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Enantioselective construction of C-B axially chiral alkenylborons by nickel-catalyzed radical relayed reductive coupling

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The catalytic asymmetric synthesis of axially chiral alkenes remains a daunting challenge due to the lower rotational barrier, especially for longer stereogenic axis (e.g. C-B axis). The asymmetric radical difunctionalization of alkynes represents an efficient strategy for these targets. Key to the success of such transformations lies in aryl-stabilized highly reactive alkenyl radical intermediates, however, it remains an elusive whether a boryl group could play a similar role. Here we report a nickel-catalyzed atroposelective radical relayed reductive coupling reaction of our designed ethynyl-azaborines with simple alkyl and aryl halides through a boron-stabilized vinyl radical intermediate. This transformation enables a straightforward access to the challenging axially chiral alkenylborons bearing a C-B axis in generally high enantioselectivity and excellent stereoselectivity.

Axially chiral scaffolds are widely found in natural products, chiral catalysts, ligands, and materials[1–5]. Over the past decades, great efforts have been made for the synthesis of atropisomers featuring abundant skeletons, and biaryl derivatives are undoubtedly the most widely studied[6–13]. Recently, several challenging skeletons of axially chiral compounds have attracted considerable interest. For example, axially chiral styrenes are one challenging family of chiral compounds due to their relatively lower rotational barrier between different atropisomers compared to their diaryl counterparts[14–16] (Fig. 1a). Despite significant achievements in the field, the investigations of axially chiral alkenes have focused on the C − C and C-N stereogenic axes. In this context and as part of our continued research interest in the C-B axial chirality[17–20], we aimed to develop an alkenylboron scaffold based on the 1,2-azaborine units for expending the structural diversity of axial chirality (Fig. 1a). The interesting structure, derived from the replacement of the C = C bond of all-carbon aromatic rings with a B-N bond, can maintain the aromatic character and show great potential in functional materials, ligands and medicinal chemistry[21–27] (Fig. 1b). For the designed alkenylboron atropisomers, their synthesis may be more challenging than the counterpart styrene atropisomers owing to the lower rotational barrier resulting from the fact that the Csp^2-B bond is longer than the Csp^2-Csp^2 bond[28–31].

Recently, tremendous progress has been made in the transition metal-catalyzed difunctionalization of alkynes via an aryl-stabilized vinyl radical intermediate, which serves as a powerful strategy to access multi-substituted alkenes[32–42]. Noteworthily, such a strategy has been successfully applied for the construction of axially chiral styrenes by Zhang[43] and Liu[44] groups respectively. Considering the feasibility of the process, we envisioned that an atroposelective difunctionalization of ethynyl-azaborines through an azaborine-stabilized vinyl radical intermediate could be an efficient approach to construct the designed C-B axially chiral alkenylborons. However, compared to the extensive studies on the α-borylalkyl radicals[45–50] (Fig. 1c, left), the research on α-borylvinyl radicals is very rare and undeveloped[51], which seems to totally be ignored by chemical community (Fig. 1c, right). Although α-borylvinyl radicals can theoretically serve as a fascinating intermediate to construct multi-substituted alkenylborons, only one example from iron-catalyzed radical addition of ethynylboronic acid pinacol ester

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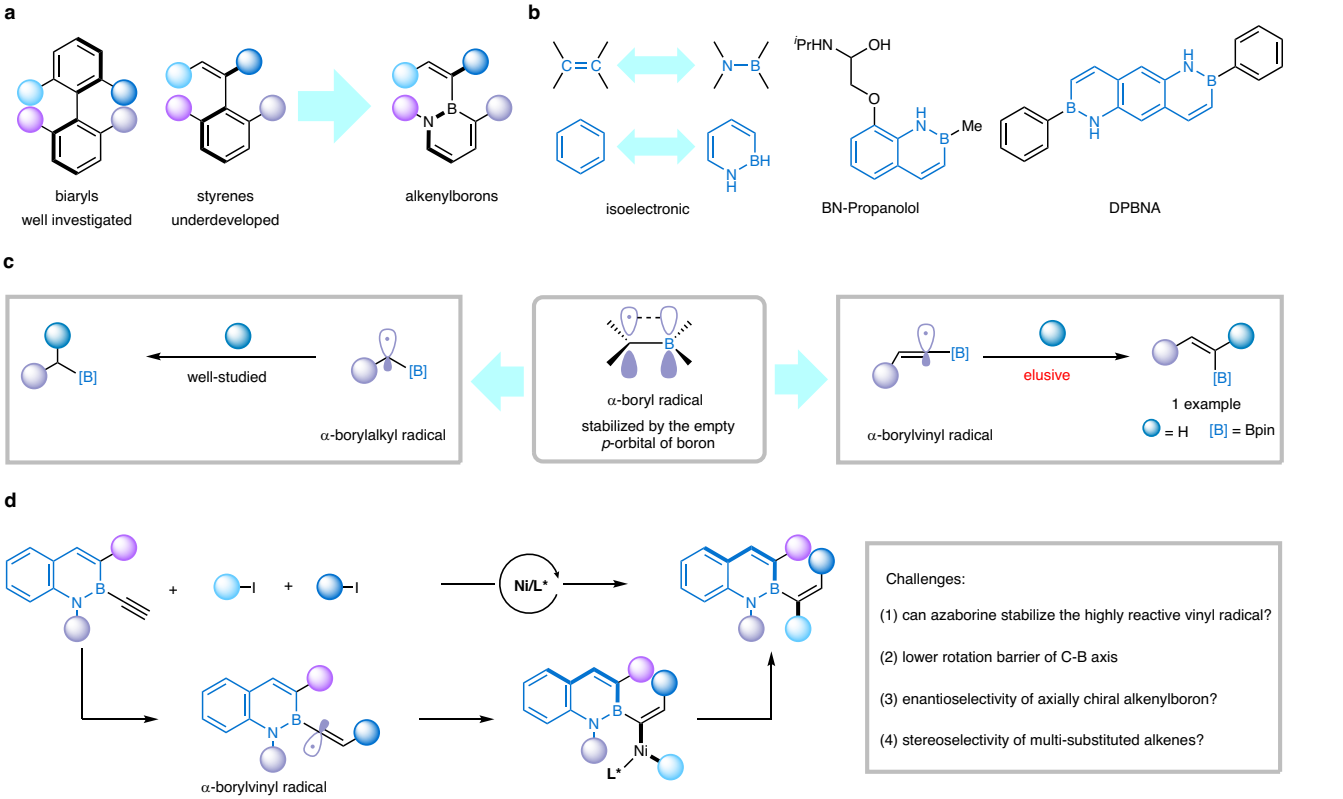

Fig. 1 | Designed nickel-catalyzed atroposelective radical alkylarylation of ethynyl-azaborines. a The design of C-B axially chiral alkenylborons. **b** Isoelectronic relationship between C = C and B-N bonds. **c** Diverse transformations via α-boryl carbon radical intermediates. **d** This work: nickel-catalyzed atroposelective relayed reductive coupling via α-borylvinyl radical. DPBNA = diphenyl-substituted 1,5-diaza-2,6- diboraanthracene.

involves such radical intermediate so far[51]. Herein, we report an atroposelective radical alkylarylation of ethynyl-azaborines to enable the axially chiral alkenylborons (Fig. 1d). Mechanistically, the catalytic protocol involves alkyl radical addition to the ethynyl moiety and cross-coupling of the resulting α-borylvinyl radical with nickel complex. This chemistry enables a straightforward access to the challenging axially chiral alkenylborons under mild conditions in generally high enantioselectivity and excellent stereoselectivity.

Results

Reaction conditions optimization

To overcome the above-mentioned challenges, we firstly designed and synthesized the sterically hindered ethynyl-azaborine **1a**[52–54]. Then, ethynyl-azaborine **1a**, 3-iodoanisole (**2a**) and *tert*-butyl iodide (**3a**) were employed to investigate the envisaged atroposelective radical relayed reductive coupling with $NiBr_2$·DME as catalyst and tetrakis(dimethylamino)ethylene (TDAE) as reductant. To our delight, when pybox **L1** was used as chiral ligand, the reaction could proceed smoothly (Table 1, entry 1), delivering the desired axially chiral alkenylboron **4a** in 39% NMR yield and −30% enantiomeric excess (ee). The preliminary result encouraged us to find a more efficient ligand for this transformation. Other pybox ligands **L2**-**L5** could efficiently promote this transformation in moderate enantioselectivities (Table 1, entries 2-5), and chlorine-substituted pybox ligand **L4** was determined to be the best one (Table 1, entry 5, 48% yield and 86% ee). Chiral quinolin-2-yl pybox **L6**, bisoxazoline ligand **L7**, and diamine ligand **L8** proved largely ineffective in this reaction (Table 1, entries 6-8). The mixed solvent (2-MeTHF/DCE) could slightly improve the yield and enantioselectivity (Table 1, entry 9), and the better enantioselectivity (89% ee) was obtained through decreased reaction temperature (Table 1, entry 10). The optimal reaction condition was furnished when $MgCl_2$ was used as an additive (Table 1, entry 11, 72% yield and 92% ee). In addition, other Ni catalysts, such as $NiCl_2$·DME and $NiBr_2$, afforded inferior results (Table 1, entries 12 and 13).

Substrate scopes

With the optimized asymmetric radical relayed reductive coupling conditions in hand, we first evaluated the substrate scope of aryl iodides (Fig. 2). Generally, aryl iodides bearing electron-donating, -neutral and -withdrawing substituents proceeded smoothly under the standard conditions, furnishing the corresponding axially chiral alkenylborons **4a**-**4v** with good to excellent enantioselectivities (83–93% ee). The lower to moderate yields for some axially chiral alkenylboron products were mainly due to the hydroalkylation process of ethynyl-azaborines[51,55]. The reaction showed good halogen compatibility, not only ethynyl-azaborine **1a** but also aryl iodines (**2c, 2i**-**2l** and **2o**), which offers valuable handles for further late-stage functionalization. Importantly, sensitive functional groups on the benzene ring, such as cyano (**4 l** and **4 m**), aldehyde (**4n**), ester (**4o**-**4s**), alkene (**4r**), ketone (**4t**), trifluoromethyl (**4 u**), and trifluoromethoxy (**4 v**), also worked well. The absolute configuration of **4 m** was determined by X-ray crystallographic analysis. Notably, aryl iodides derived from *L*(-)-borneol, geraniol and gemfibrozil were also well compatible, and furnished the desired three-component coupling products **4q**–**4 s** in moderate yields with good to excellent diasteroselective (**4q**, >20:1 dr) and enantioselectivities (89% ee and 92% ee). 2-Naphthalene iodine is also a good substrate for this atroposelective radical relayed reductive coupling reaction (**4w**). Heterocyclic derivatives, such as thiophene and pyridine, were also suitable candidates for this reductive coupling to give axially chiral alkenylborons **4x** and **4 y** with good to excellent enantioselectivities (82% and 91% ee).

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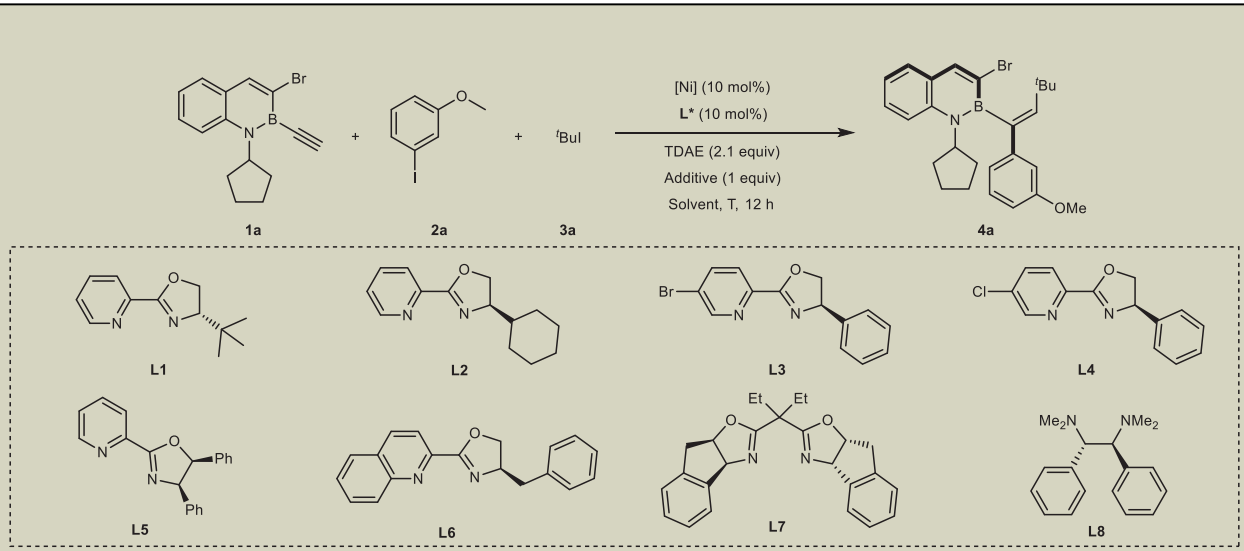
Table 1 | Optimization of reaction conditions[a]



Entry	[Ni]	L*	Additive	Solvent	Yield (%)[a]	ee (%)[b]
1	$NiBr_2$·DME	**L1**	none	THF	39	−30
2	$NiBr_2$·DME	**L2**	none	THF	42	71
3	$NiBr_2$·DME	**L3**	none	THF	33	71
4	$NiBr_2$·DME	**L4**	none	THF	48	86
5	$NiBr_2$·DME	**L5**	none	THF	39	68
6	$NiBr_2$·DME	**L6**	none	THF	trace	--
7	$NiBr_2$·DME	**L7**	none	THF	trace	--
8	$NiBr_2$·DME	**L8**	none	THF	trace	--
9[c]	$NiBr_2$·DME	**L4**	none	2-MeTHF/DCE = 10/1	57	88
10[c,d]	$NiBr_2$·DME	**L4**	none	2-MeTHF/DCE = 10/1	51	89
11[c,d]	$NiBr_2$·DME	**L4**	$MgCl_2$	2-MeTHF/DCE = 10/1	72(70)[e]	92
12[c,d]	$NiCl_2$·DME	**L4**	$MgCl_2$	2-MeTHF/DCE = 10/1	51	87
13[c,d]	$NiBr_2$	**L4**	$MgCl_2$	2-MeTHF/DCE = 10/1	18	88

[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (1.3 equiv), **3a** (3.0 equiv), $NiBr_2$·DME (10 mol%), **L*** (10 mol%), TDAE (2.1 equiv) in THF (1.0 mL) under argon at rt for 12 h. Yields were NMR yields. [b]The enantioselectivity was determined by HPLC analysis. [c]1.0 mL of 2-MeTHF and 0.1 mL of DCE. [d]-5 °C for 24 h. [e]Isolated yields. L = ligand, 2-MeTHF = 2-methyltetrahydrofuran, DCE = 1,2-dichloroethane.

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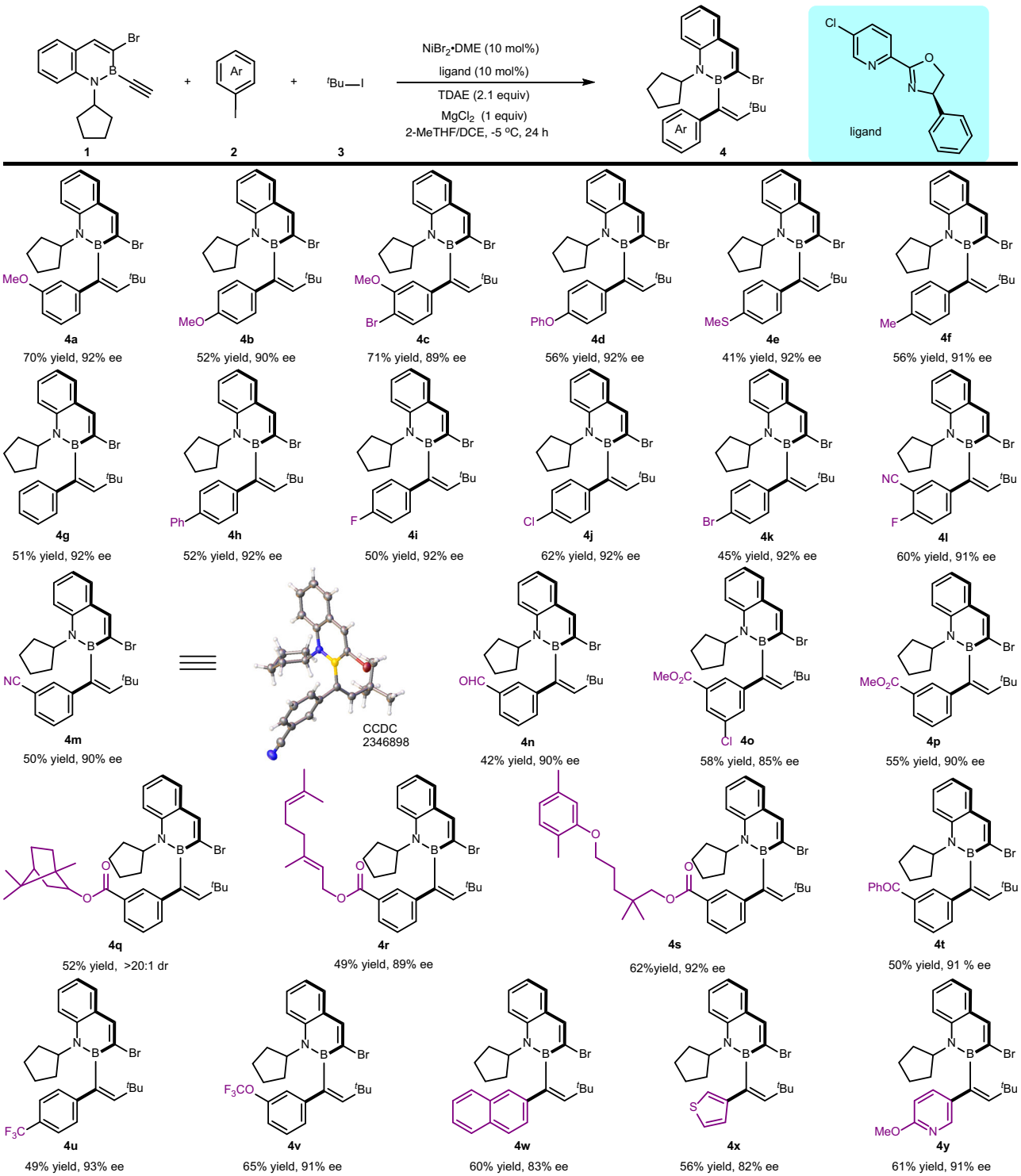

Fig. 2 | Substrate scope of aryl iodides. Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (1.3 equiv), **3a** (3.0 equiv), $NiBr_2$·DME (10 mol%), ligand (10 mol%), TDAE (2.1 equiv), $MgCl_2$ (1.0 equiv) in 1.0 mL of 2-MeTHF and 0.1 mL of DCE under argon at −5 °C for 24 h.

Next, the scope of ethynyl-azaborines in this protocol was also examined (Fig. 3). 1,2-benzazaborine ring of ethynyl-azaborines bearing alkyls, halides, and phenyl could all undergo this atroposelective coupling reaction to deliver the corresponding axially chiral alkenylborons **4z**-**4ae** in 55%–74% yields with 89%–94% ee. Notably, when the bromo group on ethynyl-azaborine was replaced by phenyl group, the reaction also performed smoothly under the standard conditions, providing the corresponding product **4af** in moderate yield and good enantioselectivity (41% yield, 83% ee). The installations of isopropyl or phenyl to the nitrogen atom had little effect on the enantioselectivities (**4ag** and **4ai**, 89% and 92% ee) for this protocol. Of note, further reduction of the steric hindrance of ethynyl-azaborine would decrease the enantioselectivity of the target product (**4ah**, 88% yield, 81% ee). Finally, the reaction of other unactivated tertiary alkyl iodides also worked well to deliver the desired axially chiral alkenylboron products **4aj**-**4al** in 42%–61% yields with 84%–87% ee.

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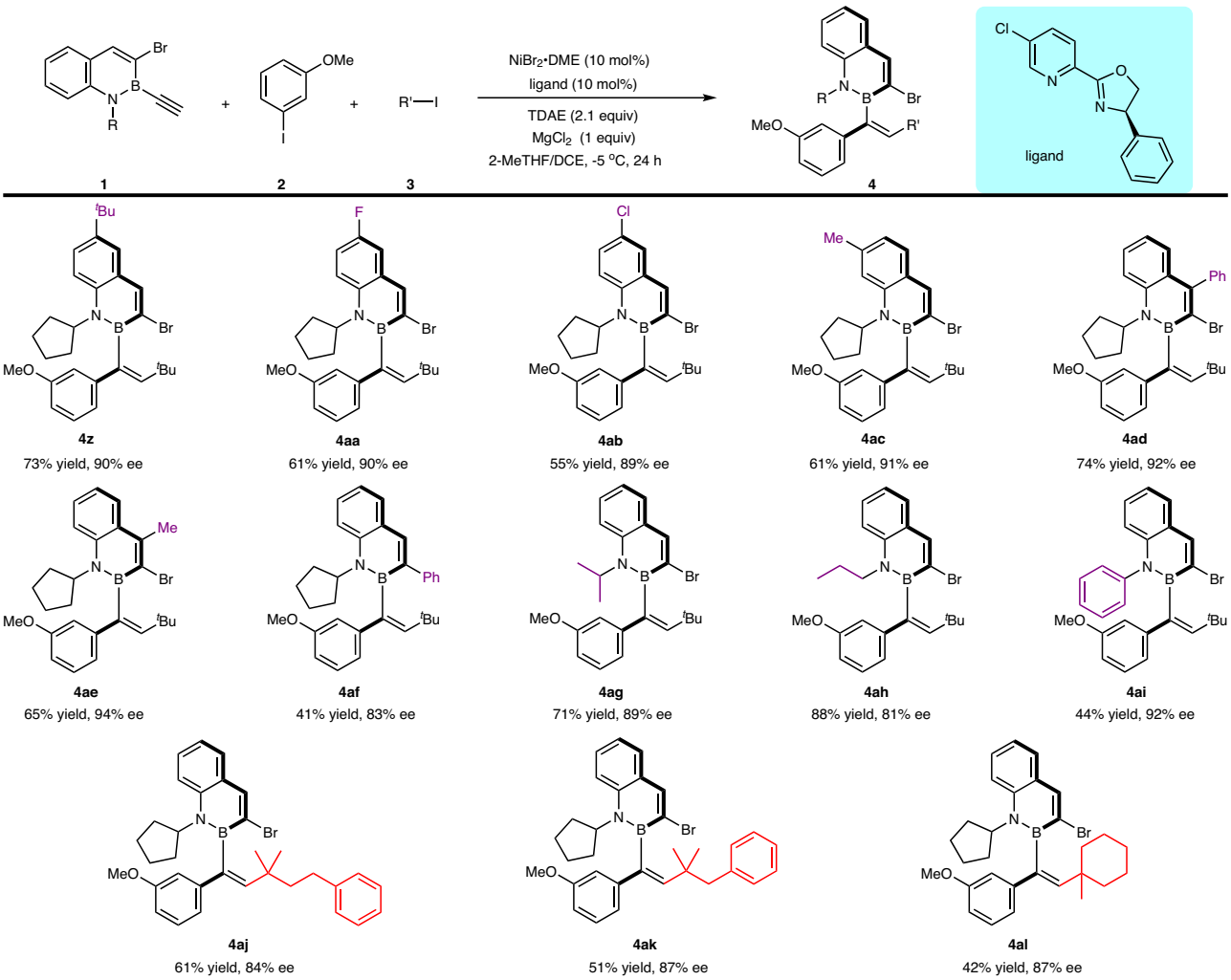

Fig. 3 | Substrate scope of ethynyl-azaborines and alkyl iodides. Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (1.3 equiv), **3a** (3.0 equiv), $NiBr_2$·DME (10 mol%), ligand (10 mol%), TDAE (2.1 equiv), $MgCl_2$ (1.0 equiv) in 1.0 mL of 2-MeTHF and 0.1 mL of DCE under argon at −5 °C for 24 h.

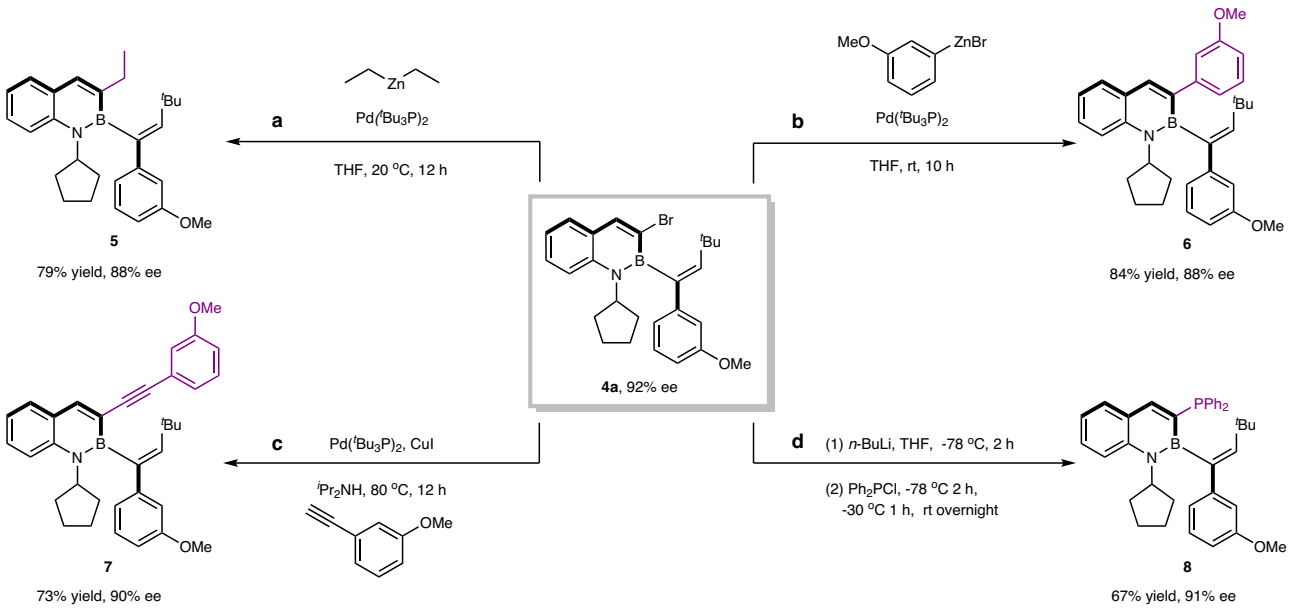

Fig. 4 | Synthetic transformations. a Pd-catalyzed Negishi cross-coupling of **4a** and alkyl zinc reagent. **b** Pd-catalyzed Negishi cross-coupling of **4a** and aryl zinc reagent. **c** Pd-catalyzed Sonogashira cross-coupling of **4a** and aryl alkyne. **d** Phosphonation reaction of **4a** via in situ axially chiral lithium intermediate.

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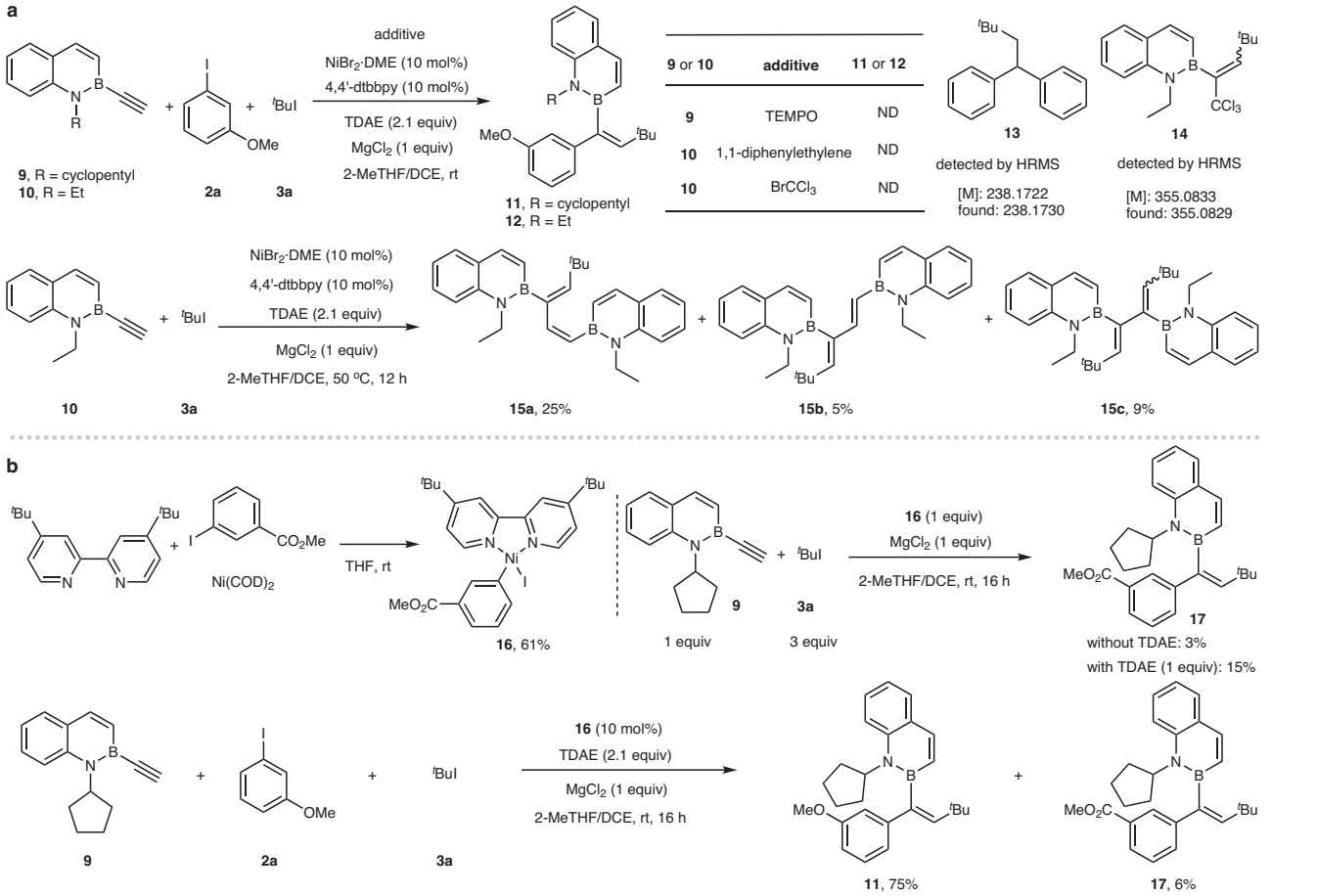

Fig. 5 | Mechanistic experiments. a Verification of the radical pathway. **b** Control reaction with Ar-Ni(II)-I complex **13**. TEMPO = 2,2,6,6-tetramethyl-1-piperinedinyloxy.

Downstream applications and transformations

The potential value of this reaction was further illustrated by synthetic transformations (Fig. 4). The resulting axially chiral alkenylboron products have been pre-installed with a bromo group, providing a handle for later functionalizations, which could undergo Negishi and Sonogashira coupling to achieve alkylation, arylation and alkynylation (**5, 6** and **7**). In addition, the new chiral (P, olefin) ligand **8** was successfully synthesized via in situ axially chiral lithium intermediate with high retention of the enantiopurity.

Mechanism investigations

To elucidate the radical process of this reductive coupling, control experiments were carried out (Fig. 5a). Firstly, TEMPO as a radical scavenger was added to the three-component reaction, and the formation of coupling product **11** was completely inhibited. Meanwhile, the addition of 1,1-diphenylethylene almost interrupted this reductive coupling reaction, whereas affording compound **13**, which may be derived from the addition of *tert*-butyl radical to 1,1-diphenylethylene. Fortunately, when the reaction of ethynyl-azaborine **10** was carried out in the presence of $BrCCl_3$, the corresponding vinyl-CCl_3 adduct (**14**) was detected by HRMS. Notably, the reaction of ethynyl-azaborine **10** with a smaller steric hindrance (ethyl group on N atom) in the absence of aryl iodide gave double addition products **15a** and **15b** as well as self-coupling product **15c**. Moreover, hydrogenation of α-borylvinyl radical intermediates was detected by GC-MS in the process of substrate investigation. These experiments suggest that an α-borylvinyl radical is involved in this coupling reaction. Then, several control experiments with nickel species were also carried out (Fig. 5b). Firstly, the stoichiometric reaction of aryl iodide, $Ni(COD)_2$ and 4,4′-dtbbpy furnished Ar-$Ni^{(II)}$-I complex **16**. Only trace amount of three-component coupling product **17** was obtained by mixing complex **16**, ethynyl-azaborine **9** and *tert*-butyl iodide, while more obvious product **17** could be observed when reductant TDAE were added. Moreover, when the catalytic amount of the complex **16** was employed in the cross-over reaction with 3-iodoanisol, compounds **11** and **17** were obtained in 75% yield and 6% yield, respectively. Overall, these results suggest that the reduction of complex **16** is necessary for this catalytic cycle.

Based on the results of the above experiments and previous literatures[43,56–58], we proposed a $Ni^{(I)}/Ni^{(II)}/Ni^{(III)}$ cycle for the asymmetric radical relayed reductive coupling (Fig. 6, left): the chiral $Ni^{(I)}$ species **A** generated in situ undergoes oxidative addition into the aryl iodine **2a** to afford the Ar-$Ni^{(III)}$L* intermediate **B**, which is reduced by TDAE to produce the Ar-$Ni^{(I)}$L* complex **C**. The activation of alkyl iodide **3a** by the Ar-$Ni^{(I)}$L* complex **C** generates an alkyl radical **D** and a Ar-$Ni^{(II)}$L* species **E**. Alkyl radical **D** undergoes regioselective addition to ethynyl-azaborine **1a** to afford the α-borylvinyl radical **F**, which can combine with Ar-$Ni^{(II)}$L* species **E** to deliver the $Ni^{(III)}$ intermediate **G**. The excellent *E*-stereoselectivity of alkene may stem from steric hindrance[32–40]. The final reductive elimination of the $Ni^{(III)}$ intermediate **G** yields axially chiral alkenylboron **4a** and regenerates the chiral $Ni^{(I)}$ catalyst. However, $Ni^{(0)}/Ni^{(I)}/Ni^{(II)}/Ni^{(III)}$ catalytic cycle can't completely rule out (Fig. 6, right), which involves the oxidative addition of Ni(0) species to aryl iodides.

In conclusion, we have developed a nickel-catalyzed atroposelective radical relayed reductive coupling reaction, leading to the formation of the challenging C-B axially chiral alkenylborons. The method features mild conditions, high enantioselectivity and excellent stereoselectivity. The key mechanistic feature of the process is the

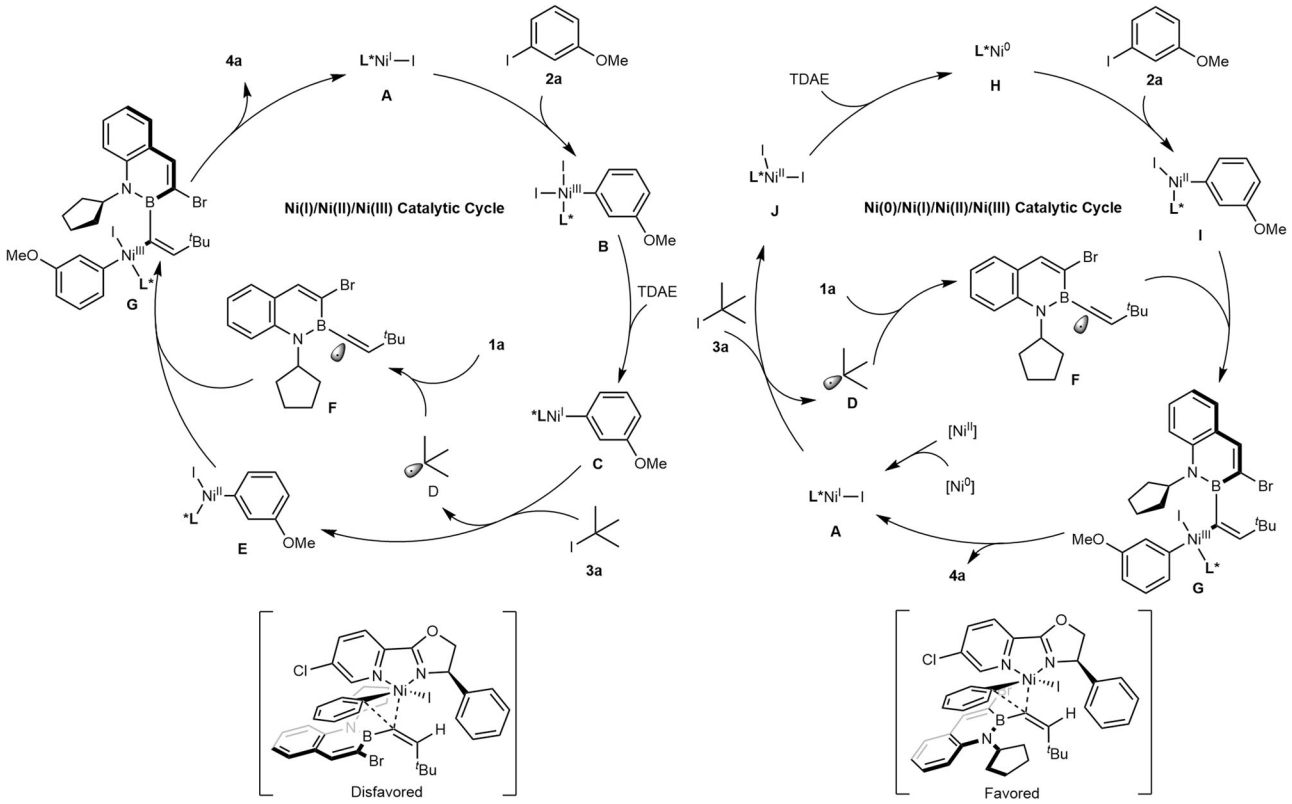

Fig. 6 | Possible reaction mechanism. Possible reaction mechanism about $Ni^{(I)}/Ni^{(II)}/Ni^{(III)}$ catalytic cycle and $Ni^{(0)}/Ni^{(I)}/Ni^{(II)}/Ni^{(III)}$ catalytic cycle. L = ligand.

generation and transformation of a boron-stabilized vinyl radical. It is expected that the concept obtained here will encourage the development of more asymmetric transformations around the multifunctional α-borylvinyl radical intermediates.

Methods

General procedure for the synthesis of C-B axially chiral alkenylborons

In a glove box, a 10 mL Schlenk tube was charged with $NiBr_2$·DME (0.01 mmol, 10 mol%), ligand (0.01 mmol, 10 mol%), the bromination of B-ethynyl-2,1-borazaronaphthalene (0.1 mmol, 1.0 equiv), aryl iodide (0.13 mmol, 1.3 equiv), alkyl iodide (0.3 mmol, 3 equiv), $MgCl_2$ (0.1 mmol, 1.0 equiv), 2-Me-THF (1 mL) and DCE (0.1 mL). The resulting mixture was stirred at room temperature for 1 min. Then TDAE (0.21 mmol, 2.1 equiv) was added. The reaction tube was taken out of the glove box and reacted at −5 °C for 24 h. Upon completion, proper amount of silica gel was added to the reaction mixture. After removal of the solvent, the crude reaction mixture was purified on silica gel to afford **4**.

Data availability

The data that support the findings of this study are available within the article and its Supplementary Information files. All other data are available from the corresponding author upon request. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers 2346898 (**4 m**). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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Q.S. and K.Y. conceived and directed the project. Q.W., T.R., H.Y., and Z.Y. performed experiments. Q.W. prepared the Supplementary Information. Q.S. and K.Y. wrote the paper. All authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

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