here required only 13 linear synthetic steps. Critical to our strategy was the application of thermodynamic stereocontrol in the dimerization of persistent free radicals, a process that we have extensively characterized. The efficiency of the route has enabled the preparation of sufficient quantities of material that the biological activities of these natural products can now be more thoroughly evaluated.

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SUPPLEMENTARY MATERIALS

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ASYMMETRIC CATALYSIS

A general, modular method for the catalytic asymmetric synthesis of alkylboronate esters

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Alkylboron compounds are an important family of target molecules, serving as useful intermediates, as well as end points, in fields such as pharmaceutical science and organic chemistry. Facile transformation of carbon-boron bonds into a wide variety of carbon-X bonds (where X is, for example, carbon, nitrogen, oxygen, or a halogen), with stereochemical fidelity, renders the generation of enantioenriched alkylboronate esters a powerful tool in synthesis. Here we report the use of a chiral nickel catalyst to achieve stereoconvergent alkyl-alkyl couplings of readily available racemic α-haloboronates with organozinc reagents under mild conditions. We demonstrate that this method provides straightforward access to a diverse array of enantioenriched alkylboronate esters, in which boron is bound to a stereogenic carbon, and we highlight the utility of these compounds in synthesis.

Organoboron compounds play an important role in fields ranging from materials science to biochemistry to organic synthesis (*1*, *2*); for example, in organic chemistry, they serve as products or as reaction partners in powerful transformations such as the hydroboration of olefins (*3*) and the Suzuki cross-coupling (*4*). Although impressive progress has been made in organoboron chemistry during the past decades, substantial opportunities remain, including expanding their role in enantioselective synthesis. For instance, the development of methods for the asymmetric synthesis of alkylboron compounds wherein boron is attached to a stereogenic carbon (Fig. 1A) is an important objective, given their utility both as end points (e.g., Velcade) (*5*, *6*) and as versatile precursors to a wide range of other valuable families of molecules, including enantioenriched amines and alcohols (*1*, *7*, *8*). In particular, alkylboronate esters (Fig. 1A) simultaneously possess desirable aspects of stability (including to air and moisture, as well as configurational stability) and of reactivity (stereospecific conversion of the C–B bond to C–C, C–N, C–O, C–halogen, and other C–heteroatom bonds).

Whereas early efforts to synthesize enantioenriched alkylboron compounds focused primarily on the use of stoichiometric chiral reagents to control the stereochemistry of the product (*8*, *9*), recent investigations have increasingly focused on exploiting chiral catalysts. Virtually all methods furnish chiral alkylboronate esters that must contain a specific functional group in a specific position—for example, an aryl, an alkenyl, or a directing group (*10*–*12*).

Matteson has developed a powerful, versatile strategy for the synthesis of alkylboronate esters through the coupling of α-haloboronates with organolithium or organomagnesium reagents (Fig. 1B) (*13*). This reaction proceeds through initial addition of the organometallic nucleophile to the electrophilic boron, followed by a 1,2-migration (substitution with inversion) to form the desired carbon-carbon bond. The Matteson reaction serves as the foundation for a general, modular method for the synthesis of alkylboronate esters, including an enantioselective process that uses a stoichiometric chiral auxiliary (Fig. 1C); moreover, the reaction can be applied in an iterative procedure

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that affords homologated alkylboronate esters (Fig. 1D). Aggarwal has developed an elegant related approach that uses enantioenriched α-lithiated benzoates to produce these targets, including in an iterative fashion (*14*).

Nevertheless, areas for improvement persist. For example, it would be attractive to exploit a chiral catalyst, rather than a stoichiometric chiral reagent, to control enantioselectivity; this is essential for the synthesis at will of any of the possible stereoisomers in the iterative strategy illustrated in Fig. 1D. Furthermore, it is desirable to use nucleophilic coupling partners other than highly reactive organolithium and organomagnesium reagents, because they limit the range of tolerated functional groups. Here we address these challenges by achieving a Matteson-like coupling in a mechanistically distinct fashion: Specifically, we use a chiral nickel catalyst to cross-couple racemic α-haloboronates with organozinc reagents, thereby generating alkylboronate esters with high enantioselectivity (Fig. 1, E to G).

We have recently established that nickel complexes catalyze the coupling of a broad range of alkyl electrophiles with a diverse array of organometallic nucleophiles, often with high levels of enantioselectivity (*15*–*17*); these cross-couplings proceed through organonickel intermediates that are generated and consumed in elementary steps such as oxidative addition, transmetalation, and reductive elimination (*18*). In pursuing a transition metal–catalyzed variant of the Matteson coupling, we used organozinc reagents as the nucleophilic coupling partner (Negishi-type reactions) because they can be generated under mild conditions, they do not require a stoichiometric activator (unlike, for example, the base in a Suzuki cross-coupling) (*4*), and they are compatible with a broad spectrum of functional groups (*19*).

Whereas treatment of the α-chloroboronate depicted in Fig. 2A with *n*-BuMgBr resulted in a rapid reaction (complete consumption of the electrophile within 15 min at room temperature in tetrahydrofuran and dimethylacetamide), replacement of *n*-BuMgBr with *n*-BuZnBr led to no coupling after 24 hours. However, through the addition of an appropriate nickel catalyst ($NiBr_2$•diglyme and a chiral 1,2-diamine), the coupling of the previously unreactive organozinc reagent could be achieved even at 0°C (entry 1 in Fig. 2A); moreover, the reaction proceeded with very good enantioselectivity [92% enantiomeric excess (ee)] from a racemic mixture of the electrophile. This new method proved versatile: A wide array of α-haloboronates and organozinc reagents could be coupled under mild conditions with good ee (Fig. 2, A and B). Essentially no desired product was observed in the absence of the diamine, consistent with a ligand-accelerated process (*20*). Although we have applied chiral nickel-diamine catalysts to stereoconvergent Suzuki cross-couplings of racemic alkyl electrophiles (*16*), they have not previously proved to be the ligands of choice for corresponding Negishi cross-couplings.

We found that a variety of organozinc reagents could be used as the nucleophilic coupling partner,

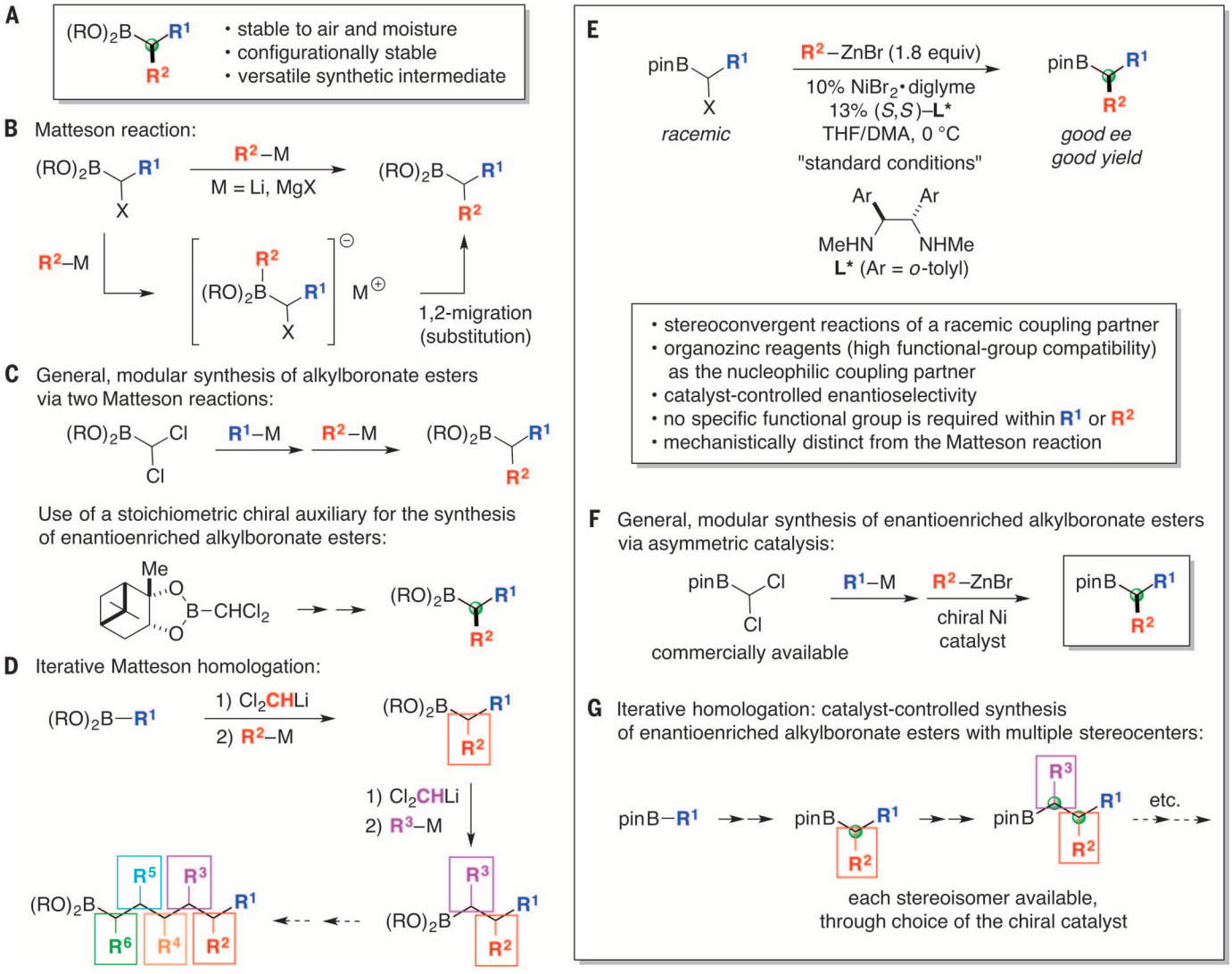


Fig. 1. Alkylboronate esters. (**A** to **D**) Background. (**E** to **G**) This study. R, alkyl group (superscripts indicate different alkyl groups); Me, methyl; pin, pinacolato; THF, tetrahydrofuran; DMA, dimethylacetamide; equiv, equivalent; ee, enantiomeric excess.

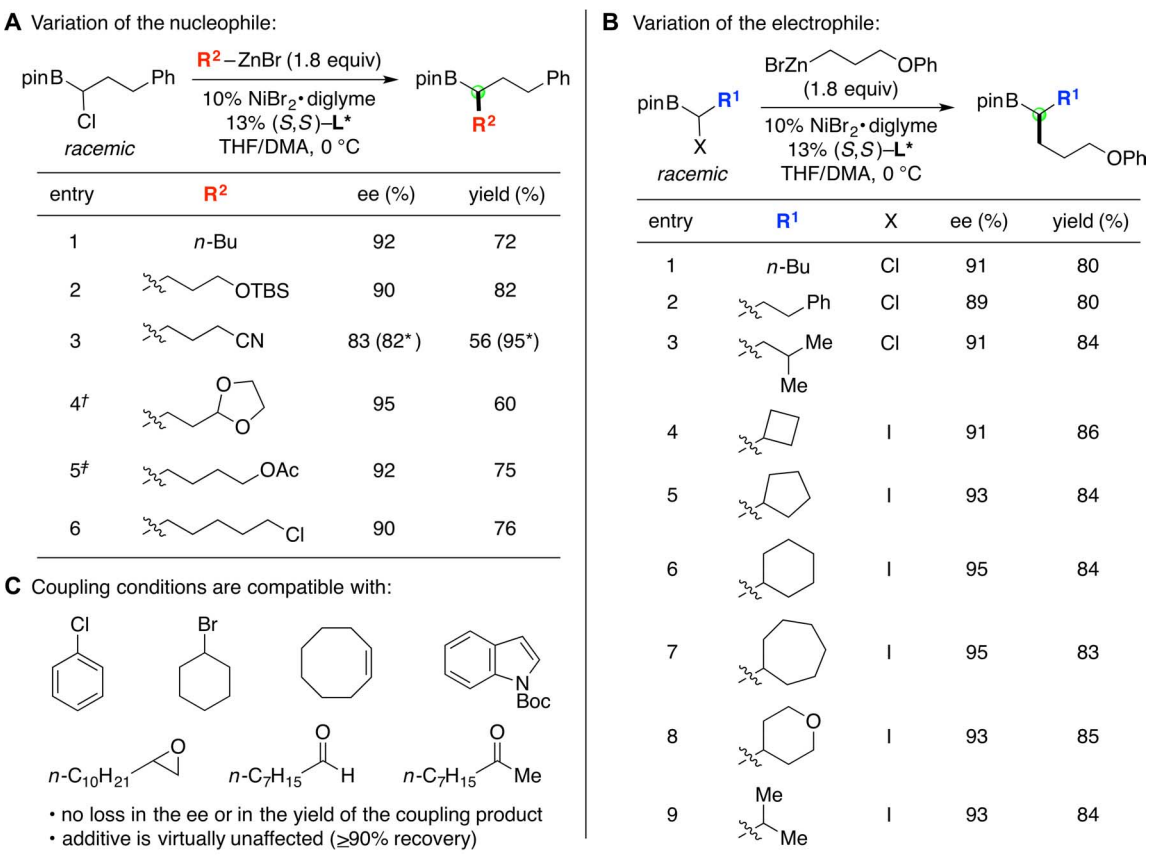


Fig. 2. Nickel-catalyzed asymmetric synthesis of alkylboronate esters. (**A** and **B**) Variation in the coupling partners. The ee was determined by chiral high-performance liquid chromatography after oxidation to the alcohol. The yield was determined by isolation after chromatographic purification. (**C**) Functional-group compatibility. (**D**) Comparison of the enantioselectivity-determining step when using a chiral auxiliary versus a chiral catalyst. All data represent the average of two experiments. *α-iodoboronate was used. †Reaction temperature, 10°C. ‡Catalyst loading, 12% $NiBr_2$•diglyme and 16% **L***. TBS, *tert*-butyldimethylsilyl; Ac, acetyl; Ph, phenyl; Boc, *t*-butoxycarbonyl.

including functionalized substrates that bear a silyl ether, a cyano group, an acetal, an ester, or a primary alkyl chloride, furnishing the target alkylboronate esters with very good enantioselectivity from a racemic α-haloboronate (Fig. 2A). Yields substantially greater than 50% of highly enantioenriched product establish the stereoconvergence of both enantiomers of the electrophile into a single enantiomer of the alkylboronate ester (in contrast to a simple kinetic resolution). Under the same conditions, a secondary alkylzinc reagent furnished a low yield and moderate ee.

Similarly, an array of α-haloboronates served as suitable electrophilic coupling partners (Fig. 2B), including sterically demanding compounds (entries 4 to 9); in the latter cases, because of the sensitivity of the reaction to steric hindrance, it proved advantageous to use a more reactive α-iodoboronate, rather than an α-chloroboronate. When the coupling of the 2-phenylethyl–substituted electrophile depicted in entry 2 was conducted on a larger scale (1.3 g of purified product), a lower catalyst loading could be used to generate the desired alkylboronate ester with comparable ee and yield (3.0% $NiBr_2$•diglyme and 3.6% chiral ligand **L***; 90% ee, 77% yield). To determine the compatibility of the process with various functional groups, we carried out the cross-coupling of the tetrahydropyran-substituted electrophile illustrated in entry 8 in the presence of a range of compounds (1.0 equivalent in individual experiments), and we established that the ee and yield of the product are essentially unaffected, as is the additive (Fig. 2C) (*21*, *22*). Organolithium and organomagnesium reagents react with functional groups such as secondary alkyl bromides, epoxides, aldehydes, and ketones.

As a consequence of the mechanistic dichotomy between the Matteson reaction and this nickel-catalyzed cross-coupling, there is a divergence in which step of the modular asymmetric synthesis leads to the stereoselective formation of product **A** (Fig. 2D). In the Matteson approach using a stoichiometric chiral auxiliary, the two chlorines of electrophile **B** are diastereotopic because of the chiral diolate ligand, and their differential reactivity in the 1,2-migration of the tetravalent boron intermediate results in the stereoselective formation of compound **C′** and then **A′** (an outline of the mechanism of the Matteson reaction is shown in Fig. 1B). In contrast, for the asymmetric nickel-catalyzed cross-coupling, racemic α-haloboronate **C** is converted by the chiral nickel-diamine catalyst into product **A** in an enantioconvergent reaction, likely through a radical generated from homolytic cleavage of the C–Cl bond (*18*).

We applied this nickel-catalyzed method for the stereoselective synthesis of alkylboronate esters to more complex partners. For example, under our standard conditions, a derivative of cholesterol

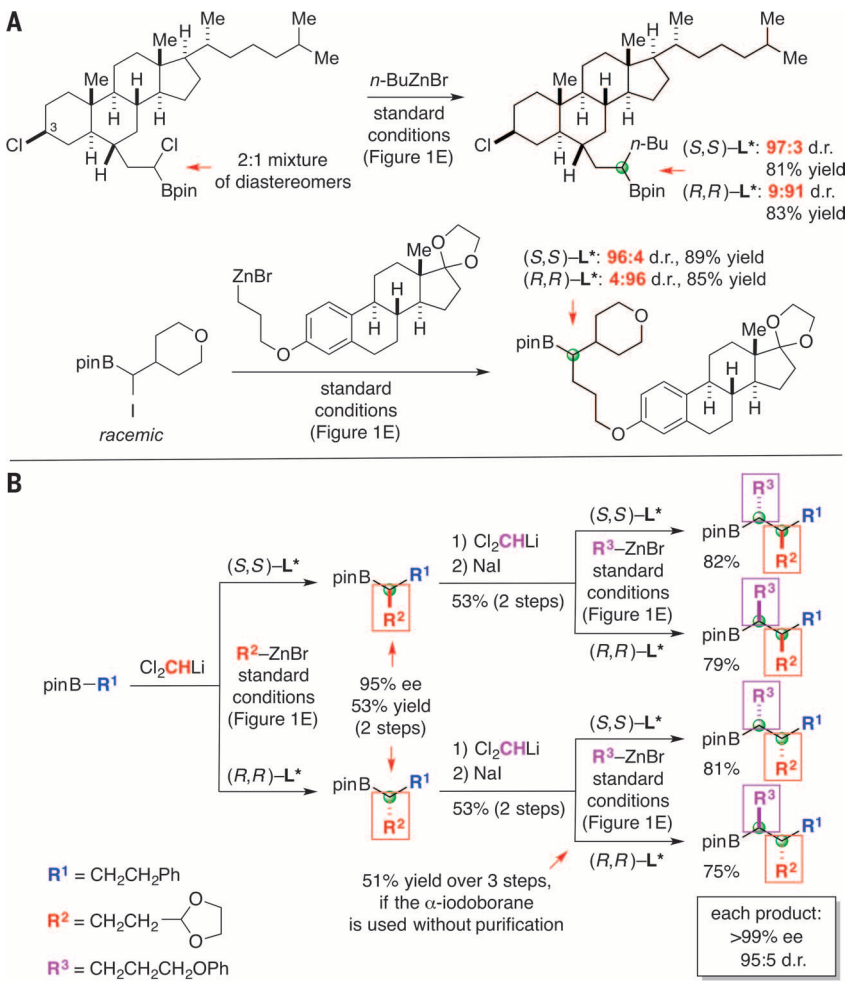


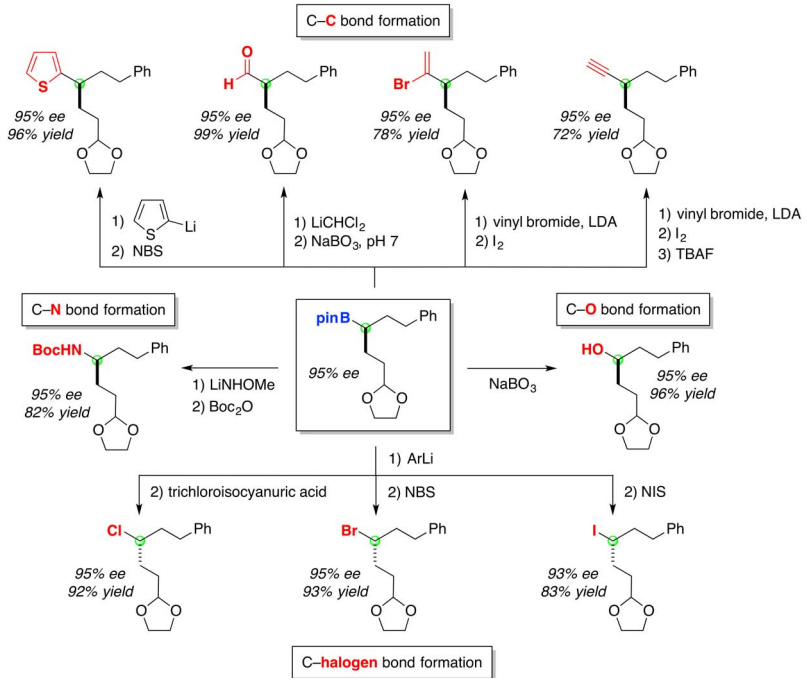
Fig. 3. Catalyst-controlled stereoselectivity in the asymmetric synthesis of alkylboronate esters. (**A**) Complex coupling partners. (**B**) Iterative homologation. d.r., diastereomeric ratio.

served as a suitable electrophile (top of Fig. 3A; selective reaction of the chloride α to boron, rather than the chloride in the 3 position), and a derivative of estrone functioned as an effective nucleophile (bottom of Fig. 3A), leading to each of the desired coupling products with high stereoselectivity and in good yield. In both cases, the stereochemistry of **L***, rather than that of the substrate, is the predominant determinant of the stereochemistry α to boron.

We also demonstrated that our method can be exploited in an iterative homologation process (Fig. 3B). Thus, in contrast to a sequence of Matteson reactions using a stoichiometric chiral auxiliary, this nickel-catalyzed asymmetric coupling can provide access to any of the four possible diastereomers of the target alkylboronate ester with excellent stereoselectivity from a single starting material, simply through the choice of the appropriate enantiomer of the nickel-**L*** catalyst for each key carbon-carbon bond-forming process. Once again, the configuration of the chiral catalyst, not that of the coupling partners, primarily dictates the stereochemistry of the products in Fig. 3B.

As noted at the outset, enantioenriched alkylboronate esters are extremely versatile intermediates in organic synthesis that can be converted into other important families of compounds with preservation of the ee at the boron-bound carbon (*1*, *7*, *8*, *23*–*26*); several illustrative examples are provided in Fig. 4. Thus, C–C, C–N, C–O, and C–halogen bond formation can be achieved in good yield, affording access to a wide array of functional groups that are common in valuable synthesis targets, including bioactive molecules (e.g., heterocycles, aldehydes, amines, alcohols, and alkyl halides), all with little or no erosion in enantiomeric excess. By providing straightforward access to a broad array of alkylboronate esters, and thereby to diverse families of enantioenriched organic

Fig. 4. Enantioenriched alkylboronate esters as versatile intermediates. The alkylboronate compounds are converted to diverse families of organic molecules through C–C, C–N, C–O, and C–halogen bond formation. NBS, *N*-bromosuccinimide; LDA, lithium diisopropylamide; TBAF, tetrabutylammonium fluoride; ArLi, [3,5-bis(trifluoromethyl)phenyl]lithium; NIS, *N*-iodosuccinimide.



compounds through subsequent functionalization (Fig. 4), our catalytic asymmetric method may have a substantial impact on the many fields that benefit from ready access to chiral molecules.

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SUPPLEMENTARY MATERIALS

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TOPOLOGICAL MATTER

Robust spin-polarized midgap states at step edges of topological crystalline insulators

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Topological crystalline insulators are materials in which the crystalline symmetry leads to topologically protected surface states with a chiral spin texture, rendering them potential candidates for spintronics applications. Using scanning tunneling spectroscopy, we uncover the existence of one-dimensional (1D) midgap states at odd-atomic surface step edges of the three-dimensional topological crystalline insulator (Pb,Sn)Se. A minimal toy model and realistic tight-binding calculations identify them as spin-polarized flat bands connecting two Dirac points. This nontrivial origin provides the 1D midgap states with inherent stability and protects them from backscattering. We experimentally show that this stability results in a striking robustness to defects, strong magnetic fields, and elevated temperature.

The recent theoretical prediction and experimental realization of topological insulators (TIs) have considerably extended the notion of a phase of matter. Within this framework, it has been shown that—based on some topological invariants—the electronic properties of materials can be classified into distinct topological classes (*1*, *2*). In topologically nontrivial materials, unconventional boundary modes have been experimentally detected by several different techniques (*3*–*9*). In two-dimensional (2D) TIs, counter-propagating spin-momentum–locked 1D edge modes develop along the sample boundary; in contrast, 3D TIs (*4*) have boundary modes that are linearly dispersing chiral surface states. Although a large variety of 3D TIs have been reported, only very few 2D TIs are known [HgTe (*3*), InAs (*10*) quantum wells, and Bi bilayers (*11*)]. These 2D TIs are delicate and difficult to realize experimentally because they all require the fabrication of precisely controlled thin film heterostructures. Properties such as small band gaps (*3*, *10*), strong substrate-induced hybridization effects (*11*), or the existence of residual trivial states (*10*, *11*) make helical edge states not only challenging to study but also of limited appeal for applications. Furthermore, their topological properties are protected only as long as time-reversal symmetry is preserved.

Here, we report that 2D topological surfaces, in turn, can be the mother state for nontrivial 1D midgap states (*12*), suggesting a dimensional hierarchy of boundary states in topological insulators. Specifically, we report on the discovery of 1D topological spin-filtered channels that naturally develop at step edges of 3D topological crystalline insulators (TCIs)—i.e., materials where the existence of surface Dirac states is guaranteed by crystal symmetries.

Figure 1A displays the rock-salt structure of $Pb_{1-x}Sn_xSe$ ($x \leq 0.4$). Depending on Sn-content x, these compounds have been reported to belong to two topologically distinct phases (*13*) that can be stoichiometrically controlled. Starting from PbSe, which is topologically trivial, the substitutional solid solution $Pb_{1-x}Sn_xSe$ turns into a topologically nontrivial phase as the Sn concentration exceeds $x \approx 0.24$ (*14*, *15*). Its bulk inverted band gap cannot be adiabatically connected to a trivial state as long as some crystal symmetries are preserved. The electronic properties of high-symmetry surfaces of these TCIs are characterized by topologically protected linearly dispersing Dirac states (*13*, *14*, *16*–*19*). Figure 1B illustrates this scenario for the nonpolar (001) surface, which is commonly exposed after cleaving bulk crystals. It hosts four Dirac cones centered in close proximity to the $\overline{X}$ and $\overline{Y}$ points of the Brillouin zone. Figure 1C shows a typical image of the (001) surface acquired by scanning tunneling microscopy (STM) on a freshly cleaved $Pb_{0.67}Sn_{0.33}Se$ bulk crystal (*20*)—i.e., a material safely within the topological regime at $x \geq 0.24$. An atomically resolved image showing the Se sublattice (*21*) is displayed as an inset. The profile taken along the gray line shows that several atomically flat terraces exist, separated by step edges of different heights.

Given the equal probability of breaking the crystal bonds at every atomic layer, all steps can be mapped onto two different classes: those corresponding to an integer number n of the conventional unit cell heights a—i.e., na, from here

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A general, modular method for the catalytic asymmetric synthesis of alkylboronate esters

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Crafting chiral boron building blocks

Carbon-boron bonds are easily transformed into a wide variety of C–C, C–N, and C–O bonds. With that flexibility in mind, Schmidt *et al.* show that nickel complexes can catalyze asymmetric alkylation of carbon centers adjacent to boron. This protocol creates chiral alkylboronates that function as stable precursors to numerous complex molecules. The reaction proceeds in stereo-convergent fashion —forming a single product from either mirror image of the α-haloboronate reagent. Successive reactions can also create chains of adjacent chiral alkyl centers with stereochemistry set by the configuration of the ligand bound to nickel.

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