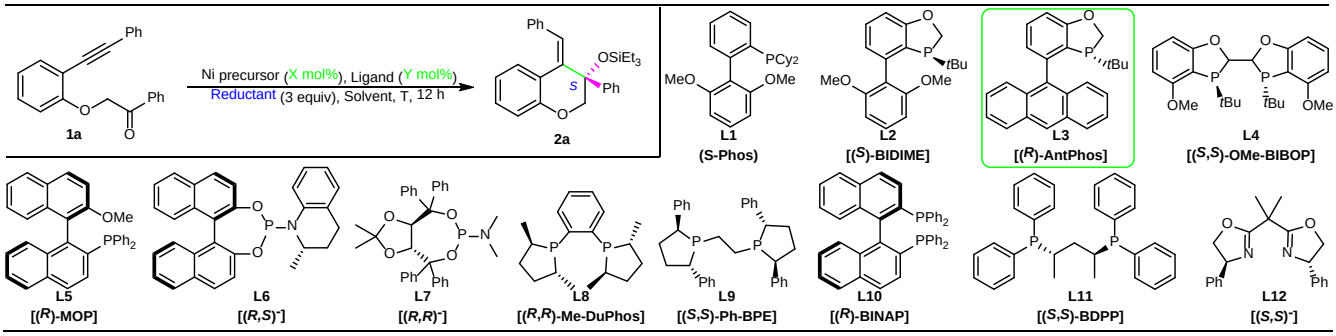
The synthesis methods of chiral chromans mainly include small molecule catalysis and transition metal catalysis. The small molecule catalysis is mainly chiral phosphoric acid, cinchona alkaloids, etc.[13-22], but they are limited by the large amount of catalyst and the restriction of the substrate. The transition metal-catalyzed asymmetric synthesis of chiral chromans is a powerful strategy in synthetic organic chemistry. Recently, transition metal Ti[23], Rh[24-28], Pd[29-35], Ru[36-38], Ir[39-40], Au[41], Sc[42-43], Cu[44-49]-catalyzed reactions have been developed. In 2004, He and coworkers developed an $AuCl_3$/AgOTf catalyzed cyclialkylation of electron-rich arenes with epoxides to prepare racemic 3-chromanols in moderate yields (Fig 1b)[50]. In 2011, Corey and coworkers reported one example of $InBr_3$ promoted cyclization of aromatic acetylenes, giving racemic 3-chromanol product in 6% yield (**Fig** 1d)[51]. In 2020, Xu and coworkers reported a $Pd(OAc)_2$/NFSI-catalyzed intramolecular C(sp^3)−H arylative cyclization to synthesis racemic 3-chromanols derivatives in high yields, which requires specific structural synergy with directing group (Fig 1c)[52]. In 2022, Wang and coworkers reported an Cu-catalyzed asymmetric hydroboration/kinetic resolution of racemic 2-aryl-chromenes to synthesis of chiral 3-hydroxychromans, but the conversion is only 50%, and the total yield of 3-hydroxychromans is about 22.5% with recovering 22.5% chiral 2-aryl-chromenes. (Fig 1e)[53]. In 2015, Lu and coworkers reported the Pd(dppp)$(H_2O)_2(BF_4)$-catalyzed cyclization of alkynones, but only one example gave two racemic 3-hydroxy chromans (Fig 1f)[54]. In the past decades, efficient enantioselective synthesis of chiral 3-hydroxychromans with quaternary allylic alcohols hasn't been reported yet.

Since 2015, an efficient Ni-catalyzed reductive cyclization strategy was developed by Tang and our group[55-58], to construct various chiral tetrahydrofurans and pyrrolidines with quaternary allylic alcohols. In view of attractive biological activities of chiral chromans, we are excited to design and synthesis of aryl chained alkynones to construct chromans with chiral quaternary allylic alcohol subunits, and further exploring their biological activities. Different kinds of aryl chained alkynones have been synthesized, and Nickel precursors with different ligands were tested for this reductive cyclization process. Fortunately, one special aryl chained alkynones could give desired chiral chromans with good yields and enantioselectivities with our privileged ligand system. Herein, we reported an efficient asymmetric stereoselective intramolecular reductive cyclization of aryl chained alkynones catalyzed by Ni(cod)$_2$ and *P*-chiral monophosphine ligand **(*R*)-AntPhos** utilizing triethylsilane (Et_3SiH) as reductant, which concisely synthesize chiral 3-hydroxyl chroman derivatives bearing quaternary stereocenters of tri-substituted allylic siloxanes in up to 97% yield, >99:1 er and >99 *E/Z* under mild conditions (Fig 1g). Up to 69 examples were successfully established with this method. To the best of our knowledge, this is the first highly asymmetric stereoselective Ni-catalyzed reductive cyclization of aryl chained alkynones for efficient synthesis of chroman derivatives with chiral quaternary carbon stereocenters of trisubstituted allylic siloxanes. This is also the first time clarified mechanism study of the excellent enantioselectivity and perfect stereoselectivity was proposed and confirmed by DFT calculations, which will definitely give future guidance for new reaction design and application. Furthermore, these corresponding 3-hydroxyl chromans was studied for their anti-tumor activities. Some of them showed good killing ability on four kinds of cancer cells (bladder cancer T24 cells, colorectal cancer SW480 cells, lung cancer A549 cells, brain glioma U251 cells), and is nontoxic to normal cells. These synthesized chiral 3-hydroxyl chromans with tertiary allylic alcohols might be one kind of important anticancer leading compounds with important research significance. Further study on structure-activity relationships of these 3-hydroxychromans is under investigation to discover new anti-cancer drugs.

Results

Ligand effects and reaction optimization. We envisioned whether chromans with tertiary allylic alcohol sillyl ether could be synthesized efficiently by Ni-catalyzed reductive cyclization of alkynyl and carbonyl groups. We began our experiments by testing the intramolecular reductive cyclization of aryl chained alkynones **1a** with Ni(cod)$_2$ and different ligands (Fig 2). The reaction was performed under nitrogen in dioxane at 25 ^oC for 12 h in the presence of a nickel catalyst prepared in situ with Ni(cod)$_2$ (5 mol %), PPh_3 (5 mol % ligand) and 3 equiv. triethylsilane (Et_3SiH). The target product 2a (Entry 1) was obtained in 18% yield (Entry 1). A series of ligands including achiral and chiral ones were investigated for their activity and enantioselectivity. (i.e., **L1**-**L12** as shown in Fig 2; for further results and ligands tested, see Supporting Information in detail). When **L1 (S-Phos)** achiral ligand was used as the ligand, only trace amounts of product were obtained (Entry 2). Using the monophosphine *P*-chiral ligand **L2 [(*S*)-BI-DIME]**, we were pleasantly surprised to find the corresponding cyclized product in excellent 98% yield with moderate enantioselectivity (32:68 er, Entry 3). Excitingly, **L3 [(*R*)-AntPhos]** provided the desired product in excellent yield and enantioselectivity (98% yield, 93:7 er, Entry 4), which indicates that the large steric hindrance of the planary anthracene group play an important role in the control of chirality. However, the bisphosphine ligand **L4 [(*S*,*S*)-OMe-BIBOP]** with the same backbone as **L3** is inactive for this reaction (Entry 5). The axially chiral monophosphine ligand **L5 [(*R*)-MOP]** afforded the product in low yield and moderate enantioselectivity (38% yield, 74:26 er, Entry 6). The chiral monophosphine nitrogen ligand **L6** and **L7** provided the product with good yields and poor enantioselectivities (**L6**: 76% yield, 37:63 er; **L7**: 54 % yield, 45:55 er; Entry 7, 8) Commercial bisphosphine chiral ligands **L8 [(*R*,*R*)-Me-DuPhos], L9 [(*S*,*S*)-Ph-BPE]**, **L10 [(*R*)-BINAP]** and **L11 [(*S*,*S*)-BDPP]** were all investigated for this transformation, only **L11** gave desired product in moderate yield (60%) and poor enantioselectivity (60:40 er), the others have no reactivity at all (Entries 9-12). The chiral bidentate oxazole ligand **L12 [(*S*,*S*)-]** is not applicable to this reaction (Entry 13). These results showed that special monophosphine ligands have better reactivity than bisphosphorus ligands, and most of common chiral bisphosphorus ligands are not applicable for this asymmetric transformation. We chose **L3 [(*R*)-AntPhos]** as the optimal ligand to use Ni(II) precursors Ni(OAc)$_2$ and $NiCl_2$, it was found that the reaction could not proceed (Entry 14-15). The reducing agent was then explored, and it was found that $(EtO)_3SiH$ as reducing agent gave the desired product in 90% yield and 91.7:8.3 er , and the reaction could not proceed using $ZnEt_2$ as the reductant (Entry 16-17). The solvent effect was also investigated, THF give moderate yield and excellent enantioselectivity, toluene gave high yield and enantioselectivity (THF: 60% yield, 93.8:6.2 er; toluene: 91% yield, 92.5:7.5 er) while protic solvent MeOH led to no conversion (Entries 18-20). When reducing the temperature to 0°C with THF, poor yield and high enantioselectivity was obtained (36% yield, 94.3:5.7 er, Entry 21) suggesting that lower temperature increases the enantioselectivity and decreases the yield. Finally, to achieve a balance between yield and enantioselectivity, we used mixed solvent as THF/dioxane (1:2) at -5 °C for 48 hours with **7.5** mol % catalyst loading of Ni(cod)$_2$ and **(*R*)-AntPhos**, the desired product was obtained with excellent yield and enantioselectivity as the optimal reaction conditions (95% yield, 95.5:4.5 er, Entry 22). Interestingly, although

different phosphine ligands were applied for this transformation, the *E/Z* stereoselectivity of the cyclized allylic product was always >99:1, no matter how much its enantioselectivity was conducted. This probably because of the chemistry specialty of this Nickel catalyzed cyclization.



Entry[a]	Ni precursor	Ligand	X	Y	Solvent	Reductant	T(°C)	Yield (%)[b]	er (%)[c]	*E/Z*[d]
1	$Ni(cod)_2$	**PPh_3**	5	5	dioxane	Et_3SiH	rt	18	50:50	>99:1
2	$Ni(cod)_2$	**L1**	5	5	dioxane	Et_3SiH	rt	–	–	–
3	$Ni(cod)_2$	**L2**	5	5	dioxane	Et_3SiH	rt	97	38:62	>99:1
4	$Ni(cod)_2$	**L3**	5	5	dioxane	Et_3SiH	rt	98	93:7	>99:1
5	$Ni(cod)_2$	**L4**	5	5	dioxane	Et_3SiH	rt	–	–	–
6	$Ni(cod)_2$	**L5**	5	5	dioxane	Et_3SiH	rt	38	74:26	>99:1
7	$Ni(cod)_2$	**L6**	5	5	dioxane	Et_3SiH	rt	76	37:63	>99:1
8	$Ni(cod)_2$	**L7**	5	5	dioxane	Et_3SiH	rt	54	45:55	>99:1
9	$Ni(cod)_2$	**L8**	5	2.5	dioxane	Et_3SiH	rt	–	–	–
10	$Ni(cod)_2$	**L9**	5	2.5	dioxane	Et_3SiH	rt	–	–	–
11	$Ni(cod)_2$	**L10**	5	2.5	dioxane	Et_3SiH	rt	–	–	–
12	$Ni(cod)_2$	**L11**	5	2.5	dioxane	Et_3SiH	rt	60	43:57	>99:1
13	$Ni(cod)_2$	**L12**	5	2.5	dioxane	Et_3SiH	rt	–	–	–
14	$Ni(OAc)_2$	**L3**	5	5	dioxane	Et_3SiH	rt	–	–	–
15	$NiCl_2$	**L3**	5	5	dioxane	Et_3SiH	rt	–	–	–
16	$Ni(cod)_2$	**L3**	5	5	dioxane	$(EtO)_3SiH$	rt	90	91.7:8.3	>99:1
17	$Ni(cod)_2$	**L3**	5	5	dioxane	$ZnEt_2$	rt	–	–	–
18	$Ni(cod)_2$	**L3**	5	5	THF	Et_3SiH	rt	60	93.8:6.2	>99:1
19	$Ni(cod)_2$	**L3**	5	5	toluene	Et_3SiH	rt	91	92.5:7.5	>99:1
20	$Ni(cod)_2$	**L3**	5	5	MeOH	Et_3SiH	rt	–	–	–
21[e]	$Ni(cod)_2$	**L3**	5	5	THF	Et_3SiH	0	36	94.3:5.7	>99:1
22[e]	$Ni(cod)_2$	**L3**	7.5	7.5	THF/dioxane (1:2)	Et_3SiH	-5	95	95.5:4.5	>99:1

Fig. 2 | Ligand effects and reaction optimization for Ni-catalyzed enantio- stereoselective reductive cyclization of aryl chained alkynone 1a. [a]The reactions were performed under nitrogen for 12h with **1a (**0.1 mmol), Ni precursor (X mol %), ligand (Y mol %), reductant (0.3 mmol), and solvent (0.5 mL); product **2a** was the only observed product. The *S* absolute configuration of **2a** was assigned on the basis of the absolute configuration of **2bh** determined by X-ray crystallography. [b]Isolated yields; [c]The enantioselectivities were determined by chiral HPLC on a Chiralcel OD-H column. [d]Isolated *E/Z* ratio confirmed by ^{1}H NMR analysis. [e]48 h.

Substrate scope. The substrate scope for the enantioselective synthesis of chroman with chiral tertiary allylic alcohol silyl ethers was then examined with ligand **L3** under the optimized reaction conditions (Fig 2, Entry 22). Firstly, different R^1 groups of aromatic and alkyl alkynes were investigated (Fig 3, **2b-2ao**, see details in SI). Aryl mono-substituents have good compatibility for the reaction with substrates of different electrical properties, different steric hindrance, and different substitution sites; the corresponding products were given in up to 97% yield, up to 96:4 er and up to 99:1 *E/Z*. However, several substrates gave lower enantioselectivity (**2h**, **2n**, **2y**, **2ai** and **2al**). Strong electron-withdrawing substituents -CN at different sites gave decreased yield and enantioselectivity (**2h**: 33%, 62:38 er; **2n**: 38%, 64:36 er), which might be caused by the coordination of -CN with the catalyst. The decreased enantioselectivity of the biphenyl alkynyl product is probably due to the far steric stretch and the large planar rigidness (**2y**: 81%, 78:22 er). The products of both disubstituted and trisubstituted aromatic alkynes have excellent enantioselectivities (**2aa**-2**ae**, 93:7-96:4 er). 2-Naphthyl-substituted alkyne was successfully cyclized to provide compound **2z** in 75% yield and 95:5 er. Heteroaromatic alkynes including thiophene, pyridine, benzofuran were also examined. Although the simple pyridine and quinolone substituted alkynes failed to obtain product **2ap** and **2ao**. Unexpectedly, *Orth*-F- substituted pyridine alkyne **1ai** could give cyclization product chiral chroman **2ai** in 44% yied with 74:26 er, which may be due to the strong electrical attraction of fluorine atom weakening the coordination ability of nitrogen atom. Benzofuran-substituted heteroaromatic alkyne **1ai** provided chroman **2ai** in 89% yield and 76:24 er, the reason is not clear. Various aliphatic alkynes were also efficiently converted into chiral chromans in excellent enantioselectivities (**2am-2ao**, 91:9-95:5 er). It was found that, most of the different alkyne products were achieved with excellent *E/Z* selectivity (*E/Z* > 99:1), some of them were obtained with both *E* and *Z* isomers. 1-naphthalene substituted alkyne **1aa,** 3-thiophene substituted alkyne **1ah** and 2-benzothiophene substituted alkyne **1aj** produced the corresponding chiral chroman **2aa, 2ah** and **2aj** as *E/Z* mixture, which could be isolated in good yield with good to excellent enantioselectivity [**2aa**: *E*/Z = 66:34, (*E*) 48%, 94:6 er, (*Z*) 25%, 92:8 er; **2ah**: *E*/Z = 82:18, (*E*) 42%, 93:7er, (*Z*) 9%, 94:6 er; **2ai**: *E/Z* = 87:13, (*E*) 52%, 90:10 er, (*Z*) 8%, 76:24 er]. It can be seen that the *Z*-configuration chroman products of 1-naphthyl and 3-thiophene have excellent enantioselectivity, while the 2-benzothiophene-substituted one has mediate enantioselectivity. This is the first time *Z*-configuration cyclized products were obtained in high enantioselectivities with these Nickel-catalyzed intramolecular coupling cyclization strategies.

To further evaluate the compatibility of this reaction, different ketone substrates were then investigated. Different phenyl, alkyl groups were examined under the same conditions as above mentioned with the best ligand **(*R*)-AntPhos**. Different R^2 groups of ketones afforded the corresponding chiral chromans bearing tertiary allylic alcohol silyl ether with high stereoselectivity and enantioselectivity in good to excellent yield (Fig 3, **2ar-2bl**, see details in SI). Aryl substituents have good compatibility for the reaction with substrates of different electrical properties, different steric hindrance, and different substitution sites; the corresponding products were given in up to 98% yield,

up to > 99:1 er and up to 99:1 *E*/*Z*. However, several substrates gave lower yield or lower enantioselectivity (**2ar**, **2aw, 2bb**, **2bf, 2bg** and **2bk**). *Ortho*-OMe substituted **1ar** gave product **2ar** in decreased yield and enantioselectivity (**2ar**: 37%, 86:14 er), *Para*-Me substituted **2aw** was obtained in 85% yield with 86:14 er, *Para*-CN substituted **2bb** was obtained in 18% yield with 84:16 er. The reason for these affects might be due to their steric hindrance with electrical properties. The cyclization product of *para*-Cl **2az** was obtained in highest yield (98%), extremely excellent enantioselectivity (>99:1 er) and *E*/*Z* (> 99:1). This asymmetric cyclization reaction is also compatible with aliphatic ketones. Three aliphatic ketones were also tested. Although bulky *t*-Bu group is not tolerable for this cyclization, no desired product **2bl** was obtained even at 100 °C (0% yield). Ethyl ketone alkyne **1bf** gave the product **2bf** in 94% yield with 82:18er, and 1-adamantyl ketone alkyne **1bg** led to chiral chroman **2bg** in 26% yield with 95:5 er at 100 °C. The heterocyclic substituents 2-benzofuran and 2-thiophene were also efficiently converted to chiral chromans with excellent enantioselectivity (**2bh**: 42%, 97:3 er; **2bi**: 93%, 94:6 er). It was noted that the *meta*-F substituted product appeared *E*/*Z* selectivity as 88:12, which could be isolated in good yield with good to excellent enantioselectivity [**2au**: *E*/*Z* = 88:12, (*E*) 78%, 96:4 er, (*Z*) 11%, 62:38 er]. Fortunately, the di-substituted 3,4-dimethoxy-substituted aromatic ketone gave the cyclized product **2bj** in 75% yield with 95:5 er, whose single crystal was prepared by crystallization with solvent heptane/EtOAc (4:1), and its absolute configuration was confirmed unambiguously by X-ray analysis. And the formed chiral center was assigned as ***S*** (see details in SI)[59].

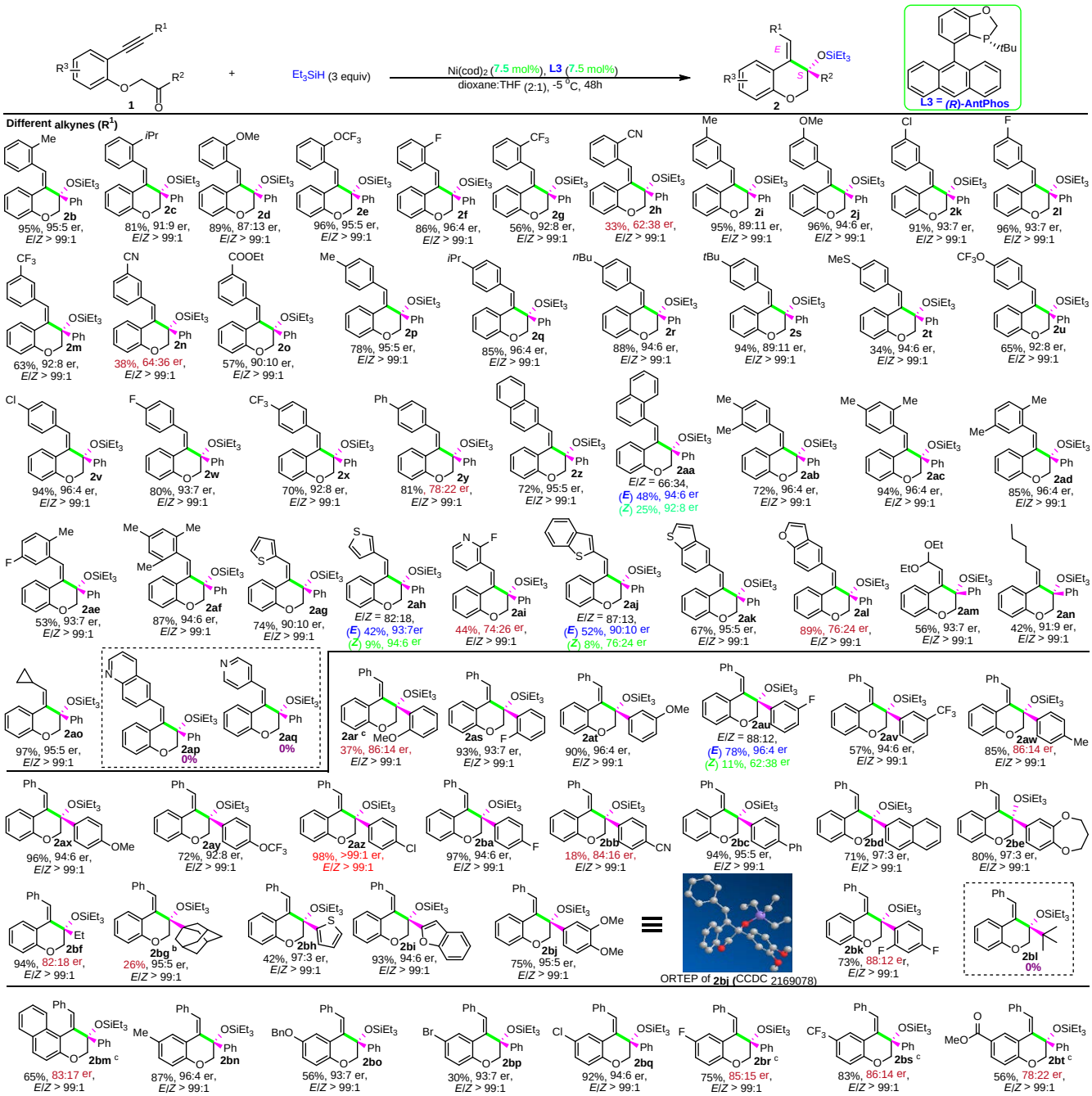


Fig. 3 | Substrate scope for Ni-catalyzed enantio- stereoselective reductive cyclization of aryl chained alkynones. [a.] The reactions were performed under nitrogen in dioxane/THF(2:1) (0.5 mL) at -5 °C.for 48 h with **1** (0.1 mmol) in the presence of Ni(cod)$_2$ (5 mol %), **L3** (5 mol %), and triethylsilane (0.3 mmol); [b.] T = 100 °C, toluene (0.5ml), er measured by removal of triethylsilyl; [c.] T = 60 °C, dioxane (0.5ml). The absolute configuration of **2b-2bq** was assigned on the basis of the absolute configuration of **2bj** determined by X-ray crystallography.

The substrate scope of the chained maternal aryl substituent R^3 was also investigated. The naphthyl-linked alkynone **1bm** has poor

reactivity at low temperature; we then adjusted the reaction temperature to 60 °C to obtain a cyclized product chiral chroman **2bm** with a yield of 65% and an enantioselectivity of 83:17 er. The methyl-and benzyloxy-substituted substrates gave the corresponding cyclized product **2bn** and **2bo** in good yields and enantioselectivities (**2bn**: 87%, 96:4 er; **2bo**: 56%, 93: 7 er). The halogen -substituted substrates could also be converted into the corresponding chiral chromans (**2bp**: 30%, 93:7 er; **2bq**: 92%, 94:6 er**; 2br**: 75%, 85:15 er), and the decrease in the yield of **2bp** might be due to the coordination of the nickel complex with bromide, the decreased enantioselectivity of the electron-withdrawing group product **2br** probably because of higher reaction temperature (60 °C) leading to unfavored enantio-control, which is the same as **2bm**, **2bs** and **2bt** (**2bs**: 83%, 86:14 er; **2bt**: 56%, 78:22 er). These four examples all could not be carried out under low temperature at 0 °C, the reason for the lower activity and enantioselectivity might for their electron withdrawing properties of naphthyl-, CF_3O- and ester groups. In general, the nickel-catalyzed synthetic chiral chroman reaction we developed is well tolerated for various aryl, heterocyclic, and aliphatic substituents.

Totally, 72 aryl chained alkynones were designed and synthesized, 69 examples were successfully applied for this Ni-catalyzed enantio-stereoselective reductive cyclization for the construction of functionalized chromans with chiral quaternary tertiary allylic alcohol silyl ethers. The substrate scope was broad and versatile. Most of the examples gave the chiral chromans in high yield (up to 98%), excellent enantioselectivities (up to >99:1 er) and perfect stereoselectivities (up to >99 *E*/*Z*). Some of the examples observed both *E*/*Z* isomers with good yield and high enantioselectivity. Some challenged alkynones could be proceeded to obtain the desired products under higher temperature with high yields and good enantioselectivities. Based on this comprehensive and in-depth research study, we are confident to working on the further explorations on organo-medicinal chemistry and chemical biology.

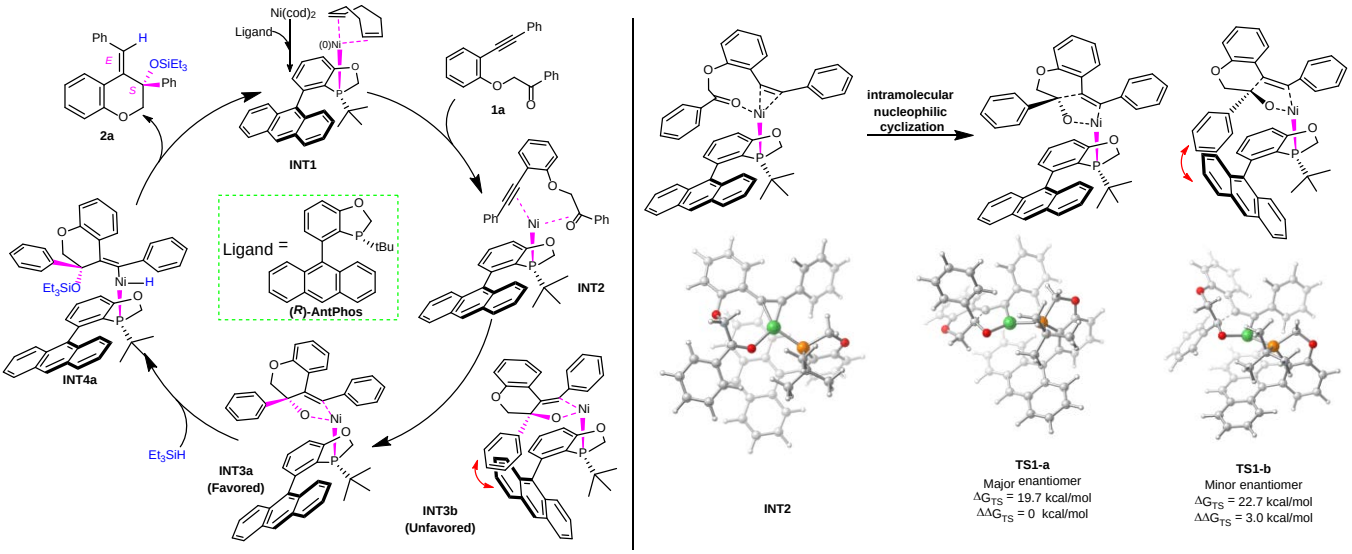


Fig. 4 | a. Proposed mechanistic pathway involving dimeric metallacyclic model of enantio- stereoselective reductive cyclization of aryl chained alkynones with Nickel^0 and (*R*)-AntPhos. b. Comparison of transition states for the formation of two enantiomers with ligand (*R*)-AntPhos.

Mechanistic and computational studies. Based on these results and our previous mechanistic studies on nickel-catalyzed intermolecular or intramolecular reductive cyclization of alkynones, we proposed the catalytic cycle of this intramolecular asymmetric reductive cyclization of **1a** as dimeric metallacyclic model, which was depicted in Fig 4a**.** Firstly, Nickel precursor $Ni(cod)_2$ coordinated with chiral monophosphorus ligand **(*R*)-AntPhos** to form Ni(0) metal complex **INT1**, and losing one cyclooctadiene. Then addition of **1a** generated the cyclization process through Ni(II) metallacycle **INT2**, which was further transformed to dimer Ni(II) metallacycle **INT3**. At this stage, the detailed stereochemical model of Ni(II) metallacycle **INT3**, presented two possible formation with opposite enantiomeric selectivity at tertiary C-O bond position. The enantioselectivity and stereoselectivity is apparently determined at this cycloaddition stage. Conformational analysis of metallacycle **INT3** with **(*R*)-AntPhos** indicates that the conformer **INT3b** is unflavored as its big steric hindrance between the phenyl group of the bicycle ring and the anthracene moiety of **(*R*)-AntPhos**, forming the stable conformer **INT3a**, which is favored, and further generate Ni(II) hydride species **INT4a** by coordination and σ-bond metathesis with reductant Et_3SiH. Final reductive elimination of **INT4a** provided the desired product **2a** and regenerated the Ni(0) catalyst **INT1**, which started new catalytic cycle afterwards. The cyclized product **2a** was then confirmed as ***S*** configuration, which is consistent with the absolute configuration of the product **2bj** determined by X-ray crystallography.

Computational studies[60] were carried out to gain more mechanistic insights into the Nickel catalyzed asymmetric intramolecular reductive cyclization of aryl chained alkynone **1a**. A ligand exchange step of $Ni(cod)_2$ with **(*R*)-AntPhos** is very facile to occur and generate the intermediate **INT1** with a free energy barrier of only 0.6 kcal/mol. Subsequent coordination rapidly generates a Ni(II) coordinated intermediate **INT2**, which can easily be transformed into complex **INT2-a** and its isomer **INT2-b**. The calculated results suggest that nucleophilic cycloaddition is not only rate-determining step but also the enantioselectivity-determining step. The relative free energy of **INT2-b** is 3.5 kcal/mol higher than that of **INT2-a**. Nucleophilic cycloaddition of the β-carbon atom of alkynyl group to the carbonyl carbon atom *via* transition state **TS1-a** gave intermediate **INT3-a**. As shown in Fig 4b, the calculated activation free energy of the first nucleophilic cycloaddition step is 19.7 kcal/mol. In another possible case, intramolecular cycloaddition via transition state **TS1-b** gives intermediate **INT3-b** with an activation free energy of 22.7 kcal/mol. The relative free energy of **TS1-b** is 3.0 kcal/mol higher than that of **TS1-a** because of the steric effect between the ligand and the substrate in **TS1-b**. The computational results reveal high diastereoselectivity, which agrees with the experimental observation. In order to provide evidence for the hypothesis that a distortion of the substrate occurs in the minor transition state due to unfavorable interactions with the anthryl group of the phosphine ligand, **(*S*)-BIDIME** (**L2**) was used in place of **(*R*)-AntPhos** (**L3**). The calculated difference of the free energy of activation values for **TS1-a'** and **TS1-b'** is only 0.9 kcal/mol [61], which suggests that poor enantioselectivity would be experimentally observed, largely because of the absence of strain repulsion between the phenyl ring of the benzoyl group and the anthancene group of the phosphine ligand.

After identifying the dominant path, the subsequent transformations are very facile to occur (Fig 5). Et_3SiH is ready to undergo insertion into the Ni-O bond to give a complex **INT4-a** through **TS2-a**, in which the Si···H distance is lengthened to 1.70 Å while Ni···H and Si···O distances are stabilized to 1.70 Å and 1.96 Å. The calculated $\Delta G^{\neq}$ for this step is 15.3 kcal/mol relative to **INT3-a** and Et_3SiH. Subsequently, the resulted Ni(II) metallacycles were then undergo an intramolecular ligand exchange step to form a Ni(II)-H species (**INT5-a**) with a free energy barrier of only 6.1 kcal/mol, suggesting the formation of the Ni(II)-H species is facile to occur after the formation of **INT4-a**. Finally, the catalytic cycle is completed by the reductive elimination of the yielded Ni(II)-H species to generate the product **2a** *via* a transition state **TS3-a** with a free energy barrier of only 10.1 kcal/mol relative to **INT4-a** and regenerate the Ni(0) catalyst. In another possible case, the **INT3-b** goes through similar processes of Si-H insertion, intramolecular ligand exchange and reductive elimination to give the isomer product **2a′**. Eventhrough, the transition state **TS3-b** showes a slight advantage in the reductive elimination, it doesn't change the enantioselectivity of the reaction.

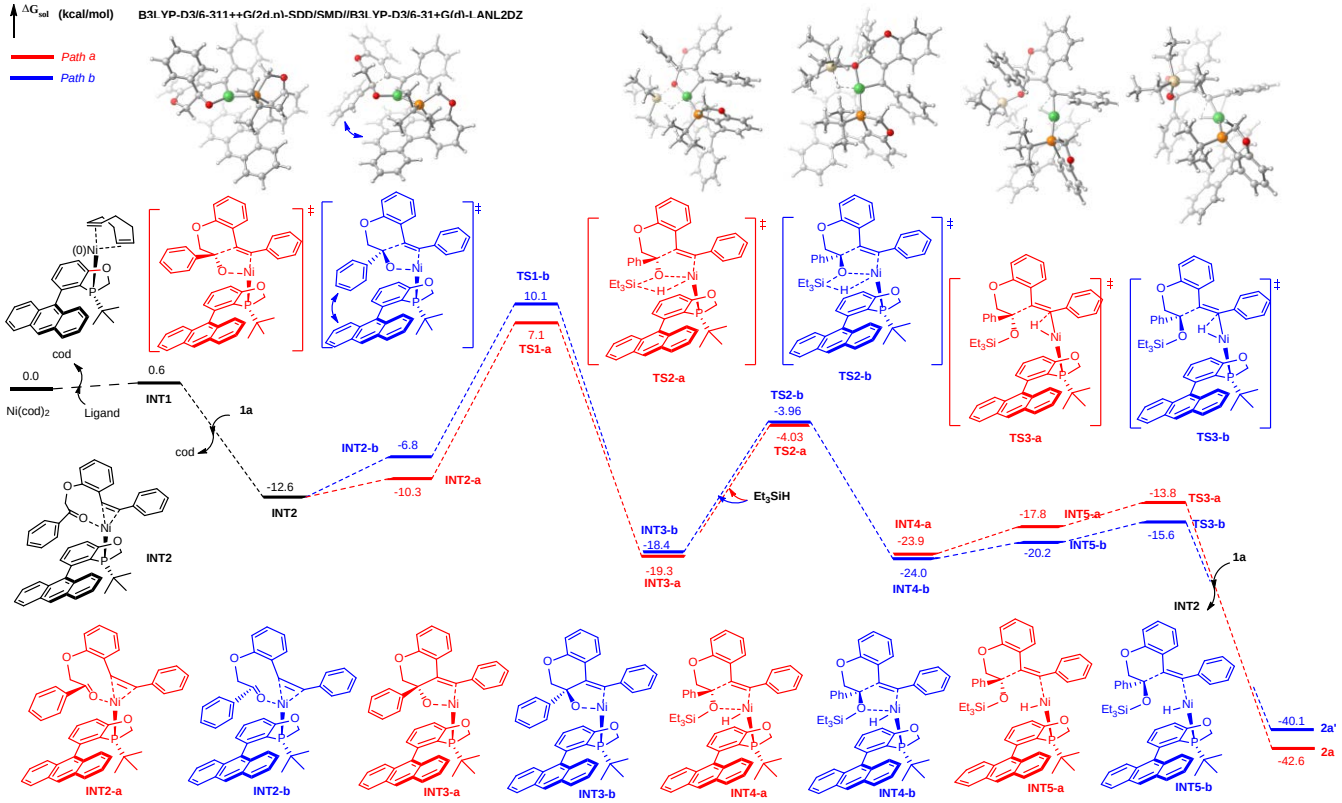


Fig. 5 | Computational study. DFT calculations with energy profiles for mechanistic pathway of asymmetric stereoselective Ni-catalyzed reductive cyclization of 1a, Bond lengths are shown in Å.

Synthetic applications. Based on the above-mentioned studies on the anticancer activity of 3-hydroxychroman derivatives, we are interested in exploring the practicability and applications of the developed nickel-catalyzed method for the synthesis of bioactive chromans with chiral tertiary alcohols. We designed and synthesized multifunctional grouped chromanol-based compounds, which were expected to have good anticancer activity. Their anticancer activity will be studied and reported in the follow-up work.

With the successful development of this efficient nickel catalyst, we are firstly curious for its practicability of this reductive cyclization process. Gram scale reaction was carried out starting from aryl chained alkynone **1bj**. As shown in Fig. 6a, under optimized reaction conditions, a gram-scale reductive cyclization of **1bj** (2.00 g) was run in THF/dioxane (1:2, 2 mL) at -5 ^{o}C for 48 h with Schlenk tube, in the presence of 5.0 mol% Ni(cod)$_2$ and 5.0 mol% **(*R*)-AntPhos** using Et_3SiH as the reductant. Product **2bj** was obtained (2.05 g) in 78% yield, 95:5 er and >99:1 *E/Z*. No loss of its reactivity, enantioselectivity and stereoselectivity were found, which proved that this Ni-catalyzed asymmetric stereoselective reductive cyclization of aryl chained alkynones is practical and efficient. Further desiliconization of **2bj** under TBAF gave the 3-hydroxychroman **T18** with chiral quaternary tertiary allylic alcohol in 98% yield. The enantioselectivity and stereoselectivity of **T18** was the same as **2bj** (95:5 er, >99:1 *E/Z*). This is very important for the further application of this methodology in medicinal chemistry.

Polymethoxy-substituted aryl compounds, such as lignans extracted from Schisandra nuts and flavonoids extracted from citrus have received extensive attention due to their excellent biological activity[61-64]. To this end, we envisioned whether it would be possible to synthesize polymethoxy-substituted chroman with better biological activity. Firstly, 2-iodophenol **3a** reacted with 2-bromo-1-(3,4-dimethoxyphenyl)ethan-1-one **3b** under alkaline conditions to obtain dimethoxy ketone **3c**. 5-bromo-1,2,3-trimethoxybenzene **3d** reacted with ethynyltrimethylsilane to achieve **3e** by sonogashira reaction, and then removal of TMS to give **3f** in two steps. **3c** coupled with **3g** by sonogashira reaction to give aryl polymethoxy-substituted alkynone **3g**, which was cyclized to polymethoxy-substituted aryl chiral chroman **3h** in 94% yield, 95:5 er and >99:1 *E/Z* through our developed asymmetric Nickel-catalyzed cyclization. Largely hindered alkynone substrate **3g** is also suitable for this nickel-catalyzed cyclization method, illustrating the utility of our developed method (Fig 6b).

Amino acids are an important part of life, the structural unit of polypeptide drugs, and an important direction of life and medical research[65-68]. We proceeded from 3-monoiodo-*L*-tyrosine as starting material to protect the amino group and carboxyl group to obtain **3i** in two steps, and then **3i** was subjected to the same two-steps procedures as the synthetic route of standard substrate to obtain the alkynone **3k**. Compound **3k** was run the nickel-catalyzed reductive coupling to give chiral chromans with chiral tertiary alcohol silyl ether chroman **3l** in 86% yield, 92:8 er and >99:1 *E/Z* (Fig 6c). It was showed that the nickel catalyzed cyclization method is tolerant to amino acid substrates,

which provides more possibilities for the synthesis of multifunctional chroman with tertiary alcohol, and also facilitates the development of potential bioactive molecules based on this skeleton.

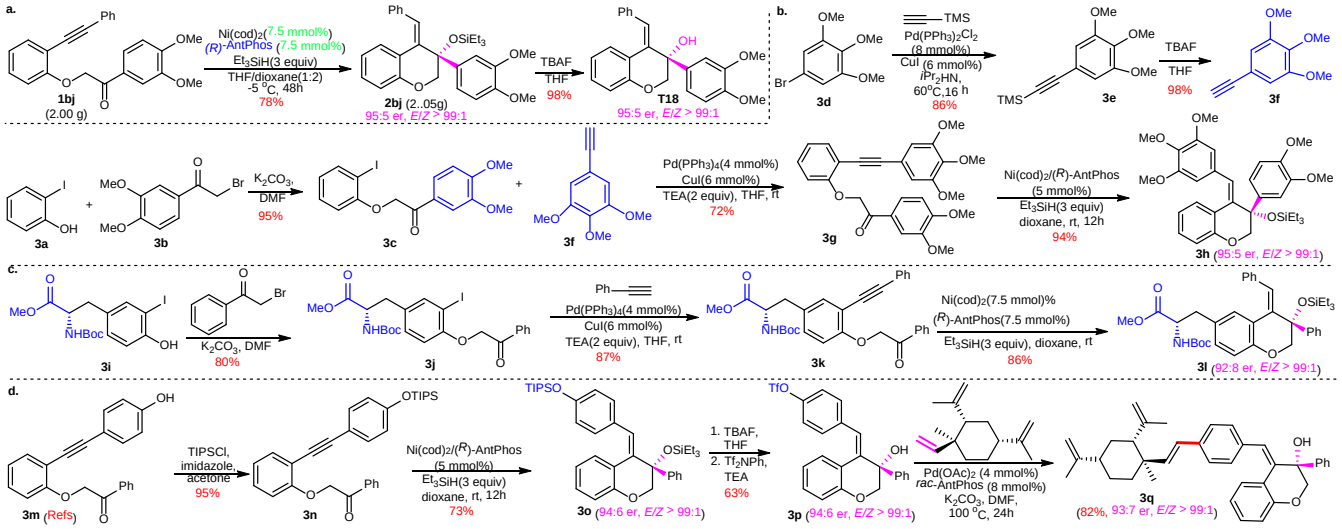
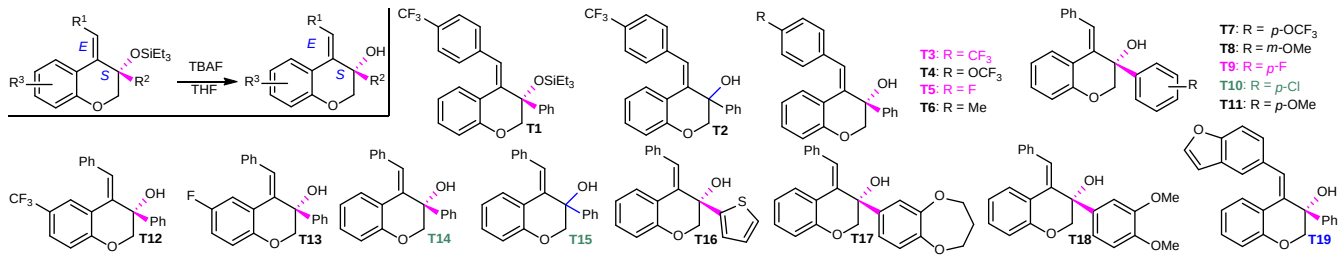
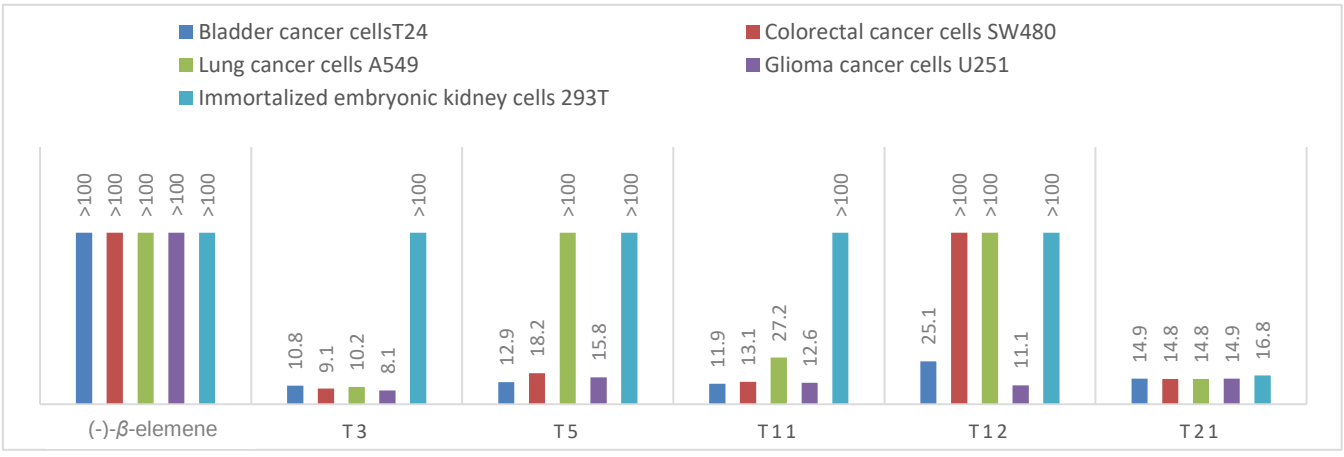


Fig. 6 | Gram-scale reaction and synthesis of multifunctionalized chiral chromans.

(-)-*β*-elemene[69-72] is an active anticancer ingredient extracted from the ginger plant turmeric. It has been clinically used in various malignant tumors to enhance the curative effect and reduce the toxic and side effects of radiotherapy and chemotherapy. We envisioned whether two fragments of elemene and chroman could be linked together and expected to exhibit unique and better anticancer activities. The phenolic hydroxyl group of **3m** (synthesized by reference route) was firstly protected by TIPS to give **3n**. Then **3n** was ring-closed under the standard nickel asymmetric catalytic process to achieve **3o** in 73% yield, 94:6 er and >99:1 *E*/*Z*. TBAF was used to remove -TIPS and -$SiEt_3$ protecting groups in one step to generate dihydroxy intermediate. Since the acidity of phenolic hydroxyl group is stronger than that of aliphatic alcohol, this dihydroxy intermediate could selectively react with Tf_2NPh under alkaline conditions to form compound **3p** in 63% yield. Finally, compound **3p** is coupled with (-)-*β*-elemene through Heck reaction to obtain the final elemene and chroman-linked product **3q** in 82% yield, 93:7 er and >99:1 *E*/*Z* (Fig 6d). Subsequential work will conduct biological activity tests on these three 3-hydroxychroman-based compounds to expect better biological activities, and the test results will be reported in follow-up work.





Samples[a]	Bladder cancer cells T24	Colorectal cancer cells SW480	Lung cancer cells A549	Glioma cancer cells U251	Immortalized embryonic kidney cells 293T
T1	>100	>100	>100	>100	>100
T2	>100	>100	>100	>100	>100
T3	10.8	9.1	10.2	8.1	>100
T4	20	29.5	>100	19.1	>100
T5	12.9	18.2	>100	15.8	>100

T6	>100	>100	>100	21.7	>100
T7	>100	>100	>100	17.2	>100
T8	>100	>100	>100	>100	>100
T9	11.9	13.1	27.2	12.6	>100
T10	25.1	>100	>100	11.1	>100
T11	>100	>100	>100	>100	>100
T12	28.1	>100	>100	18.6	>100
T13	>100	>100	>100	>100	>100
T14	28.2	>100	>100	17.3	>100
T15	24.8	>100	>100	16.3	>100
T16	>100	>100	>100	>100	>100
T17	>100	>100	>100	>100	>100
T18	>100	>100	>100	>100	>100
T19	14.9	14.8	14.8	14.9	16.8
(-)-*β*-elemene	>100	>100	>100	>100	>100

Fig. 7 | Antitumor activity of chromans with chiral tertiary alcohols. [a]The numbers in the table represent IC50/uM

Antitumor studyies. Chroman fragments with chiral alcohols are the backbone of some natural products and drugs with important anticancer activities. From chromans with chiral tertiary alcohols silyl ethers developed by our nickel-catalyzed asymmetric coupling methodology, chiral 3-hydroxychromans could be easily accessed by desilanization, which are highly likely to have anticancer activity. Bladder cancer cells T24, colorectal cancer cells SW480, lung cancer cells A549 and brain glioma cancer cells U251 were selected as the anticancer activity research objects, and immortalized embryonic kidney cells 293T normal cells was chose as the reference. As shown in the Fig 7, 19 samples were synthesized and tested. To our surprise the results showed that multiple compounds had better anti-cancer activity than (-)-*β*-elemene, which was consistent with our original assumptions and proved the practicality of our developed method. Comparing the anticancer activities of the three compounds **T1**, **T2** and **T3**, it can be seen that the chiral triethylsilyl ether compound **T1** and its racemic alcohol **T2** have no anticancer activity, while the IC50 of their chiral alcohol **(*R*)-T3** on the four cancer cells is 10.8 μM, 9.1 μM, 10.2 μM and 8.1 μM respectively, indicating that chiral **(*R*)-T3** with *p*-CF_3 has good antitumor activities, while the IC50 of normal immortalized embryonic kidney cells 293T is above 100 μM. Chiral **T5** showed inhibitory ability against T24 (IC50 = 12.9 μM), SW480 (IC50 = 18.2 μM) and U251 tumor cells (IC50 = 15.8 μM). Chiral **T9** showed inhibitory activity to four tumor cells as 11.9 μM (IC50), 13.1 μM (IC50), 27.2 μM (IC50) and 12.6 μM (IC50) respectively. Chiral **T10**, **T14** and racemic **T15** have similar anticancer activities as they all not active to SW480 and A549, but have antitumor activities to T24 (IC50 = 25-30 μM) and U251 (IC50 = 10-20 μM). Especially Chiral **T10** has good anticancer activity only against U251 (IC50 = 11.1 μM), but has no toxicity to normal cell 293T (IC50 > 100 μM), showing specificity of anticancer activity to Glioma tumor. All these six leading compounds showed no toxicity to normal cells. Chiral **T19** has anticancer activity against all four cancer cells, the IC50 of the four cancer cells is around 14 μM, but the IC50 of normal cell 293T is also around 16 μM. Overall, the compounds with good anticancer activity mostly contain fluorine (-F, CF_3) group at *p*-position of benzyl ring, which is one spot worth paying attention to. In general, the asymmetric synthesis of chroman compounds with chiral tertiary allylic alcohols was developed by us. These new 3-hydroxychromans with chiral quaternary stereocenters are a class of leading compounds with good anticancer activities. Further medicinal chemistry studies of all the obtained chroman compounds are investigated on the way, and will be published soon in the following work.

Conclusions

Asymmetric synthesis of chiral chromans with tertiary allylic alcohols is a long-standing problem in the area of asymmetric catalysis, and this challenge has not been accomplished in the past decades. Herein we firstly reported the practical asymmetric stereoselective intramolecular reduction cyclization of aryl chained alkynones to synthesize a series of chroman derivatives with chiral tertiary allylic alcohol silyl ether in high yield (up to 98%), excellent enantioselectivity (up to > 99:1 er) and stereoselectivity (up to > 99:1 *E*/*Z*) catalyzed by $Ni(cod)_2$ and **(*R*)-AntPhos**. This method was proved to be a practical process for concise synthesis of chromans with chiral tertiary allylic alcohols, and totally 69 examples were successfully established with this method. Detailed mechanism studies were carried on by DFT calculations of computational science. In the rational stereo-chemical catalytic cycle, the cycloaddition stage dimer Ni(**II**) metallacycle **INT3** is the enantioselectivity-determining step, while the ligand **(*R*)-AntPhos** played an important role by a large π-conjugated system and steric interactions and is the only efficient ligand for this asymmetric transformation. We designed and synthesized several polymethoxy substituted, amino acid substituted and (-)-*β*-elemene linked 3-hydroxychroman derivatives for further anticancer studies. It was found that the easily desilylation of obtained products could give 3-hydroxychroman derivatives with tertiary alcohols, which have good anticancer activity and no toxicity to normal cells. Molecules with different configurations have great differences in anticancer activity and some molecules show specificity to different cancer cells. 3-Hydroxychroman derivatives with quaternary stereocenters are a class of anticancer leading compounds with important research significance. The more in-depth anticancer activity of these compounds is under study and will be reported in detail in the future. Further exploration on more efficient nickel catalyst, its detailed mechanistic study, and development of various efficient nickel-catalyzed asymmetric reactions are under investigation in our laboratory.

Methods

Procedure for Asymmetric Nickel-Catalyzed Intramolecular Reductive cyclization of Alkynone: $Ni(cod)_2$ (0.075 mmol, 7.5 mol %), **(*R*)-AntPhos** (**L3**, 0.075 mmol, 7.5 mol %), and THF/dioxane (1:2) (0.5 mL) were added to a 4 mL screw-cap vial equipped with a magnetic stirring bar in the glove box. Substrate **1** (0.1 mmol, 1.00 equiv.) was added to the solution in one portion, followed by the addition of triethylsilane (Et_3SiH, 0.1 mL, 0.3 mmol, 3.00 equiv.). The vial was closed with a screw-cap, and the resulting mixture was stirred at -5 ^oC for 24 h. Quenched with saturated sodium bicarbonate ($NaHCO_3$), extracted with ethyl acetate (EtOAc), washed with saturated NaCl, dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by column chromatography (1% petroleum ether/EtOAc) to afford compound **2**.

Data availability

The authors declare that all other data supporting the findings of this study are available within the article and Supplementary Information files, and also are available from the corresponding author upon reasonable request. The X-ray crystallographic coordinates for structures that support the findings of this study have been deposited at the Cambridge Crystal-lographic Data Centre (CCDC) with the accession code CCDC2169078 (**2bj**) These data can be obtained free of charge via

www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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Acknowledgements

We are grateful to the financial support provided by National Natural Science Foundation of China (22061032), Natural Science Foundation of Inner Mongolia (2020MS02022), Science and Technology Program of Inner Mongolia (2020GG0134), Opening-fund from State Key Laboratory of Bio-organic and Natural Products Chemistry of SIOC (21300-5206002), "JUN-MA" High-level Talents Program of Inner Mongolia University (21300-5185121), "Grassland Talents" Program of Inner Mongolia (12000-12102414) and High-level Recruit Program of Inner Mongolia (12000-13000603). Key Project at Central Government Level: the ability establishment of sustainable use for valuable Chinese medicine resources (2060302) is sincerely acknowledged. We gratefully thank Dr. He Meng (Inner Mongolia University) for NMR and HRMS assistance, Prof. Ning Zhu and Dr. Yuanyuan Gao (Inner Mongolia Technology University) for X-ray crystallographic assistance

Author contributions

G. L. conceived, designed, directed the project and wrote the manuscript with input from all other authors. Under the guidance of G. L., T. Z. and R. L. developed the methods and performed the synthetic experiments with the help of Y. C. and L. Z. In addition, S. Z. performed the DFT calculations on mechanism under the guidance of G. L. and helped to revise this manuscript. J. Y. gave many helpful discussions for anti-tumor experiments. All the authors participated in the discussion and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41929-023-XXXX-x.
Correspondence and requests for materials should be addressed to Guodu Liu. **Peer review information** *Nature Catalysis* thanks xxx and the other anonymous reviewer(s) for their contribution to the review of this work.
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