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Regiocontrolled Reductive Vinylation of Aliphatic 1,3-Dienes with Vinyl Triflates by Nickel Catalysis

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ABSTRACT: The regiocontrolled functionalization of 1,3-dienes has become a powerful tool for divergent synthesis, yet it remains a long-standing challenge for aliphatic substrates. Herein, we report a reductive approach for a branch-selective 1,2-hydrovinylation of aliphatic 1,3-dienes with R−X electrophiles, which represents a new selectivity pattern for diene functionalization. Simple butadiene, aromatic 1,3-dienes, and highly conjugated polyene were also tolerated. The combination of Ni(0) and the phosphine−nitrile ligand generally resulted in >20:1 regioselectivity with the retention of the geometry of the $C_3{-}C_4$ double bonds. This reaction proceeds with a broad substrate scope, and it allows for the conjugation of two biologically active units to form more complex polyene molecules, such as tetraene and pentaene as well as heptaene.

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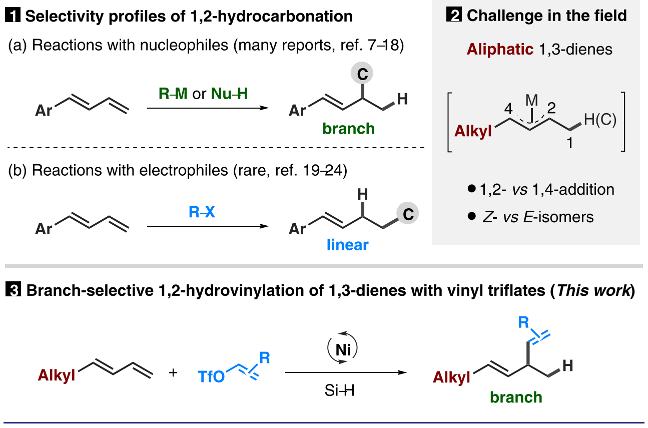
The transition-metal-catalyzed hydrofunctionalization of 1,3-dienes has emerged as a promising method to produce value-added molecules.[1−6] In particular, hydrocarbonation reactions offer straightforward access to alkene-containing building blocks with high regio- and stereochemical diversity. Generally, the reactions of 1,3-dienes with nucleophiles afford 1,2-addition products with branch selectivity, which is a major advance in this field (Scheme 1(1a)).[7−18] However, there are very few reports on the coupling of R−X electrophiles with dienes, which typically results in linear selectivity (Scheme 1(1b)).[19−24] The discovery of novel selectivity patterns would provide new opportunities for research in this field, but it remains largely unexplored.[25−28]

Scheme 1. 1,2-Hydrocarbonation of 1,3-Dienes



The reactions of 1,3-dienes typically involve the intermediacy of η^3-π-allyl species (Scheme 1(2)).[5] The unsymmetrical metal-π-allyl complexes could be attacked at either C_2 or C_4, resulting in the 1,2- or 1,4-addition products. Moreover, the Z- and E-isomers may be formed since these intermediates may be in equilibrium during the reactions. These properties of diene chemistry make it particularly challenging to control the selectivity. Previous studies have shown that the selectivity is closely dependent on the electronic and steric nature of the diene substrate.[7] Therefore, to date, the majority of reports on highly selective transformations have focused on the reactions of aromatic 1,3-dienes.[1−28] The use of aliphatic dienes typically results in a complex mixture of 1,2- and 1,4-adducts and Z-/E-isomers, except for cyclic[29,30] and highly sterically hindered substrates.[7,9,13,16,19] A general method to account for the selective hydrocarbonation of common aliphatic 1,3-dienes is still to be developed.

Herein, we report a branch-selective 1,2-hydrovinylation of aliphatic 1,3-dienes by a nickel-catalyzed reductive vinylation reaction (Scheme 1(3)). Aliphatic dienes with diverse steric properties and simple butadiene and aromatic derivatives were all tolerated. The success of this effort depends on the use of phosphine−nitrile ligands, which have rarely been used in the area of transition-metal catalysis.[31] It thus offers an approach to skipped dienes (1,4-dienes) with a scope that is complementary to the established methodologies.[22,23,29,30,32−39]

Skipped dienes are key structural elements found in various natural products,[40−42] and the importance of this class of compounds has spurred the development of many useful methods,[32] including the coupling of 1,3-dienes with alkenes[29,30,33−38] or vinyl electrophiles.[22,23] These reactions provide very efficient access to linear 1,4-addition products. As part of our ongoing studies on reductive vinylation

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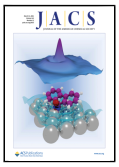

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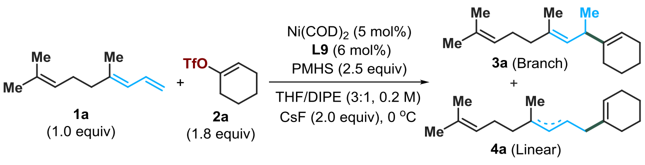
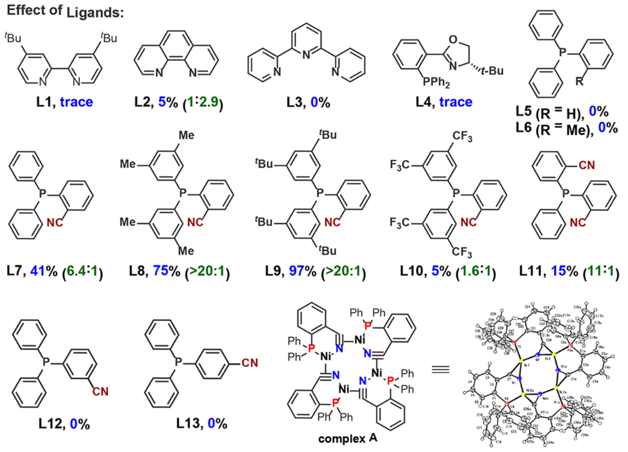
reactions,[43−47] we wondered whether 1,3-dienes could couple with vinyl triflates to offer new selectivity profiles for skipped diene synthesis.

We began our investigation by studying the reaction of diene **1a** with vinyl triflate **2a** (Table 1). After numerous trials, we determined that the combination of Ni(COD)$_2$, **L9** and polymethylhydrosiloxane (PMHS) gave the best result, affording **3a** in 94% isolated yield with >20:1 regioselectivity (entry 1). The use of Ni(II) precatalysts also gave good results (entries 2−4), but they required remarkably long induction periods (details in Scheme S3). The hydride source plays an essential role. The reactions worked well in the presence of Si−H (entries 1, 5, and 6); by contrast, the reactions with HCO$_2$Na, HCO$_2$H, or ^{i}PrOH were completely ineffective (entries 7−9), even though they are frequently employed in Ni/Pd-catalyzed hydrocarbonation reactions.[48] The reactions with the metal reductant afforded no desired product (entry 10). Control experiments revealed that the Ni catalyst and PMHS were all required for the vinylation of 1,3-dienes (entry 11). The reaction of vinyl bromide did not yield any desired product, and the use of vinyl iodide gave **3a** in 35% yield with a 7:1 regioselectivity (entries 12 and 13).

Table 1. Optimization of the Reaction Conditions[a]



entry	change from standard conditions	**3a** (%)	**3a**/**4a**
1	none	97 (94)[b]	>20:1
2	NiBr$_2$ instead of Ni(0)	81	>20:1
3	Ni(acac)$_2$ instead of Ni(0)	85	>20:1
4	Ni(dppp)Cl$_2$ instead of Ni(0)	88	>20:1
5	(EtO)$_3$SiH instead of PMHS	81	>20:1
6	Ph$_2$MeSiH instead of PMHS	51	>20:1
7	HCO$_2$Na instead of PMHS	0	n/a
8[c]	HCO$_2$H instead of PMHS	0	n/a
9[d]	^{i}PrOH instead of PMHS	0	n/a
10	Mn/Zn instead of PMHS	0	n/a
11	no Ni or PMHS	0	n/a
12	Vinyl bromide instead of **2a**	0	n/a
13	Vinyl iodide instead of **2a**	35	7:1



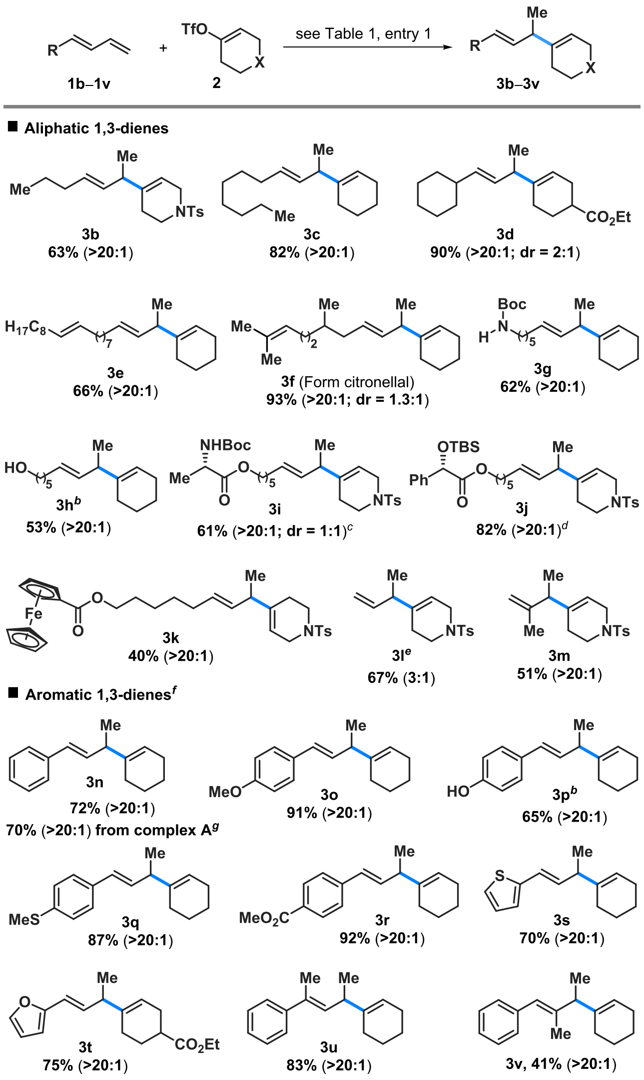
[a]Reaction conditions: **1a** (0.1 mmol) and **2a** (0.18 mmol) were used; the yields and the ratio of **3a**/**4a** were determined by GC analysis using dodecane as an internal standard. [b]Isolated yields obtained from **1a** (0.2 mmol) and **2a** (0.36 mmol) are given in parentheses. [c]Et$_3$N (2.5 equiv) was used instead of CsF. [d]KOH (2.5 equiv) was used instead of CsF.

The ligands had a substantial effect on the reaction (Table 1). Although nitrogen ligands have found broad applications in the reductive hydrofunctionalization of alkenes,[49] they gave either no or low yields of the desired product (**L1**−**L4**). In these cases, most of the vinyl triflate was recovered, and diene **1a** was reacted to form a mixture of 1,2-/1,4-hydrogenation products in 87% yield for **L1** and approximately 20% yield for **L2**/**L4**. While no reaction was observed in the presence of phosphine ligand **L5** or **L6**, the use of phosphine−nitrile ligand **L7** gave a promising result. The reaction efficiency appeared to be governed by the electronic and steric nature of the ligands. The use of electron-rich **L8** improved the yield to 75% and gave a ratio of **3a**/**4a** of >20:1, whereas its electron-poor counterpart, **L10**, yielded trace amounts of **3a**. More sterically hindered **L9** increased the yield (97%) further. Bis(2-cyanophenyl) phenylphosphine (**L11**) gave a low yield of the desired product. No reaction was observed when the cyano group was placed at either the meta or para position (**L12** or **L13**). Further studies revealed that the combination of Ni(COD)$_2$ and **L7** gave tetrameric complex **A**, which clearly shows the essential role of the cyano group at the ortho position.[50] The reaction using this complex gave results comparable to those from standard conditions (see **3n** in Table 2).

With the optimal reaction conditions in hand, we studied the scope of the reaction for 1,3-dienes (Table 2). The less sterically hindered aliphatic 1,3-dienes, such as those bearing linear alkyl chains,[51] which have proved to be very challenging with respect to the control of selectivity,[7] worked well to afford skipped dienes **3b** and **3c** with regioisomeric ratios of >20:1. The reaction of cyclohexanyl diene afforded **3d** in high yield. Polyenes [1,3,12-henicosatriene (**3e**) and 6,10-dimethylundeca-1,3,9-triene (**3f**)] were selectively vinylated to afford the skipped trienes. The presence of acidic amide (**3g**) and alcohol (**3h**) groups was tolerated. 1,3-Dienes derived from amino acid (**3i**), α-oxyacid (**3j**), and ferrocenecarboxylic acid (**3k**) were coupled well. Butadiene is one of the highest volume bulk chemicals in the world, and its functionalization is of considerable interest. Reported methods for the hydrovinylation of 1,3-butadienes generally yield the 1,4-addition products.[33−38] Alternatively, our method offers access to the 1,2-adducts (**3l** and **3m**). When aromatic substrates were employed, ligand **L7** was required to give high yields of the desired products. Under these conditions, aromatic 1,3-dienes, bearing electron-neutral (**3n**), electron-rich (**3o**−**3q**) and electron-poor (**3r**) arenes, were all coupled well. Heteroaryl substrates (**3s** and **3t**) and multisubstituted 1,3-dienes (**3u** and **3v**) were tolerated.

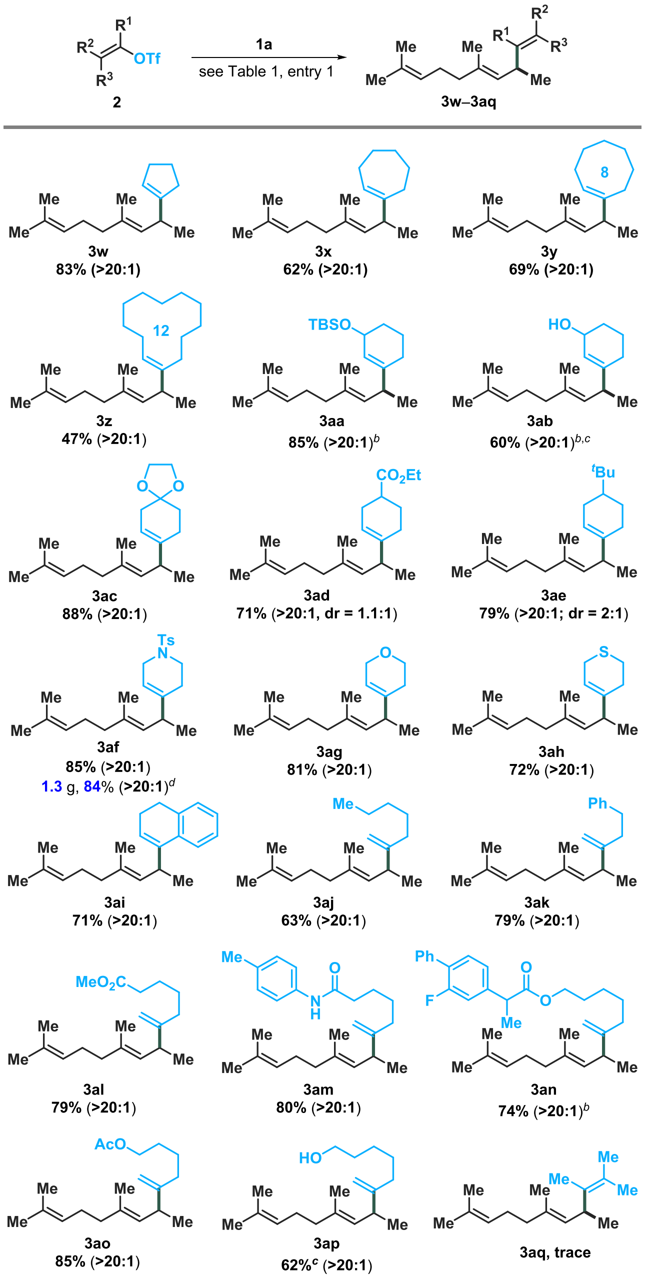
The substrate scope of the reaction with vinyl triflates is shown in Table 3. Regioisomeric ratios of >20:1 were obtained for all of the cases studied. Cyclic vinyl triflates, ranging from five- to eight-membered rings, were coupled with **1a** to afford

Table 2. Scope of the Reaction with 1,3-Dienes[a]



[a] Conditions as shown in Table 1, entry 1; diene **1** (0.2 mmol) was used; reactions were run for 48 h, and isolated yields are given; only E isomers were observed; the regioisomeric and diastereomeric ratios were determined by ^{1}H NMR and ^{13}C NMR, respectively; 1-tosyl-1,2,3,6-tetrahydropyridin-4-yl triflate (**2b**) was used for volatile molecules and for the purpose of isolation. [b] TBAF (0.2 mmol) was added after 48 h to cleave the O−Si bond formed in situ. [c] The dr value was determined by HPLC. [d] The dr value was not assigned. [e] Butadiene (0.4 mmol), vinyl triflate (2.0 equiv), PMHS (1.25 equiv), and CsF (1.0 equiv) were used; 1,2-/1,4-addition ratio of 9:1. [f] **L7** was used. [g] Complex **A** (2 mol %) was used instead of Ni(COD)$_2$ and **L7**.

Table 3. Scope of the Reaction with Vinyl Triflates[a]

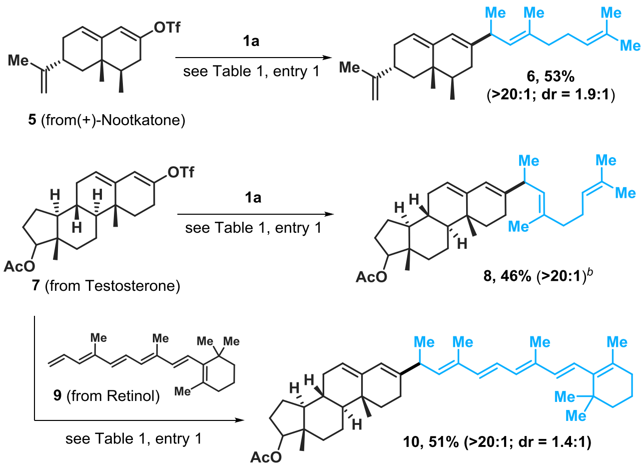


[a] Conditions are the same as shown in Table 1, entry 1; diene **1a** (0.2 mmol) was used; reactions were run for 48 h, and isolated yields are given; only E-isomers were observed; the regioisomeric and diastereomeric ratios were determined by ^{1}H NMR and ^{13}C NMR, respectively. [b] The dr value was not assigned. [c] TBAF (0.2 mmol) was added after 48 h to cleave the O−Si bond formed in situ. [d] Diene **1a** (4 mmol) was used; the reaction was run for 72 h.

target products **3w−y** in good yields. A larger ring-sized substrate, cyclododecenyl triflate, afforded triene **3z** in moderate yield. Cyclic vinyl triflates, with substituents at the 3- and 4-positions, afforded respective products **3aa−ae** in good to high yields. Nonaromatic heterocycles are key structural motifs found in various pharmaceuticals; however, their introduction through C−C bonds is challenging. Our method provides a way of producing nonaromatic heterocycle-containing polyenes, such as the trienes of 3-piperideine (**3af**), 3,6-dihydro-2*H*-pyran (**3ag**), and 3,6-dihydro-2*H*-thiopyran (**3ah**). The reaction could be run on the gram scale without a loss of efficiency (**3af**). A benzene-fused substrate, 3,4-dihydronaphthalenyl triflate, was also tolerated (**3ai**). Besides cyclic substrates, acyclic vinyl triflates also coupled well (**3aj−ap**). Functionalities, including silyl ether (**3aa**), alcohols (**3ab** and **3ap**), ketal (**3ac**), ester (**3ad**, **3al** and **3ao**), heterocycles (**3af−ah**) and amide (**3am**), were tolerated. However, fully substituted vinyl triflate was not found to be effective (**3aq**).

The modification of biologically active molecules offers a promising approach to altering the pharmacological profiles of compounds. This method allows for the conjugation of two biologically active units into one polyene[52] (Scheme 2). For example, vinyl triflates derived from (+)-nootkatone **5** and

Scheme 2. Modification of Biologically Active Molecules[a]

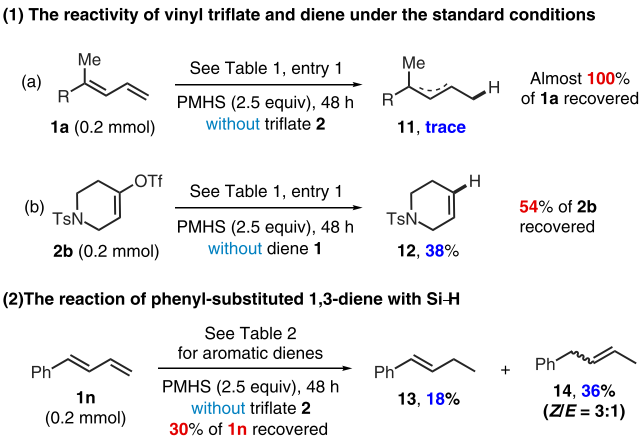


[a]Conditions as shown in Table 1, entry 1; **1a**/**9** (0.2 mmol) and triflates (0.36 mmol) were used; reactions were run for 60 h, and isolated yields are given; the regioisomeric and diastereomeric ratios were determined by ^{1}H NMR and ^{13}C NMR, respectively. [b]The dr value was not assigned.

testosterone **7** were coupled with geraniol-derived triene **1a** to afford pentaene **6** and tetraene **8** in moderate yields. Highly conjugated polyene, retinol-derived **9**, was coupled with **7** at the terminal alkene moiety to afford heptaene **10** with good regioselectivity.

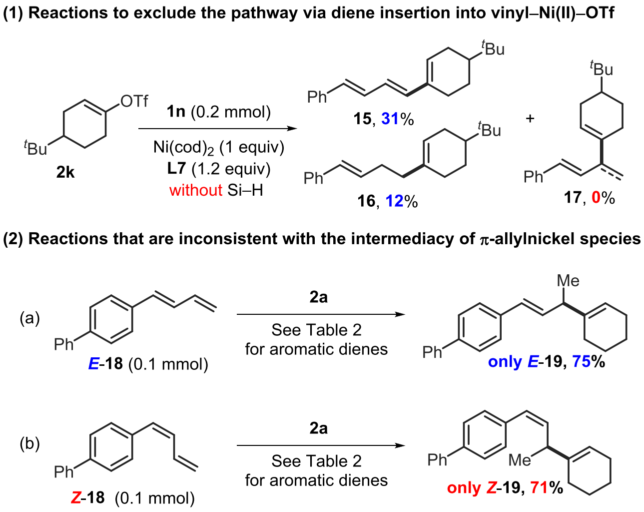
The reaction can be initiated by NiH, which is usually generated from Ni(II) and Si–H.[49] It is also possible that the reaction begins with Ni(0) and R–X.[53,54] Our control experiments indicate that the latter might be involved in this reaction. (1) The Ni(0) catalyst was found to work more efficiently than the Ni(II), and the latter required a long induction period (Scheme S3). (2) Vinyl triflates showed higher activity toward Ni(0) than aliphatic dienes and Si–H. For example, under standard conditions, vinyl triflate **2c** reacted well to form vinyl–H **12** in 38% yield, whereas aliphatic diene **1a** remained intact even after 48 h (Scheme 3(1)). (3) For cases in which the reaction started with diene **1n** and Si–H, a mixture of 1,2-/1,4-addition products and Z-/E-isomers was afforded (Scheme 3(2)). Such selectivity is not consistent with that observed for the hydrovinylation products.

Scheme 3. Insight into the Initial Step of This Reaction



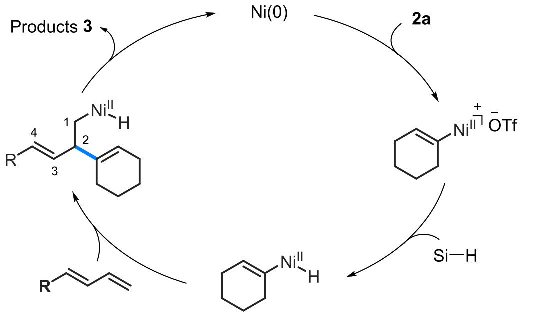
The formed vinyl–Ni(II)–OTf may undergo migratory insertion, followed by protonation with Si–H, to afford the desired products (the reductive Heck reaction pathway).[53,54] If this is the case, then Si–H should have little or no effect on the regioselectivity. However, in the absence of Si–H, the reaction of vinyl triflate **2k** with diene **1n** and Ni(0) (1.0 equiv) gave only linear products **15** and **16**, without any branch adduct observed (Scheme 4(1)).[55] Moreover, because alkyl–NiX can be terminated by various hydride/proton sources,[48] such as HCO_2Na, HCO_2H, and $^{i}PrOH$, we expected that the reaction with these reagents instead of Si–H would also yield the desired product. However, none of these reactions proceeded (Table 1, entries 7–9). These results suggest that Si–H should react with Ni before the migratory insertion step, which very likely forms the vinyl–Ni(II)–H intermediate.[56−59] The presence of CsF may facilitate this process.[60,61]

Scheme 4. Insight into the Migratory Insertion of the Diene



On the basis of the above-mentioned results and the previous reports, we tentatively propose a catalytic cycle for the reductive vinylation of 1,3-dienes (Scheme 5). Oxidative addition of vinyl–OTf to Ni(0) affords R–Ni(II)–OTf, which undergoes transmetalation with Si–H to afford an R–Ni(II)–H intermediate.[56−59] The migratory insertion of the 1,3-diene into the vinyl–Ni(II)H bond, followed by C–H reductive elimination, affords the desired product.[62,63] Alternatively, the insertion of a 1,3-diene into a vinyl Ni(II)–H bond may also result in the desired product via the intermediacy of an allyl–Ni(II)–vinyl species (Scheme

Scheme 5. Proposed Mechanism



S4).[64] Our control experiments suggest that the former process might be favored. The reactions of ***E*-18** and ***Z*-18** exclusively afforded ***E*-19** and ***Z*-19** in 75 and 71% yields, respectively (Scheme 4(2)). Retention of the geometry of the $C_3{-}C_4$ double bond was also observed when aliphatic substrate **1a** was used (Scheme S2). These results suggest that the reaction may not proceed through the intermediacy of a π-allylnickel species.[7,64]

In conclusion, we have developed a new hydrovinylation reaction of 1,3-dienes with vinyl triflates and thereby established a method for producing skipped dienes with a scope that is complementary to that of established methodologies. This reaction demonstrates a new selectivity pattern for diene functionalization, namely, branch-selective 1,2-addition with R−X electrophiles. It also offers a method to account for the regiocontrolled hydrocarbonation of common aliphatic 1,3-dienes, which has been a long-standing challenge in this field. Work on the further expansion of the scope of coupling partners is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00142.

> Parts of the mechanistic studies, detailed experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for new compounds, and computational methods and data (PDF)

Accession Codes

CCDC 2067720 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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