ORGANIC CHEMISTRY

Catalyst-controlled doubly enantioconvergent coupling of racemic alkyl nucleophiles and electrophiles

Haohua Huo, Bradley J. Gorsline, Gregory C. Fu*

Stereochemical control in the construction of carbon-carbon bonds between an alkyl electrophile and an alkyl nucleophile is a persistent challenge in organic synthesis. Classical substitution reactions via S_N1 and S_N2 pathways are limited in their ability to generate carbon-carbon bonds (inadequate scope, due to side reactions such as rearrangements and eliminations) and to control stereochemistry when beginning with readily available racemic starting materials (racemic products). Here, we report a chiral nickel catalyst that couples racemic electrophiles (propargylic halides) with racemic nucleophiles (β-zincated amides) to form carbon-carbon bonds in doubly stereoconvergent processes, affording a single stereoisomer of the product from two stereochemical mixtures of reactants.

Transition metal catalysts for the construction of aryl-aryl bonds have revolutionized organic synthesis (*1*, *2*), particularly in the pharmaceutical industry, where these reactions have enabled the straightforward diversification of lead structures and thereby greatly facilitated drug development. Nevertheless, there is growing recognition in medicinal chemistry that, to improve the prospect for clinical success, it may be advantageous to incorporate more sp^3-hybridized carbons and more stereocenters into drug candidates (*3*, *4*). Furthermore, from a broader perspective, alkyl-alkyl bonds are even more pervasive in organic molecules than are aryl-aryl bonds.

A particularly straightforward strategy for the construction of alkyl-alkyl bonds is the nucleophilic substitution reaction of an alkyl electrophile with an alkyl nucleophile. Unfortunately, classical pathways for nucleophilic substitution (S_N1 and S_N2 reactions) are effective for only a very small subset of the possible electrophiles and nucleophiles, with side reactions such as elimination (loss of H–X; X, leaving group) or rearrangement often intervening instead (*5*). Furthermore, products of alkyl-alkyl coupling often bear a stereocenter at one or both carbons of the new bond, whereas uncatalyzed S_N1 and S_N2 reactions typically produce racemic products from racemic reactants.

Recently, we and others have demonstrated that transition metals, in particular earth-abundant nickel, can catalyze nucleophilic substitution reactions of alkyl electrophiles and address key shortcomings (reactivity and stereoselectivity) of classical S_N1 and S_N2 pathways for the construction of alkyl-alkyl bonds (*6*–*12*). Because the simultaneous control of two stereocenters in reactions between two racemic partners is an especially challenging goal (Fig. 1A, iii), efforts have until now focused on the two individual components of this ultimate objective, specifically, enantioconvergent substitution reactions of either racemic electrophiles or racemic nucleophiles, each with achiral reaction partners (Fig. 1A, i and ii, respectively). To date, a range of examples of enantioconvergent substitutions of racemic electrophiles have been described (Fig. 1A, i) (*6*, *7*), whereas in the case of alkyl-alkyl couplings of racemic nucleophiles (Fig. 1A, ii), success has been restricted to a single nucleophile, 2-zincated-*N*-Boc-pyrrolidine (*13*–*15*).

Here, we describe progress in addressing the two key stereochemical challenges remaining in such alkyl-alkyl bond formations (Fig. 1A, ii and iii). First, we develop a catalyst that effects enantioconvergent substitutions of achiral alkyl electrophiles by a family of racemic nucleophiles (Fig. 1B, i). Then, building on this foundation, we establish that doubly enantioconvergent substitution reactions of racemic electrophiles by racemic nucleophiles can be accomplished, whereby the chiral catalyst achieves alkyl-alkyl bond formation while simultaneously controlling the stereochemistry at both termini of the newly formed bond (Fig. 1B, ii).

The catalytic enantioselective synthesis of carbonyl compounds that bear a β,β-dialkyl stereocenter is a topic of substantial interest, owing to the presence of such subunits in a variety of bioactive molecules (e.g., valnoctamide) (*16*, *17*). Unfortunately, one particularly powerful strategy for the generation of such targets, the conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds, requires comparatively reactive nucleophiles (Grignard reagents) in the case of α,β-unsaturated amides, because of their relatively low electrophilicity (*18*). Because Grignard reagents have somewhat poor functional-group compatibility, the development of complementary approaches to the direct catalytic asymmetric synthesis of amides that bear such β stereocenters is a worthwhile objective.

In the initial phase of this program, we determined that a chiral nickel/(pyridine-oxazoline) catalyst can achieve enantioconvergent substitution reactions of achiral alkyl iodides by racemic β-zincated amides with good enantioselectivity and yield (Fig. 2). Thus, under our optimized conditions, a β-zincated pentanamide coupled with *n*-hexyl iodide in 90% enantiomeric excess (ee) and 95% yield (entry 1). The ee and yield values together establish that the catalyst is providing enantioselectivity not via a simple kinetic resolution of the racemic nucleophile but instead by selective conversion of both enantiomers of the nucleophile into a single enantiomer of the product.

A wide array of primary alkyl iodides served as suitable electrophiles in this nickel-catalyzed enantioconvergent substitution reaction by a racemic nucleophile (Fig. 2, entries 1 to 17). Substitution proceeded with good ee and yield with electrophiles that varied in steric demand (entries 1 to 4) and bore a broad range of functional groups (entries 5 to 17: an olefin, a silyl ether, a trifluoromethyl group, an acetal, an ester, a ketone, a nitrile, an alkyl chloride, an alkyl bromide, an imide, an amide, and a thiophene). Furthermore, through additive studies (see table S3), we determined that groups such as an aldehyde, an aryl bromide, an aryl chloride, a benzofuran, an epoxide, an indole, and a tertiary amine are compatible with the method.

To achieve the challenging goal of catalyst-controlled doubly enantioconvergent couplings of racemic electrophiles with racemic nucleophiles (Fig. 1A, iii), it is necessary for secondary electrophiles to undergo substitution by secondary nucleophiles; to date, examples of metal-catalyzed secondary-secondary couplings are still scarce (*13*, *14*, *19*–*22*), with the exception of allylation reactions (*23*). When the conditions developed for nickel-catalyzed enantioconvergent substitution reactions of primary alkyl iodides (conditions 1 in Fig. 2) were applied to cyclohexyl iodide, good enantioselectivity but moderate yield were observed (93% ee, 49% yield at 52% conversion). Small modifications of the reaction conditions (conditions 2 in Fig. 2) led to improved yield with essentially identical enantioselectivity (entry 18: 87% yield, 92% ee). With this method, the chiral nickel/(pyridine-oxazoline) catalyst achieved the enantioconvergent substitution of a range of secondary alkyl iodides, including saturated oxygen and nitrogen heterocycles, by the racemic nucleophile with good ee and yield (entries 18 to 23).

As described above, a single racemic alkyl nucleophile (2-zincated *N*-Boc-pyrrolidine) has previously been shown to engage in enantioconvergent substitution reactions with alkyl

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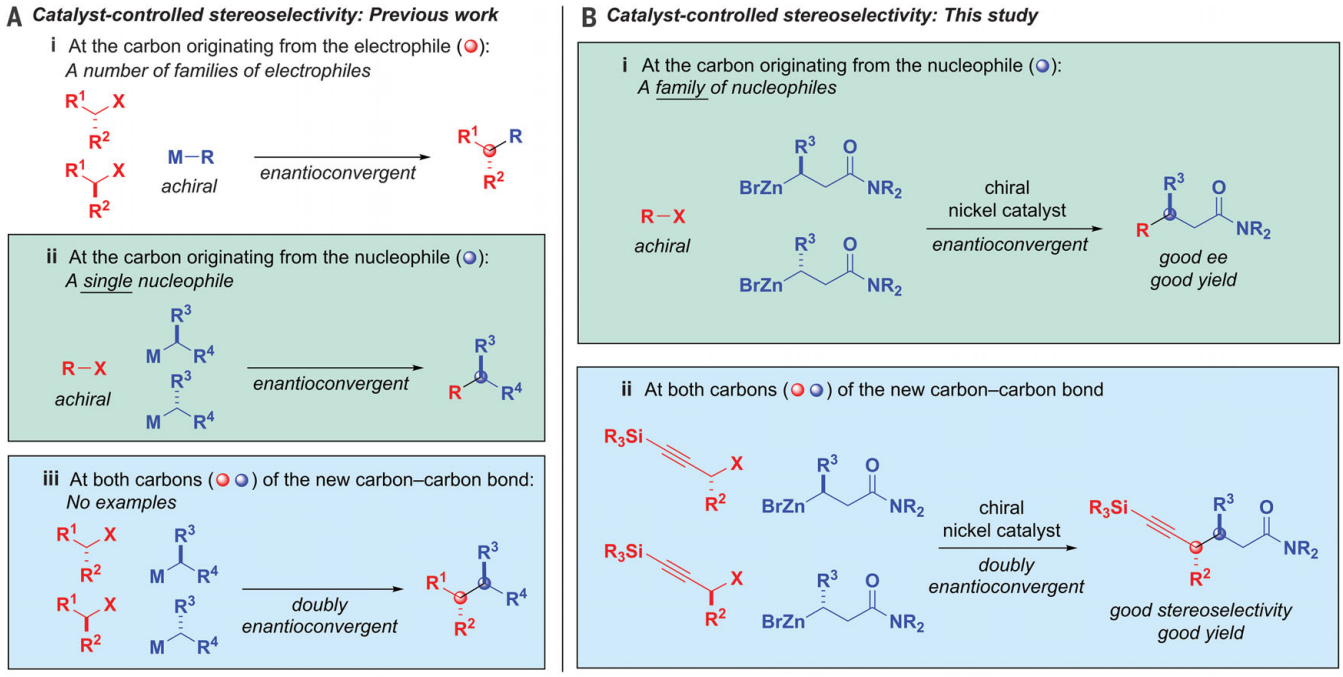

Fig. 1. Alkyl-alkyl bond formation. (**A**) Catalyst-controlled stereoselectivity—previous work. (**B**) Catalyst-controlled stereoselectivity—this study. ee, enantiomeric excess; M, metal; R, substituent; X, leaving group.

electrophiles (Fig. 1A, ii) (*13*, *14*). In contrast, the present method is effective for nucleophilic substitutions by a family of racemic nucleophiles, with both primary and secondary alkyl iodides as electrophiles (Fig. 2, entries 24 to 38). For example, the R^3 substituent of the nucleophile can vary in size or bear a functional group, and good enantioselectivities were consistently observed (entries 24 to 33). Furthermore, the standard conditions can be applied to a variety of amides, including Weinreb amides (*24*) (entries 34 to 38).

Turning next to doubly enantioconvergent alkyl-alkyl bond formation (Fig. 1A, iii), we hypothesized that we might enhance the likelihood for success if we focused our efforts on the use of electrophiles and nucleophiles that have successfully participated in the individual dimensions of this challenge (Fig. 1A, i and ii). We therefore examined the coupling of a racemic propargylic electrophile (*25*) with a racemic β-zincated amide. Although the nickel/(pyridine-oxazoline)–based conditions that we developed to control one stereocenter with a racemic β-zincated amide (Fig. 2) could not be applied directly to the doubly enantioconvergent substitution reaction, we were able to achieve our goal with a related nickel/(pyridine-oxazoline)–based method (Fig. 3).

Under these conditions, the chiral nickel catalyst coupled a 1.0:1.0 mixture of a racemic electrophile and a racemic nucleophile to provide the substitution product with good enantioselectivity, diastereoselectivity, and yield [Fig. 3, entry 1: 92% ee, 98:2 diastereomeric ratio (dr), 74% yield]. Together, the values for stereoselectivity and yield establish that this substitution reaction is indeed a doubly enantioconvergent process, whereby the catalyst is transforming both enantiomers of the two racemic starting materials into a particular stereoisomer of the desired product with good stereoselectivity.

On a gram scale, the doubly enantioconvergent substitution reaction illustrated in entry 1 of Fig. 3 proceeded with essentially identical stereoselectivity and yield as for a reaction conducted on a 0.5-mmol scale. A higher turnover number but a lower yield were observed when half of the standard loading of the nickel catalyst was used. The method was not highly sensitive to traces of moisture or air—the addition of 0.1 equivalent of water or 0.5 ml of air led to similar stereoselectivity and only a modest drop in yield.

The scope of the method proved fairly broad with respect to both the propargylic halide and the β-zincated amide. In the case of the propargylic halide, the R^2 substituent could vary in steric demand (Fig. 3, entries 1 to 4) and bear functional groups such as an ether, an acetal, an alkyne, an alkene, an ester, an alkyl chloride, and a furan (entries 5 to 15). Furthermore, a variety of silicon substituents on the alkyne were tolerated (entries 16 to 18).

Similarly, good stereoselectivity and yield were observed with a variety of β-zincated amides. For example, the β substituent (R^3) could range in size and include a variety of functional groups (Fig. 3, entries 21 to 30). Furthermore, different substituents on the nitrogen of the amide [including a Weinreb amide (*24*)] were tolerated (entries 19 and 20).

Although we have not yet carried out in-depth mechanistic studies of this process, we have determined that no EPR-active species were observed during a reaction in progress, which is consistent with our previous mechanistic investigations of nickel-catalyzed enantioconvergent coupling reactions of racemic electrophiles, wherein a diamagnetic organonickel(II) complex was suggested to be the primary resting state of nickel during catalysis (*26*, *27*). Furthermore, when a coupling was conducted in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), adducts derived from both the electrophile and the nucleophile were observed, consistent with the generation of organic radicals from each reaction partner (Fig. 3, mechanistic data); the intermediacy of organic radicals provides a pathway for enantioconvergence of the two racemic reactants. In order for the chiral nickel catalyst to achieve good stereoselectivity in the case of the nucleophile, it must distinguish between two alkyl substituents (R^3 and CH_2CONR_2 in Fig. 3), which can be challenging in asymmetric synthesis. We hypothesize that bidentate **L2**, rather than a tridentate ligand [e.g., a pybox (*7*)], is effective, because the lower coordination number of the ligand facilitates complexation of the oxygen of the amide to nickel in the stereochemistry-determining step, thereby enabling differentiation of the alkyl groups.

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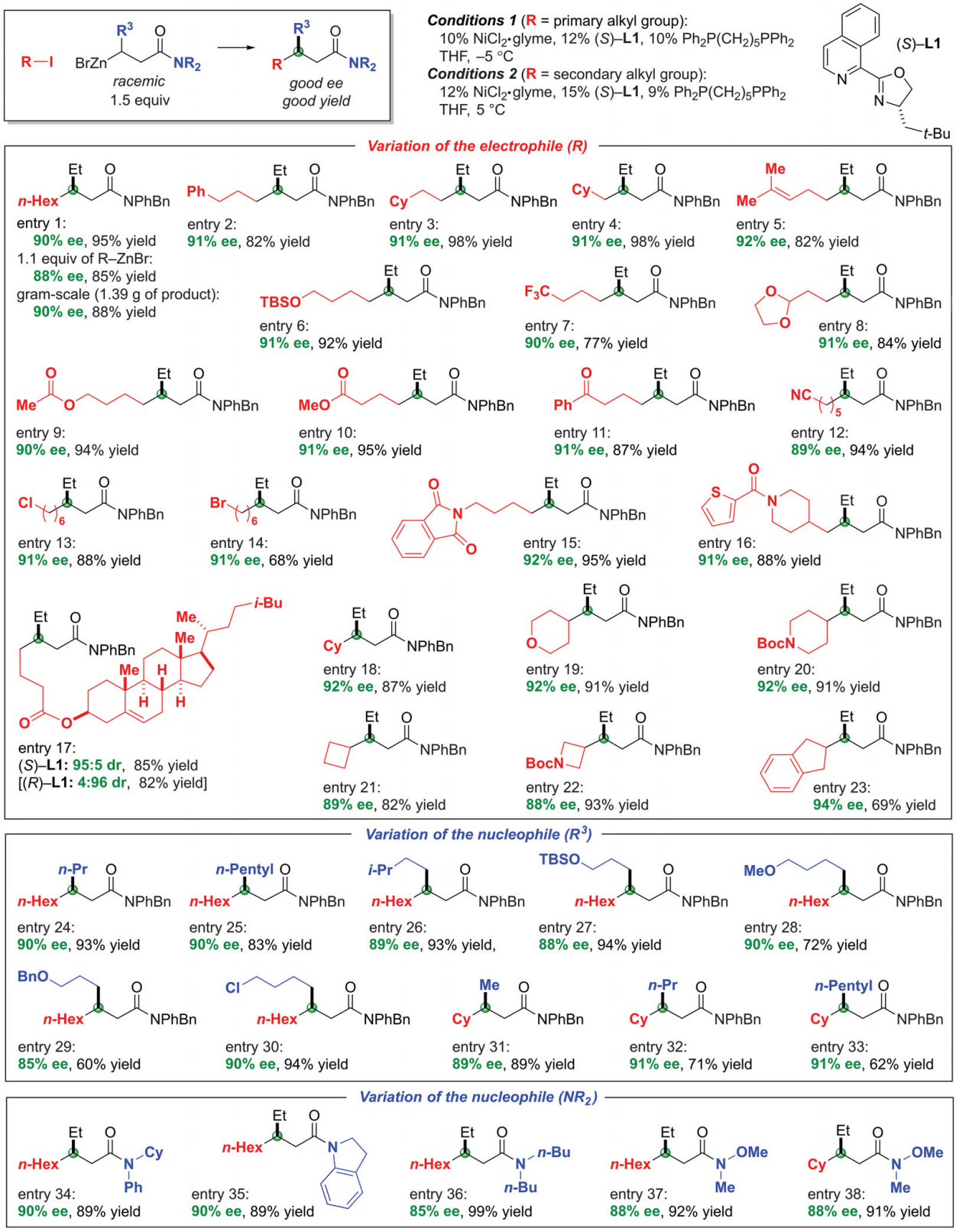

Fig. 2. Enantioconvergent substitution reactions of racemic nucleophiles. Couplings were generally conducted using 0.6 mmol of the electrophile. All data represent the average of two experiments. The percent yield represents purified product. Bn, benzyl; Boc, *tert*-butoxycarbonyl; *i*-Bu, isobutyl; *t*-Bu, *tert*-butyl; Cy, cyclohexyl; Et, ethyl; *n*-Hex, *n*-hexyl; Me, methyl; Ph, phenyl; *i*-Pr, isopropyl; *n*-Pr, *n*-propyl; TBS, *tert*-butyldimethylsilyl.

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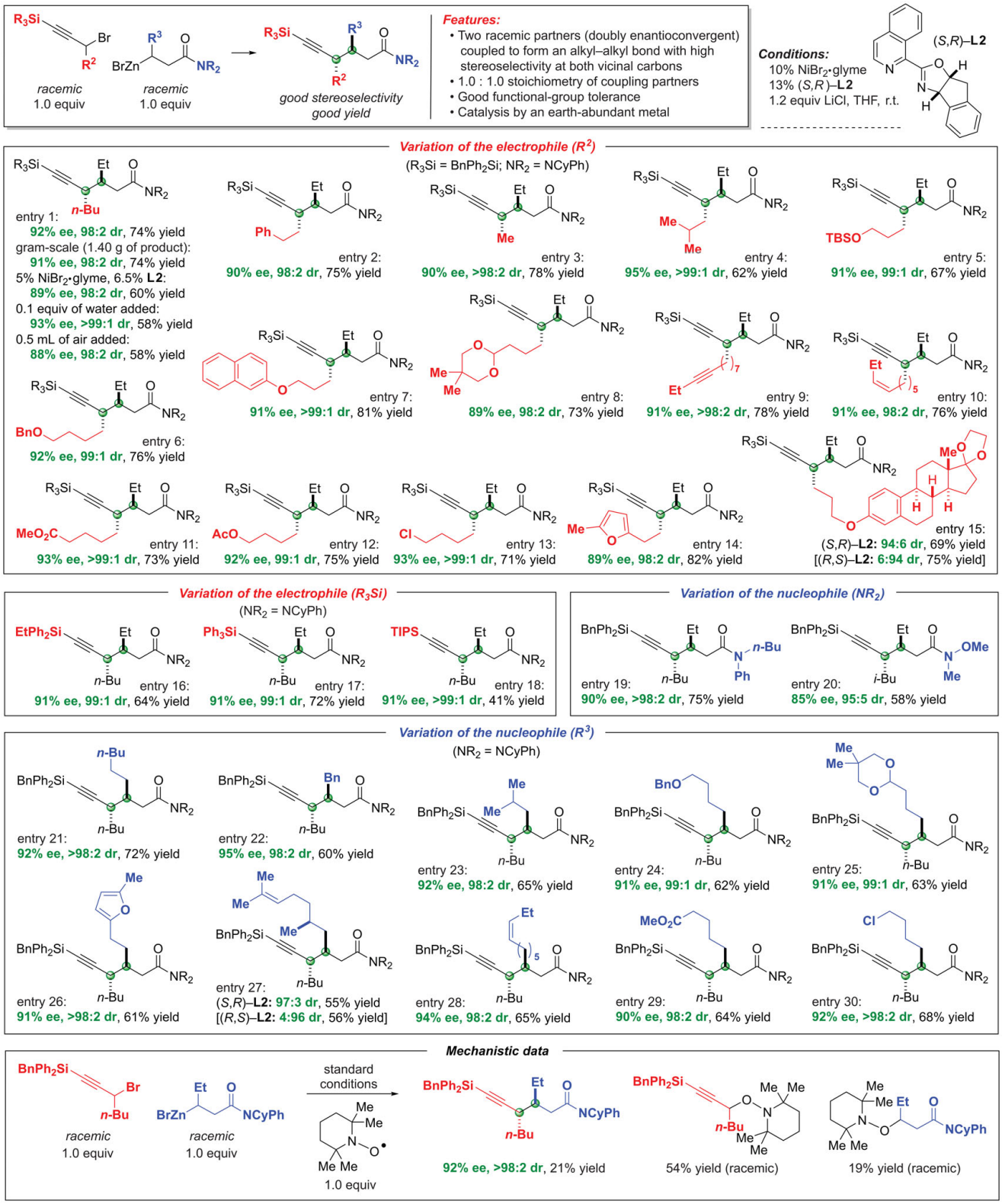

Fig. 3. Doubly enantioconvergent substitution reactions of racemic electrophiles by racemic nucleophiles. Couplings were generally conducted using 0.5 mmol of the electrophile. All data represent the average of two experiments. The percent yield represents purified product. dr, diastereomeric ratio; Ac, acetyl; TIPS, triisopropylsilyl.

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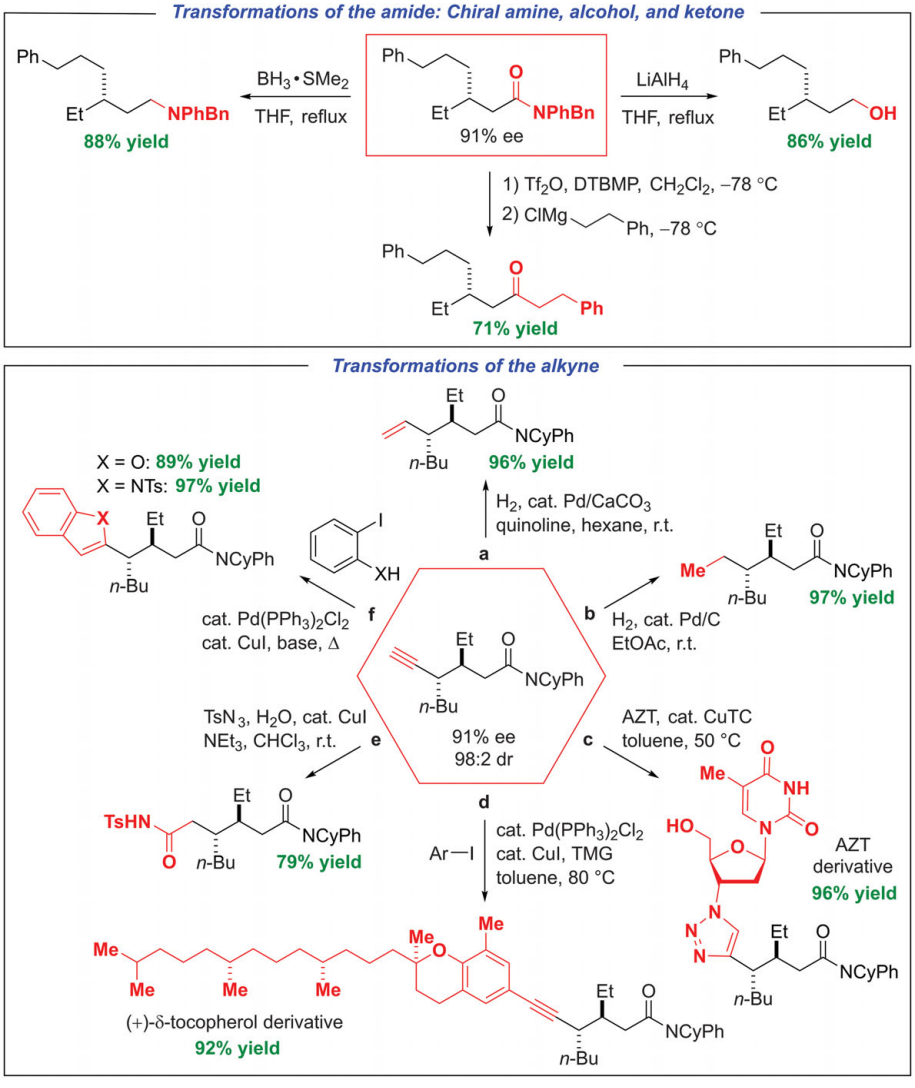

Fig. 4. Transformations into other useful families of enantioenriched compounds. The percent yield represents purified product (average of two experiments). Tf, triflate; DTBMP, 2,6-di-*t*-butyl-4-methylpyridine; AZT, azidothymidine; TC, thiophene-2-carboxylate; TMG, 1,1,3,3-tetramethylguanidine.

The products of these enantioconvergent couplings were readily converted into other useful families of enantioenriched compounds (Fig. 4). For example, *N*-aryl–*N*-alkylamides could be directly transformed in good yield without racemization into tertiary amines, primary alcohols, and dialkylketones (*28*). Furthermore, alkynes are highly versatile synthetic handles that are suitable for elaboration into a wide variety of useful functional groups (*29*). Thus, the terminal alkyne (removal of the silicon protecting group: tetra-*n*-butylammonium fluoride, tetrahydrofuran, room temperature; 91% yield) could be reduced to an alkene or an alkane (Fig. 4, reactions a and b, respectively); engaged in an azide cycloaddition (reaction c) (*30*, *31*) or a Sonogashira reaction (reaction d); or converted into an amide (reaction e) (*32*), an indole, or a benzofuran (reaction f) (*33*).

Future studies will focus on expanding the scope of these doubly enantioconvergent alkyl-alkyl couplings to include a wide range of activated and unactivated electrophiles, as well as a broad array of conjugated and nonconjugated nucleophiles. Success in these endeavors could transform the enantioselective synthesis of organic compounds.

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ACKNOWLEDGMENTS

We thank S. H. Jungbauer, S. C. Virgil, L. M. Henling, D. G. Vander Velde, H. Yin, D. J. Freas, W. Zhang, and Z. Yang for assistance and discussions. **Funding:** Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, R37–GM62871). H.H. thanks the Resnick Sustainability Institute at Caltech for fellowship support. **Author contributions:** H.H. and B.J.G. performed all experiments. H.H. and G.C.F. wrote the manuscript. All authors contributed to the analysis and the interpretation of the results. **Competing interests:** The authors declare no competing interests. **Data and materials availability:** The data that support the findings of this study are available in the paper, in its supplementary materials (experimental procedures and characterization data), and from the Cambridge Crystallographic Data Centre (CCDC) (www.ccdc.cam.ac.uk/structures; crystallographic data are available free of charge under CCDC reference numbers 1935944 and 1935945).

SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
Figs. S1 and S2
Tables S1 to S5
Spectral Data
References (*34*–*40*)

4 September 2019; accepted 26 November 2019
10.1126/science.aaz3855

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Science

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Science **367** (6477), 559-564.
DOI: 10.1126/science.aaz3855

Convergent coupling

Metal-catalyzed coupling of two flat aromatic rings is one of the most versatile and widely applied chemical reactions. Efforts to extend this protocol to alkyl-alkyl coupling are complicated by the prospect of forming two different three-dimensional configurations at each carbon center, corresponding to four possible products. Huo *et al.* now report that a chiral nickel catalyst can convergently link two mirror-image pairs of alkyl reactants into just one product (see the Perspective by Xu and Watson). The specific reaction couples propargylic halides to zinc-activated aliphatic amides.

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