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Communication

Asymmetric *anti*-Selective Borylalkylation of Terminal Alkynes by Nickel Catalysis

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ABSTRACT: Selective transformation of alkyne triple bonds to double bonds serves as an efficient platform to construct substituted alkenes. While significant advances have been made in its spatiotemporal regulation, achieving a multicomponent enantioselective reaction that requires multifaceted selectivity issues to be overcome is still uncommon. Here, we report an unprecedented asymmetric *anti*-stereoselective borylcarbofunctionalization of terminal alkynes by nickel catalysis. The utilization of an inexpensive chiral diamine ligand enables the three-component cross-coupling of terminal alkynes, a diboron reagent, and prochiral alkyl electrophiles with high levels of regio-, stereo-, and enantioselectivities. This reaction provides an efficient protocol to access enantioenriched alkenyl esters bearing an α-stereogenic center, is remarkably practical, and has a broad scope and an outstanding functional group compatibility. In addition, the value of this method has been highlighted in a diversity of follow-up stereoretentive derivatizations and the stereoselective concise synthesis of complex drug molecules.

Alkynes, as some of the most fundamental and versatile functional groups, are widely exploited as starting precursors in organic synthesis.[1] The development of catalytic methods that enable their transformation into other value-added functionalities or structures is a highly interesting yet challenging topic from both academic and industrial perspectives.[2] In this regard, the selective difunctionalization of alkynes has been explored as an important strategic entry to access stereodefined alkenes[3] and is frequently utilized in assembling complex pharmaceutical molecules.[4] Regio- and stereoselective control comprise the central challenges in the quest of transforming linear entities into tetrahedral ones (Figure 1A).[5] To address regioselectivity issues, electronically biased[6] or directing-auxiliary-containing alkynes[7] have been used. The spatiotemporal selectivity of the two introduced functional groups is generally dictated by reaction mechanistic manifolds: if the reaction undergoes alkyne migratory insertion into a nucleophilic organometallic species, a *syn*-selective difunctionalized product is usually obtained;[8] if the reaction is initiated by the addition of a radical species to the alkyne, a product with *anti*-selective control is favored.[9] Furthermore, in a handful of cases a reaction initiated by a *syn*-addition was followed by a *Z*/*E* isomerization, particularly in the case of intramolecular annulation reactions,[10] as well as with the assistance of coordinating groups.[11] Additionally, ligands[12] or reaction conditions[13] can also modulate the reaction stereoselectivity. Transition-metal-catalyzed difunctionalization of alkynes that simultaneously creates polysubsituted olefins and stereocenters with complete regio- and stereocontrol is a highly challenging task; currently the state of the art is limited to a dicarbofunctionalization reaction by using prochiral imines.[14] The borylative difunctionalization of unsaturated π-bond chemicals[15] serves as a platform to assemble organoboron compounds.[16] Merging the borylative difunctionalization of alkynes with a stereoconvergent cross-coupling of prochiral electrophiles[17] constitutes transformations of great synthetic potential (Figure 1B, top line), yet it is still an underexplored topic in the blueprint of alkyne difunctionalization reactions.

As an extension of our success in a series of nickel-catalyzed borylcarbofunctionalization of alkenes,[18] we moved our attention to exploring the synthetic potential of the same reaction with alkynes. However, the implementation of this concept, especially the search for one chiral ligand able to simultaneously modulate the regio-, diastereo-, and enantioselectivity in a multicomponent reaction, poses formidable challenges. Furthermore, another competition is from the radical outer-sphere bond formation pathway, which results in the formation of racemic products with reversed regioselectivity (Figure 1B, bottom line). Herein, we report our success in circumventing these obstacles via the development of a Ni-catalyzed enantioselective intermolecular borylalkylation of unactivated terminal alkynes (Figure 1C). Unexpectedly, a high level of *E*-stereoselectivity rather than *Z*-stereoselectivity was obtained in this transformation. This reaction features a simple and inexpensive chiral ligand and high regio- and enantioselective controls. Moreover, this study builds up a synthetic method by the combination of aliphatic terminal alkynes, abundant carboxylic acids, and B_2pin_2, providing efficient access to highly valuable enantioenriched α-vinyl esters.

We commenced this study by exploring the three-component cross-coupling of an unactivated alkyne (**1a**),

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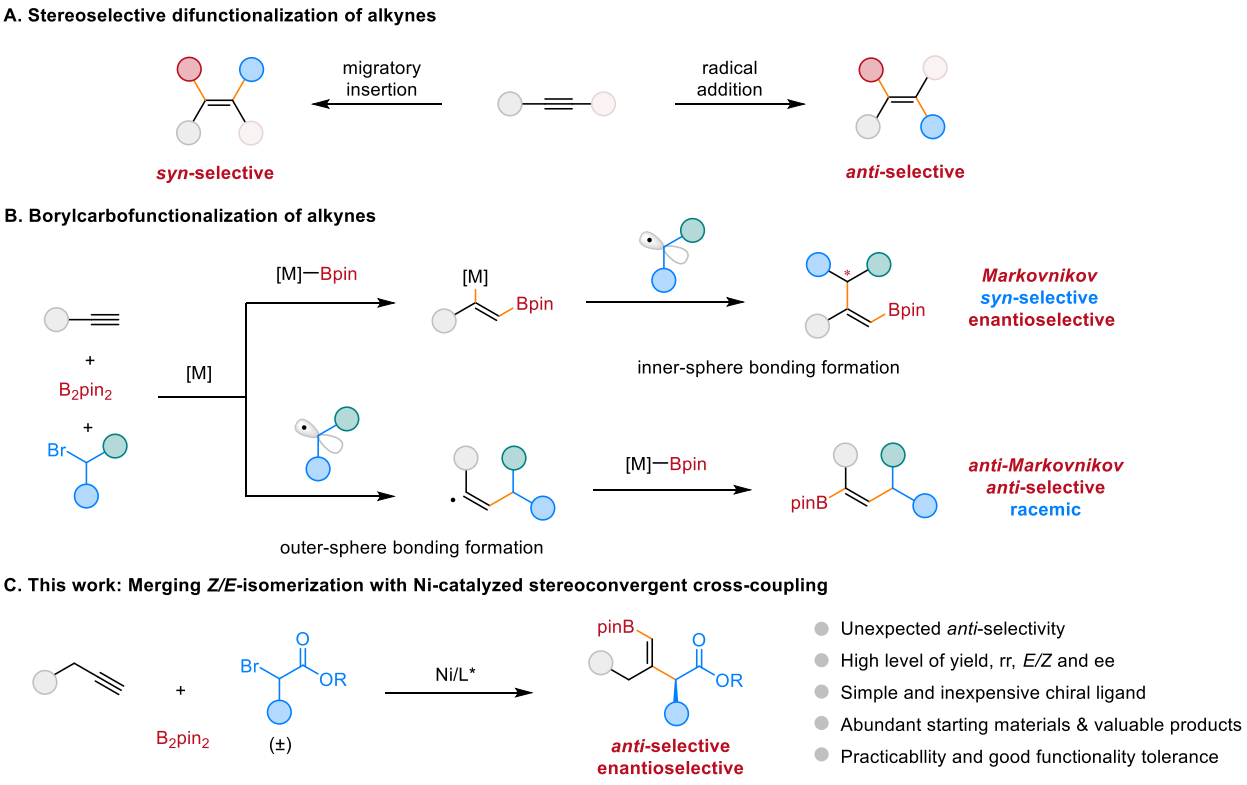
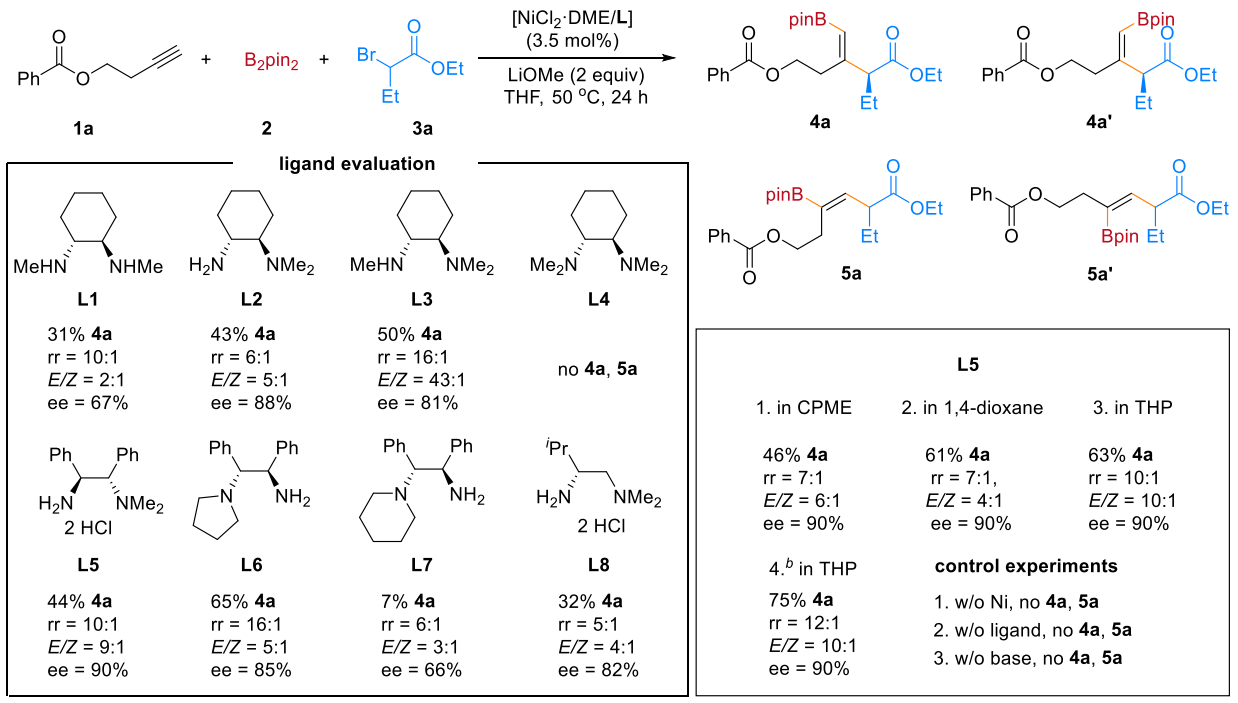


Figure 1. Difunctionalization of alkynes.

Table 1. Reaction Development[a]



[a]Reaction conditions unless specified otherwise: $NiCl_2$·DME (3.5 mol %), **L** (3.5 mol %), **1a** (0.4 mmol, 1.0 equiv), **2** (0.8 mmol, 2 equiv), **3a** (0.8 mmol, 2 equiv), and LiOMe (0.8 mmol, 2 equiv) in solvent (2.0 mL), stirred at 50 °C for 24 h. GC yield, rr, and *E*/*Z* were determined by GC analysis of the crude reaction mixture. Enantiomeric excess (ee) was determined by chiral HPLC analysis. [b]**2** (1.2 mmol, 3.0 equiv) and LiOMe (1.2 mmol, 3.0 equiv) were used; the given yield is the isolated yield of **4a** on a 0.4 mmol scale.

B_2pin_2 (**2**), and ethyl 2-bromobutyrate (**3a**). After extensive experiments, we found that the ligand is a paramount parameter to enable this three-component reaction. As shown in Table 1, the simple chiral 1,2-diamine ligand **L1** was effective for promoting the formation of enantioenriched Markovnikov-borylative alkylation products. Unexpectedly, the

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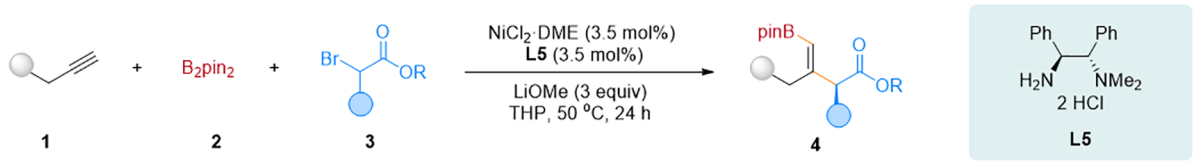
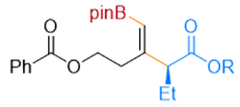
Table 2. Substrate Scope[a]



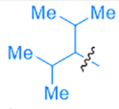
Scope of alkyl bromides



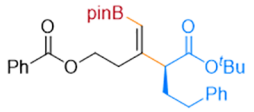
4a: 75%, 90% ee
E/*Z* = 10:1, rr = 12:1

4b: 79%, 91% ee
E/*Z* = 8:1, rr = 13:1

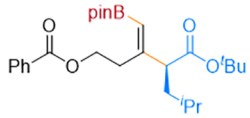
4c: 80%, 93% ee
E/*Z* = 11:1, rr = 15:1



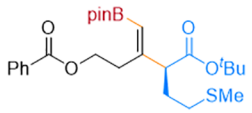
4d: 65%, 95% ee
E/*Z* =10:1, rr = 38:1
enti-**4d:** 62%[e], 92% ee
E/*Z* = 9:1, rr > 20:1



4e: 68%, 89% ee
E/*Z* = 11:1, rr > 20:1



4f: 61%[c], 92% ee
E/*Z* > 20:1, rr > 20:1



4g: 45%[d], 90% ee
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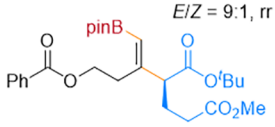
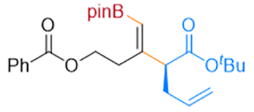
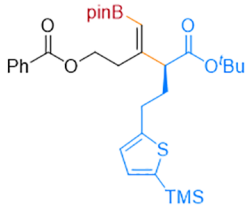


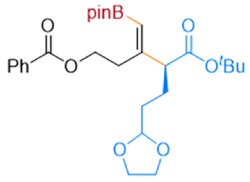
4h: 55%, 90% ee
E/*Z* = 8:1, rr > 20:1



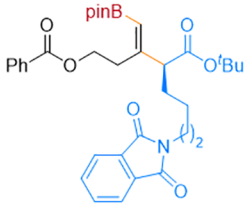
4i: 41%[d], 86% ee
E/*Z* = 8:1, rr > 20:1



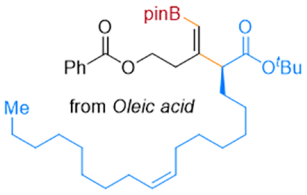
4j: 52%[b], 89% ee
E/*Z* = 10:1, rr > 20:1



4k: 70%, 90% ee
E/*Z* = 11:1, rr > 20:1

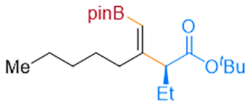


4l: 59%[b], 95% ee
E/*Z* = 15:1, rr = 11:1

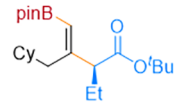


4m: 55%[b], 81% ee
E/*Z* = 12:1, rr > 20:1

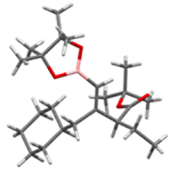
Scope of alkynes



4n: 76%, 87% ee
E/*Z* = 51:1, rr = 16:1



4o: 65%, 91% ee
E/*Z* = 9:1, rr = 14:1



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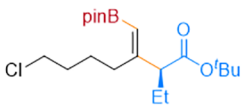
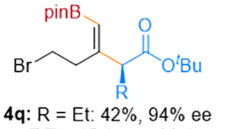
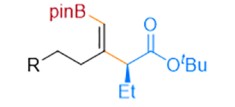


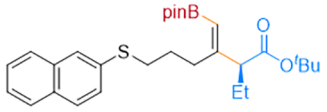
4p: 71%, 88% ee
E/*Z* =8:1, rr = 12:1



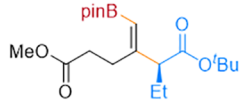
4q: R = Et: 42%, 94% ee
E/*Z* = 15:1, rr = 20:1
4r: R = Me: 53%, 87% ee
E/*Z* = 24:1, rr = 26:1



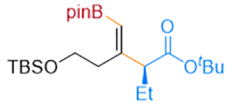
R = Ph **4s:** 71%, 87% ee
E/*Z* = 15:1, rr = 20:1
R = OPh **4t:** 55%, 98% ee
E/*Z* = 15:1 , rr = 20:1



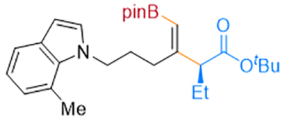
4u: 58%, 89% ee
E/*Z* = 10:1, rr > 20:1



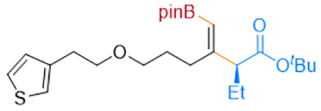
4v: 77%, 92% ee
E/*Z* = 12:1, rr = 15:1
enti-**4v:** 79%[e], 92% ee
E/*Z* = 12:1, rr = 16:1



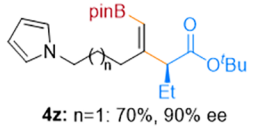
4w: 72%, 95% ee
E/*Z* = 14:1, rr = 20:1
10 mmol scale: 3.12 g
67%, 94% ee
E/*Z* = 13:1, rr > 20:1



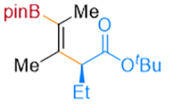
4x: 80%, 88% ee
E/*Z* = 10:1, rr > 20:1



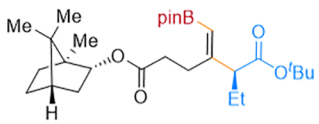
4y: 72%, 92% ee
E/*Z* > 20:1, rr = 8:1



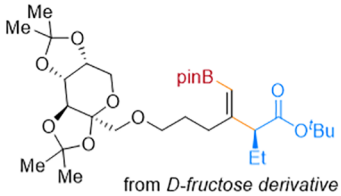
4z: n=1: 70%, 90% ee
E/*Z* = 8:1, rr = 15:1
4aa: n=2 : 64%, 94% ee
E/*Z* = 8:1, rr = 14:1



4ab: 25%, 81% ee
Z/*E* > 20:1, rr > 20:1



from *Borneol derivative*
4ac: 65%, 83% de
E/*Z* = 8:1, rr = 10:1



from *D-fructose derivative*
4ad: 70%, 90% de
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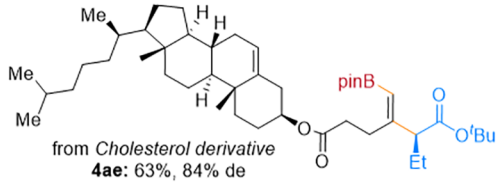

from *Cholesterol derivative*
4ae: 63%, 84% de
E/*Z* = 8:1, rr = 10:1

[a]General reaction conditions: $NiCl_2$·DME (3.5 mol %), **L5** (3.5 mol %), **1** (0.4 mmol, 1.0 equiv), **2** (1.2 mmol, 3.0 equiv), **3** (0.8 mmol, 2.0 equiv) and LiOMe (1.2 mmol, 3.0 equiv) in THP (2.0 mL), stirred at 50 °C for 24 h. The given isolated yield refers to the single isomeric product. [b]Reaction was conducted on 0.2 mmol scale. [c]THF was used instead of THP as solvent. [d]Isolated yield of the product from following Suzuki cross-coupling. [e](*R*,*R*)-**L5** was used.

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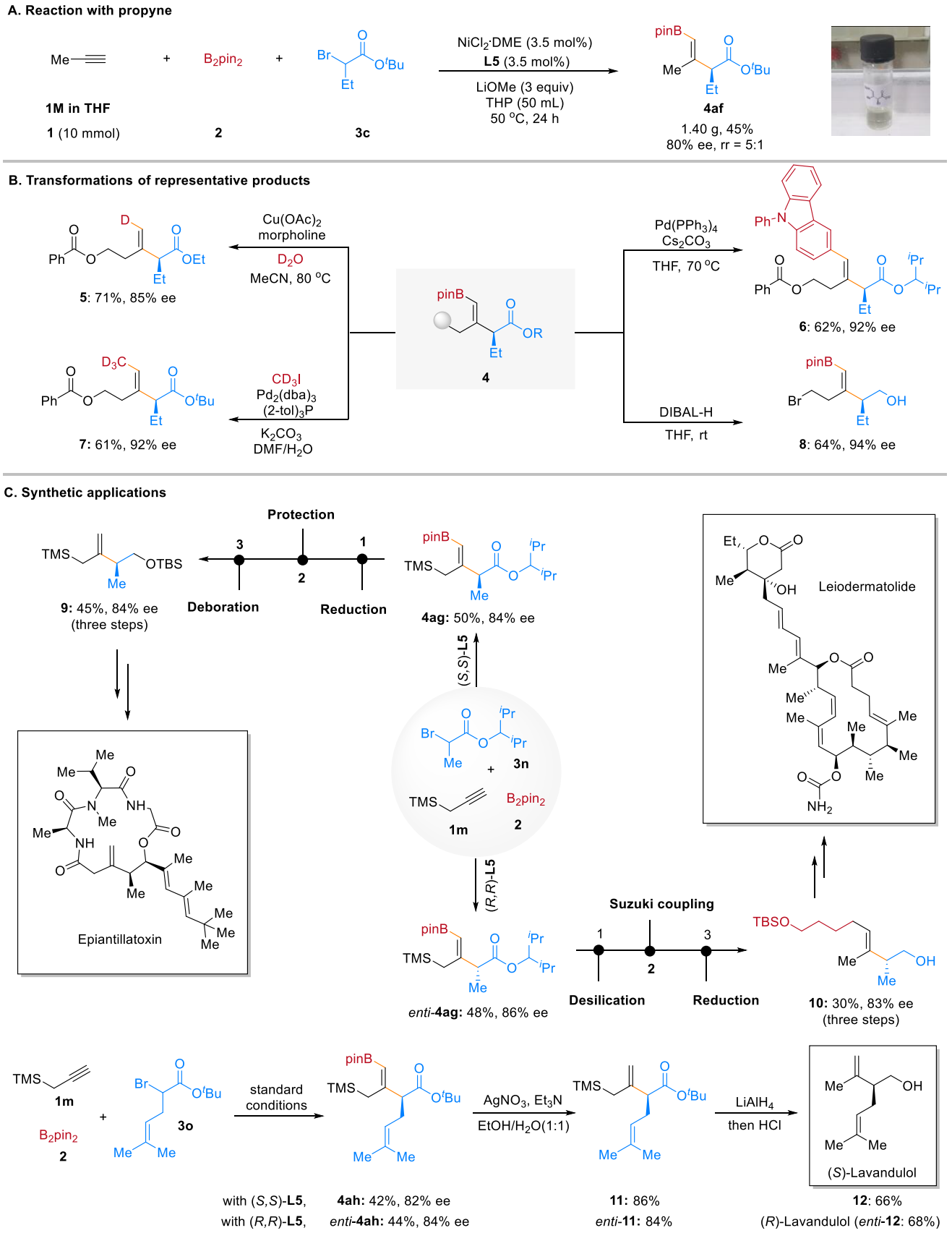

Figure 2. Transformations of products and synthetic applications.

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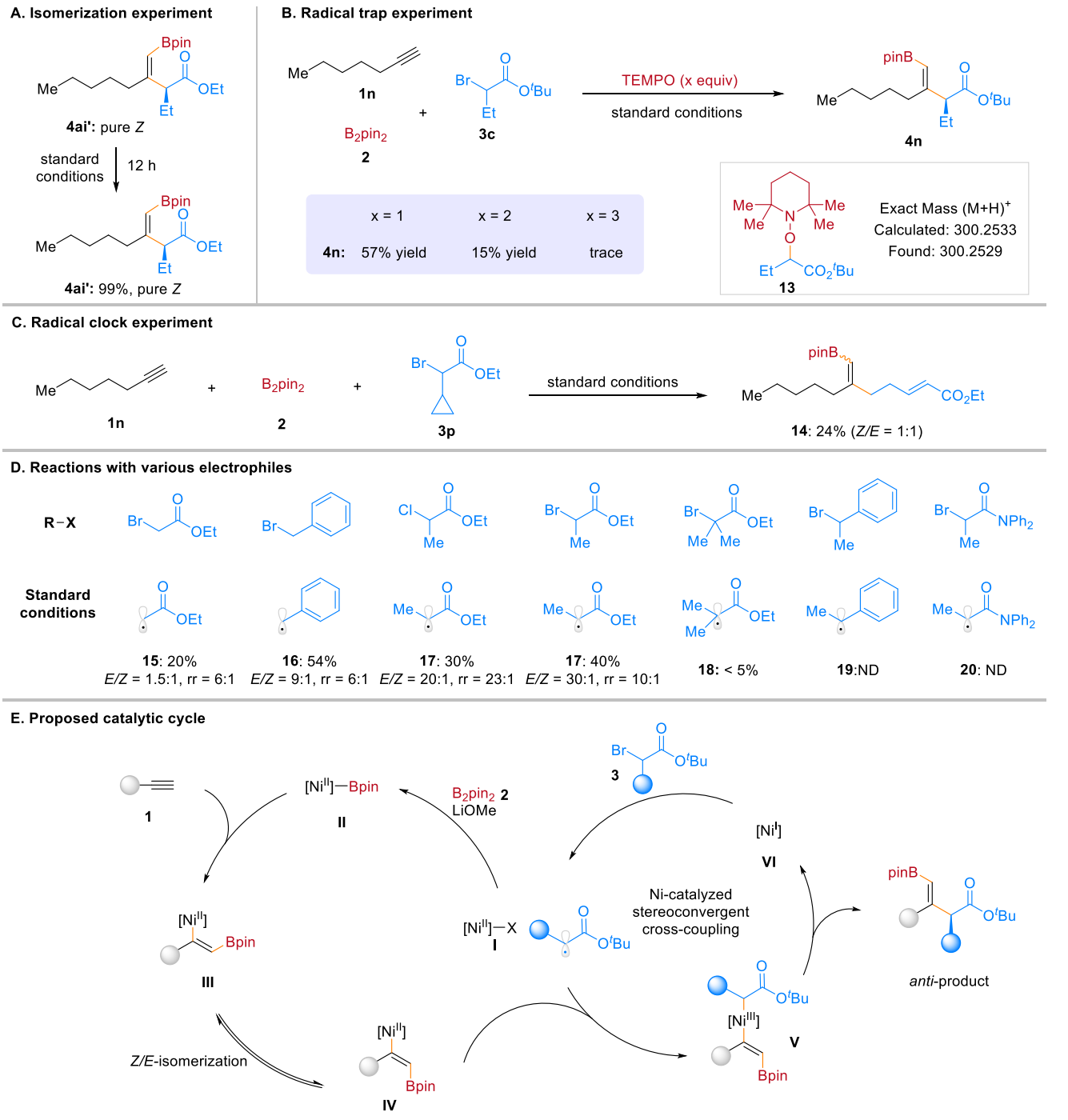

Figure 3. Mechanistic studies and the proposed catalytic cycle.

reaction led to the *E*-product **4a** as the preferred isomer, rather than the *Z*-product **4a′**. Modification of the *N*-substituents revealed no clear trend. For example, when comparing **L1**−**L3**, the reactivity and *E*/*Z* ratio increased with an increasing number of methyl substituents, but the regio- and enantioselectivity did not, **L2** affording a better ee but a worse rr. These results reflect the difficult reaction optimization. The fully methyl-substituted diamine **L4** failed to offer any three-component coupling products. Among the ligands with a modified backbone, **L5** with a 1,2-diphenylethylene backbone provided a slightly better result. A subsequent solvent survey identified tetrahydropyran (THP) as the optimal choice. The reactivity was further improved by increasing the boron reagent and base loadings. Under these optimized conditions, **4a** was isolated in 75% yield with good chemo- and enantioselectivity (12:1 rr, 10:1 *E*/*Z* and 90% ee).

With the optimal reaction conditions in hand, we shifted our attention to a scope study. As outlined in Table 2, the ester alkyl group was investigated first. Both regio- and enantioselectivity gradually increased as the size of the alkyl group also increased, while the *Z*/*E* ratio was hardly affected (**4a**−**d**). We selected *tert*-butyl as a protecting group to access the scope of prochiral electrophiles. A set of *α*-bromoesters bearing diverse substituents, which were readily prepared from the corresponding aliphatic carboxylic acids,[19] were tested in combination with **1a**. All participated in this reaction to successfully afford

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the enantioenriched alkenyl esters in good yields with excellent enantiomeric excesses (81−95% ee) (**4e**−**m**). A wide range of transformable and coordinating functional groups, including thioether, ester, olefin ketyl, and imide, were well tolerated and did not affect the reactivity and selectivity. Next, the alkyne part was assessed in combination with *tert*-butyl 2-bromobutyrate as a model partner (**4n**−**ae**). A series of unactivated terminal alkynes containing a broad range of pendant groups, including aliphatic chains (**4n**,**o**), transformable heteroatoms (**4p**−**r**) and functional groups (**4s**−**w**), and heterocycles (**4x**−**aa**) were examined, all smoothly undergoing this nickel-catalyzed reaction to deliver the borylated alkenyl esters in good yields and with high levels of chemo- and enantioselectivity (83−98% ee). The absolute configuration was unambiguously confirmed by X-ray analysis for product **4o**. Notably, 2-butyne, a simple internal alkyne, was also able to produce the *anti*-selective borylalkylation product (**4ab**) with good enantioselectivity under identical reaction conditions, albeit in a low yield. Complex substrates derived from natural products (**4m**,**ac**−**ae**), could also furnish the corresponding enantioenriched products with satisfying results under the standard reaction conditions. Moreover, the product **4w** was isolated in a similar yield and selectivity in a larger scale experiment (10 mmol), demonstrating the practicability of this reaction. Propyne could also afford the product **4af** in moderate yield with a good ee in a larger scale experiment (Figure 2A). Particularly noteworthy is that a terminal aryl alkyne selectively afforded the *anti*-Markovikov borylalkylation product under the same reaction conditions (see SI Section 4 for more details). In addition, alkyne trimers mainly accounted for the mass balance of the reactions with low yields (see SI Section 5 for more details).

To show the synthetic potential of this asymmetric reaction in creating diverse chiral structures, follow-up derivatizations were conducted. In particular, the incorporation of the boron group provides extensive opportunities for subsequent stereospecific manipulations (Figure 2B).[20] For example, the product **4a** underwent deborylative deuteration to produce the D-labeled terminal olefin **5**. Products **4c**,**d** participated in Pd-catalyzed Suzuki−Miyaura cross-couplings[21] to afford stereodefined trisubstituted alkenes **6** and **7**, respectively. Moreover, reduction of the ester group furnished enantioenriched homoallyl alcohol **8**.

Additional investigations were conducted to demonstrate the value of this methodology in the buildup of complex functional molecules, simplifying the synthetic routes of important intermediates and biologically active targets (Figure 2C). Intriguingly, both enantiomers accessible from the reaction with **1m** and **3n** are key intermediates, through three-step routes, of the epiantillatoxin[22] (**4ag**) and leiodermatolide[23] (*enti*-**4ag**) syntheses. Moreover, a concise synthetic route through only three steps to (*S*)-lavandulol (**12**)[24] or (*R*)-lavandulol (*enti*-**12**)[25] from **1m** and **3o** was developed by this chemistry.

To gain insight into the mechanistic details of the unique *E*-selectivity in this nickel-catalyzed three-component reaction, a series of mechanistic experiments were designed. The *E*/*Z* ratio remains constant during the time course of the reaction (see SI Section 7.1 for details) and no *Z*/*E*-isomerization was detected in a control experiment with pure *Z*-isomeric product (Figure 3A). These results indicate that the *E*-stereoselectivity in this transformation is not derived from the product *Z*/*E*-isomerization. Radical trapping experiments showed that the reaction is greatly inhibited by the addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), and the alkyl radical was identified as a TEMPO-trapped adduct (Figure 3B). Moreover, cyclopropane-opening products were isolated from a radical clock experiment using alkyl bromide derivative **3p** (Figure 3C). These results agree with the fact that the alkyl radical is involved in the catalytic cycle. Furthermore, when a series of alkyl electrophiles are examined, we found that the *E*/*Z* ratio varies with the identity of the electrophile (Figure 3D). Notably, secondary benzyl bromide and substituted α-bromo amide failed to produce the corresponding borylalkylation products in the current system. Finally, we propose a mechanism for this multicomponent transformation based on precedent reports.[26] As shown in Figure 3E, the reaction is proposed to be initiated by a Ni(II) species (**I**), which could undergo transmetalation and Markovnikov addition to generate a *syn*-alkenyl-Ni(II) intermediate (**III**). Subsequent *Z*/*E*-isomerization could deliver the *anti*-isomer (**IV**), which is proposed to capture the free radical faster than the *syn*-isomer (**III**). Finally, reductive elimination from the high-valence Ni(III) species (**V**) would give the product (**4**) and a Ni(I) species (**VI**), which could generate the alkyl radical from the prochiral electrophile (**3**). The chiral ligand is hypothesized to modulate radical addition or reductive elimination to produce the stereoconvergent outcome.[17,27] There are precedents for the isomerization of alkenyl nickel intermediates.[28] A carbene-type intermediate[28a−c] and η^2-vinyl intermediate[28d−f,29] have been proposed. It is still unclear if the *anti*-isomer is thermodynamically favored or a Curtin−Hammett situation[29] is involved in this case. Further efforts to elucidate the mechanistic details are still ongoing in our laboratory.

In conclusion, we have developed an asymmetric intermolecular borylcarbofunctionalization of unactivated alkynes by combining an uncommon *syn*-/*anti*-isomerization and a nickel-catalyzed stereoconvergent cross-coupling. This reaction provides an efficient approach to enantioenriched α-vinyl esters from easily accessible terminal alkynes, prochiral α-bromoesters, and B_2pin_2, in a highly chemo- and enantioselective manner. This method shows a broad scope and an outstanding functional group compatibility. The synthetic value of this methodology has been highlighted with shortened synthetic routes to drug molecules. We expect the present study to find broad utility in future sophisticated target syntheses and to stimulate a wider interest in enantioselective syntheses from alkynes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c05969.

Experimental procedures and spectral data for all new products (PDF)

Accession Codes

CCDC 2232129 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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