Published in final edited form as:

Science. 2020 January 31; 367(6477): 559–564. doi:10.1126/science.aaz3855.

Catalyst-controlled asymmetric substitution reactions by racemic nucleophiles: From singly to doubly enantioconvergent processes

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

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA

Abstract

The construction of carbon–carbon bonds and the control of product stereochemistry are two of the most important challenges in organic synthesis. The substitution reaction of an alkyl electrophile by an alkyl nucleophile is a potentially powerful, convergent strategy for organic synthesis; however, in practice, classical mechanisms for substitution reactions (S_N1 and S_N2 pathways) are limited in their ability to generate carbon–carbon bonds and to control product stereochemistry when beginning with readily available racemic starting materials. We have developed a chiral nickel catalyst that couples, for the first time, racemic electrophiles with racemic nucleophiles to form carbon–carbon bonds in doubly stereoconvergent processes (i.e., affording a single stereoisomer of the product from two stereochemical mixtures of starting materials).

One Sentence Summary:

The nickel-catalyzed coupling of two racemic partners to form a new carbon–carbon bond as a single stereoisomer is described.

The development of effective methods for the synthesis of carbon–carbon bonds is a central challenge in organic chemistry. Transition-metal catalysts for the construction of aryl–aryl bonds have revolutionized organic synthesis (1, 2), particularly in the pharmaceutical industry, where they have enabled the straightforward diversification of lead structures and thereby greatly facilitated drug development. Nevertheless, there is a 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. In this report, we describe a new

*Correspondence to: gcfu@caltech.edu.

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 within the paper, its Supplementary Materials (experimental procedures and characterization data) and from the Cambridge Crystallographic Data Centre (<https://www.ccdc.cam.ac.uk/structures>; crystallographic data are available free of charge under CCDC reference numbers 1935944 and 1935945).

dimension in metal-catalyzed nucleophilic substitution reactions, wherein a nickel catalyst not only forges an alkyl–alkyl bond, but also controls the stereochemistry at both carbons of the new bond, beginning with a 1:1 mixture of a racemic electrophile and a racemic nucleophile, in a doubly enantioconvergent process.

A particularly straightforward strategy for the construction of alkyl–alkyl bonds is the nucleophilic substitution of an alkyl electrophile by an alkyl nucleophile; if this approach were entirely general, synthetic organic chemistry would be greatly simplified (e.g., Figure 1A). 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) often intervening instead (5).

When constructing alkyl–alkyl bonds via nucleophilic substitution, in addition to the challenge of reactivity, in many instances there is also the challenge of stereoselectivity, since the product can bear a stereocenter at one or both carbons of the new bond (e.g., Figure 1B). Again, uncatalyzed S_N1 and S_N2 reactions are not able to properly address this challenge, as readily available racemic starting materials lead to racemic products.

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 of classical S_N1 and S_N2 pathways for the construction of alkyl–alkyl bonds, both in terms of reactivity and stereoselectivity (6, 7, 8, 9, 10, 11). Because the simultaneous control of two stereocenters, beginning with two racemic partners, is an especially challenging goal (Figure 1B–3), efforts to date have focused on the two individual components of this ultimate objective, specifically, enantioconvergent substitution reactions of racemic electrophiles and of racemic nucleophiles, each with achiral reaction partners (Figure 1B–1 and Figure 1B–2, respectively). To date, a number of examples of enantioconvergent substitutions of racemic electrophiles have been described (Figure 1B–1) (6, 7), whereas, in the case of racemic nucleophiles (Figure 1B–2), success has been restricted to a single nucleophile, 2-zincated-*N*-Boc-pyrrolidine (12, 13).

In this report, we describe progress in addressing both of the key remaining stereochemical challenges (Figure 1B–2 and Figure 1B–3). First, we develop a catalyst that effects the enantioconvergent substitution of alkyl electrophiles by a family of racemic nucleophiles (Figure 1C–1). Then, building on this foundation, we establish that doubly enantioconvergent substitution reactions of racemic electrophiles by racemic nucleophiles can be accomplished wherein the chiral catalyst achieves alkyl–alkyl bond formation while simultaneously controlling the stereochemistry at both termini of the newly formed bond (Figure 1C–2).

The catalytic enantioselective synthesis of carbonyl compounds that bear a β,β -dialkyl stereocenter is a topic of substantial interest, due to the presence of such subunits in a variety of bioactive molecules (e.g., valnoctamide (14)) (15). Unfortunately, one particularly powerful strategy for the generation of such targets, the conjugate addition of carbon nucleophiles to α,β -unsaturated carbonyl compounds, requires relatively reactive nucleophiles (Grignard reagents) in the case of α,β -unsaturated amides, due to their

relatively low electrophilicity (16). Because Grignard reagents have comparatively poor functional-group compatibility, the development of complementary approaches to the catalytic asymmetric synthesis of amides that bear such β stereocenters is an important 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 (Figure 2). Thus, under our optimized conditions, a β -zincated pentanamide couples with *n*-hexyl iodide with 90% ee and 95% yield (entry 1; 1.1 equiv of R–ZnBr: 88% ee, 85% yield). The high ee and high yield, taken together, establish that the catalyst is providing enantioselectivity not via a simple kinetic resolution of the racemic nucleophile, but that instead both enantiomers of the nucleophile are being converted to the product with good ee.

A wide array of primary alkyl iodides serve as suitable electrophiles in nickel-catalyzed enantioconvergent substitution reactions by the racemic nucleophile (Figure 2, entries 1–17). Substitution proceeds with good ee and yield with electrophiles that vary in steric demand (entries 1–4) and that bear a broad range of functional groups (entries 5–17: 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 the Supplementary Materials), we have 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 (Figure 1B–3), it is necessary that secondary electrophiles undergo substitution by secondary nucleophiles; to date, examples of metal-catalyzed secondary–secondary couplings are still quite scarce (12, 13, 17, 18, 19, 20), with the exception of allylation reactions (21). When the conditions developed for nickel-catalyzed enantioconvergent substitution reactions of primary alkyl iodides (Conditions 1 in Figure 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 Figure 2) led to improved yield with essentially identical enantioselectivity (entry 18: 87% yield, 92% ee). With this method, the chiral nickel/(pyridine–oxazoline) catalyst can achieve the enantioconvergent substitution of an array of secondary alkyl iodides, including saturated oxygen and nitrogen heterocycles, by the racemic nucleophile with good ee and yield (entries 18–23).

As described above, a single racemic nucleophile (2-zincated *N*-Boc-pyrrolidine) has been shown to date to engage in enantioconvergent substitution reactions of alkyl nucleophiles with alkyl electrophiles (Figure 1B–2) (12, 13). 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 (Figure 2, entries 24–38). For example, the R³ substituent of the nucleophile can vary in size or bear a functional group, and good enantioselectivities are consistently observed (entries 24–33). Furthermore, the standard

conditions can be applied to a variety of amides, including Weinreb amides (22) (entries 34–38).

Clearly, the difficulty in developing an effective catalyst increases quite considerably as the challenge progresses from: (1) simple (non-asymmetric) alkyl–alkyl bond formation (e.g., Figure 1A) → (2) bond formation plus control of stereochemistry at one terminus of the new carbon–carbon bond (Figure 1B–1 or Figure 1B–2) → (3) bond formation plus control of stereochemistry at both termini of the new carbon–carbon bond (Figure 1B–3). We hypothesized that we might enhance the likelihood of accomplishing doubly enantioconvergent alkyl–alkyl bond formation (Figure 1B–3) if we focused our effort on the use of electrophiles and nucleophiles that have successfully participated in the individual dimensions of this challenge (Figure 1B–1 and 1B–2). We therefore examined the coupling of a racemic propargylic electrophile (23) with a racemic β -zincated amide (this study). Although the nickel/(pyridine–oxazoline)-based conditions that we developed to control one stereocenter with a racemic β -zincated amide (Figure 2) could not be applied directly to a doubly enantioconvergent substitution reaction, we were able to achieve our goal with a related nickel/(pyridine–oxazoline)-based method (Figure 3).

Under these conditions, the chiral nickel catalyst couples 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 (Figure 3, entry 1: 92% ee, 98:2 dr, 74% yield). Together, the values for stereoselectivity and yield establish that this substitution reaction is indeed a doubly enantioconvergent process, wherein the catalyst is transforming both enantiomers of the two racemic starting materials into a particular stereoisomer of the desired product with good stereoselectivity.

A few practical points are worthy of note. On a gram scale, the doubly enantioconvergent substitution reaction illustrated in entry 1 of Figure 3 proceeds with essentially identical stereoselectivity and yield as does a reaction conducted on a 0.5-mmol scale. A higher turnover number, although a lower yield, is observed when half of the standard loading of the nickel catalyst is used. Finally, the method is not highly sensitive to traces of moisture or air—the addition of 0.1 equiv of water or 0.5 mL of air leads to similar stereoselectivity and only a modest drop in yield.

The scope of the method is 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 can vary in steric demand (entries 1–4), and it can bear functional groups such as an ether, an acetal, an alkyne, an alkene, an ester, an alkyl chloride, and a furan (entries 5–15). Furthermore, a variety of silicon substituents on the alkyne are tolerated (entries 16–18).

Similarly, good stereoselectivity and yield are observed with a variety of β -zincated amides. For example, the β substituent (R^3) can range in size and can include a variety of functional groups (Figure 3, entries 21–30). Furthermore, different substituents on the nitrogen of the amide (including a Weinreb amide (22)) are tolerated (entries 19 and 20).

The products of these enantioconvergent couplings are readily converted into other useful families of enantioenriched compounds (Figure 4). For example, *N*-aryl–*N*-alkylamides can

be directly transformed in good yield without racemization into tertiary amines, primary alcohols, and dialkylketones (24). Furthermore, alkynes are highly versatile synthetic handles that are suitable for elaboration into a wide variety of useful functional groups (25). Thus, the terminal alkyne (removal of the silicon protecting group: TBAF, THF, r.t.; 91% yield) can be reduced to an alkene or an alkane (reactions **a** and **b**, respectively), engaged in an azide cycloaddition (reaction **c**) (26, 27) or a Sonagashira reaction (reaction **d**), or converted into an amide (reaction **e**) (28), an indole, or a benzofuran (reaction **f**) (29).

In summary, we have described new dimensions for metal-catalyzed enantioconvergent nucleophilic substitution reactions. In initial work, we have established that a family of racemic secondary nucleophiles can couple with achiral electrophiles to form alkyl–alkyl bonds with good enantioselectivity and yield (Figure 1C–1). Building upon this development, we have also achieved doubly enantioconvergent substitutions of racemic secondary electrophiles by racemic secondary nucleophiles, thereby controlling vicinal stereochemistry at both termini of the new carbon–carbon bond (Figure 1C–2). This study thus demonstrates the viability of a retrosynthetic disconnection that has substantial strategic potential in asymmetric synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS:

We thank Dr. Stefan H. Jungbauer, Dr. Scott C. Virgil, Lawrence M. Henling, Dr. David G. Vander Velde, Dr. Haolin Yin, Dylan J. Freas, and Wanji Zhang for assistance and discussions.

Funding: Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, R01–GM62871). H. H. thanks the Resnick Sustainability Institute at Caltech for fellowship support.

REFERENCES AND NOTES:

1. Suzuki A, Cross-coupling reactions of organoboranes: an easy way to construct C–C bonds. *Angew. Chem. Int. Ed* 50, 6722–6737 (2011).
2. Negishi E.-i, Magical power of transition metals: past, present, and future. *Angew. Chem. Int. Ed* 50, 6738–6764 (2011).
3. Lovering F, Bikker J, Humblet C, Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem* 52, 6752–6756 (2009). [PubMed: 19827778]
4. Lovering F, Escape from flatland 2: complexity and promiscuity. *Med. Chem. Commun* 4, 515–519 (2013).
5. Hartshorn SR, *Aliphatic Nucleophilic Substitution* (Cambridge University Press: New York, 1973).
6. Choi J, Fu GC, Transition metal-catalyzed alkyl–alkyl bond formation: another dimension in cross-coupling chemistry. *Science* 356, eaaf7230 (2017). [PubMed: 28408546]
7. Fu GC, Transition-metal catalysis of nucleophilic substitution reactions: a radical alternative to SN1 and SN2 processes. *ACS Cent. Sci* 3, 692–700 (2017). [PubMed: 28776010]
8. Kaga A, Chiba S, Engaging radicals in transition metal-catalyzed cross-coupling with alkyl electrophiles: recent advances. *ACS Catal.* 7, 4697–4706 (2017).
9. Iwasaki T, Kambe N, Ni-catalyzed C–C couplings using alkyl electrophiles. *Top. Curr. Chem* 374, 66 (2016).
10. Geist E, Kirschning A, Schmidt T, sp³–sp³ Coupling reactions in the synthesis of natural products and biologically active molecules. *Nat. Prod. Rep* 31, 441–448 (2014). [PubMed: 24573302]

11. Pitre SP, Weires NA, Overman LE, Forging C(sp³)-C(sp³) bonds with carbon-centered radicals in the synthesis of complex molecules. *J. Am. Chem. Soc* 141, 2800–2813 (2019). [PubMed: 30566838]
12. Cordier CJ, Lundgren RJ, Fu GC, Enantioconvergent cross-couplings of racemic alkylmetal reagents with unactivated secondary alkyl electrophiles: catalytic asymmetric Negishi α -alkylations of *N*-Bocpyrrolidine. *J. Am. Chem. Soc* 135, 10946–10949 (2013). Because one of the atoms on the carbon that bears zinc is a nitrogen, rather than a carbon, 2-zincated-*N*-Boc-pyrrolidine may not be considered a secondary nucleophile. [PubMed: 23869442]
13. Mu X, Shibata Y, Makida Y, Fu GC, Control of vicinal stereocenters through nickel-catalyzed alkyl-alkyl cross-coupling. *Angew. Chem. Int. Ed* 56, 5821–5824 (2017).
14. Shekh-Ahmad T, Hen N, McDonough JH, Yagen B, Bialer M, Valnoctamide and sec-butylpropylacetamide (SPD) for acute seizures and status epilepticus. *Epilepsia* 54, 99–102 (2013). [PubMed: 24001086]
15. Cordova A (ed.), *Catalytic Asymmetric Conjugate Reactions* (Wiley-VCH: Weinheim, Germany, 2010).
16. Rodríguez-Fernández M, Yan X, Collados JF, White PB, Harutyunyan SR, Lewis acid enabled copper-catalyzed asymmetric synthesis of chiral β -substituted amides. *J. Am. Chem. Soc* 139, 14224–14231 (2017). [PubMed: 28960071]
17. Malosh CF, Ready JM, Catalytic cross-coupling of alkylzinc halides with α -chloroketones. *J. Am. Chem. Soc* 126, 10240–10241 (2004). [PubMed: 15315425]
18. Smith SW, Fu GC, Nickel-catalyzed Negishi cross-couplings of secondary nucleophiles with secondary propargylic electrophiles at room temperature. *Angew. Chem. Int. Ed* 47, 9334–9336 (2008).
19. Yang C-T, Zhang Z-Q, Liang J, Liu J-H, Lu X-Y, Chen H-H, Liu L, Copper-catalyzed cross-coupling of nonactivated secondary alkyl halides and tosylates with secondary alkyl Grignard reagents. *J. Am. Chem. Soc* 134, 11124–11127 (2012). [PubMed: 22734716]
20. Binder JT, Cordier CJ, Fu GC, Catalytic enantioselective cross-couplings of secondary alkyl electrophiles with secondary alkylmetal nucleophiles: Negishi reactions of racemic benzylic bromides with achiral alkylzinc reagents. *J. Am. Chem. Soc* 134, 17003–17006 (2012). [PubMed: 23039358]
21. Kazmaier U (ed.), *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis* (Springer: Berlin, 2012).
22. Balasubramaniam S, Aidhen IS, The growing synthetic utility of the Weinreb amide. *Synthesis* 3707–3738 (2008).
23. Smith SW, Fu GC, Nickel-catalyzed asymmetric cross-couplings of racemic propargylic halides with arylzinc reagents. *J. Am. Chem. Soc* 130, 12645–12647 (2008). [PubMed: 18763769]
24. Huang P-Q, Wang Y, Xiao K-J, Huang Y-H, A general method for the direct transformation of common tertiary amides into ketones and amines by addition of Grignard reagents. *Tetrahedron* 71, 4248–4254 (2015).
25. Trost BM, Li C-J (eds), *Modern Alkyne Chemistry* (Wiley-VCH: Weinheim, Germany, 2015).
26. Rostovtsev VV, Green LG, Fokin VV, Sharpless KB, A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective “ligation” of azides and terminal alkynes. *Angew. Chem. Int. Ed* 41, 2596–2599 (2002).
27. Tornøe CW, Christensen C, Meldal M, Peptidotriazoles on solid phase: [1,2,3]-triazoles by regiospecific copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. *J. Org. Chem* 67, 3057–3064 (2002). [PubMed: 11975567]
28. Cho SH, Yoo EJ, Bae I, Chang S, Copper-catalyzed hydrative amide synthesis with terminal alkyne, sulfonyl azide, and water. *J. Am. Chem. Soc* 127, 16046–16047 (2005). [PubMed: 16287290]
29. Schumacher RF, Honraedt A, Bolm C, Synthesis of *N*-methyl-2-indolyl- and *N*-methyl-2-benzo[*b*]furylsubstituted sulfoximines by Pd/Cu co-catalyzed domino cross-coupling/cyclization reactions. *Eur. J. Org. Chem* 3737–3741 (2012).
30. Binder JT, Cordier CJ, Fu GC, Catalytic enantioselective cross-couplings of secondary alkyl electrophiles with secondary alkylmetal nucleophiles: Negishi reactions of racemic benzylic

- bromides with achiral alkylzinc reagents. *J. Am. Chem. Soc.* 134, 17003–17006 (2012). [PubMed: 23039358]
31. Krout MR, Mohr JT, Stoltz BM, Preparation of (S)-tert-ButylPHOX (oxazole, 4-(1,1-dimethylethyl)-2-[2-(diphenylphosphino)phenyl]-4,5-dihydro- (4S)-). *Org. Synth* 86, 181–193 (2009). [PubMed: 20072718]
32. Smith SW, Fu GC, Nickel-catalyzed asymmetric cross-couplings of racemic propargylic halides with arylzinc reagents. *J. Am. Chem. Soc.* 130, 12645–12647 (2008). [PubMed: 18763769]
33. Zhu Q, Graff DE, Knowles RR, Intermolecular anti-Markovnikov hydroamination of unactivated alkenes with sulfonamides enabled by proton-coupled electron transfer. *J. Am. Chem. Soc.* 140, 741–747 (2018). [PubMed: 29268020]
34. Krasovskiy A, Knochel P, Convenient titration method for organometallic zinc, magnesium, and lanthanide reagents. *Synthesis* 890–891 (2006).
35. Dolomanov OV, Bourhis LJ, Gildea RJ, Howard JAK, Puschmann H, OLEX2: A complete structure solution, refinement and analysis program. *J. Appl. Cryst.* 42, 339–341 (2009).
36. Sheldrick GM, SHELXT - Integrated space-group and crystal-structure determination. *Acta Cryst.* A71, 3–8 (2015).
37. Sheldrick GM, Crystal structure refinement with SHELXL. *Acta Cryst.* C71, 3–8 (2015).
38. Tosatti P, Campbell AJ, House D, Nelson A, Marsden SP, Catalyst control in sequential asymmetric allylic substitution: Stereodivergent access to *N,N*-diprotected unnatural amino acids. *J. Org. Chem.* 76, 5495–5501 (2011). [PubMed: 21563816]

(A) A potentially powerful retrosynthetic disconnection **(C) Catalyst-controlled stereoselectivity: This study**

(C-1) At the carbon originating from the nucleophile (○):
A family of nucleophiles

(C-2) At both carbons (○●) of the new carbon-carbon bond

(B) Catalyst-controlled stereoselectivity: Previous work

(B-1) At the carbon originating from the electrophile (○):
A number of families of electrophiles

(B-2) At the carbon originating from the nucleophile (○):
A single nucleophile

(B-3) At both carbons (○●) of the new carbon-carbon bond:
No examples

Fig. 1. Alkyl-alkyl bond formation.

(A) A potentially powerful retrosynthetic disconnection. (B) Catalyst-controlled stereoselectivity: Previous work. (C) Catalyst-controlled stereoselectivity: This study. ee = enantiomeric excess, M = metal, R = substituent, X = leaving group.

Fig. 4. Transformations into other useful families of enantioenriched compounds

[All data represent the average of two experiments. The percent yield represents purified product.].