

# Convergent Catalytic Asymmetric Synthesis of Esters of Chiral Dialkyl Carbinols

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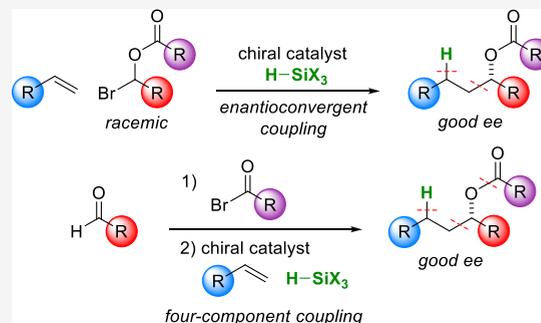


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**ABSTRACT:** Because chiral dialkyl carbinols, as well as their derived esters, are significant as intermediates and end points in fields such as organic, pharmaceutical, and biological chemistry, the development of efficient approaches to their asymmetric synthesis is an important endeavor. In this report, we describe a method for the direct catalytic enantioselective synthesis of such esters, beginning with an alkyl halide (derived from an aldehyde and an acyl bromide), an olefin, and a hydrosilane, catalyzed by nickel, an earth-abundant metal. The method is versatile, tolerating substituents that vary in size and that bear a range of functional groups. We further describe a four-component variant of this process, wherein the alkyl halide is generated in situ, thus obviating the need to isolate either an alkyl electrophile or an alkylmetal, while still effecting an alkyl–alkyl coupling. Finally, we apply our convergent method to the efficient catalytic enantioselective synthesis of three esters that are bioactive themselves or that have been utilized in the synthesis of bioactive compounds.



## INTRODUCTION

Esters of enantioenriched dialkyl carbinols, as well as the dialkyl carbinols themselves, are frequently encountered in organic chemistry, pharmaceutical science, biochemistry, and related fields (e.g., Figure 1A). With regard to catalytic asymmetric approaches to the generation of such esters, the dynamic kinetic resolution of racemic alcohols is one attractive strategy, although the scope of suitable partners is somewhat limited.<sup>1</sup> Another straightforward retrosynthesis involves the acylation of an enantioenriched alcohol, which might in turn be synthesized via the reduction of a ketone or via the addition of an organometallic nucleophile to an aldehyde. However, the asymmetric reduction of dialkyl ketones that bear two alkyl groups of similar size typically proceeds with poor enantioselectivity,<sup>2</sup> and studies of the asymmetric addition of alkylmetals to aliphatic aldehydes have largely focused on relatively simple nucleophiles.<sup>3</sup> Consequently, alternative approaches to the catalytic asymmetric synthesis of enantioenriched dialkyl carbinols and/or their ester derivatives have been pursued.<sup>4</sup>

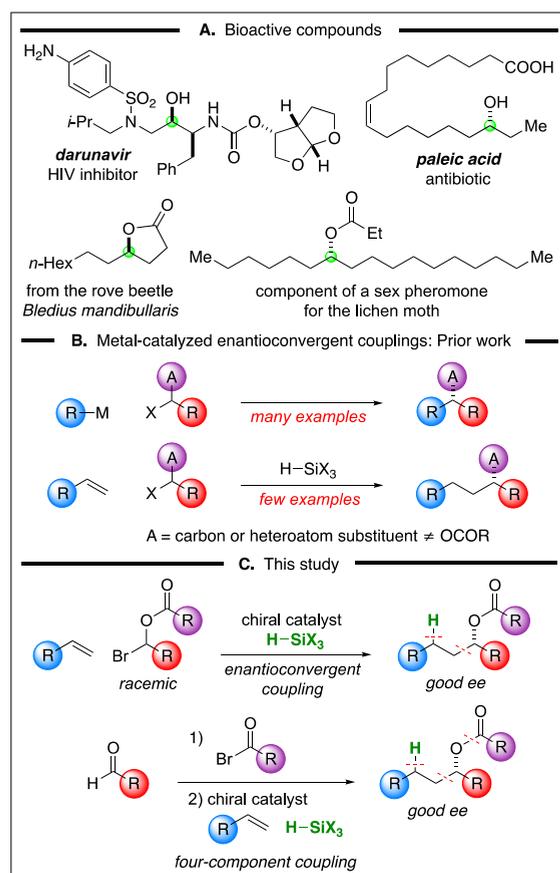
The metal-catalyzed enantioconvergent coupling of racemic alkyl electrophiles with alkyl nucleophiles has begun to emerge as a powerful strategy in asymmetric synthesis (top of Figure 1B).<sup>5</sup> Recently, it has been established that, in certain instances, an olefin (in combination with a hydrosilane) can be used in place of an alkyl nucleophile as the coupling partner (bottom of Figure 1B), thereby obviating the need to synthesize a discrete alkylmetal reagent,<sup>6,7</sup> which can afford significant practical advantages.

We have begun to explore whether the metal-catalyzed enantioconvergent coupling of racemic alkyl electrophiles with olefins can be applied to interesting new families of electrophiles to generate useful new classes of products. For example, we envisioned that it might be possible to accomplish a direct catalytic asymmetric synthesis of esters derived from enantioenriched dialkyl carbinols (top of Figure 1C).<sup>8</sup> In this report, we describe the achievement of this objective as well as the development of a variant wherein the same products are generated in a four-component coupling of readily available reaction partners (aldehyde, acyl bromide, olefin, and hydrosilane; bottom of Figure 1C).<sup>9</sup>

## RESULTS AND DISCUSSION

In an initial study, we examined the coupling of racemic 1-bromopropyl benzoate with vinyl cyclohexane (Figure 2A), and we determined that NiBr<sub>2</sub>·diglyme and chiral bis(oxazoline) ligand L\* can accomplish the desired enantioconvergent reductive coupling in good yield and ee (78% yield, 92% ee; entry 1). In the absence of NiBr<sub>2</sub>·diglyme or of ligand L\*, essentially no carbon–carbon bond formation is observed (entries 2 and 3). An array of other ligands are less effective

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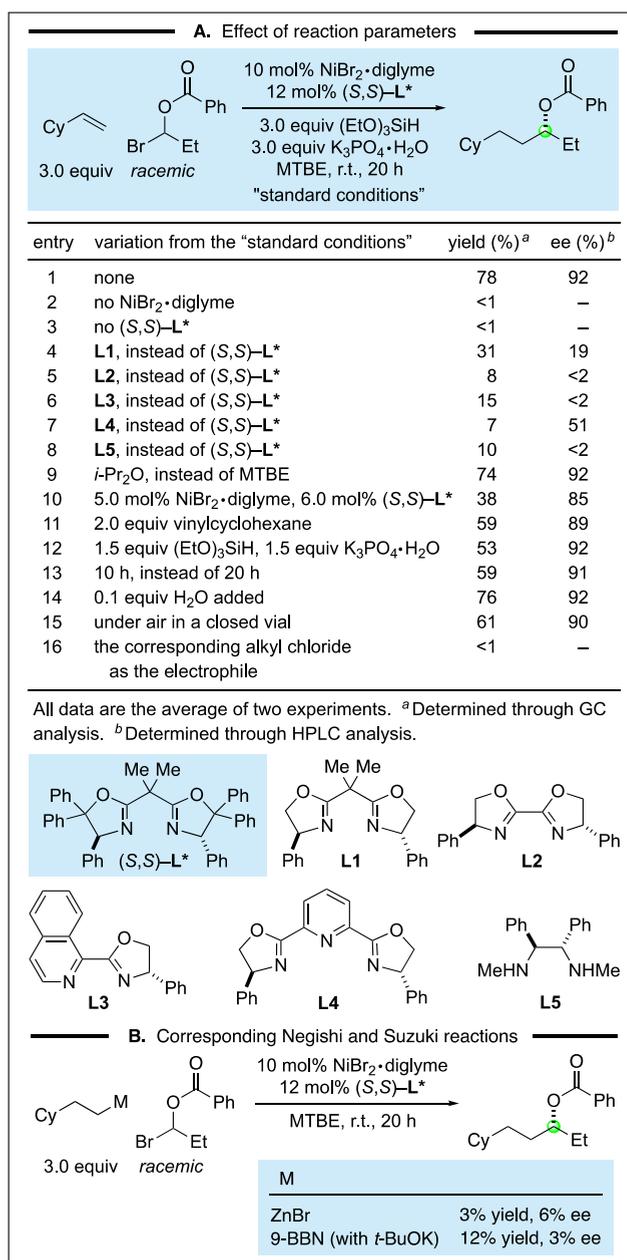


**Figure 1.** (A) Examples of bioactive compounds that include a chiral dialkyl carbinol, free or acylated. (B) Approaches to metal-catalyzed enantioconvergent alkyl–alkyl couplings of racemic electrophiles. (C) This study.

than ligand  $L^*$  (entries 4–8), whereas the use of  $i\text{-Pr}_2\text{O}$  in place of MTBE leads to a similar outcome (entry 9). If the coupling is conducted with less catalyst, less olefin, less hydrosilane/base, or for less time, then a lower yield and/or ee are obtained (entries 10–13). The presence of a small amount of water (0.1 equiv) has virtually no effect on the coupling (entry 14), and a reaction run under air in a closed vial proceeds relatively smoothly (entry 15). Under these conditions, the corresponding alkyl chloride (entry 16) and a 1,1-disubstituted olefin (methylene-cyclohexane) are not suitable coupling partners.

It is interesting to note that, if the olefin/hydrosilane are replaced with an alkylmetal reagent (an alkylzinc or an alkylborane), carbon–carbon bond formation proceeds with poor yield and enantioselectivity (Figure 2B). Thus, in addition to the practical advantage of not having to generate a stoichiometric quantity of an alkylmetal reagent, the use of an olefin/hydrosilane may enable couplings that are not readily achieved via the traditional nucleophile–electrophile approach.

The scope of this method for the catalytic enantioconvergent synthesis of acylated dialkyl carbinols is fairly broad with respect to the various substituents (Figure 3). For example, the alkyl substituent  $\alpha$  to bromine can vary in size from methyl to neopentyl to isopropyl, and consistently good yields and ee's are observed (entries 1–8). A variety of functional groups, including an ether and an unactivated primary alkyl chloride and bromide, are compatible with the method (entries 9–12). In the case of an electrophile that bears a nearby stereocenter,

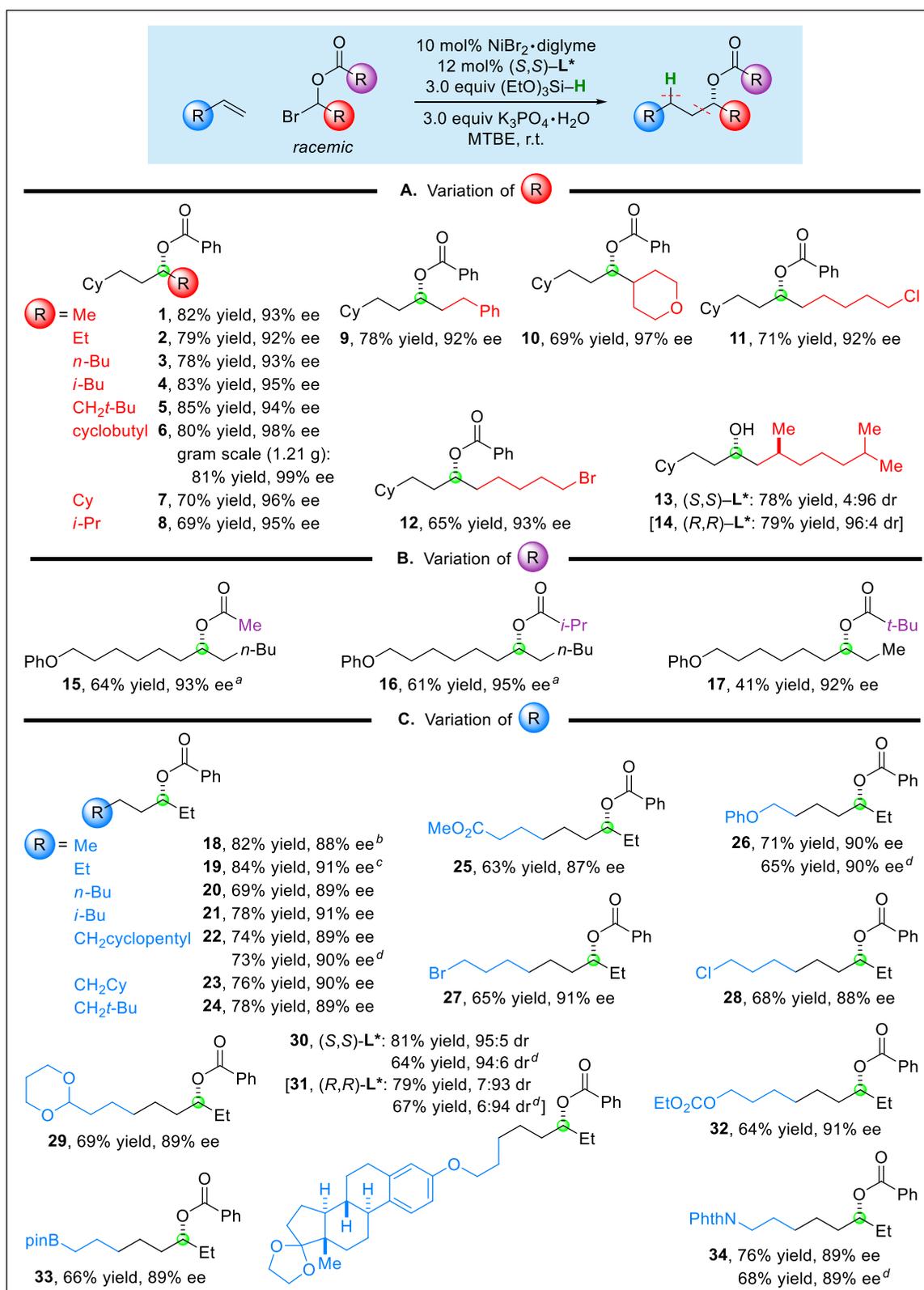


**Figure 2.** Catalytic asymmetric synthesis of an ester of a chiral dialkyl carbinol. (A) Effect of reaction parameters. (B) Comparison with the corresponding Negishi and Suzuki reactions.

the stereochemistry of the catalyst, rather than that of the substrate, predominantly controls the stereochemistry of the product (entries 13–14). On a gram-scale (1.21 g of product), the coupling illustrated in entry 6 proceeds in similar yield and ee as for a reaction conducted on a 0.8 mmol scale.

With regard to the acyl substituent of the electrophile, not only an aryl group (Figure 3, entries 1–14) but also an alkyl group (entries 15–17) can be present. For these electrophiles, less  $(\text{EtO})_3\text{SiH}$  and  $\text{K}_3\text{PO}_4 \cdot \text{H}_2\text{O}$  may be used (2.0 equiv), and a small enhancement in yield is observed when the coupling is conducted in  $i\text{-Pr}_2\text{O}$ . However, in the case of a  $t$ -butyl substituent, a modest yield (but good enantioselectivity) is observed under either conditions (entry 17).

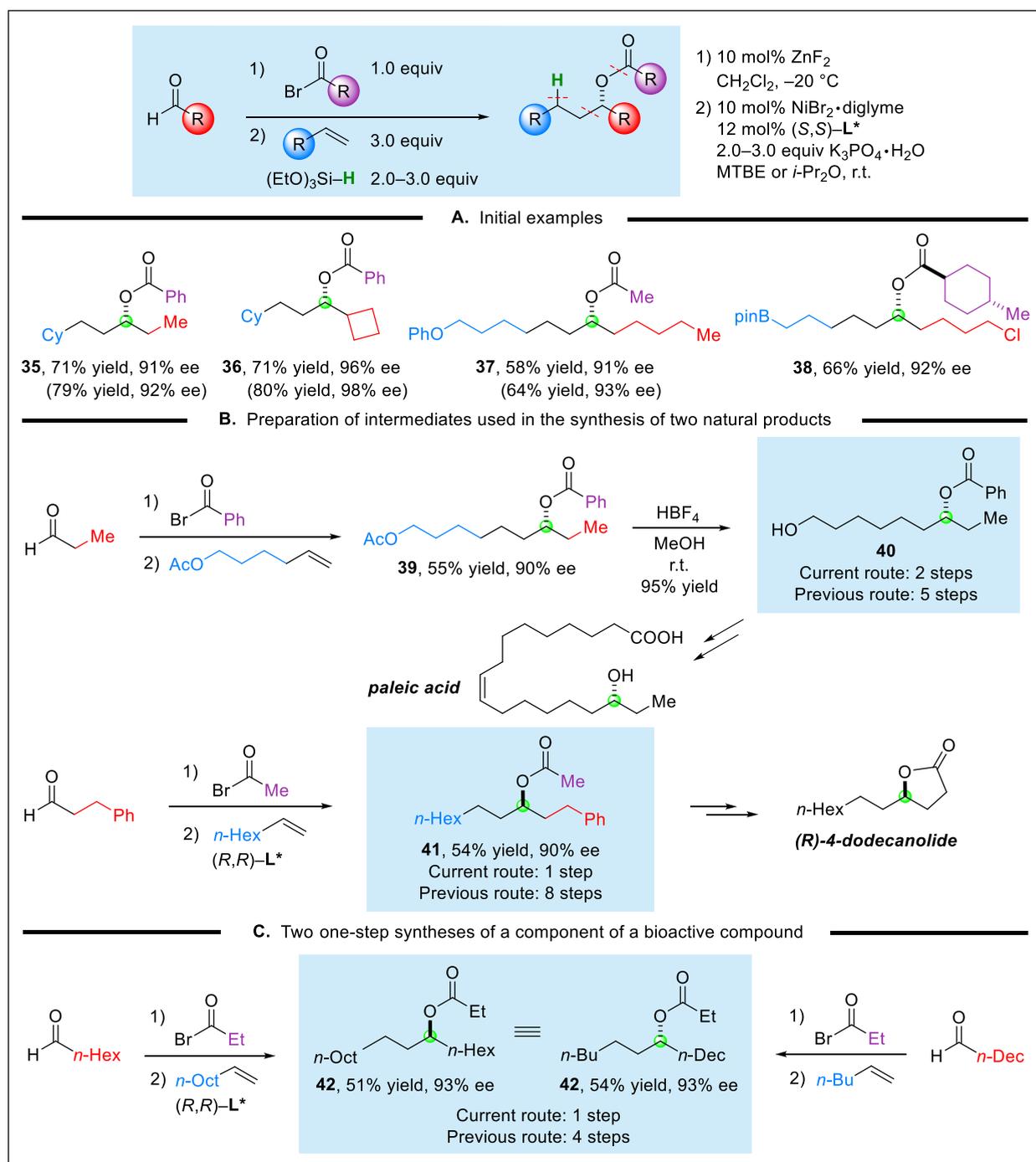
The scope of the enantioconvergent coupling is broad with respect to the olefin, leading to an array of products with ~90%



**Figure 3.** Catalytic asymmetric synthesis of esters of chiral dialkyl carbinols: Scope. All data are the average of two experiments. Unless otherwise noted, couplings were conducted on a 0.8 mmol scale. <sup>a</sup>In place of the standard conditions, 2.0 equiv of (EtO)<sub>3</sub>SiH and 2.0 equiv of K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O were used with *i*-Pr<sub>2</sub>O as the solvent. <sup>b</sup>In place of the standard conditions, a balloonful of propylene was used. <sup>c</sup>In place of the standard conditions, 5.0 equiv of 1-butene (bp 21 °C) was used. <sup>d</sup>In place of the standard conditions, 2.0 equiv of the olefin was used.

ee. For example, the substituent can range in size from methyl to neopentyl (Figure 3, entries 18–24; for Cy, see entries 1–14), and a variety of functional groups can be present,

including an acetal, carbonate, boronate ester, and imide (entries 25–34). Additive studies establish that an aldehyde, aniline, aryl bromide, aryl chloride, aryl tosylate, aryl triflate,



**Figure 4.** Catalytic asymmetric four-component couplings. (A) Initial examples. (B) Preparation of intermediates used in the synthesis of paleic acid and *(R)*-dodecanolide. (C) One-step syntheses of *(S)*-heptadecan-7-yl propionate, a component of a sex pheromone for the lichen moth. All data are the average of two experiments.

benzofuran, benzothiophene, epoxide, ketone, *N*-methylindole, thioether, and unactivated secondary alkyl bromide are fully compatible with the reaction conditions (see the [Supporting Information](#)). Consistent with the data provided in entry 11 of [Figure 2A](#), the use of 2.0, rather than 3.0, equivalents of the olefin generally leads to a modest loss in yield, but little change in enantioselectivity ([Figure 3](#), entries 22, 26, 30, 31, and 34; drop in yield: 1–17%).

These three-component reactions can also be conducted as four-component reactions (aldehyde, acyl bromide, olefin, and hydrosilane) by preparing the alkyl bromide in situ. As

illustrated in [Figure 4A](#), the four-component reactions proceed in good yield, leading to the formation of a C–H, a C–C, and a C–O bond, as well as the creation of a stereocenter with good enantioselectivity.

This nickel-catalyzed four-component coupling provides efficient access to enantioenriched compounds that have been applied by others in the synthesis of natural products ([Figure 4B](#)). Thus, benzoate ester **40**, an intermediate in the synthesis of paleic acid, an antimicrobial agent that is effective against *Mannheimia* and *Pasteurella*, can be generated from commercially available compounds in two steps and 90% ee via

our catalytic asymmetric coupling, whereas it had previously been synthesized in five steps.<sup>10</sup>

Enantioenriched ester **41** (Figure 4B), generated earlier in eight steps via a lipase-catalyzed kinetic resolution of a racemic alcohol, has served as an intermediate in a synthesis of (*R*)-4-dodecanolide, which is part of a defensive secretion of rove beetle *Bledius mandibullaris*.<sup>11</sup> Using our catalytic enantioselective four-component coupling, we can produce ester **41** in one step and 90% ee from commercially available building blocks.

Finally, we applied our method to the catalytic asymmetric synthesis of (*S*)-heptadecan-7-yl propionate (Figure 4C; **42**), which is a component of a sex pheromone for lichen moths.<sup>12</sup> Ester **42** has previously been synthesized in four steps via a Jacobsen kinetic resolution of a racemic epoxide; using our method, we produced ester **42** in one step by two different disconnections from commercially available compounds.

## CONCLUSIONS

We developed an efficient and versatile method for the direct synthesis of esters of enantioenriched dialkyl carbinols via a nickel-catalyzed enantioconvergent coupling of a racemic alkyl halide with an olefin in the presence of a hydrosilane. The method tolerates substituents of varying size on the electrophile and on the olefin, and it displays good functional-group tolerance.

Furthermore, we demonstrated the viability of a four-component variant of this method wherein the alkyl halide is generated in situ, and we applied this convergent approach to the efficient synthesis of enantioenriched esters that are bioactive themselves or that have been employed as intermediates in previous syntheses of bioactive natural products. In contrast to traditional alkyl–alkyl couplings of electrophiles and nucleophiles, in this approach, the alkyl electrophile is generated in situ and the need to synthesize a stoichiometric alkylmetal nucleophile is obviated. Additional efforts to apply earth-abundant metals to useful coupling reactions are underway.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.0c01324>.

Procedures, characterization data, and additional references (PDF)

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## Notes

The authors declare no competing financial interest.

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## REFERENCES

- (1) For a review, see: Verho, O.; Bäckvall, J.-E. Chemoenzymatic Dynamic Kinetic Resolution: A Powerful Tool for the Preparation of Enantiomerically Pure Alcohols and Amines. *J. Am. Chem. Soc.* **2015**, *137*, 3996–4009.
- (2) For overviews, see: (a) Arai, N.; Ohkuma, T. Reduction of Carbonyl Groups: Hydrogenation. *Science of Synthesis, Stereoselective Synthesis*; De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Georg Thieme Verlag: Stuttgart, 2011; Vol. 2, pp 9–57. (b) Zaidlewicz, M.; Pakulski, M. M. Reduction of Carbonyl Groups: Transfer Hydrogenation, Hydrosilylation, Catalytic Hydroboration, and Reduction with Borohydrides, Aluminum Hydrides, or Boranes. *Science of Synthesis, Stereoselective Synthesis*; De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Georg Thieme Verlag: Stuttgart, 2011; Vol. 2, pp 59–131. (c) Stefane, B.; Pozgan, F. Advances in Catalyst Systems for the Asymmetric Hydrogenation and Transfer Hydrogenation of Ketones. *Catal. Rev.: Sci. Eng.* **2014**, *56*, 82–174.
- (3) Ramon, D. J.; Yus, M. Alkylation of Carbonyl and Imino Groups. *Science of Synthesis, Stereoselective Synthesis*; De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Georg Thieme Verlag: Stuttgart, 2011; Vol. 2, pp 349–400.
- (4) For illustrative examples, see: (a) León, F.; González-Liste, P. J.; García-Garrido, S. E.; Arribas, I.; Rubio, M.; Cadierno, V.; Pizzano, A. Broad Scope Synthesis of Ester Precursors of Nonfunctionalized Chiral Alcohols Based on the Asymmetric Hydrogenation of  $\alpha,\beta$ -Dialkyl-,  $\alpha,\beta$ -Diaryl-, and  $\alpha$ -Alkyl- $\beta$ -aryl-vinyl Esters. *J. Org. Chem.* **2017**, *82*, 5852–5867. (b) Schmidt, J.; Choi, J.; Liu, A. T.; Slusarczyk, M.; Fu, G. C. A General, Modular Method for the Catalytic Asymmetric Synthesis of Alkylboronate Esters. *Science* **2016**, *354*, 1265–1269.
- (5) (a) Fu, G. C. Transition-Metal Catalysis of Nucleophilic Substitution Reactions: A Radical Alternative to  $S_N1$  and  $S_N2$  Processes. *ACS Cent. Sci.* **2017**, *3*, 692–700. (b) Choi, J.; Fu, G. C. Transition Metal-Catalyzed Alkyl–Alkyl Bond Formation: Another Dimension in Cross-Coupling Chemistry. *Science* **2017**, *356*, eaaf7230. (c) Kaga, A.; Chiba, S. Engaging Radicals in Transition Metal-Catalyzed Cross-Coupling with Alkyl Electrophiles: Recent Advances. *ACS Catal.* **2017**, *7*, 4697–4706. (d) Iwasaki, T.; Kambe, N. Ni-Catalyzed C–C Couplings using Alkyl Electrophiles. *Top. Curr. Chem.* **2016**, *374*, 66. (e) Geist, E.; Kirschning, A.; Schmidt, T.  $sp^3$ - $sp^3$  Coupling Reactions in the Synthesis of Natural Products and Biologically Active Molecules. *Nat. Prod. Rep.* **2014**, *31*, 441–448.
- (6) For a pioneering study of a nonasymmetric nickel-catalyzed coupling, see: Lu, X.; Xiao, B.; Zhang, Z.; Gong, T.; Su, W.; Yi, J.; Fu, Y.; Liu, L. Practical Carbon–Carbon Bond Formation from Olefins Through Nickel-Catalyzed Reductive Olefin Hydrocarbonation. *Nat. Commun.* **2016**, *7*, 11129.
- (7) (a) Wang, Z.; Yin, H.; Fu, G. C. Catalytic Enantioconvergent Coupling of Secondary and Tertiary Electrophiles with Olefins. *Nature* **2018**, *563*, 379–383. (b) He, S.-J.; Wang, J.-W.; Li, Y.; Xu, Z.-Y.; Wang, X.-X.; Lu, X.; Fu, Y. Nickel-Catalyzed Enantioconvergent Reductive Hydroalkylation of Olefins with  $\alpha$ -Heteroatom Phosphorus or Sulfur Alkyl Electrophiles. *J. Am. Chem. Soc.* **2020**, *142*, 214–221. (c) For a related process, see: Zhou, F.; Zhang, Y.; Xu, X.; Zhu, S.

NiH-Catalyzed Remote Asymmetric Hydroalkylation of Alkenes with Racemic  $\alpha$ -Bromo Amides. *Angew. Chem., Int. Ed.* **2019**, *58*, 1754–1758.

(8) For a report of the use of the corresponding alkyl iodides as radical precursors for additions to alkynes, see: Wang, L.; Lear, J. M.; Rafferty, S. M.; Fosu, S. C.; Nagib, D. A. Ketyl Radical Reactivity via Atom Transfer Catalysis. *Science* **2018**, *362*, 225–229.

(9) For reductive coupling strategies that introduce allyl and other unsaturated groups to aldehydes and other electrophiles, see: Holmes, M.; Schwartz, L. A.; Krische, M. J. Intermolecular Metal-Catalyzed Reductive Coupling of Dienes, Allenes and Enynes with Carbonyl Compounds and Imines. *Chem. Rev.* **2018**, *118*, 6026–6052.

(10) (a) Watanabe, T.; Kurata, I.; Hayashi, C.; Igarashi, M.; Sawa, R.; Takahashi, Y.; Akamatsu, Y. The Synthesis of Paleic Acid, an Antimicrobial Agent Effective Against *Mannheimia* and *Pasteurella*, and its Structurally Related Derivatives. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5843–5846. (b) Jones, G. B.; Huber, R. S.; Chapman, B. J. Catalytic Enantioselective Synthesis of Macrolides via Asymmetric Alkylation. *Tetrahedron: Asymmetry* **1997**, *8*, 1797–1809.

(11) (a) Vlasyuk, A. L.; Voblikova, V. A.; Gamalevich, G. D.; Serebryakov, E. P. The Absolute Configuration of (+)- and (–)-Phenylundec-4-yn-3-ols. Synthesis of (*R*)-4-Dodecanolide, a Component of the Defensive Secretion of Rove Beetle *Bledius Mandibularis*. *Russ. Chem. Bull.* **2013**, *62*, 2032–2036. (b) Vlasyuk, A. L.; Gamalevich, G. D.; Ignatenko, A. V.; Serebryakov, E. P.; Struchkova, M. I. Lipase-Mediated Deracemization of Secondary 1-Phenyl-Substituted Propargylic Alcohols of Different Topology. *Russ. Chem. Bull.* **2004**, *53*, 693–702.

(12) Fujii, T.; Yamakawa, R.; Terashima, Y.; Imura, S.; Ishigaki, K.; Kinjo, M.; Ando, T. Propionates and Acetates of Chiral Secondary Alcohols: Novel Sex Pheromone Components Produced by a Lichen Moth *Barsine Expressa* (Arctiidae: Lithosiinae). *J. Chem. Ecol.* **2013**, *39*, 28–36.