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Communication

Enantioselective Reductive Divinylation of Unactivated Alkenes by Nickel-Catalyzed Cyclization Coupling Reaction

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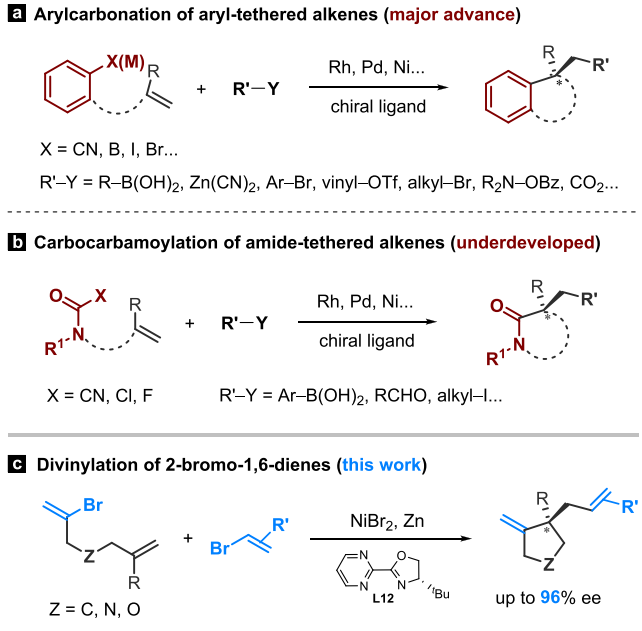
ABSTRACT: Catalytic asymmetric dicarbofunctionalization of tethered alkenes has emerged as a promising tool for producing chiral cyclic molecules; however, it typically relies on aryl-tethered alkenes to form benzene-fused compounds. Herein, we report an enantioselective cross-electrophile divinylation reaction of nonaromatic substrates, 2-bromo-1,6-dienes. The approach thus offers a route to new chiral cyclic architectures, which are key structural motifs found in various biologically active compounds. The reaction proceeds under mild conditions, and the use of chiral *t*-Bu-pmrox and 3,5-difluoro-pyrox ligands resulted in the formation of divinylated products with high chemo-, regio-, and enantioselectivity. The method is applicable for the incorporation of chiral hetero- and carbocycles into complex molecules.

Asymmetric difunctionalization of alkenes catalyzed by transition metals has been recognized as a powerful tool for the construction of chiral molecules.[1] Particularly, dicarbofunctionalization of tethered alkenes offers efficient access to enantioenriched carbo- and heterocyclic compounds.[2] The majority of reports have focused on the reactions of aryl-tethered alkenes, in which the rigid aromatic ring is incorporated to improve the selectivity (Scheme 1a). Over the past few years, studies along these lines have progressed significantly, with the scope expanded from single-molecule to two-component reactions,[3] from activated substrates[4,6] to unactivated alkenes,[5,7] and from nucleophile−electrophile reactions[4,5] to cross-electrophile couplings.[6,7] In short contrast, the reactions of nonaromatic substrates remain elusive, and the major advances have been limited to carbamoyl-tethered alkenes for producing chiral pyrrolidinone (Scheme 1b).[8] The development of new tethered alkenes for asymmetric dicarbofunctionalizations is essential for improving the structural diversity of chiral cyclic compounds.

Scheme 1. Dicarbofunctionalization of Tethered Alkenes Catalyzed by Transition Metals



3-Methylene five-membered rings (e.g., pyrrolidine, tetrahydrofuran, and cyclopentane) are key structural motifs of numerous biologically active compounds.[9] Among various approaches for their synthesis, the cyclization of 2-(pseudo)-halo-1,6-dienes is of great interest.[10] These methods have found broad applications in the total synthesis of various natural products.[9] Despite formidable advances, asymmetric variants of these processes are rare. The most reliable methods depend on pre-generation of chiral 2-(pseudo)halo-1,6-dienes, which undergo diastereoselective cyclization to afford chiral cyclic derivatives.[11] There are also a few reports demonstrating the stereoselective cyclization of olefinic organolithium compounds by using stoichiometric amounts of chiral ligands.[12] Alternatively, catalytic enantioselective cyclization and C−C coupling of 2-(pseudo)halo-1,6-dienes would provide an approach to this class of molecules with improved molecular diversity, but it remains to be disclosed.

Herein, we report a nickel-catalyzed enantioselective cyclization-vinylation reaction of 2-bromo-1,6-dienes and thus establish a new method for the synthesis of chiral 3-methylene five-membered hetero- and carbocycles (Scheme

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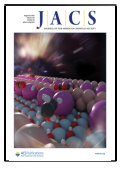

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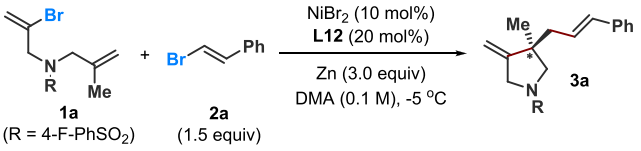
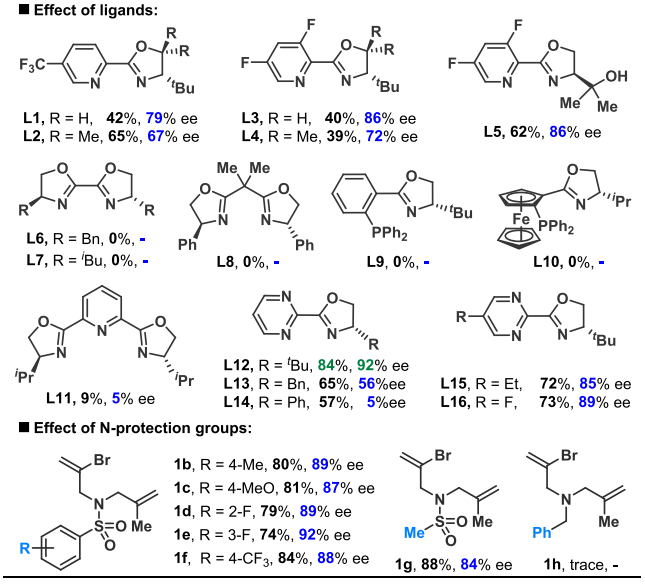
1c). This work represents the first asymmetric divinylation reaction of alkenes. High chemo-, regio-, and enantioselectivity was generally obtained by using chiral *t*-Bu-pmrox (**L12**)[13] and 3,5-difluoro-pyrox ligands **L3**–**L5**,[14] which have not previously been realized in the field of alkene functionalization.

Cross-electrophile coupling has recently emerged as a promising tool for forging the C–C bonds.[15] Our group has an ongoing interest in developing new and unconventional coupling partners for this type of chemistry.[16] Very recently, we reported a nickel-catalyzed enantioselective cross-electrophile aryl-vinylation reaction of unactivated alkenes.[7a] We wondered whether nonaromatic tethered substrate could be involved and afford new chiral cyclic architectures. We then focused on the reaction of 2-bromo-1,6-diene **1a** with vinyl bromide **2a** (Table 1, also see Table S1 for details). After

Table 1. Optimization of the Reaction Conditions[a]



entry	change of conditions	yield (%)	ee (%)
1	none	84 (78)[b]	92
2	$Ni(cod)_2$ instead of $NiBr_2$	62	88
3	$NiCl_2$ instead of $NiBr_2$	70	87
4	NiI_2 instead of $NiBr_2$	72	86
5	Mn instead of Zn	32	60
6	no Ni or Zn	0	



[a]**1a** (0.1 mmol) and **2a** (0.15 mmol) were used; reactions proceeded for 24 h. The yields were determined by GC analysis with dodecane as internal standard. [b]**1a** (0.2 mmol) was used; the isolated yield is given.

numerous trials, we determined that the combination of $NiBr_2$, *t*-Bu-pmrox **L12**, and Zn in DMA at −5 °C gave the best result; the reaction afforded **3a** in 78% isolated yield and 92% ee (entry 1). The reactions also worked in the presence of other nickel sources but resulted in decreased yields and slightly lower ee values (entries 2–4). Unlike previous observations with aryl-vinylation reactions,[7a] the use of Mn instead of Zn gave **3a** in low yield, and the reaction afforded a significant amount of cyclized protonation byproduct **12** (see below) (entry 5). The $MnBr_2$ formed in situ may account for the decreased yield and enantioselectivity (see Table S3). No reaction was observed in the absence of a nickel catalyst or reductant (entry 6).

The choice of ligand had a substantial effect on the reaction (Table 1). The 5-CF_3-pyrox ligands, which are highly effective for enantioselective cross-electrophile aryl-vinylation reactions of alkenes,[6b,7a] gave **3a** in low yield and moderate ee (**L1** and **L2**). In the case of reaction with **L1**, the protonation of cyclized intermediate was determined as the major side reaction. Further studies in the field of pyrox ligands revealed that 3,5-difluoro-pyrox ligands[14] could be used to improve the yield and enantioselectivity (**L3**–**L5**), and indeed, the use of **L5** gave **3a** in 62% yield and 86% ee. While chiral ligands, including (*S*,*S*)-Bn-biOx (**L6**),[17] (*S*,*S*)-^{i}Bu-biOx (**L7**),[1j,m] (*S*,*S*)-Ph-box (**L8**),[18] (S)-Ph-Phox (**L9**),[6c] and (*S*,*Sp*)-*i*Pr-Phosferrox (**L10**),[6a,d] proved highly effective for asymmetric cross-electrophile difunctionalization of alkenes and cross-coupling reactions, they failed to give any desired product. The reaction of (*S*,*S*)-Ph-PyBox (**L11**) gave **3a** in 9% yield and 5% ee. Finally, we found that pmrox ligands **L12**–**L16** were effective for this reaction, and the use of *t*-Bu-pmrox (**L12**) gave the best result.[13]

The sulfonate groups had little effect on the reaction. In general, the reactions of fluorinated aryl sulfonates gave slightly higher enantioselectivity than those of electron-rich derivatives (**1b**–**e**). However, the enantioselectivity decreased slightly when the more electron-poor CF_3 group was used (**1f**). Mesylated substrate **1g** gave the desired product in 88% yield and 84% ee. *N*-Benzyl diene **1h** did not give any desired product, and most of staring materials were recovered.

With the optimal reaction conditions in hand, we studied the scope of the reaction for vinyl electrophiles (Table 2). Styrenyl bromides, bearing either electron-rich or -poor groups, coupled with **1a** efficiently to afford **3i**–**p** in moderate to high yields and 88–95% ee. Substituents at the *para*-, *meta*-, or *ortho*-positions of the aryl group were tolerated (**3i**–**k**). The absolute configuration of **3k** was determined by X-ray analysis, and that of all other products was assigned accordingly.[19] Functionalities, including silyl ether (**3l**), aryl fluoride (**3m**), chloride (**3n**), and trifluoromethyl and ester groups (**3o** and **3p**), were tolerated. The reactions of heteroaryl and polyaryl substrates afforded the divinylation products **3q**–**t** in good yields and high ee. The reaction of dienyl bromide afforded triene **3u** in 68% yield and 93% ee. *cis*-*β*-Bromostyrene gave **3v** in 54% yield with partial retention of alkene stereochemistry but a decreased ee value. Trisubstituted vinyl bromide also worked and gave **3w** in 87% ee. However, when *α*-bromostyrene was employed, the reaction resulted in recovery of **1a** and **2q** (**3x**). Internal vinyl triflates are more readily available than bromide derivatives. Their reactions afforded the target products with a scope that is complementary to those of vinyl bromides. Cyclic vinyl triflates, including five-, six-, and eight-membered rings, were coupled well; the reactions delivered **3y**–**ab** in high enantioselectivity. Acyclic vinyl triflates also worked. For example, the reactions of *gem*-substituted substrates afforded **3ac**–**ad** in moderate yields with good to high enantioselectivity.

In comparison to aryl-tethered alkenes, the chemo- and enantioselectivity of cross-electrophile divinylation of nonaromatic substrate is much more difficult to control. This agrees with the fact that due to the inherent similarity in the

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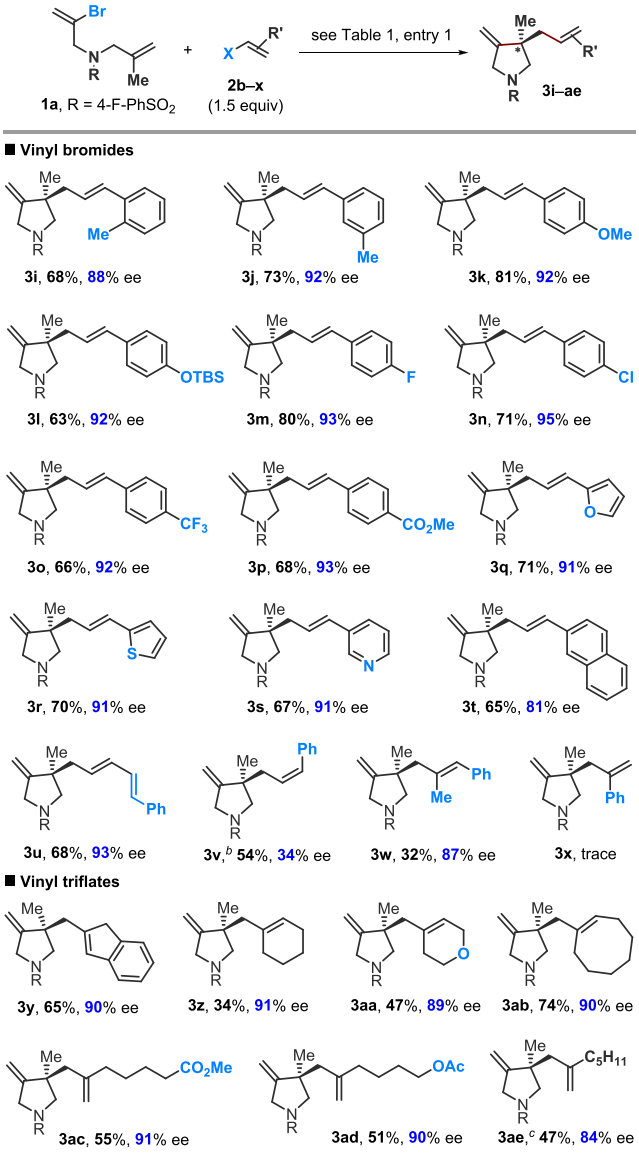
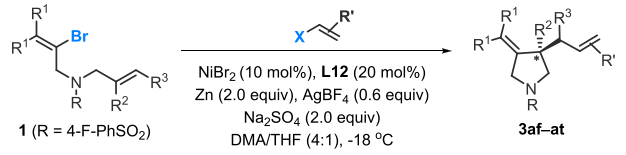
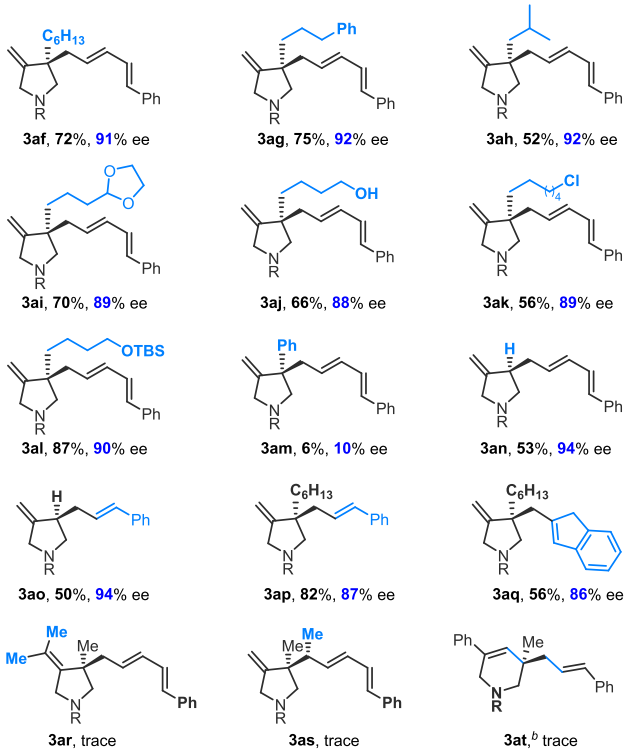
Table 2. Reactions of Vinyl Electrophiles[a]



[a]Reaction conditions are as shown in Table 1, entry 1. **1a** (0.2 mmol) and **2** (0.3 mmol) were used; the isolated yields are given. [b]*Z*-Bromostyrene was used; **3v** (*Z*/*E* = 8:1) was obtained. [c]Reaction at room temperature.

Table 3. Reactions of *N*-Tethered Bromodienes[a]





[a]Bromodienes **1** (0.2 mmol) and vinyl electrophiles (0.3 mmol) were used. Dienyl bromide **2n** was used for **3af**–**an**, **3ar**, and **3as**; styrenyl bromide **2a** was used for **3ao**, **3ap**, and **3at**. 1*H*-Inden-2-yl triflate **2r** was used for **3aq**. Reactions proceeded for 48 h; isolated yields are given. [b]Tethered terminal vinyl iodide **1w** was used.

reactivity of the two coupling partners reaction involving two vinyl electrophiles remains a significant challenge in cross-coupling arena.[20] Indeed, when the methyl group was replaced with a more sterically hindered C_6H_{13} substituent, the cyclization of 2-bromo-1,6-dienes was partially blocked; the reaction afforded **3af** in 53% yield and 84% ee, along with 21% yield of cross vinyl−vinyl coupling byproduct. The selectivity for the cyclization product could be improved by using $AgBF_4$ as an additive, and rescreening of the reaction conditions resulted in the formation of **3af** with 72% yield and 91% ee (see Table S2). Under these conditions, various pyrrolidines that contain an enantioenriched quaternary stereocenter were produced in high enantioselectivity (Table 3). The more sterically hindered isobutyl substituent was tolerated (**3ah**). The reactions were compatible with acid-, base-, and nucleophile-sensitive functionalities, such as acetal (**3ai**), alcohol (**3aj**), and alkyl chloride (**3ak**). The reaction of TBS-protected alcohol afforded **3al** in 87% yield and 90% ee. However, when a styrene component was employed, the reaction afforded **3am** in low yield with most of the starting material being recovered. The reaction of monosubstituted alkene afforded the desired product **3an** in moderate yield and with high enantioselectivity. The substrate scope of vinyl coupling partners could be expanded from dienyl to styrenyl bromides (**3ao** and **3ap**) and vinyl triflate (**3aq**). Tethered internal vinyl bromide (**3ar**) or alkene (**3as**) did not give the desired product, with most of starting materials being recovered. Terminal iodide gives no six-membered cycle **3at** but does give a large amount of vinyl−H and vinyl−vinyl byproducts.

The *O*-tethered 2-bromo-1,6-dienes coupled well with various vinyl bromides, and high enantioselectivity was achieved when 3,5-difluoro-pyrox **L5** was employed (Table 4). Bromostyrenes, bearing electron-neutral, -rich, and -poor substituents, were tolerated (**3au**−**ay**). The reactions of heteroaryl substituted vinyl bromide afforded bis-heterocycle compounds **3az** and **3ba** in 95 and 94% ee, respectively. The reactions of vinyl triflate and dienyl bromide afforded **3bb** and **3bc** in 90 and 92% ee, respectively. Monosubstituted alkene substrate gave **3bd** in 94% ee. The *C*-tethered 2-bromo-1,6-

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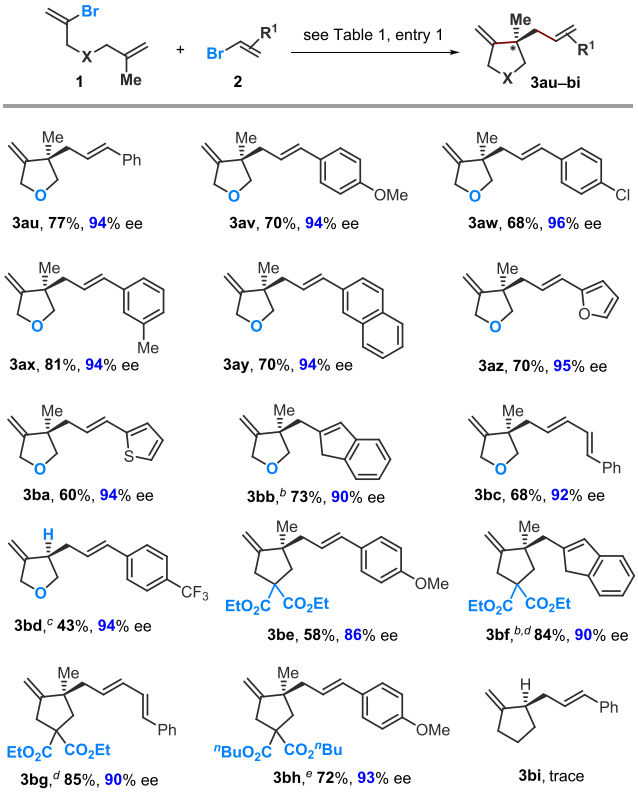
Table 4. Reactions of *O*-/*C*-Tethered Bromodienes[a]



[a]Reaction conditions are as shown in Table 1, entry 1. Bromodienes **1** (0.2 mmol) and vinyl bromide **2** (0.3 mmol) were used; the isolated yields are given. Ligand **L5** and 4 Å MS (40 mg) were used for *O*-tethered substrates; ligand **L2** was used for *C*-tethered substrates. [b]Vinyl triflate **2r** was used. [c]Reaction at 0 °C. [d]Reaction at −10 °C. [e]Reaction at −18 °C.

diene also worked well; the reactions afforded **3be**–**bh** in moderate to high yields with high enantioselectivity obtained in the presence of ligand **L2**. However, the reaction of 2-bromohepta-1,6-diene only afforded cyclized-protonation product (**3bi**), indicating the coordinating tether may have positive impact on the selectivity for the cross-product.

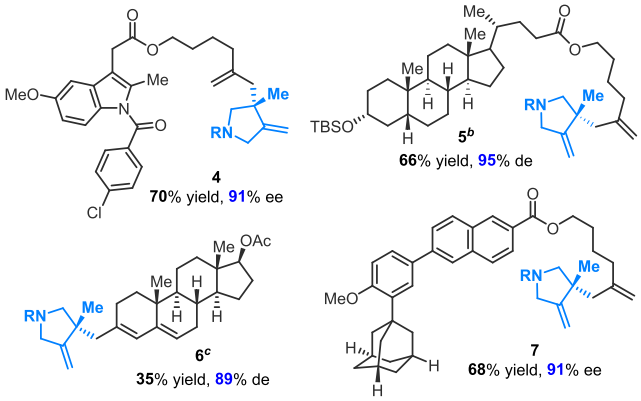
The modification of biologically active compounds offers a promising approach to altering their pharmacological profiles. This method allows for the incorporation of chiral five-membered ring structures into complex molecules (Scheme 2). For example, vinyl triflates derived from indometacin (**4**), lithocholic acid (**5**), testosterone (**6**), and adapalene (**7**) could undergo divinylation reactions with **1a**, and chiral pyrrolidine-containing complex molecules were obtained with high enantioselectivity.

The derivatization of formed product is shown in Scheme 3, which offers opportunities for increasing molecular diversity. The sulfonyl group could be removed, and the reaction afforded **8** in 82% yield. The two alkenes are differentiated synthetically. For example, hydrogenation and epoxidation reactions of compound **3a** selectively afforded **9** and **10** in 68 and 78% yields, respectively, leaving the *exo*-methylene group available for further derivatization. The tandem deprotection and cyclization reaction afforded polycyclic compound **11** in 76% yield as a single isomer.

Mechanistic studies on this process are summarized in Scheme 4. The stoichiometric reaction of Ni(0) with **1a** (4.0 equiv) and **2a** (4.0 equiv) showed that 40% yield of cyclized protonation product **8** was formed from **1a**, and most vinyl bromide **2a** was recovered (Scheme 4a, entry 1). This result suggests a reaction pathway involving 2-bromo-1,6-dienes first react with nickel to form complex **B** (see below) and then undergo C−C coupling with vinyl bromides. This reaction pathway is supported further by the following findings: (1) When above mixture was treated with Zn (2.4 mmol) instead of H_2O and stirred for another 24 h, protonation byproduct **12** was significantly decreased with **3a** being isolated in 65% yield (Scheme 4a, entry 2). (2) In the presence of MeOH (3.0 equiv), the reaction of **1j** and **2n** afforded target product **3ag** and protonation byproduct **13** with the same enantioselectivity (Scheme 4b).

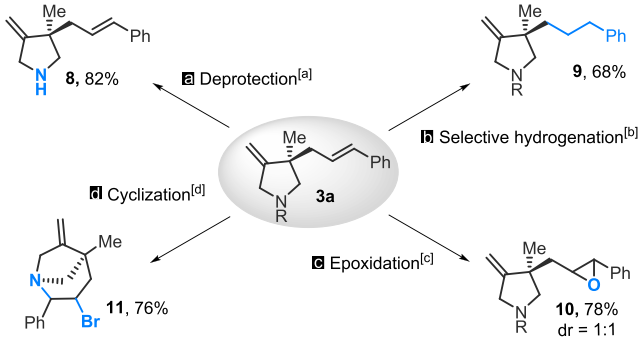
On the basis of the above results and on reported work,[6a,7a,21] we tentatively suggest the catalytic cycle shown in Scheme 5. The reaction of **1** with Ni(0) affords complex **A**, which undergoes an enantioselective migratory insertion process to afford complex **B**.[6a,7a] Reduction of complex **B** gives a Ni(I) species, which undergoes oxidative addition with **2**, followed by reductive elimination to afford desired product **3**.[21] The bidentate coordination of dienes to nickel may favor

Scheme 2. Catalytic Functionalization of Complex Molecules[a]



[a]Reaction conditions are as shown in Table 1, entry 1. **1a** (0.2 mmol) and vinyl triflates (0.24 mmol) were used; isolated yields are given. [b]Ligand **L3** was used. [c]Ligand **L4** was used.

Scheme 3. Derivatization of Product 3a



[a]**3a** (0.2 mmol) and Mg turning (6.0 mmol) in MeOH (3.0 mL) was ultrasonicated for 3 h. [b]**3a** (0.2 mmol) and Pd/C (15 mg, 10% w/w) in DCM (0.5 mL). [c]**3a** (0.2 mmol) and *m*-CPBA (0.3 mmol) in $CHCl_3$ (6.0 mL) at room temperature (rt). [d]**3a** (0.2 mmol), $Et_3N{\cdot}3HF$ (0.3 mmol), and NBS (0.3 mmol) in DCM (3.0 mL) at rt; the absolute stereochemistry of **11** was not assigned.

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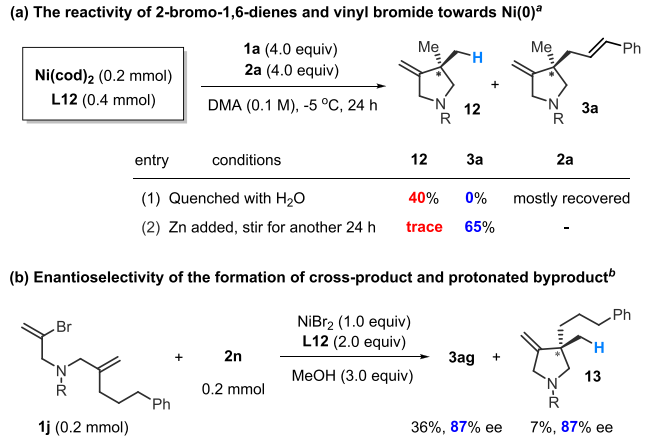
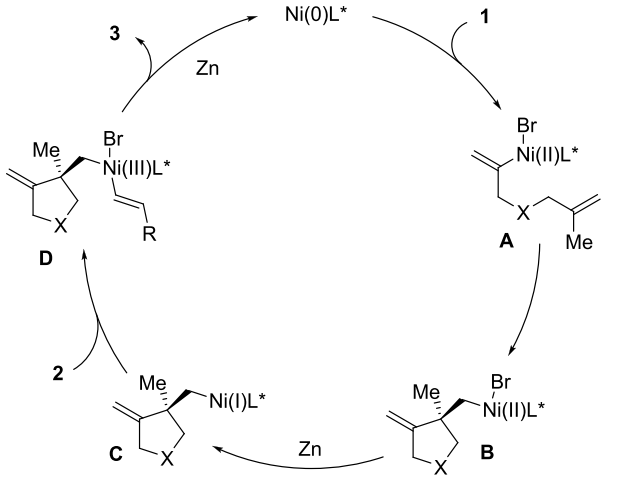
Scheme 4. Mechanistic Investigation



[a]Reaction conditions are as shown in Table 1, entry 1, but $Ni(cod)_2$ (0.2 mmol, 1.0 equiv), **L12** (2.0 equiv), **1a** (4.0 equiv), and **2a** (4.0 equiv) were used. Zn (2.4 mmol) was added after 24 h in entry 2; isolated yields are with respect to the amount of Ni in entry 1 and **1a** in entry 2. [b]Reaction conditions are as shown in Table 3, but $NiBr_2$ (1.0 equiv), **L12** (2.0 equiv) and MeOH (3.0 equiv) were used.

Scheme 5. Proposed Mechanism



this process, which may allow Ni(0) to first undergo oxidative addition reaction with 2-bromo-1,6-dienes. Moreover, the coordination of tether to nickel may stabilize complex **B** and thus contribute to the success of the reaction.[22]

In summary, we have reported a nickel-catalyzed cross-electrophile cyclization-vinylation reaction of 2-bromo-1,6-dienes with vinyl bromides. This work represents the first asymmetric divinylation reaction of alkenes and demonstrates the use of a new nonaromatic tethered alkene for enantioselective difunctionalization reactions. The approach thus offers a route to new chiral cyclic architectures that are otherwise difficult to form. Further expansion of the scope of the asymmetric cross-electrophile difunctionalization of 2-bromo-1,6-dienes is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c05670.

General information, experimental procedures, new compound characterization, spectroscopic data, HPLC chromatograms and NMR spectra (PDF)

Accession Codes

CCDC 2001088 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

The authors declare no competing financial interest.

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