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Ni-catalysed assembly of axially chiral alkenes from alkynyl tetracoordinate borons via 1,3-metallate shift

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Asymmetric synthesis based on a metallate shift of tetracoordinate borons is an intriguing and challenging topic. Despite the construction of central chirality from tetracoordinate boron species via a 1,2-metallate shift, catalytic asymmetric synthesis of axially chiral compounds from such boron 'ate' complexes is an ongoing challenge. Axially chiral alkenes have received great attention due to their unique characteristics and intriguing molecular scaffolds. Here we report an enantioselective nickel-catalysed strategy for the construction of axially chiral alkenes via a 1,3-metallate shift of alkynyl tetracoordinate boron species. The chemoselectivity, regioselectivity and atroposelectivity can be regulated and well-controlled from readily accessible starting materials with a cheap transition-metal catalyst. Downstream transformations indicate the powerful conversion ability of such compounds in this protocol, and late-stage elaborations of bioactive compounds can also be achieved. Mechanistic experiments reveal that regioselective *syn*-addition of an aryl–Ni complex with a carbon–carbon triple bond and subsequent 1,3-phenyl migration are the two key steps for the synthesis of axially chiral alkenes.

Tetracoordinate boron species, as the key intermediates in organoboron chemistry, have gained substantial attention in modern synthetic chemistry[1–8]. Migration reactions and transmetallation are two important reaction modes of tetracoordinate borons that have been extensively studied[9–12]. Among all of the transformations based on such compounds, asymmetric synthesis is particularly appealing and attractive, because chiral compounds exist widely in natural products and biologically relevant compounds, chiral ligands and catalysts[13–18]. However, enantioselective transformations based on tetracoordinate borons are relatively rare and elusive[19–23]. There are typically three types of protocol for the synthesis of enantioenriched compounds via a metallate shift based on tetracoordinate borons. In the first, a chiral carbon centre adjacent to the boron atom of tetracoordinate boron either undergoes a stereoinvertive migration on the carbon centre bearing a leaving group or a stereoretentive shift on the migrating carbon centre, thus giving a stereospecific rearrangement leading to enantioenriched compounds (Fig. 1a, type I)[22,24–30]. As a representative example, Aggarwal's group have developed a series of elegant 1,2-metallate shift reactions based on tetracoordinate boron species originating from chiral lithium carbenoid reagents and organoborons, affording chiral borylated compounds bearing a carbon stereocentre via in situ stereospecific rearrangement[22,25–28]. In the second type, alkenyl tetracoordinate boron is activated by a chiral metal complex to enable an enantioselective 1,2-metallate shift to render chiral molecules (Fig. 1a, type II)[31–37]. Morken and colleagues, for example, reported an enantioselective transition-metal-catalysed 1,2-metallate rearrangement of alkenylboronates to provide myriad chiral organoborons[31]. In the third protocol, a chiral auxiliary-controlled stereoselective 1,2-metallate shift leads to chiral products (Fig. 1a, type III)[19,20,38–41]. The well-known enantioselective Matteson homologation reaction belongs to this type.

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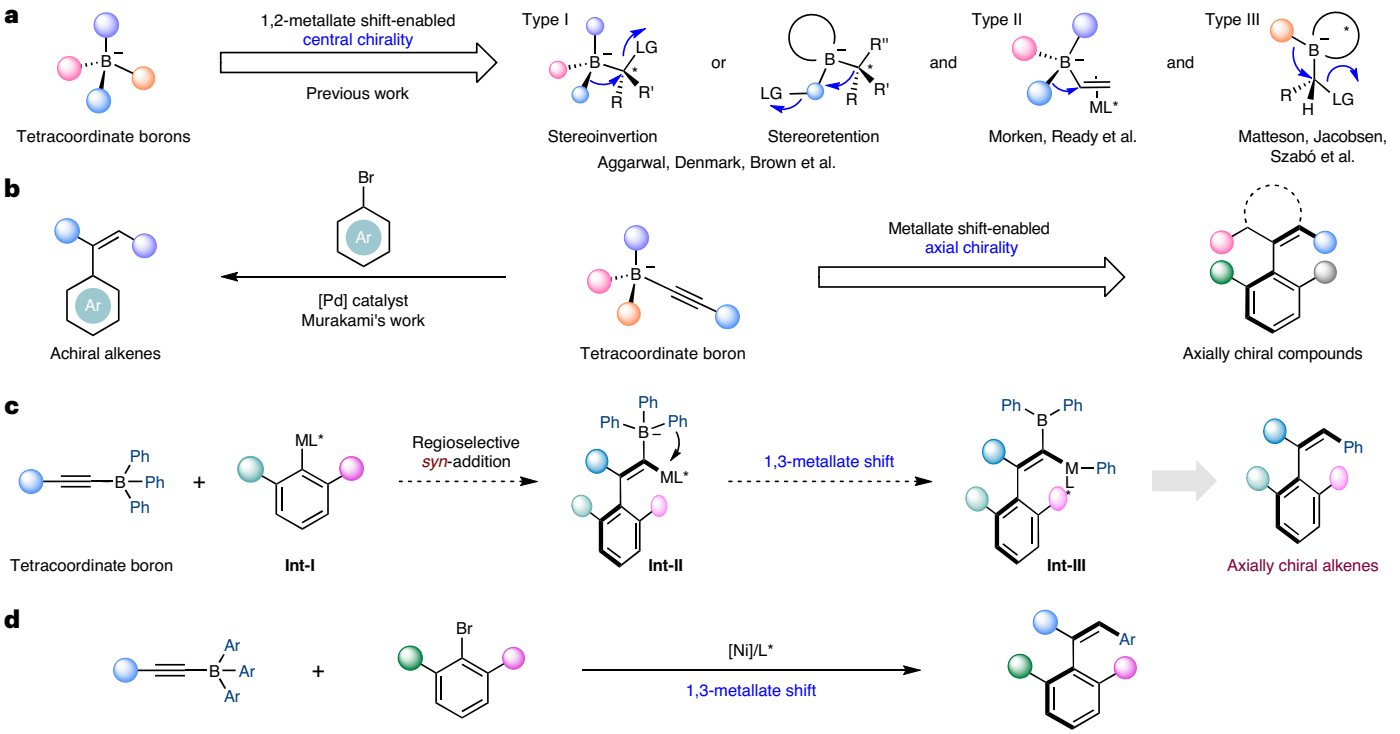

Fig. 1 | Background, hypothesis and our strategy. a, Asymmetric synthesis based on tetracoordinate borons affords chiral compounds via a metallate shift. **b**, Pd-catalysed reactions of tetracoordinate borons with aryl halides and our design. **c**, Proposed mechanism for our design. M, metal catalyst; L, chiral ligand. **d**, Atroposelective construction of axially chiral alkenes from alkynyl tetracoordinate borons via 1,3-metallate shift (this work).

In 2021, Jacobsen and colleagues disclosed a catalytic enantioselective 1,2-metallate shift of tetracoordinate borons using an in situ-generated chiral auxiliary, delivering a range of chiral α-Cl borons[38]. Of note, all of the aforementioned transformations are limited to construction of the carbon central chirality via a 1,2-metallate shift.

The well-known axial chirality structure is widely present in nature and our everyday lives[42–46]. However, the metallate shift-enabled assembly of axial chirality based on tetracoordinate boron species has not yet been reported. As atropisomers, axially chiral alkenes, which bear a chiral axis between a substituted alkene and an aryl ring, have received great attention in recent years due to their unique characteristics and intriguing molecular scaffolds. Not only can they be employed as synthons for total synthesis[47,48], but they can also be applied to asymmetric synthesis as chiral catalysts or ligands[49–52]. However, their efficient synthesis remains in its infancy, with the challenge lying in the low rotational barrier and the flexible framework of such compounds[42,46,53]. There was no progress in the assembly of this class of chiral compounds until 2017, when Tan and colleagues reported an organocatalytic asymmetric Michael addition reaction to alkynals, providing a pioneering example of the catalytic atroposelective synthesis of axially chiral acyclic alkenes[54]. Since then, several tactics have been successively developed into fundamental tools for accessing such chiral compounds[46,55–57], but, to the best of our knowledge, current known synthetic strategies for the construction of axially chiral alkenes either depend on special substrate design (organocatalytic protocols) or need expensive transition-metal catalysis (transition metal-promoted methods). There has been no report of the construction of atropisomeric alkenes by a migration process, especially from readily accessible starting materials with abundant and inexpensive transition-metal catalysis. Murakami and colleagues developed a Pd-catalysed functionalization of alkynyl tetracoordinate borons with aryl halides, affording trisubstituted alkenes (Fig. 1b, left)[58], but this transformation requires an expensive catalyst and features achiral products.

As part of our ongoing interest in the development of migration reactions on tetracoordinate boron species[5,9,59–64], we wondered whether axially chiral alkenes could be constructed from tetracoordinate borons via metallate migration reactions (Fig. 1b, right), in what is a highly desirable and appealing process. Inspired by previous works[9,58], we speculated that alkynyl tetracoordinate boron species would be the most suitable substrates to afford this class of atropisomers, in which regioselective *syn*-addition of an aryl–metal complex (**Int-I**) to the C–C triple bond of alkynyl tetracoordinate boron would deliver the reaction intermediate **Int-II** specifically and enantioselectively under an appropriate chiral environment. The subsequent 1,3-metallate shift of **Int-II** could generate the key intermediate **Int-III**, which would eventually render the axially chiral alkenes after reductive elimination (Fig. 1c). However, there are several inherent and difficult challenges to overcome (Fig. 1c): (1) how to avoid C–B bond cleavage of the tetracoordinate borons in the presence of the metal catalyst (chemoselectivity); (2) how to promote a specific model of addition (*syn*-addition versus *anti*-addition, as well as the position of the metal on the alkenes) with the aryl metal species (regioselectivity); (3) how to generate axially chiral alkenes with good enantioselectivity (stereoselectivity). If successful, this strategy would offer an approach for the rapid construction of axially chiral alkenes from bench stable solids—alkynyl tetracoordinate borons—and achieve metallate shift to access axially chiral molecules.

In this Article we establish an enantioselective Ni-catalysed construction of axially chiral alkenes from readily available alkynyl tetracoordinate borons and sterically hindered aryl bromides, in which *syn*-addition of the aryl–Ni complex and a 1,3-metallate shift are the key steps (Fig. 1d). This approach provides a powerful and straightforward synthetic route towards substituted axially chiral acyclic alkene derivatives from a readily accessible raw material—alkynyl tetracoordinate boron. In sharp contrast to the previous central chirality assembly, this is an example of accessing axial chirality via a metallate shift of tetracoordinate borons, and, unlike previous 1,2-metallate shift studies,

this strategy undergoes an unusual 1,3-metallate shift. This reaction features excellent regioselectivity, exclusive *Z*/*E*-selectivity and good atroposelectivity. Inexpensive transition-metal catalysis, valuable chiral products and versatile synthetic transformations on the target products add further value to our strategy.

Results and discussion

Optimization of the reaction conditions

To validate our hypothesis, we chose alkynyl tetracoordinate boron hept-1-yn-1-yltriphenylborate (**1**) and methyl 2-bromo-3-methylbenzoate (**2**) as model substrates to investigate the transformation (Table 1). Initially, various metal catalysts (Fe, Co, Ni, Cu and Pd) and several common racemic ligands were examined (Table 1; details are provided in Supplementary Tables 1–3). Theoretically, a reaction intermediate may be produced in the presence of a suitable aryl–metal species via regioselective *syn*-addition with alkynyl tetracoordinate boron, and suppress cleavage of the C–B bond. To our delight, nickel and palladium catalysts can accomplish this transformation to afford the desired racemic product **3′** in moderate yields (Table 1 and Supplementary Tables 2 and 3). The palladium catalysts presented better reactivity than their counterpart nickel catalysts for this transformation. We therefore decided to use a palladium catalyst to evaluate the enantioselective reaction conditions for the assembly of chiral product **3** with versatile privileged chiral ligands (Table 1, entries 1–7 and Supplementary Tables 4 and 5). Chiral BOX ligands (**L1** and **L2**) could generate the target chiral product **3** with 25% and 17% yields and 54.2:46.8 and 51.0:49.0 e.r., and chiral thiourea (**L3**) led to the desired product **3** in 26% yield with 53.5:46.5 e.r. When (*S*)-BINOL (**L4**), (*S*)-BINAM (**L5**) and (*S*)-NOBIN (**L6**) were investigated as chiral ligands, (*S*)-BINAM (**L5**) produced the best results, with the desired product **3** obtained in 68% yield and 74.5:25.5 e.r. The P-chiral phosphorus ligand (**L7**) was also tested in this system, but gave a low yield and poor enantioselectivity of the desired axially chiral product **3** (entry 7). Further experiments were performed for the optimization of the conditions, but, unfortunately, no improvements were achieved (for details see Supplementary Tables 6–10).

Because palladium catalysis could not provide satisfactory results even after extensive condition screening, we decided to reevaluate nickel catalysis, because it also demonstrated reasonable reactivity in the racemic transformation. However, no reaction occurred when chiral ligands **L1**, **L2**, **L5** and **L8** were used in this reaction system (entries 8 and 10). Gratifyingly, although the chiral phosphorus ligand (*S*)-NOBIN (**L6**) and the phosphoramidite ligand (**L9**) gave poor results for this atroposelective process (entries 9 and 11), chiral pyridine-BOX ligands (**L10**–**L15**) performed very well in this transformation. Among them, ligand **L14** showed the best reactivity, delivering the axially chiral styrene **3** in 90% yield with 94.0:6.0 e.r. (entries 12–17). Encouraged by this exciting result, we assessed further different nickel catalysts, such as $NiBr_2$, $Ni(acac)_2$ and $NiCl_2(dppp)_2$ with **L14** as the chiral ligand, and found that $Ni(acac)_2$ was the best catalyst, affording desired product **3** in 93% yield and 95.5:4.5 e.r. (entries 18–20). In addition, when the additive LiCl was replaced with KCl or LiI, the former could not make the reaction proceed smoothly, but LiI had an effect similar to that of LiCl in enantioselective control (entries 21 and 22). Finally, the solvent effect was investigated, revealing that tetrahydrofuran was still the best choice (entry 23; for details see Supplementary Tables 11–14).

Substrate scopes

With the optimized conditions in hand, we examined the scope of this Ni-catalysed enantioselective construction of axially chiral alkenes (Table 2). A series of aryl bromides were first investigated. In general, all the substrates were compatible with the reaction conditions, affording the corresponding products in good to excellent yields and 94.0:6.0 to 96.0:4.0 e.r. values (Table 2). Aryl bromides with different aliphatic chain benzoates (methyl, ethyl, *n*-butyl, *iso*-butyl, *iso*-propyl and *tert*-butyl) were investigated under the standard conditions, and the corresponding axially chiral alkenes (**3**–**8**) were provided in excellent yields (87–93%) and with good enantioselectivities (95.0:5.0 to 96.0:4.0 e.r.). It is worth noting that 3-bromopropyl 2-bromo-3-methylbenzoate could also give the desired product **9** under the above reaction conditions in 79% yield and with a good e.r. value. In addition, cyclic alkyl groups (cyclopropyl, cyclobutyl and cyclopentyl) were also compatible, giving the desired products **10**, **11** and **12** in 83–87% yields with 94.8:5.2 to 96.0:4.0 e.r. values. We then evaluated the different aryl-containing ester substituents. The phenethyl 2-bromo-3-methylbenzoate underwent the standard reactions to obtain the wanted axially chiral product **13** in 82% yield with good enantioselectivity (94.8:5.2 e.r.). Both electron-donating groups and electron-withdrawing groups, including fluoro and chloro, were well-tolerated in the catalytic system, and gave excellent results in terms of chemical yields (**14**–**16**, 81–83%) and atroposelectivities (95.0:5.0 to 96.0:4.0 e.r.). Furthermore, a 3-substituted group on the aromatic ring of aryl bromide (3-chlorophenethyl 2-bromo-3-methylbenzoate) could proceed smoothly to form the target product **17** with good results (86% yield and 94.8:5.2 e.r.). The reaction conditions were also compatible with 4-phenylbutyl 2-bromo-3-methylbenzoate, which afforded compound **18** with good yield and good enantioselectivity.

We next explored the scope of alkynyl tetracoordinate boron species for the assembly of axially chiral alkenes. First, alkynyl tetracoordinate borons with different aliphatic chains (*n*-propyl, *n*-butyl and *n*-hexyl) underwent the reaction with methyl 2-bromo-3-methylbenzoate under the same conditions, giving the corresponding desired products (**19**–**21**) with steady enantiomeric ratios (~95.0:5.0 e.r.) and excellent yields (89–92% yield). Substrates with a cyclic alkyl group were also examined under viable reaction conditions to access the target products **22** and **23** in 88% and 95% yields, respectively, with good atroposelectivity. Axially chiral styrenes **24** and **25** were obtained in good yields with 95.3:4.7 and 94.8:5.2 e.r. values under the above reaction conditions when R was a phenylethyl or 4-chlorophenyl group. Various ether-containing aliphatic alkynyl tetracoordinate borons were investigated. In general, the reaction tolerated an array of substituents with different steric and electronic properties. In spite of electron-neutral groups, electron-donating and electron-withdrawing groups were all suitable, under standard conditions, for accessing the corresponding chiral products (**26**–**33**) in moderate to good yields with good e.r. values. In addition, disubstituted, trisubstituted and fused-ring substrates could generate the target products (**34**–**36**, 61–78% yields) with good results under standard conditions. The substrate tetramethylammonium (5-(benzyloxy) pent-1-yn-1-yl)triphenylborate also underwent the above reaction conditions to render the desired chiral product **37** with good results. Moreover, aza-containing aliphatic substrate tetramethylammonium (5-(3-methyl-1*H*-indol-1-yl)pent-1-yn-1-yl)triphenylborate reacted with **2** to provide a similar result (**38**, 80% yield, 95.0:5.0 e.r.) under the standard reaction conditions.

Next, thioether-containing substrates were evaluated in this system. Various thioether-containing axially chiral styrenes (**39**–**43**) were procured in moderate to good yields (68–82%) with good atroposelectivities under the same conditions. Subsequently, other multi-substituted aryl bromides, such as methyl 2-bromo-3,4-dimethylbenzoate, methyl 2-bromo-3,5-dimethylbenzoate and methyl 2-bromo-3-ethylbenzoate, were investigated in this system under the standard reaction conditions, and the desired axially chiral products **44**–**46** were obtained in excellent yields with high enantioselectivities. Axially chiral product 2,6-dimethylphenyl (*Z*)-3-methyl-2-(1-phenylhept-1-en-2-yl)benzoate (**47**) was also successfully formed with excellent results (83% yield, 96.2:3.8 e.r.) under viable reaction conditions. Finally, many aryl amido bromides ((2-bromo-3-methylphenyl)(pyrrolidin-1-yl)methanone, 2-bromo-*N*-isopropyl-3-methylbenzamide, 2-bromo-*N*-cyclopropyl-3-methylbenzamide and 2-bromo-*N*-cyclopentyl-3-methylbenzamide)

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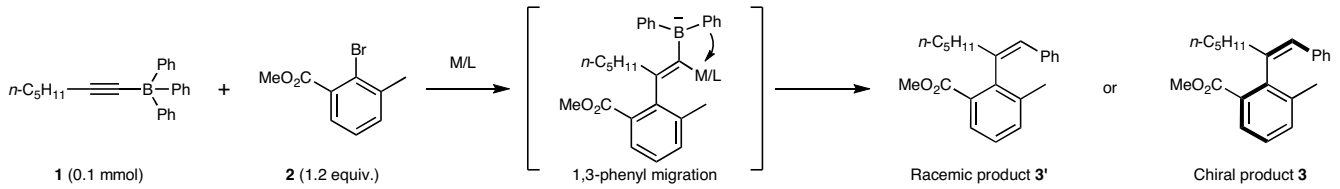
Table 1 | Initial attempt and optimization of the reaction conditions



1 (0.1 mmol) **2** (1.2 equiv.) 1,3-phenyl migration Racemic product **3'** Chiral product **3**

$FeCl_2$/Fe(acac)$_3$/$CoCl_2$/Co(acac)$_3$/$CuCl_2$/Cu(acac)$_2$/$CuBr_2$/CuCl as catalyst[a]

L1'	L2'	L3'	L4'	L5'	L6'
NR	NR	NR	NR	NR	NR

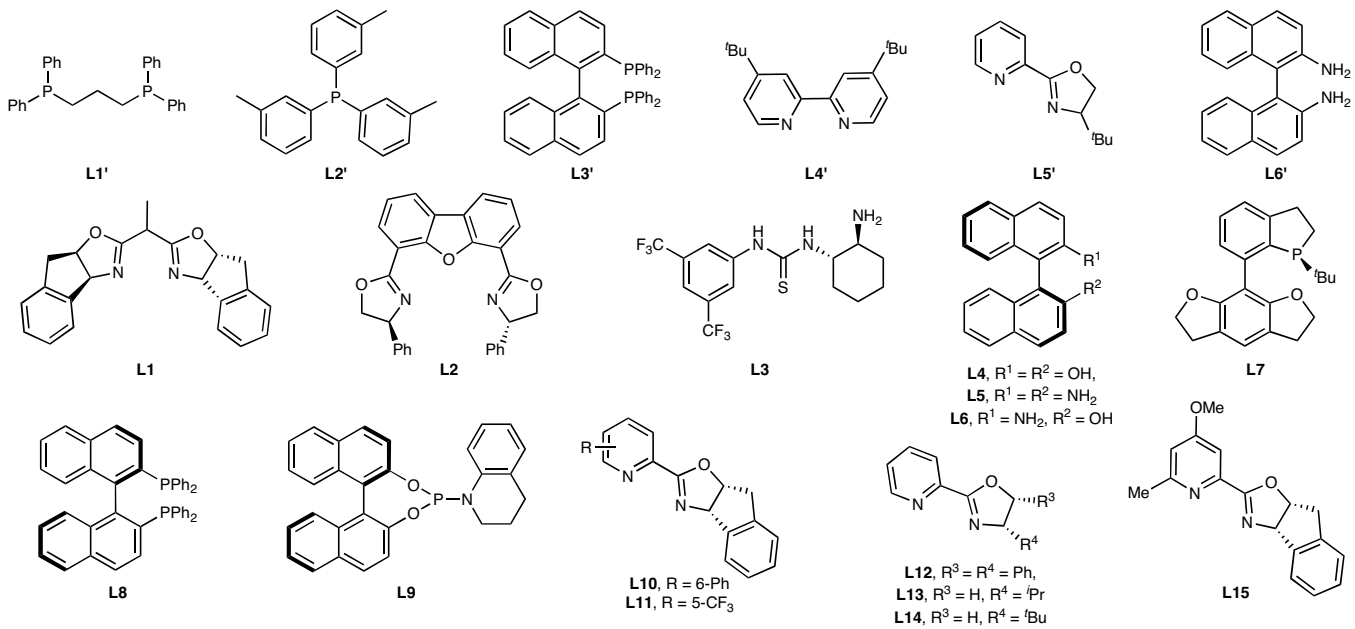
$Pd_2(dba)_3$ ($Pd(OAc)_2$) as catalyst[a]

L1'	L2'	L3'	L4'	L5'	L6'
61%	72% (62%)	78% (54%)	9% (trace)	13% (trace)	64%

$Ni(PPh_3)_2Br_2$ ($Ni(cod)_2$) as catalyst (LiCl as additive)[a]

L1'	L2'	L3'	L4'	L5'	L6'
NR	NR	NR	32%	58% (32%)	NR

Entry	Variation from conditions	Yield of **3** (%)	E.r. value of **3**
1[b]	**L1** as ligand	25	54.2:46.8
2[b]	**L2** as ligand	17	51.0:49.0
3[b]	**L3** as ligand	26	53.5:46.5
4[b]	**L4** as ligand	19	50.4:49.6
5[b]	**L5** as ligand	68	74.5:25.5
6[b]	**L6** as ligand	25	53.5:46.5
7[b]	**L7** as ligand	26	32.9:67.1
8[c]	**L1** or **L2** or **L5** as ligand	–	–
9[c]	**L6** as ligand	50	52.5:47.5
10[c]	**L8** as ligand	–	–
11[c]	**L9** as ligand	23	55.0:45.0
12[c]	**L10** as ligand	75	52.0:48.0
13[c]	**L11** as ligand	72	81.0:19.0
14[c]	**L12** as ligand	79	78.5:21.5
15[c]	**L13** as ligand	85	86.0:14.0
16[c]	**L14** as ligand	90	94.0:6.0
17[c]	**L15** as ligand	78	86.0:14.0
18[d]	$NiBr_2$ as catalyst	91	32.9:67.1
19[d]	$Ni(acac)_2$ as catalyst	93	95.5:4.5
20[d]	$NiCl_2(dppp)_2$ as catalyst	72	94.0:6.0
21[e]	KCl instead of LiCl	–	–
22[e]	LiI instead of LiCl	67	95.0:5.0
23[e]	CH_3CN as solvent	54	74.0:26.0



Unless otherwise noted, all reactions were performed under an argon atmosphere with tetramethylammonium hept-1-yn-1-yltriphenylborate (**1**, 0.1 mmol) and methyl 2-bromo-3-methylbenzoate (**2**, 1.2 equiv.). NR, no reaction; acac, acetylacetone; dba, dibenzylideneacetone; cod, 1,5-cyclooctadiene. [a]Metal catalyst (10 mol%), L (20 mol%) at room temperature or 80 °C for 12 h, isolated yield. [b]$Pd_2(dba)_3$ (10 mol%), L* (20 mol%), at room temperature for 12 h, isolated yield. [c]$NiCl_2(PPh_3)_2$ (6 mol%), L* (12 mol%), LiCl (3 equiv.) at 80 °C for 12 h, isolated yield. [d]$NiCl_2(PPh_3)_2$ was replaced and **L14** used as ligand. [e]$Ni(acac)_2$/**L14** system.

were converted into the desired products **48**–**51** with similar efficiencies and selectivities under the same reaction conditions. The structure and absolute configuration of **51** were confirmed by X-ray crystallographic analysis after recrystallization (Table 2). In addition, target product **52** was isolated in 86% yield with 94.0:6.0 e.r. under the above reaction conditions.

The entire process was readily extended to a reaction utilizing a fused-ring system—with naphthalene as substrate—via further condition optimizations, in which **L15** acted as the optimal chiral ligand (Table 3). Subsequently, we explored the amenability of this type of substrate to the reaction system. A series of chain alkyl 1-bromo-2-naphthoates, such as methyl, ethyl and isobutyl, were

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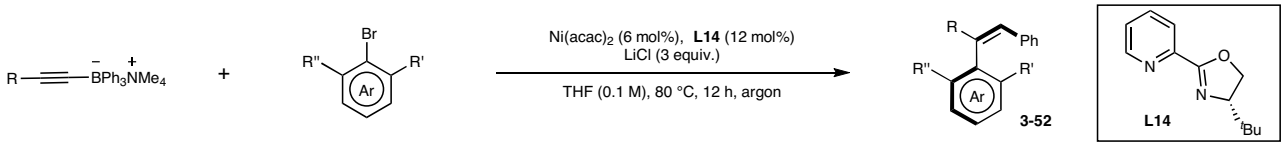
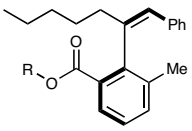
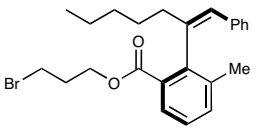
Table 2 | Substrate scope for the construction of axially chiral styrenes

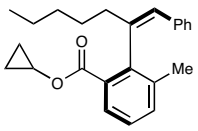




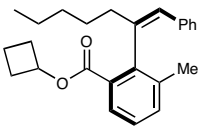
3, R = Me 93% yield, 95.5:4.5 e.r.
4, R = Et 91% yield, 95.0:5.0 e.r.
5, R = ^{n}Bu 89% yield, 95.1:4.9 e.r.
6, R = ^{t}Bu 91% yield, 96.0:4.0 e.r.
7, R = ^{i}Pr 87% yield, 95.2:4.8 e.r.
8, R = ^{t}Bu 92% yield, 95.4:4.6 e.r.



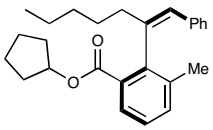
9, 79% yield, 94.9:5.1 e.r.



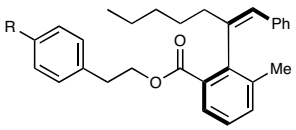
10, 85% yield, 94.8:5.2 e.r.



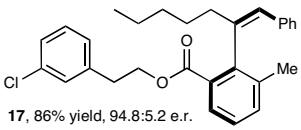
11, 87% yield, 95.4:4.6 e.r.



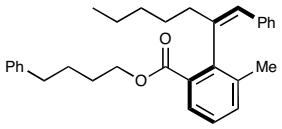
12, 83% yield, 96.0:4.0 e.r.



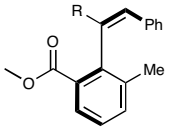
13, R = H 82% yield, 94.8:5.2 e.r.
14, R = Me 83% yield, 96.0:4.0 e.r.
15, R = F 82% yield, 95.0:5.0 e.r.
16, R = Cl 81% yield, 95.1:4.9 e.r.



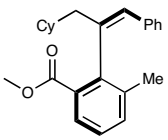
17, 86% yield, 94.8:5.2 e.r.



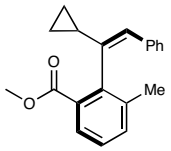
18, 71% yield, 95.1:4.9 e.r.



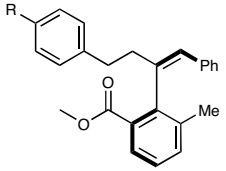
19, R = ^{n}Pr 92% yield, 95.2:4.8 e.r.
20, R = ^{n}Bu 89% yield, 95.2:4.8 e.r.
21, R = *n*-hexyl 91% yield, 95.0:5.0 e.r.



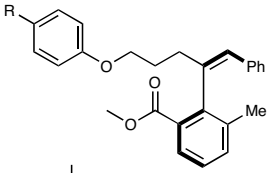
22, 88% yield, 96.2:3.8 e.r.



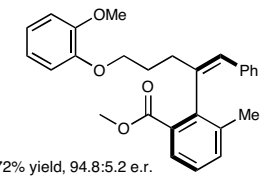
23, 95% yield, 95.6:4.4 e.r.



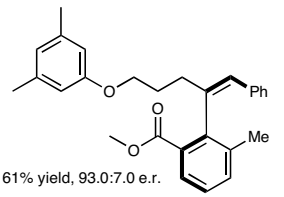
24, R = H 91% yield, 95.3:4.7 e.r.
25, R = Cl 82% yield, 94.8:5.2 e.r.



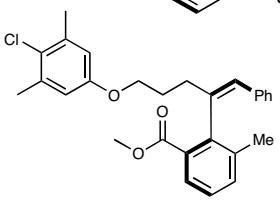
26, R = H 72% yield, 95.9:4.1 e.r.
27, R = Me 73% yield, 94.9:5.1 e.r.
28, R = Et 88% yield, 94.8:5.2 e.r.
29, R = ^{t}Bu 85% yield, 95.5:4.5 e.r.
30, R = OMe 62% yield, 95.0:5.0 e.r.
31, R = F 63% yield, 95.5:4.5 e.r.
32, R = Cl 72% yield, 94.9:5.1 e.r.



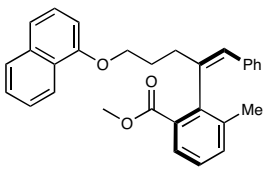
33, 72% yield, 94.8:5.2 e.r.



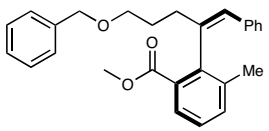
34, 61% yield, 93.0:7.0 e.r.



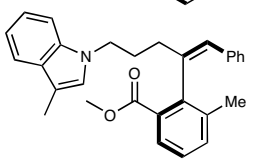
35, 75% yield, 95.2:4.8 e.r.



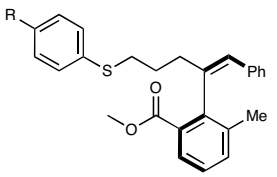
36, 78% yield, 95.1:4.9 e.r.



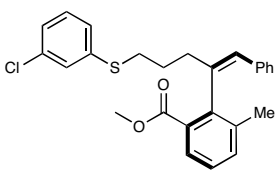
37, 81% yield, 95.3:4.7 e.r.



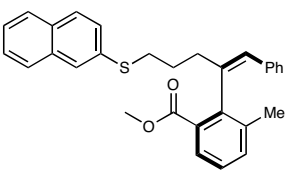
38, 80% yield, 95.0:5.0 e.r.



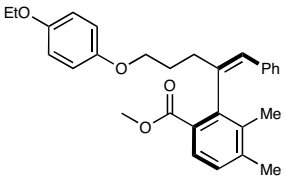
39, R = Me 75% yield, 95.8:4.2 e.r.
40, R = F 79% yield, 95.7:4.3 e.r.
41, R = Cl 76% yield, 96.0:4.0 e.r.



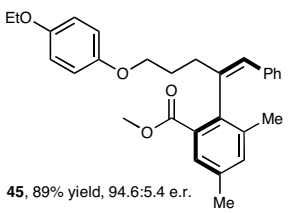
42, 82% yield, 95.8:4.2 e.r.



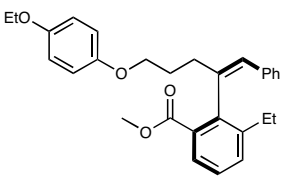
43, 68% yield, 95.8:4.2 e.r.



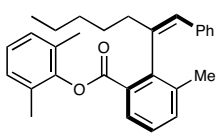
44, 89% yield, 94.7:5.3 e.r.



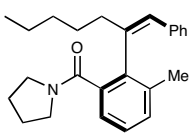
45, 89% yield, 94.6:5.4 e.r.



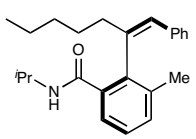
46, 90% yield, 95.5:4.5 e.r.



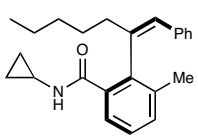
47, 83% yield, 96.2:3.8 e.r.



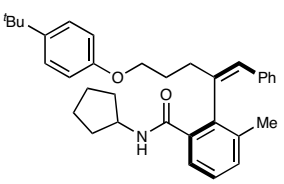
48, 72% yield, 91.7:8.3 e.r.



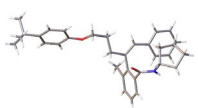
49, 68% yield, 95.6:4.4 e.r.



50, 80% yield, 94.0:6.0 e.r.



51, 82% yield, 94.8:5.2 e.r.



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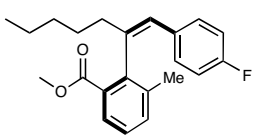

52, 86% yield, 94.0:6.0 e.r.

Unless otherwise noted, all reactions were performed using alkynyl tetracoordinate boron (1.2 equiv.), aryl bromide (0.1 mmol), Ni(acac)$_2$ (6 mol%), **L14** (12 mol%) and LiCl (3 equiv.) under an argon atmosphere at 80 °C for 12 h, isolated yield.

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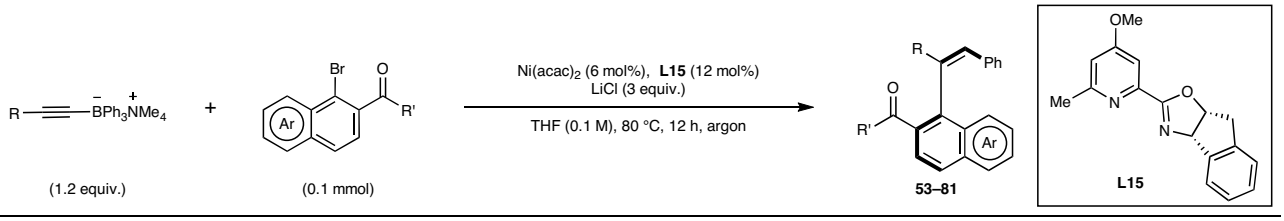
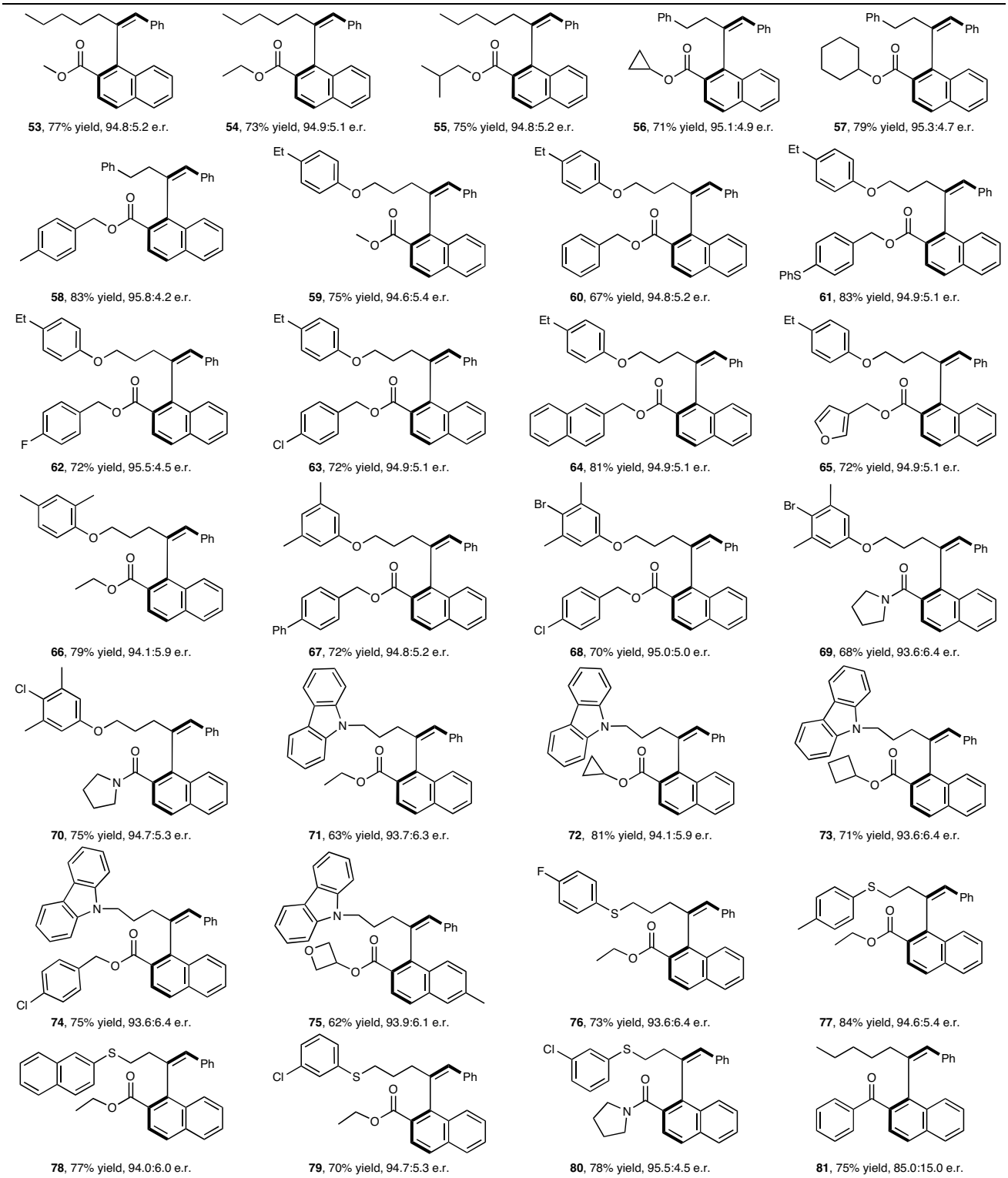
Table 3 | Substrate scope for the construction of axially chiral naphthalenyl alkenes





Unless otherwise noted, all reactions were performed using alkynyl tetracoordinate boron (1.2 equiv.), aryl bromide (0.1 mmol), $Ni(acac)_2$ (6 mol%), **L15** (12 mol%) and LiCl (3 equiv.) under an argon atmosphere at 80 °C for 24 h, isolated yield.

https://doi.org/10.1038/s41557-023-01396-7

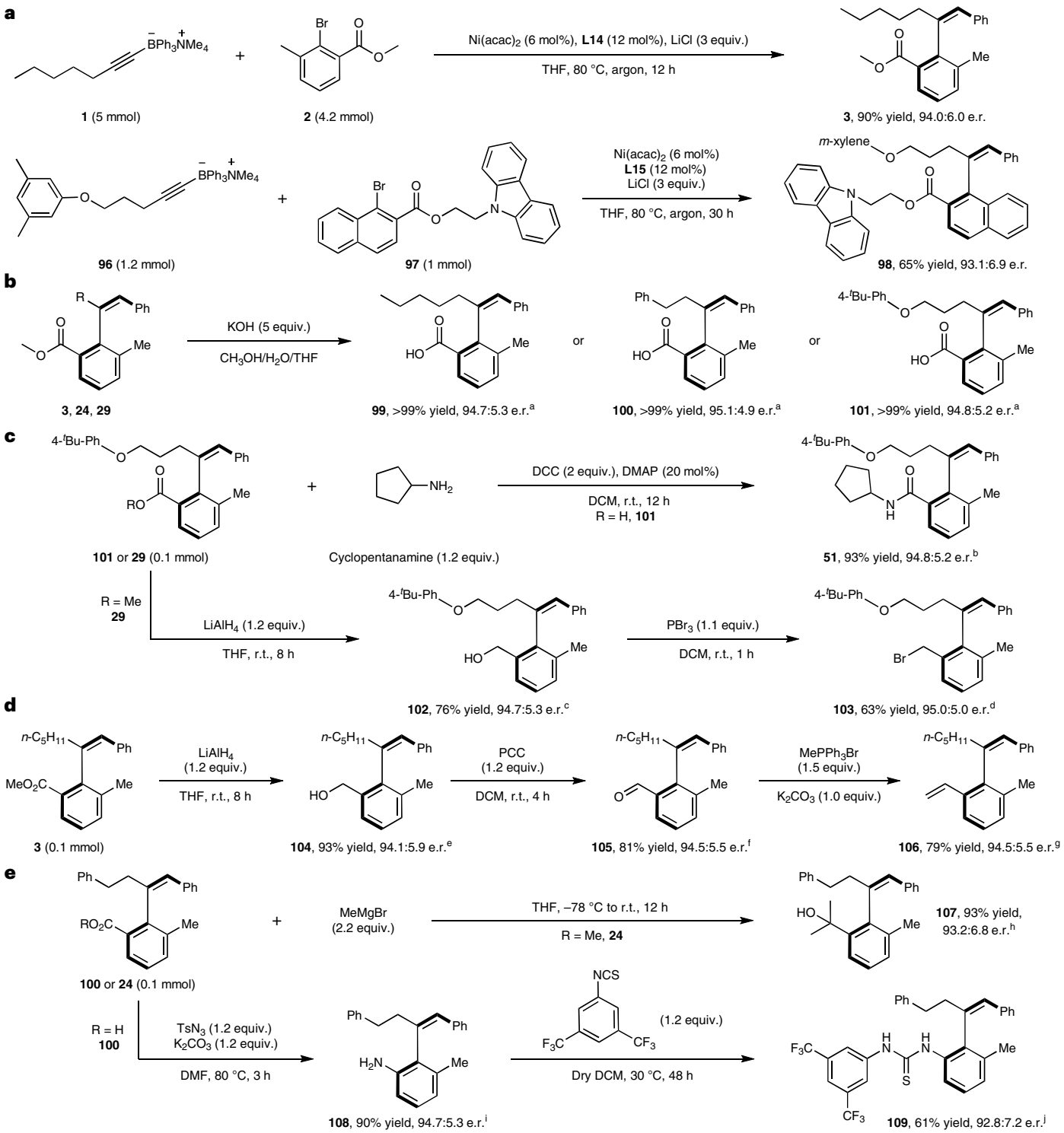
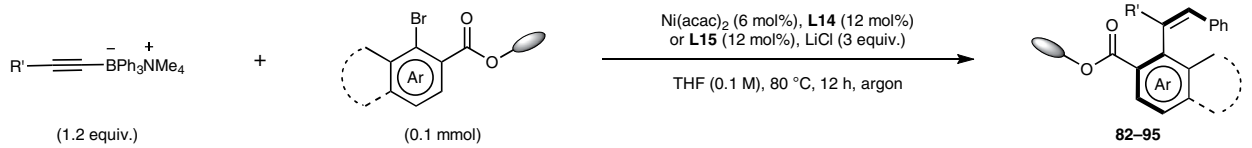
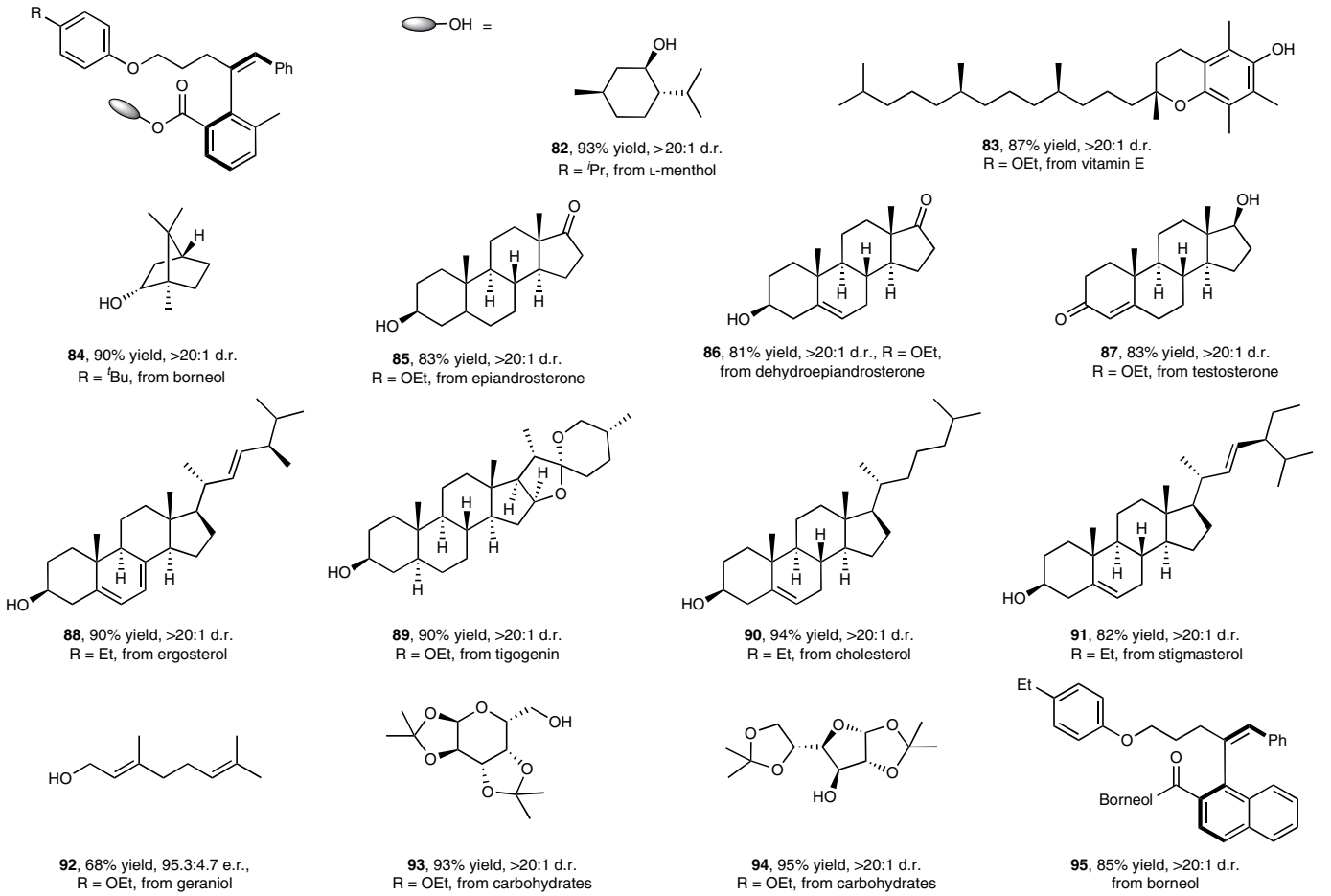


Fig. 2 | Synthetic applications. a, Scale-up reaction for the model reaction and substrate **96** with **97**. **b**, Hydrolysis of the products. **c**, Amidation, reduction and bromination reaction of the products. **d**, Olefinization process for **3**. **e**, Electrophilic substitution and amination reactions of the products. [a]Axially chiral product (**3**, **24** and **29**, 0.1 mmol) and KOH (5 equiv.) in THF, MeOH and H_2O at 60 °C for 12 h; [b]**101** (0.1 mmol), cyclopentanamine (1.2 equiv.), DCC (2 equiv.), and DMAP (20 mol%) in DCM at room temperature (r.t.) for 12 h; [c]**29** (0.1 mmol) and $LiAlH_4$ (1.2 equiv.) in THF at r.t. for 8 h; [d]**102** (0.1 mmol) and PBr_3 (1.1 equiv.) in DCM at r.t. for 1 h; [e]**3** (0.1 mmol) and $LiAlH_4$ (1.2 equiv.) in THF at r.t. for 8 h; [f]**104** (0.1 mmol) and PCC (0.12 mmol) in DCM at r.t. for 4 h; [g]**105** (0.1 mmol), $MePPh_3Br$ (1.5 equiv.) and K_2CO_3 (0.1 mmol) in 1,4-dioxane at 80 °C for 12 h; [h]**24** (0.1 mmol), MeBrMg (2.2 equiv.) in dry THF at −78 °C to r.t. for 12 h; [i]**100** (0.1 mmol), TsN_3 (1.2 equiv.) and K_2CO_3 (1.2 equiv.) in DMF at 80 °C for 3 h; [j]**108** (0.05 mmol) and 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (1.2 equiv.) in dry DCM at 30 °C for 48 h. DCC, dicyclohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; PCC, pyridinium chlorochromate; TsN_3, 4-methylbenzenesulfonyl azide.

https://doi.org/10.1038/s41557-023-01396-7

Table 4 | Late-stage functionalizations of bioactive compounds or drug molecules





Unless otherwise noted, all reactions were performed using alkynyl tetracoordinate boron (1.2 equiv.), aryl bromide (0.1 mmol), $Ni(acac)_2$ (6 mol%), **L14** or **L15** (12 mol%) and LiCl (3 equiv.) under an argon atmosphere at 80 °C for 12 h or 24 h, isolated yield.

investigated, and the corresponding chiral products **53**–**55** were delivered in 73–77% yields with good enantioselectivities. Tetramethylammonium triphenyl(4-phenylbut-1-yn-1-yl)borate reacted with cycloalkyl 1-bromo-2-naphthoates, such as cyclopropyl 1-bromo-2-naphthoate and cyclohexyl 1-bromo-2-naphthoate, affording desired products **56** and **57** with good outcomes (71% and 79% yields, 95.1:4.9 and 95.3:4.7 e.r.). Chiral product 4-methylbenzyl (*Z*)-1-(1,4-diphenylbut-1-en-2-yl)-2-naphthoate (**58**) was also smoothly obtained in 83% yield with 95.8:4.2 e.r.

Next, we selected tetramethylammonium (5-(4-ethylphenoxy) pent-1-yn-1-yl)triphenylborate as the substrate to react with various alkyl 1-bromo-2-naphthoates, including methyl 1-bromo-2-naphthoate, benzyl 1-bromo-2-naphthoate and 4-(phenylthio)benzyl 1-bromo-2-naphthoate, and the corresponding target products **59**–**63** were rendered in good yields with high enantioselectivities. The reactions of 1-bromo-2-naphthoates, including the naphthalene and heterocycle (furan) with tetramethylammonium (5-(4-ethylphenoxy)pent-1-yn-1-yl)triphenylborate, proceeded smoothly under the standard conditions, affording corresponding products **64** and **65** with good results. The disubstituted aromatic ring of alkynyl tetracoordinate boron was also tolerated in this system, thus allowing the preparation of axially chiral compound ethyl (*Z*)-1-(5-(2,4-dimethylphenoxy)-1-phenylpent-1-en-2-yl)-2-naphthoate (**66**) and [1,1′-biphenyl]-4-ylmethyl (*Z*)-1-(5-(3,5-dimethylphenoxy)-1-phenylpent-1-en-2-yl)-2-naphthoate (**67**) in 79% and 72% yields with 94.1:5.9 e.r. and 94.8:5.2 e.r., respectively. Additionally, 1-bromo-2-naphthamides reacted with the trisubstituted aromatic ring of alkynyl tetracoordinate boron under the above reaction conditions to generate products **68**–**70** in 68–75% yields with good enantioselectivities. Moreover, aza-containing aliphatic substrate, such as carbazole, reacted with various alkyl 1-bromo-2-naphthoates to access the desired products (**71**–**75**) in moderate to good yields with 94:6 e.r. values. Thioether-containing alkynyl tetracoordinate boron as a substrate also worked well under the standard reaction conditions to provide the final axially chiral products (**76**–**80**) with good results. Of note, when the ketone compound (1-bromonaphthalen-2-yl)(phenyl) methanone was subjected to the standard conditions, the target product **81** was obtained in good yield with moderate enantioselectivity.

The good compatibility of this system was further highlighted by its amenability to the late-stage functionalization of bioactive compounds or drug molecules. We selected various alkynyl tetracoordinate

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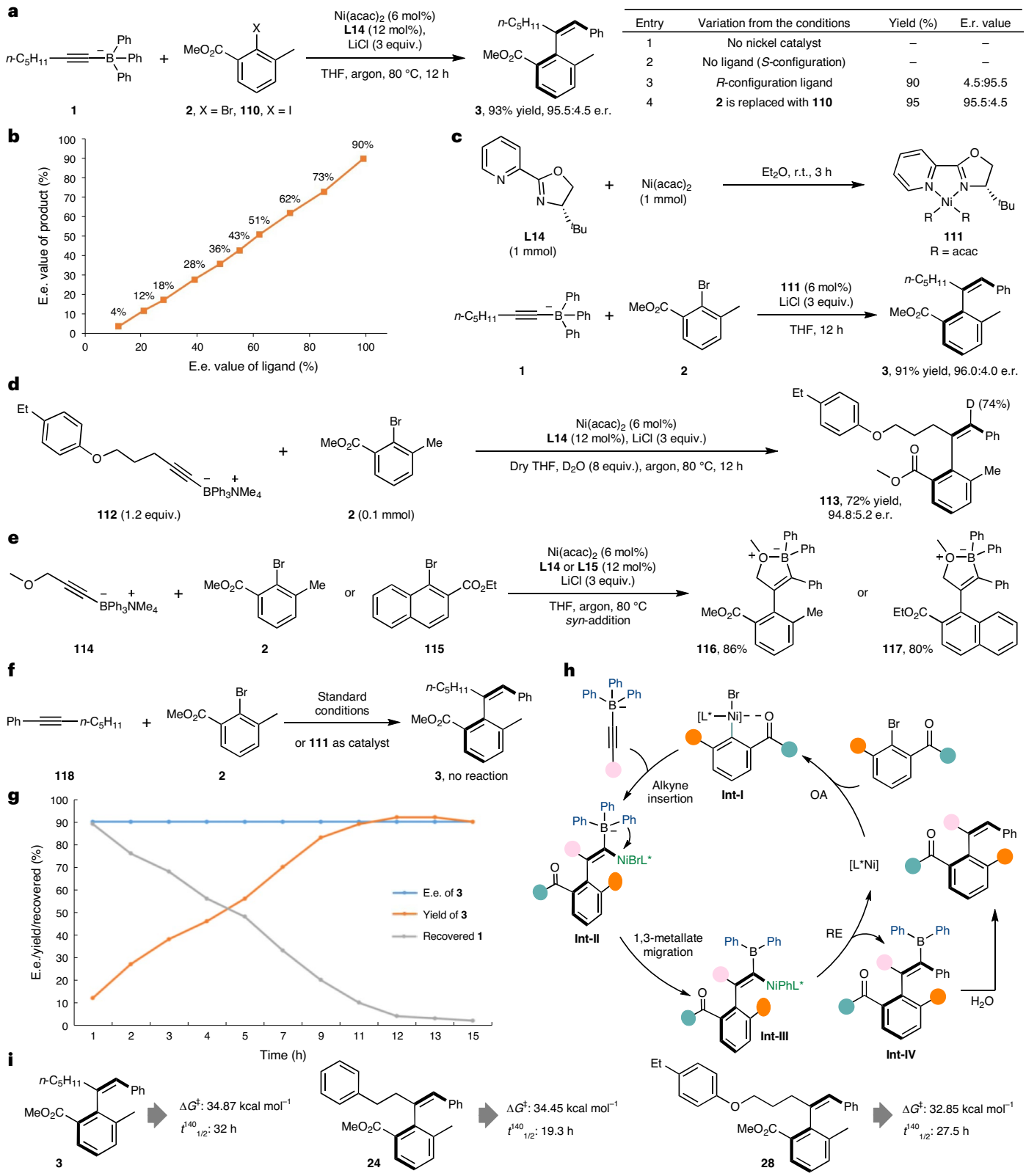

Entry	Variation from the conditions	Yield (%)	E.r. value
1	No nickel catalyst	–	–
2	No ligand (*S*-configuration)	–	–
3	*R*-configuration ligand	90	4.5:95.5
4	**2** is replaced with **110**	95	95.5:4.5

Fig. 3 | Mechanistic control experiments and possible catalytic cycle. **a**, Control experiments and configuration change of ligand. **b**, Non-linear effect experiments for e.e. values between ligand and product. **c**, Reaction of ligand with catalyst and transformation. **d**, Deuterium experiment. **e**, Initial addition mode of tetracoordinate boron with aryl bromide. **f**, The internal alkyne **118** was subjected to the standard conditions leading to no reaction occurred, ruling out its possibility as a potential intermediate for this process. **g**, Monitoring the model reaction: the e.e. values and yields of product **3** or raw material recovery over time, revealing e.e. values of product were steady and yields of product **3** gradually increased as the raw material recovery gradually decreased. **h**, Proposed mechanism for this Ni-catalysed assembly of axially chiral alkenes: oxidative addition (OA) of NiL* with aryl bromide generates aryl nickel species **Int-I**. Regioselective syn-addition of **Int-I** across the carbon–carbon triple bond of alkynyl tetracoordinated boron affords the intermediate **Int-II**. Subsequently, 1,3-metallate migration of **Int-II** occurs to render the **Int-III**, and then, the axially chiral product **Int-IV** is obtained via reductive elimination (RE) along with the regeneration of catalyst nickel to complete catalytic cycle. **i**, Thermal racemization studies and enantiomerization barrier determination of **3**, **24** and **28**.

borons as reaction partners (Table 4), and it was found that this nickel-catalysed atroposelective reaction performed very well with aryl bromides derived from L-menthol, vitamin E, borneol, epiandrosterone, dehydroepiandrosterone, restosterone, ergosterol and tigogenin, as well as cholesterol, which contained one or more stereocentres, delivering the corresponding axially chiral products **82**–**90** in excellent yields with high enantioselectivities. Remarkably, the bioactive complexes that contain C=C double bonds, such as stigmasterol and geraniol, were also compatible in this system, and the desired products **91** and **92** were delivered with good outcomes under standard conditions. In addition, aryl bromides derived from carbohydrates such as ((3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-*b*:4′,5′-d]pyran-5-yl)methanol and (3a*R*,5*S*,6*S*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]di-oxol-6-ol were good reaction partners, and the targeted products **93** and **94** were obtained in excellent yields with good enantioselectivity and excellent diastereselectivity. (1*R*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 1-((*Z*)-5-(4-ethylphenoxy)-1-phenylpent-1-en-2-yl)-2-naphtho-ate (**95**) was also formed with good outcomes under viable reaction conditions. The above results suggest that our strategy for the construction of axially chiral alkenes has excellent functional-group tolerance, making it potentially useful in the late-stage elaborations of bioactive molecules and also beneficial for pharmaceuticals.

Downstream applications and transformations

To demonstrate synthetic utility, a gram-scale synthesis of **3** was performed under the optimal reaction conditions, and an excellent yield was obtained with high enantioselectivity (Fig. 2a). In addition, a scale-up reaction of tetramethylammonium (5-(3,5-dimethylphenoxy)pent-1-yn-1-yl)triphenylborate (**96**) with 2-(9*H*-carbazol-9-yl)ethyl 1-bromo-2-naphthoate (**97**) was carried out, affording target product **98** in moderate yield with good enantioselectivity (Fig. 2a). Considering the importance of chiral carboxylic acids, which have been widely used as chiral ligands in asymmetric reactions, we decided to hydrolyse our products bearing ester groups and, to our delight, chiral carboxylic acids **99**–**101** were obtained in almost quantitative yields (Fig. 2b). The reaction of chiral (*Z*)-2-(5-(4-(*tert*-butyl)phenoxy)-1-phenylpent-1-en-2-yl)-3-methylbenzoic acid (**101**) with cyclopentanamine afforded the chiral amide **51** in good yield (93% yield, 94.8:5.2 e.r.) by amidation[55] (Fig. 2c). In addition, chiral benzyl alcohol **102** and chiral benzyl bromide **103** were smoothly obtained in 76% and 63% yields, respectively, with high enantioretentive control from compound **29**[55,65] (Fig. 2c). Similarly, chiral benzyl alcohol **104** was afforded by reduction from compound **3** with quantitative yield and no loss in enantioselectivity, and further oxidation of **104** delivered the corresponding chiral aromatic aldehyde **105** in good yields with high enantioretention. Vinyl aromatic compound **106** could be generated when a Wittig reaction was applied to aldehyde **105**, once again with good yield and enantioselectivity (Fig. 2d). Moreover, an electrophilic substitution reaction could be initiated to generate tertiary alcohol **107** with good yield and identical enantioselectivity using MeMgBr. Aniline compound **108** was also provided with a good outcome (90% yield, 94.7:5.3 e.r.)[66]. Of note, chiral thiourea **109** was smoothly produced in 61% yield with 92.8:7.2 e.r. when aniline **108** was treated with 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene, which gives such molecules the potential to act as chiral ligands in asymmetric catalytic reactions (Fig. 2e)[67]. The above results clearly demonstrate that our functionally enriched axially chiral alkenes could serve as alternative synthetic building blocks that possess axial chirality, offering potential applications in the synthesis of structurally diverse multi-substituted axially chiral alkenes.

Mechanism investigations

To gain insights into the mechanism of this methodology, a series of evaluation experiments were performed (Fig. 3). First, we carried out control experiments and found that the reaction was dependent on the participation of the Ni(acac)$_2$ and (*S*)-ligand (Fig. 3a, entries 1 and 2). When the (*S*)-configuration ligand was replaced by the (*R*)-configuration, the opposite conformation product was obtained in 90% yield and 4.5:95.5 e.r. under the standard reaction conditions (entry 3). Similar results were obtained when methyl 2-bromo-3-methylbenzoate (**2**) was replaced with methyl 2-iodo-3-methylbenzoate (**110**) as the substrate, suggesting that oxidative addition of NiL* with aryl halides is not the step to determine enantioselectivity (entry 4). A linear relationship between catalyst enantiomeric purity and product enantiomeric purity was observed (Fig. 3b), suggesting that the catalyst may be a mono-nuclear Ni(II)·(*R*)–ligand complex. Consequently, a prefabricated catalyst ($^{t\mathrm{Bu}}$pyrox)Ni(acac)$_2$ (**111**) species was prepared using Ni(acac)$_2$ and (*S*)-4-(*tert*-butyl)-2-(pyridin-2-yl)-4,5-dihydrooxazole according to the reported literature[68] and subjected to the model reaction in the absence of an individual Ni catalyst and chiral ligand **L14**, giving target product **3** in 91% yield with 96.0:4.0 e.r. (Fig. 3c), providing evidence that complex **111** could be the precatalyst in this transformation.

To find the proton source, an isotope-labelling experiment was conducted with D_2O, and the corresponding deuterated product **113** was afforded in 72% yield and 74% deuteration ratio with 94.8:5.2 e.r. (Fig. 3d), suggesting that the hydrogen atom in the product originates from H_2O. The initial addition mode of tetracoordinate boron with aryl bromide in the presence of a nickel catalyst was also investigated (Fig. 3e). When the substrate tetramethylammonium (3-methoxyprop-1-yn-1-yl)triphenylborate (**114**) reacted with either methyl 2-bromo-3-methylbenzoate (**2**) or ethyl 1-bromo-2-naphthoate (**115**) under standard conditions, the corresponding cyclic intermediates methyl 3-methyl-2-(1-methyl-2,2,3-triphenyl-2,5-dihydro-1*H*-1λ^3,2λ^4-oxaborol-4-yl)benzoate (**116**) or ethyl 1-(1-methyl-2,2,3-triphenyl-2,5-dihydro-1*H*-1λ^3,2λ^4-oxaborol-4-yl)-2-naphthoate (**117**) were obtained in 86% and 80% yields, respectively (Fig. 3e). The above results show the occurrence of *syn*-addition between the reaction of alkyne and aryl bromide. In addition, by subjecting internal alkyne **118** to the standard conditions[69], we could rule out its possibility as a potential intermediate for this process because no reaction took place (Fig. 3f). We also monitored the model reaction for e.e. values and the yields of product **3** or raw material recovery over time; this revealed that the e.e. values of the product were steady, and the yields of product **3** gradually increased as the raw material recovery gradually decreased (Fig. 3g).

Based on the above mechanistic experiments and previous literature[58,70,71], a possible catalytic cycle is proposed as shown in Fig. 3h. First, oxidative addition of NiL* with aryl bromide generates aryl nickel species **Int-I**. Regioselective *syn*-addition of **Int-I** across the carbon–carbon triple bond of alkynyl tetracoordinated boron affords intermediate **Int-II**. Subsequently, 1,3-metallate migration of **Int-II** occurs to give **Int-III**, then the axially chiral product **Int-IV** is obtained via reductive elimination along with the regeneration of catalyst nickel to complete the catalytic cycle. Finally, the target product is afforded in the presence of H_2O (Fig. 3h). To explore the configurational stability of our obtained axially chiral alkenes, we selected representative examples (**3**, **24** and **28**) and conducted racemization experiments in isopropanol at 140 °C, as shown in Fig. 3i (Supplementary Figs. 5–7).

Conclusions

In summary, we have developed an efficient strategy for the construction of axially chiral alkenes via a 1,3-metallate shift based on alkynyl tetracoordinate boron species, giving an example of axial chirality assembly from tetracoordinate borons species. The reaction proceeds smoothly with chiral Ni catalysis and shows broad substrate scope, affording the desired axially chiral alkenes with excellent chemoselectivity, exclusive *E*/*Z* selectivity and high enantioselectivities in good yields. Additionally, late-stage elaborations of bioactive compounds or drug molecules were achieved. Applications of axially chiral alkenes have been demonstrated by a series of transformations to construct axially chiral olefin derivatives without erosion of atroposelectivities,

suggesting that this protocol has potential for the synthesis of versatile axially chiral compounds with valuable structures. Control experiments carried out with specifically designed substrates indicate that the initial model of addition between aryl–Ni species and alkynyl tetracoordinate boron is regioselective and enantioselective *syn*-addition. This strategy will contribute to tetracoordinate boron chemistry and enrich the platform with an alternative approach to construct axially chiral alkene derivatives.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-023-01396-7.

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Methods

General procedure for the construction of axially chiral alkenes

To an oven-dried 10-ml Young's tube vial equipped with a magnetic stirring bar were added alkynyl tetracoordinate borons (0.12 mmol, 1.2 equiv.), aryl bromides (0.10 mmol, 1.0 equiv.), $Ni(acac)_2$ (6 mol%), **L14** or **L15** (12 mol%) and LiCl (0.3 mmol, 3 equiv.). Argon was then pumped through three times, and tetrahydrofuran (0.10 ml) was added. The reaction mixture was then stirred at 80 °C for 12–24 h. After the reaction was completed, the mixture was filtered through a short plug of silica gel and washed with EtOAc. The crude residue was purified by flash silica gel chromatography (EtOAc/petroleum ether) to afford the desired products.

Data availability

The data that support the findings of this study are available within the Article and its Supplementary Information. The X-ray crystallographic coordinates for structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition no. 2243354 (**51**). The data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Author contributions

Q.S. designed and directed the project. X.M. performed the experiments and developed the reactions. M.T., L.L., Z.Z., P.L. and J.L. helped with the collection of some experimental data. Q.S. and X.M. wrote the manuscript. All authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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