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Stereoselective Functionalization of Racemic Cyclopropylzinc Reagents via Enantiodivergent Relay Coupling

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ABSTRACT: Efficient construction of optically pure molecules from readily available starting materials in a simple manner is an ongoing goal in asymmetric synthesis. As a straightforward route, transition-metal catalyzed enantioconvergent coupling between widely available secondary alkyl electrophiles and organometallic nucleophiles has emerged as a powerful strategy to construct chiral center(s). However, the scope of racemic secondary alkylmetallic nucleophiles for this coupling remains limited in specific substrates due to the difficulties in stereoselective formation of the key alkylmetal intermediates. Here, we report an enantiodivergent strategy to efficiently achieve an array of synthetically useful chiral cyclopropanes, including chiral fluoroalkylated cyclopropanes and enantiomerically enriched cyclopropanes with chiral side chains, from racemic cyclopropylzinc reagents. This strategy relies on a one-pot, two-step enantiodivergent relay coupling (EDRC) process of the racemic *cis*-cyclopropylzinc reagents with two different electrophiles, which involves kinetic resolution of racemic *cis*-cyclopropylzinc reagents through a nickel-catalyzed enantioselective coupling with alkyl electrophiles, followed by a stereospecific relay coupling of the remaining enantiomeric cyclopropylzinc reagent with various electrophiles, to produce two types of functionalized chiral cyclopropanes with opposite configuration on the cyclopropane ring. These chiral cyclopropanes are versatile synthons for diverse transformations, rendering this strategy effective to structurally diversified molecules of medicinal interests.

INTRODUCTION

The development of new and efficient methods to access optically pure compounds is one of the core research areas in organic synthesis and related industries.¹ Among various elegant approaches in asymmetric synthesis, nickel catalyzed enantioconvergent cross-coupling reactions developed by Fu and coworkers have emerged as a powerful strategy (Figure. 1a).² This strategy efficiently access various chiral molecules through the coupling of widely available racemic secondary alkyl halides with readily synthesized organometallic nucleophiles.³ However, the scope of racemic secondary alkylmetallic nucleophiles for this enantioconvergent coupling remains limited.^{2a,4} To date, only rare examples via this strategy have been described,⁵ using specific racemic nucleophiles, such as benzylic Grignard reagent (PhCHMeMgCl)^{5a} and α -zincated *N*-Boc-pyrrolidine^{5b,c}, to stereoselectively control their configurations by chiral nickel catalyst. Very recently, an elegant nickel-catalyzed doubly enantioconvergent coupling of racemic β -zincated amides with alkyl halides was reported, providing an efficient access to chiral molecules.⁶ Using well-defined enantioenriched alkylmetallic nucleophiles is an alternative strategy,^{4,7} but requires additional steps to prepare the enantiomerically enriched nucleophiles,⁷ restricting widespread synthetic applications of these methods. We envisioned that, instead

of an enantioconvergent process involving one racemic electrophile to produce one chiral product (one-to-one), an enantiodivergent process involving one racemic alkylmetallic reagents to produce two chiral products (one-to-two) would be a new strategy for asymmetric coupling chemistry (Figure 1b). In contrast to the traditional parallel kinetic resolution process,⁸ this process relies on a one-pot two-step enantiodivergent relay coupling via nickel catalysis, which has not been reported so far. In this process, the chiral nickel catalyst enables enantioselective coupling of one enantiomer from the racemic alkylmetallic nucleophiles with an electrophile via kinetic resolution to produce one chiral product. Subsequently, the remaining nucleophilic enantiomer undergoes a stereospecific coupling with another electrophile, which is added after the first step, to afford the corresponding functionalized chiral product, bearing a chiral center opposite to that in the first product. This one-pot, two-step enantiodivergent relay coupling (EDRC) can provide an array of structure and chirality diversified molecules in a straightforward and synthetically simple manner.

In this study, we chose racemic cyclopropylzinc reagents as the nucleophiles, because the resulting chiral cyclopropane rings are of great interest both in organic synthesis and medicinal chemistry.⁹ For example, bioactive molecules bearing a cyclopropane structural motif have

been used as anti-HCV (hepatitis C virus),^{10a} anti-HIV,^{10b} and anti-cancer agents^{10c,d} (Figure 1c). In this context, various useful asymmetric synthesis of functionalized cyclopropanes, including enantioselective cyclopropanation of alkenes,^{11a} asymmetric transformations of cyclopropenes,^{11b} and enantioselective C-H bond functionalization of cyclopropanes,^{11c} have been developed previously. For more synthetic diversity and simplicity, the aforementioned hypothesized EDRC between racemic cyclopropyl nucleophiles and electrophiles would be a promising strategy to access diversified chiral cyclopropanes, which enables to enantioselectively and stepwisely form two types of *cis*-cyclopropanes bearing opposite configuration on the cyclopropane ring. In particular, this strategy is also compatible to racemic secondary alkyl electrophiles and enables access to enantiomerically enriched cyclopropanes with chiral side chains, which otherwise are difficult to prepare through conventional methods.

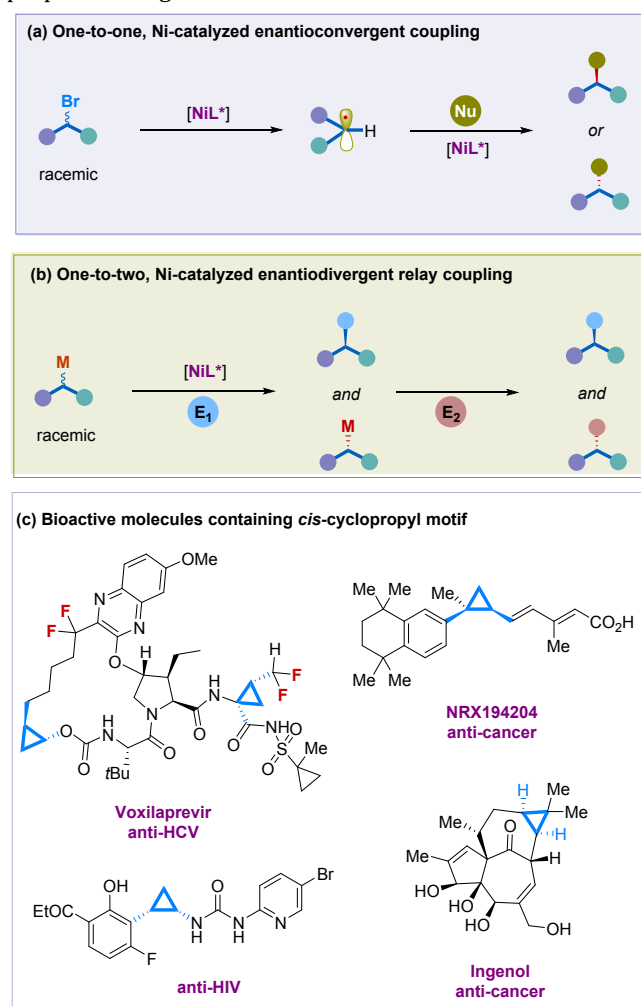


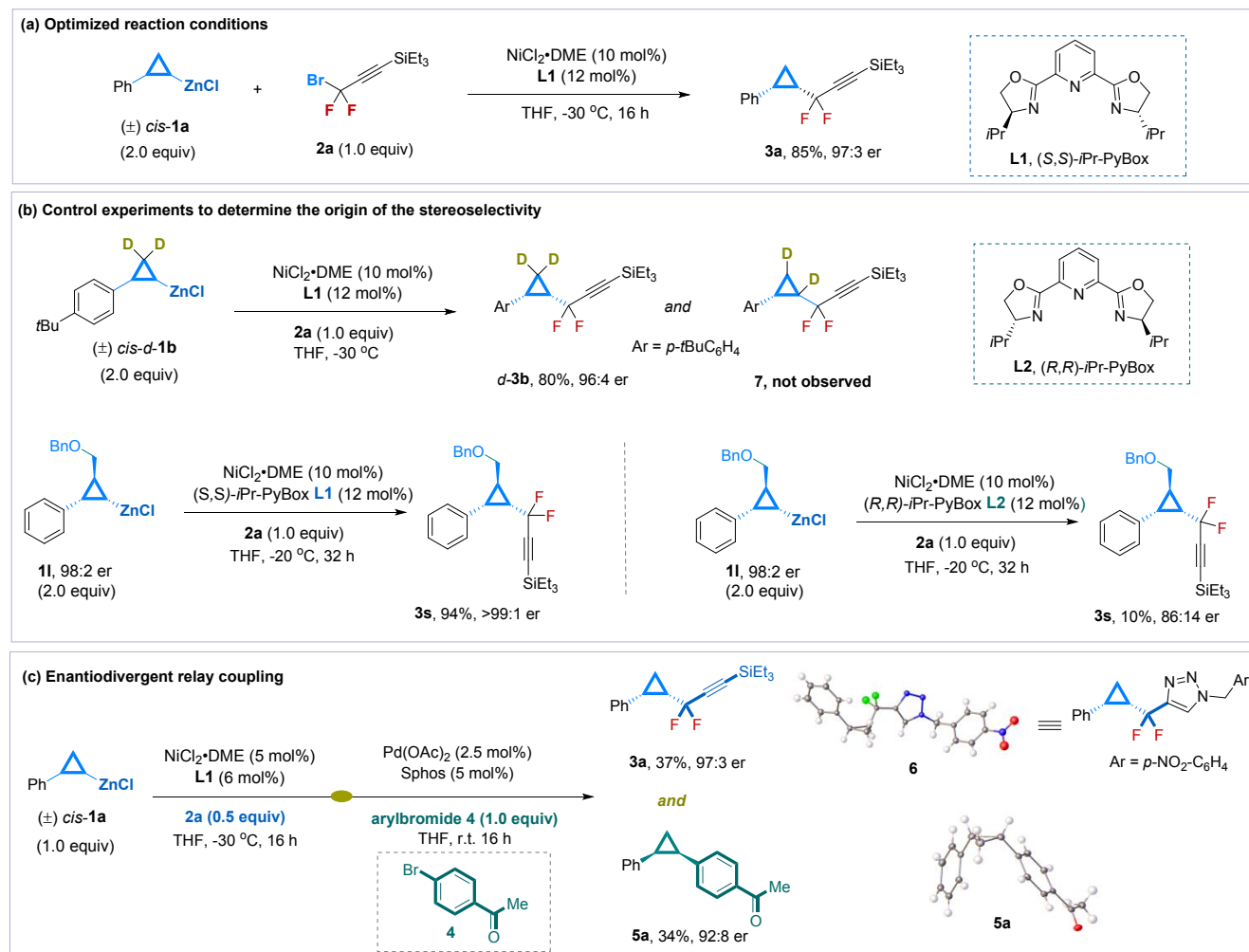
Figure 1. (a) Nickel-catalyzed enantioconvergent coupling of racemic alkyl electrophiles with organometallic nucleophiles, one-to-one strategy. (b) Outline of the current one-to-two strategy for enantiodivergent reaction of racemic alkylmetallic nucleophiles with two different

electrophiles (E_1 and E_2) stepwise. (c) Selected bioactive molecules containing *cis*-cyclopropyl structural motif.

RESULTS AND DISCUSSION

To investigate the advances of such an EDRC reaction, initially, we focused on nickel catalyzed kinetic resolution of racemic *cis*-cyclopropylzinc reagent (\pm) *cis*-**1a**^{9c} in the presence of *gem*-difluoropropargyl bromide **2a** (Scheme 1a). To date, the catalytic asymmetric fluoroalkylation remains a challenging topic¹² and the asymmetric coupling of α -*gem*-difluoroalkyl electrophiles via transition-metal catalysis has not been reported yet.^{13, 14} We found that the combination of nickel catalyst $\text{NiCl}_2\cdot\text{DME}$ (DME, dimethoxyethane), a tridentate chiral ligand (*S,S*)-*i*Pr-PyBox (**L1**, PyBox, pyridine-2,6-bis(oxazoline)), 2.0 equiv of *cis*-**1a** and 1.0 equiv of **2a** achieved the *gem*-difluoropropargylated cyclopropane **3a** in 85% yield with 97:3 er value at $-30\text{ }^\circ\text{C}$ (Scheme 1a). PyBox ligands bearing bulky substituents or a rigid skeleton diminished the enantioselectivity (For details, see the Supporting Information). This kinetic resolution process was supported by the results of several control experiments. As depicted in Scheme 1b, the reaction result of *gem*-deuterated cyclopropylzinc (\pm) *cis*-*d*-**1b** with **2a** excluded the β -H elimination/alkene insertion pathway, as no deuteride-migration product **7** was observed. The individual reaction of **2a** with enantioenriched cyclopropylzinc **11**¹⁵ using either enantiomer of *i*Pr-PyBox provided configuration retained product **3s**, where **L1** provided **3s** with much higher yield (94%) and er value (>99:1) than its enantiomer (*R,R*)-*i*Pr-PyBox **L2** (10% yield, 87:13 er). These results demonstrate that the kinetic resolution by the proper chiral nickel catalyst is the key aspect to dominate the enantioselectivity to form the chiral cyclopropane. Thus, this nickel-catalyzed coupling offers a good opportunity for the stereospecific relay coupling of the remaining enantiomer to produce another chiral cyclopropane.

Encouraged by these results, we next performed EDRC to assess the viability of the hypothesized enantiodivergent process (Scheme 1c). After nickel-catalyzed enantioselective coupling of 1.0 equiv of (\pm) *cis*-**1a** with **2a** (0.5 equiv), catalytic amount of palladium catalyst $\text{Pd}(\text{OAc})_2$, phosphine ligand Sphos, and another electrophile arylbromide **4** (1.0 equiv) were then used for the relay coupling with the remaining nucleophilic enantiomer. The coupling proceeded smoothly at room temperature, with good tolerance to the nickel catalyst previously added in the system. The overall reaction finally produced two chiral functionalized cyclopropanes **3a** and **5a** in good yields and high optical purities. The single-crystal X-ray diffraction studies of **5a** and **6**, derived from **3a** by a [3+2] cycloaddition, showed that compounds **3a** and **5a** possess opposite configuration on the cyclopropane (Scheme 1c), thus confirming the stereochemistry of the current enantiodivergent process.



Scheme 1. (a) Optimized reaction conditions of nickel-catalyzed enantioselective coupling of racemic (\pm) *cis*-**1a** with **2a**. (b) Control experiments to determine the origin of the stereoselectivity in the nickel-catalyzed coupling (c) Enantiodivergent relay coupling of racemic (\pm) *cis*-**1a** with **2a** and aryl bromide **4**.

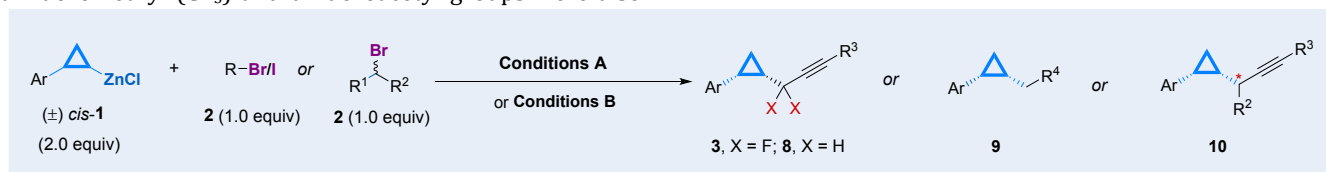
With the optimized reaction conditions in hand, we examined the scope of this nickel-catalyzed enantioselective coupling of racemic cyclopropylzinc reagents (\pm) *cis*-**1** with a variety of propargyl and allyl bromides (Scheme 2a). Overall, aromatic ring on (\pm) *cis*-**1** bearing either electron-donating or electron-withdrawing substituents underwent the coupling efficiently with high enantioselectivities (**3a-3i**). A range of *gem*-difluoropropargyl bromides **2** were applicable to the reaction (**3j-3p**) (Scheme 2a). Notably, propargyl bromides with aliphatic chains underwent the coupling smoothly without formation of allenic side products (**3l-3n**). Various functionalities, including trifluoromethoxyl, silyl, chloro, benzyloxyl, silyl ether, and carbamate moieties (**3e-3h**, **3l-3n**) were well tolerated. Even complex molecules derived substrates, such as carbohydrate- and steroid-containing *gem*-difluoropropargyl bromides, were also competent coupling partners (**3o** and **3p**). Trisubstituted cyclopropanes with three vicinal chiral centers could be efficiently accessed by the current nickel-catalyzed process with high enantioselectivities and good yields (**3q-3s**). In addition to *gem*-difluoropropargyl bromides, non-fluorinated substrates, propargyl and allyl bromides, also provided the corresponding products efficiently with comparable

enantioselectivities (**8a-8e**, **9a-9c**). In the case of unactivated alkyl halide, the corresponding product **9d** was obtained in 60% yield and 81:19 er, indicating that an alkyl electrophile with a rigid side chain may benefit the enantioselectivity. The reaction of racemic *trans*-cyclopropylzinc reagent (\pm) *trans*-**1a** with **2a** was also examined, providing the desired product in 82% yield with a low er value (65:35) (see the Supporting Information). Additionally, replacing the aryl group on the cyclopropyl ring with an alkyl substituent led to low enantioselectivity (60:40 er) (see the Supporting Information) and no reaction occurred with cyclobutyl- or cyclopentylzinc reagents as the nucleophiles. These results suggest that the use of aryl substituted *cis*-cyclopropylzinc reagents is critical for the current asymmetric coupling.

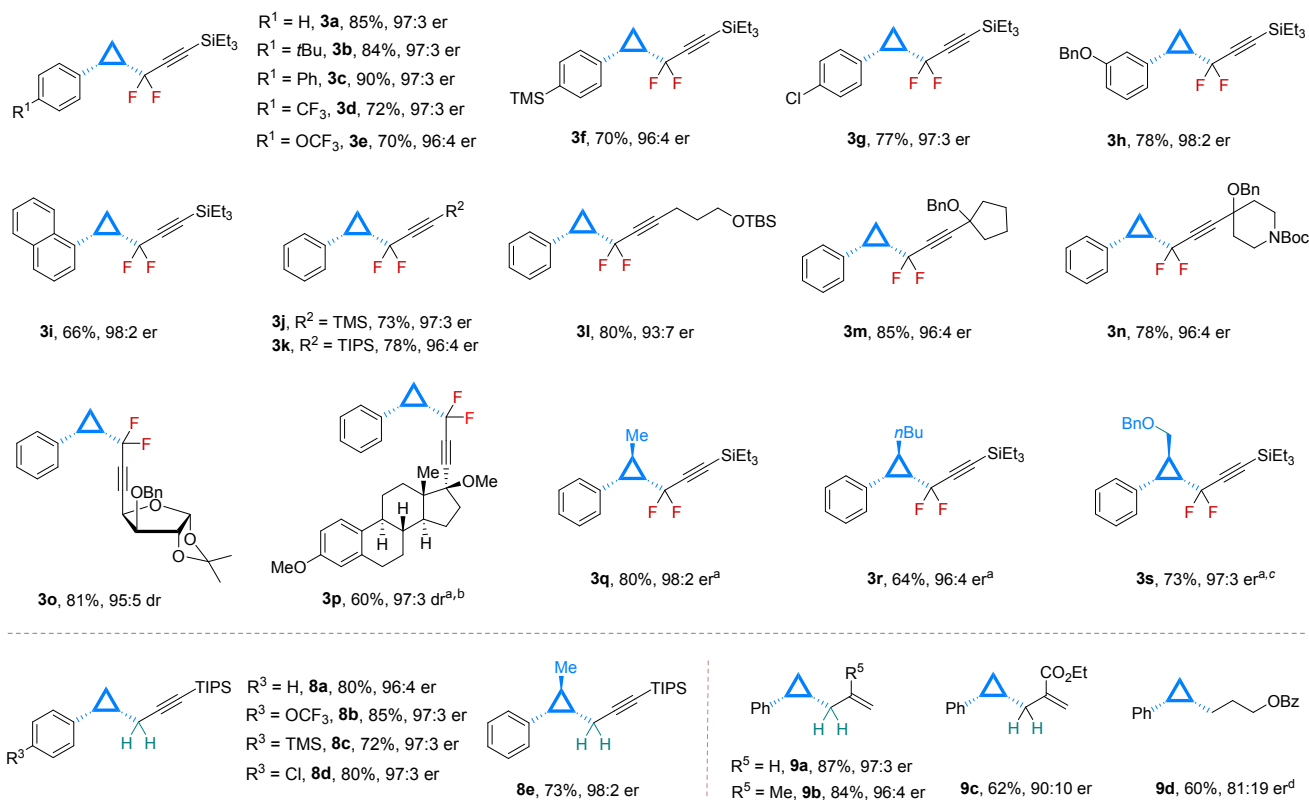
We next examined the cross-coupling of secondary alkyl electrophiles, racemic secondary propargyl bromides, with (\pm) *cis*-**1** (Scheme 2b). Because four possible stereoisomeric products would be formed, catalytic asymmetric cross-coupling of two racemic coupling partners is challenging for controlling stereoselectivity.^{5c,6} In the current process, excellent optical purities and high diastereoselectivities were obtained from the reaction of racemic secondary

difluoromethylated propargyl bromides with (\pm) *cis*-**1**, using NiBr₂·DME (10 mol%) and (*R,R*)-CyPybox (13 mol%) in dioxane at -20 °C (**10a**–**10g**). Substrates bearing trifluoromethyl (CF₃) and difluoroacetyl groups were also

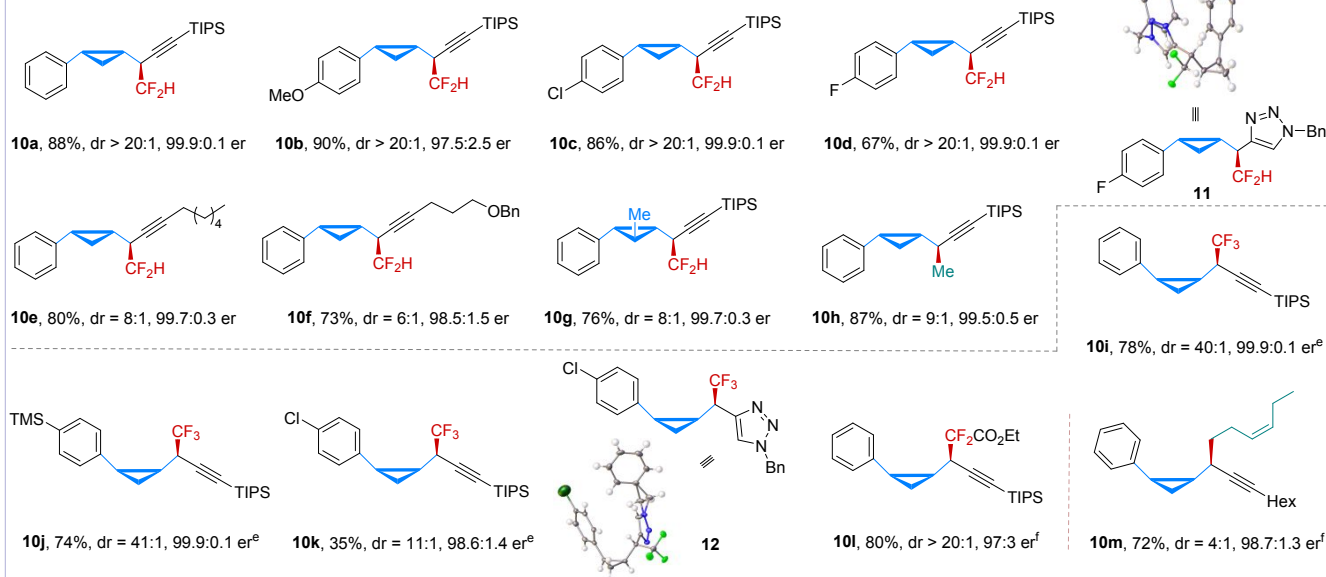
applicable to the reaction, providing the corresponding products **10i**–**10l** with excellent enantioselectivities and high diastereoselectivities.



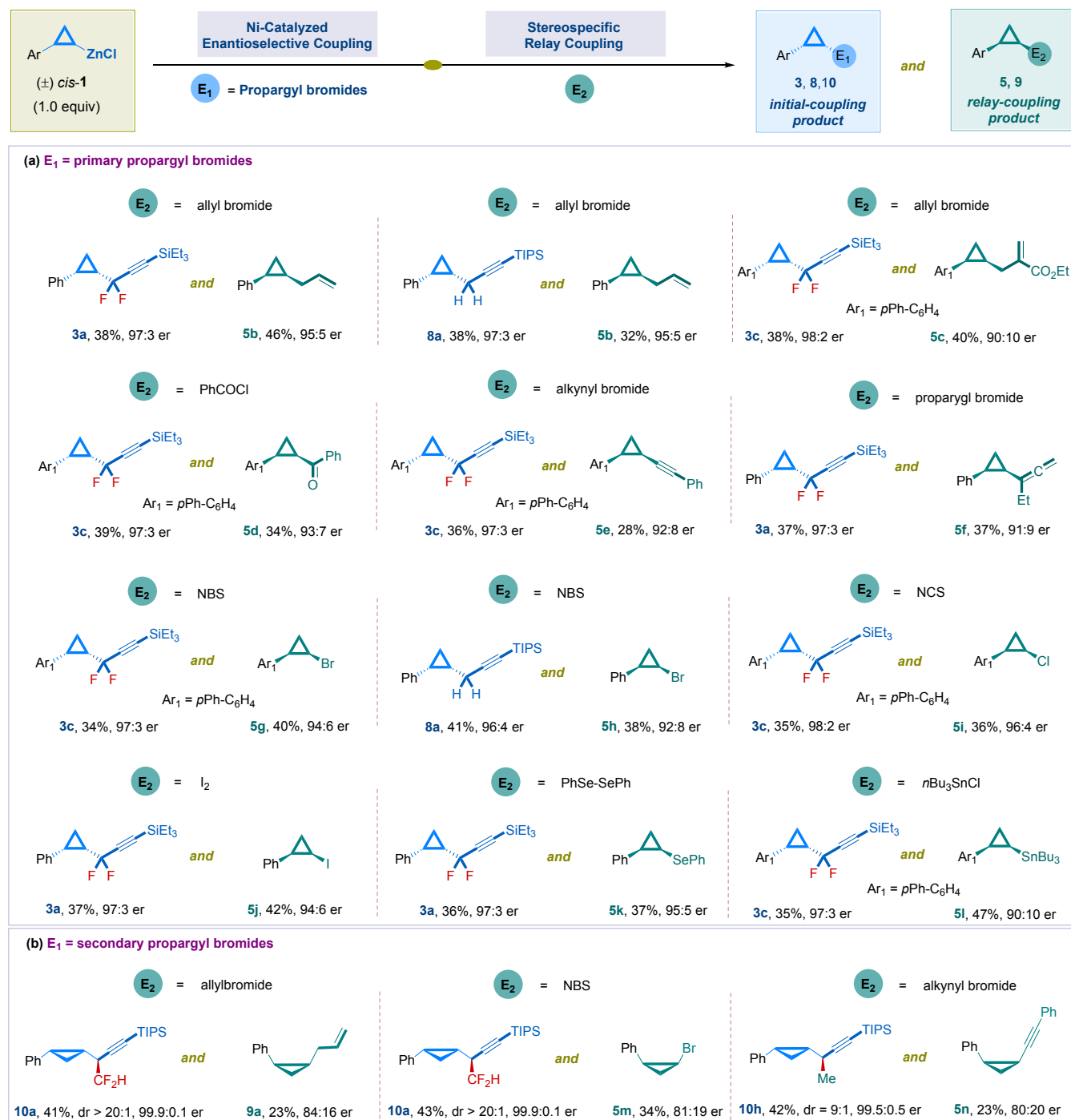
a Primary alkyl electrophiles (Conditions A)



b Racemic secondary alkyl electrophiles (Conditions B)



Scheme 2. Reaction conditions (unless otherwise specified): **(a)** Reaction with primary alkyl electrophiles. **Conditions A:** (\pm) *cis*-**1** (0.30~0.34 M in THF, 1.0 mmol, 2.0 equiv), **2** (0.5 mmol, 1.0 equiv), NiCl₂·DME (10 mol%), (*S,S*)-*i*Pr-Pybox **L1** (12 mol%), THF (3 mL), -30 °C, 32 h. ^aReaction run at -20 °C. ^bReaction run on 0.3 mmol scale. ^cReaction run on 0.2 mmol scale. ^dAlkyl iodide and CH₂Cl₂ (3 mL) were used. **(b)** Reaction with racemic secondary alkyl electrophiles. **Conditions B:** (\pm) *cis*-**1** (0.33 M in THF, 0.6 mmol, 2.0 equiv), **2** (0.3 mmol, 1.0 equiv), NiBr₂·DME (10 mol%), (*R,R*)-CyPybox (13 mol%), -20 °C, 1,4-dioxane (1 mL), 24 h. ^eReaction run at -30 °C with **L1** (13 mol%). ^fReaction run at -20 °C with **L1** (13 mol%).



Scheme 3. Substrate scope of the EDRC of racemic (\pm) *cis*-**1** with diverse electrophiles. **(a)** Reactions with primary propargyl bromides and other electrophiles. **(b)** Reactions with secondary propargyl bromides and other electrophiles. See Supporting Information for details.

These fluorine-containing groups play privileged roles in drug discovery and development, as they can improve the

metabolic stability, enhance the lipophilicity and increase the dipole moments of the bioactive molecules.¹⁶

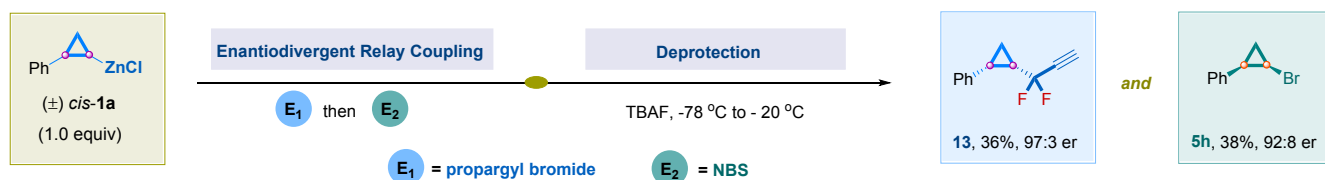
Consequently, these transformations provide useful tools for applications in the synthesis of interesting new biological active molecules. The coupling can also extend to the nonfluorinated propargyl bromides with excellent enantioselectivities and moderate diastereoselectivities (**10h** and **10m**). Remarkably, compound **10g** containing four contiguous stereocenters, which is difficult to prepare by conventional methods from simple starting materials in one step, can be expediently accessed with high stereoselectivity and high efficiency, demonstrating the advantages of this process further. The absolute configurations of the final enantiomerically enriched products **3**, **8-10** were assigned by crystallographic characterization of compounds **6**, **11** and **12**, which were derived from compounds **3a**, **10d**, and **10k**, respectively, through a [3+2] cyclization with azides.

The high enantioselectivity and reaction efficiency of this nickel-catalyzed process encourages evaluating the scope of the EDRC with (\pm) *cis*-**1** and a variety of readily available carbon and halogen electrophiles as well as organometallic and chalcogen reagents. As depicted in Scheme 3, besides the arylbromide (Scheme 1c), a range of allyl bromides, benzoyl chloride, alkynyl bromide, and propargyl bromide (**5b-5f**), were able to undergo the stereospecific relay

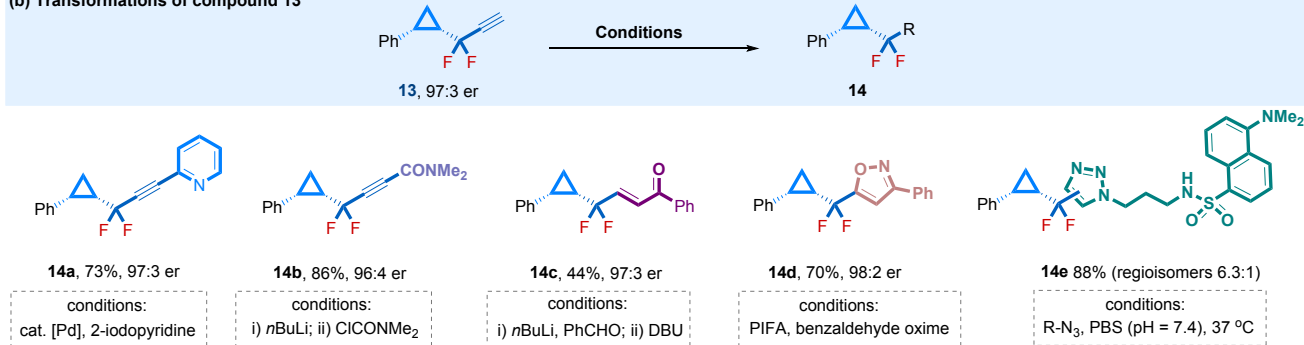
coupling in the presence of copper after the nickel-catalyzed enantioselective coupling of (\pm) *cis*-**1** with primary propargyl bromides.

High enantioselectivities and good yields of compounds **3**, **5** and **8** were achieved (**3a**, **3c**, **5b-5f**, **8a**). In particular, the allenic product **5f**, instead of propargylic compound, was obtained in high optical purity when using propargyl bromide as an electrophile, which is in contrast to the preceding nickel catalyzed propargylic coupling. In addition to carbon electrophiles, *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), and iodine (I_2) were also applicable to the current process and expediently provided the widely used chiral halogenated cyclopropanes **5g-5j**. This one-pot, two-step enantiodivergent process was further exploited by addition of diphenyl diselenide (PhSe-SePh) or tributyltin chloride (*n*Bu₃SnCl) to achieve versatile synthetic synthons, chiral cyclopropylselenium and cyclopropyltin reagents (**5k** and **5l**), respectively. With respect to the secondary alkyl electrophiles (Scheme 3b), the EDRC reactions also proceeded smoothly with allyl bromide, NBS, and alkynyl bromide as trapping reagents (**9a**, **5m**, **5n**), thus demonstrating the generality of this strategy.

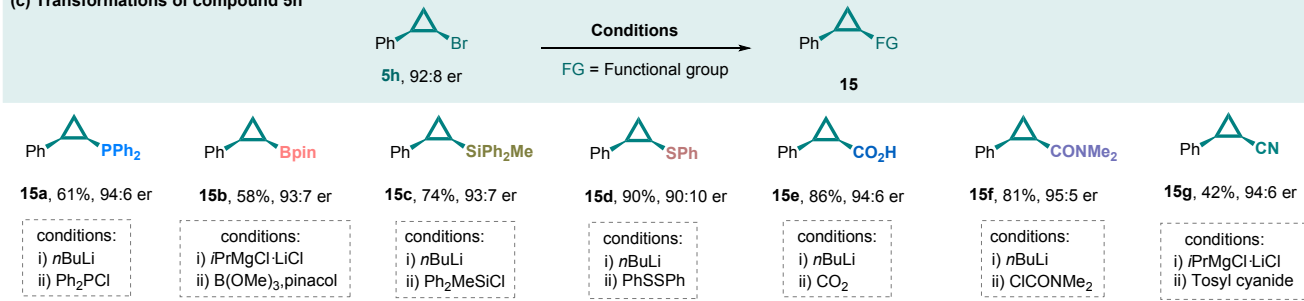
(a) One pot synthesis of compound **13** and **5h**



(b) Transformations of compound **13**



(c) Transformations of compound **5h**



Scheme 4. Diverse transformations of chiral cyclopropanes. (a) One-pot synthesis of compound **13** and **5h**. (b) Transformations of chiral *gem*-difluoropropargylated cyclopropane **13**. (c) Transformations of chiral cyclopropyl bromide **5h**. See Supporting Information for details.

To demonstrate the utility of this enantiodivergent process further, diverse transformations of the chiral cyclopropanes generated from EDRC of racemic (\pm) *cis*-**1a** with **2a** and NBS were conducted (Scheme 4). After deprotection of silyl group by tetrabutylammonium fluoride (TBAF), the resulting chiral terminal alkyne **13** was used for the diversity-oriented synthesis through transformations of carbon-carbon triple bond (Scheme 4b). Pyridyl and amide moieties were directly connected to the terminal alkyne **13** by Sonogashira reaction (**14a**) and nucleophilic addition of alkynyllithium to carbamic chloride (**14b**), respectively. The carbon-carbon triple bond can also be converted into a synthetically useful handle α,β -unsaturated ketone **14c**^{17a} or a heteroarene isoxazole **14d** of medicinal interest^{17b} via simple transformations. In particular, the copper-free click reaction of **13** with dansyl fluorophore derived azide proceeded smoothly in phosphate buffered saline (PBS, pH 7.4) at 37 °C (**14e**). In contrast, the analogous non-fluorinated alkynes usually lead to poor yields under identical reaction conditions, demonstrating the importance of CF₂ moiety adjacent to alkyne for the high reactivity.¹⁸

As a useful chiral pool and versatile linchpin, chiral cyclopropyl bromide **5h** with opposite configuration to **13** was used to install an array of functionalities, including phosphine, boronate, silyl, thiophenyl, carboxylic acid, amide, and nitrile moieties through lithium-bromide or magnesium-bromide exchange, followed by trapping with corresponding electrophiles (Scheme 4c). These transformations proceeded smoothly with retention of the configuration¹⁹ (Supporting Information Figures S1-S4). Specifically, the resulting chiral cyclopropyl phosphine may serve as a novel chiral ligand for asymmetric synthesis (**15a**);²⁰ the direct formation of enantioenriched boronic ester **15b** provides an alternative route to prepare chiral cyclopropanes by Suzuki reaction or other transformations. Additionally, the installation of silyl and thiophenyl groups is also of synthetic advantage (**15c**, **15d**) for subsequent derivatization.²¹ Finally, the efficient synthesis of **15e-15g** also illustrates the synthetic utility of this method further, as chiral cyclopropyl carboxylic acid, amide, and cyanide are the important building blocks in the synthesis of bioactive molecules.

CONCLUSIONS

In conclusion, we have developed an enantiodivergent strategy to stereoselectively access chiral cyclopropanes based on nickel-catalyzed enantioselective coupling of racemic *cis*-cyclopropylzinc reagents. These transformations demonstrate that this one-to-two enantiodivergent process is a useful strategy for asymmetric synthesis of diversified cyclopropanes that are valuable in organic synthesis and medicinal chemistry. The nickel-catalyzed enantioselective coupling of racemic cyclopropylzinc reagents with alkyl electrophiles, particularly, with racemic secondary alkyl electrophiles as well as the following stereospecific relay coupling, provides a new strategy for asymmetric synthesis.

ASSOCIATED CONTENT

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/xxxx>. Experimental procedures, characterization of new compounds, X-ray data, and computational details (PDF).

X-ray crystal structure of compound **5a** (CIF)

X-ray crystal structure of compound **5g** (CIF)

X-ray crystal structure of compound **6** (CIF)

X-ray crystal structure of compound **11** (CIF)

X-ray crystal structure of compound **12** (CIF)

X-ray crystal structure of compound **15f** (CIF)

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Author Contributions

[†]Lun An and Fei-Fei Tong contributed equally.

Notes

The authors declare no competing financial interest.

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