Diao and coworkers have developed a reductive coupling reaction to convert 1,6-dienes into cyclic molecules with trans-vicinal disubstituents. This method is readily applicable to the syntheses of biologically active molecules with high efficiency. Mechanistic studies revealed that the reaction proceeds via a classic, two-electron transfer mechanism mediated by paramagnetic Ni(I) and Ni(III) intermediates. The identification of the well-defined Ni(I) catalyst and elucidation of the mechanism will facilitate future development of Ni-catalyzed cross-coupling reactions.
Ni(I)-Catalyzed Reductive Cyclization of 1,6-Dienes: Mechanism-Controlled trans Selectivity

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SUMMARY
A Ni-catalyzed reductive cyclization of 1,6-dienes affords 3,4-disubstituted cyclopentane and pyrrolidine derivatives with high trans diastereoselectivity. This cyclization reaction enables the efficient synthesis of trans-3,4-dimethyl gababutin, a pharmaceutical lead for treating neuropathic pain, and trans-3,4-dimethylpyrrolidine, a precursor to drug candidates and pesticides. The trans selectivity distinguishes this reaction from relevant precedents that proceed via hydrogen-atom transfer and lead to cis products. Mechanistic investigation, including kinetic, spectroscopic, and radical clock studies, attributes the trans diastereoselectivity to a classic, organometallic catalytic cycle mediated by Ni(I) and Ni(III) intermediates. The electron-rich Ni(I) intermediate, stabilized by a redox-active α-diimine ligand, is responsible for the chemoselectivity toward reductive cyclization as opposed to the redox-neutral cycloisomerization observed with previous Ni(II) catalysts.

INTRODUCTION
Contemporary nickel-catalyzed cross-coupling reactions have found widespread applications in organic synthesis.1,2 The mechanisms of these reactions frequently invoke single-electron transfer steps and Ni(II) and Ni(III) intermediates.3,4 In contrast to radical pathways, the mechanism for Ni(0)-catalyzed reductive coupling of unsaturated molecules, developed by Montgomery and colleagues,5 proceeds through classic oxidative cycloaddition of Ni(0) to form Ni(II) metallocycles. Although these reactions provide an appealing way to functionalize alkynes, similar reactivity has not been observed with unactivated alkenes. Here, we report a reductive cyclization of dienes that proceeds via a mechanism distinct from those of previous reports. A well-defined Ni(I) intermediate mediates two-electron transfer pathways via a Ni(I)–Ni(III) catalytic cycle, without single-electron transfers and organic radical intermediates.

Alkenes are versatile functional groups in organic synthesis. Catalytic functionalization of alkenes represents one of the most powerful synthetic strategies in contemporary pharmaceutical synthesis. Cyclization reactions of olefins can rapidly construct cyclic molecules and have been practiced extensively. Among a variety of approaches, ring-closing metathesis is the most widespread, giving rise to unsaturated ring systems (Scheme 1A).6,7 In addition, [2 + 2] cycloaddition and ene reactions provide access to a variety of cycles.8,9 A number of catalytic conditions have been developed to carry out the cycloisomerization of dienes to form exo-methylene-necyclopentanes (Scheme 1B).10,11 In particular, Widenhoefer and DeCarli12 and
Perch et al. used Pd(II) catalysts to perform cyclization of dienes, followed by a tandem coupling with silanes to afford trans-disubstituted silylated products. A recent report by Crossley et al. shows that Co catalyzes cycloisomerization via hydrogen atom transfer (HAT) to afford cis-3,4-disubstituted cyclopentanes. Reductive coupling of unactivated alkenes can install two adjacent stereocenters at once, but such reactivity has been historically challenging.

trans-3,4-Disubstituted cyclopentane and pyrrolidine motifs are commonplace in natural products and pharmaceutical leads. Synthesis of trans-3,4-disubstituted five-membered rings, however, often requires multiple steps or stoichiometric metal reagents. Using the Ni(I)/Ni(III)-mediated two-electron mechanism, we developed a reductive cyclization of 1,6-dienes, which provides trans-3,4-disubstituted cyclopentane and pyrrolidine derivatives. The trans diastereoselectivity depicted here complements previous reductive olefin coupling methods reported by Molander and Hoberg and Baran and colleagues, which proceed through organolanthanide and radical intermediates, respectively. Our mechanistic studies reveal that the unique two-electron mechanism and the radical nature of the Ni(I) catalyst are responsible for the high reductive chemoselectivity and trans diastereoselectivity.

RESULTS

Catalyst Development

Our catalyst optimization focused on dimethyl malonate-derived 1,6-heptadiene as the substrate. The combination of Fe(acac)₃ and PhSiH₃ has been reported to reductively couple activated olefins. This condition led to reductive cyclization to form a mixture of cis and trans diastereoisomers, with the cis isomer as the major product. Conditions based on a Co catalyst developed by Crossley et al. were ineffective for the cyclization of 1. (α-Dimine)Ni complexes have been developed for olefin polymerization and oligomerization. We anticipated that catalysts of this class could effect intramolecular coupling of alkenes. In the presence of Et₂SiH₂, (α-dimine)NiBr₂ catalyzed reductive cyclization of 1 in hexafluorooisopropanol (HFIP) to generate trans-3,4-dimethylcyclopentane 2 in 50% yield. The reaction did not produce the cis diastereomer as a by-product. This exquisite selectivity for the trans diastereomer prompted us to investigate different catalyst precursors in order to improve the yield. (α-Dimine)Ni(Me₃) failed to activate and resulted in no product formation. The extensive participation of Ni(I) and Ni(III) intermediates in

![Scheme 1. Cyclization Reactions of 1,6-Dienes](image-url)
catalysis led us to evaluate Ni(I) precursors. Indeed, [(a-diimine)Ni(m-Br)]_2 exhibited the highest reactivity (Figures S7 and S8), giving rise to 2 in 79% yield (entry 5). A similar Ni(I) precursor, [(a-diimine)Ni(m-H)]_2, afforded 2 in a slightly lower yield (entry 6).

To probe the effect of ligands on this reaction, we prepared less hindered (2,6-diisopropylphenyl) substituents of 5 were replaced by benzyl groups. With an increased catalyst loading of 10 mol %, we achieved a good yield of 2 with catalyst 7 (entry 7). Notably, catalyst 7 is synthetically more accessible than 5 because it requires no glovebox manipulations. [(dtbpe)Ni(m-Br)]_2 exhibited substantially lower reactivity than (a-diimine)Ni complexes (entry 8). Evaluation of other reductants revealed that tertiary silanes (entry 9) and hydrogen were inactive (entry 11), whereas primary silanes afforded some 2 accompanied by saturated molecules resulting from the reduction of the substrate (entry 10).

**Scope**

With the reaction conditions optimized, we investigated the scope of the reductive cyclization. A number of electronically unbiased 1,6-dienes (Figures S7–S20) underwent cyclization in good yields (Figure 2; see also Figures S21–S65). In all cases,
**Figure 2. Substrate Scope**

Isolated yields: unless specified, only 3,4-trans-product was observed. Solvent for 11, 18–21, and 23–25: acetone/iPrOH (5/1). Catalyst loading for 10, 20, 22, and 25 = 5 mol %. Catalyst loading for 21 = 10 mol %. NMR yield for 11 and 14: side products from the reduction and decomposition of the substrates were not separated from the cyclized product. 25: after reduction with H₂ in the presence of Pd/C.
only trans-3,4-disubstituted products were observed. The substrate scope generally resembles that of classic cycloisomerization reactions.\textsuperscript{10,11} The Thorpe-Ingold effect is crucial to assist in the formation of cyclopentane derivatives.\textsuperscript{32} The conditions tolerate a number of functional groups, including esters, acetals, and amines. When a crotyl-substituted malonate was used, the cyclization proceeded with slightly reduced reactivity to afford 14 in 59% yield. Substituents at the allylic position could give rise to 2,3-diastereo-isomers on the basis of the relative positions of the substituent and the methyl groups formed. This diastereoselectivity was dependent on the size of the substituent, favoring 2,3-anti-diastereomers (15–17).

Cyclization of diallylamines was best performed in a mixture of acetone and iPrOH as the solvent, giving rise to a variety of pyrrolidine derivatives (18–25). 3,4-Dimethylpyrrolidine 18 formed in 15:1 diastereoselectivity, favoring the trans product. Substitution on the olefin exhibited a modest inhibitory effect. Cyclization of a crotyl substrate afforded pyrrolidine 19 in high yield, whereas bulkier substituents led to reduced yields (20–22). In the preparation of pyrrolidine 21, both cis- and trans-alkenes gave the desired product, but the cis-alkene exhibited higher reactivity. Cyclization of a dicrotyl substrate generated trans-diethyl pyrrolidine 23 in 31% yield, suggesting more difficult cyclization with two internal olefins. Cyclization of a geminal-disubstituted olefin proceeded to afford trisubstituted pyrrolidine 24 with a quaternary carbon in 47% yield. When a cyclohexene derivative was used as the substrate, the standard conditions gave a mixture of reductive and redox-neutral cyclization products in a 1:1 ratio, which was then converted to the single diastereomer 25 upon hydrogenation.

Applications

The current reductive coupling reaction found appealing applications in preparing bioactive molecules. trans-Dimethyl-pyrrolidine product 18 can be readily deprotected to generate trans-3,4-dimethylpyrrolidine 26, which serves as the precursor to pesticide 27\textsuperscript{33} and selective estrogen receptor modulator 28 (Scheme 2A).\textsuperscript{19} Previous methods to prepare 18 require multiple steps from the commercially available dimethylmaleic anhydride 29, and give a mixture of cis and trans diastereomers.\textsuperscript{34} In contrast, our cyclization reaction provides exclusive access to the trans diastereomer. The volatile nature of 26 prompted us to treat it with acid after deprotection.

\begin{scheme}
Scheme 2. Synthetic Applications of trans-Selective Reductive Cyclization
\end{scheme}

(A) Derivation of trans-dimethyl-pyrrolidine 18 to pesticide 27 and selective estrogen receptor modulator 28.
(B) Synthesis of dimethyl gababutin derivative 36 via Ni-catalyzed reductive cyclization.
and purify it via recrystallization (Figures S66 and S67). Resolution methods are readily available to separate the two enantiomers of 26.\textsuperscript{34}

The (R,R) enantiomer of gababutin derivative 36 exhibits superior efficacy toward relieving neuropathic pain and anxiety in in vivo models (Scheme 2B).\textsuperscript{18} The previous synthesis required 13 steps with less than 14% overall yield. The chiral centers were established in the first step with (-)-menthol as a chiral auxiliary.\textsuperscript{18} Our reductive cyclization enables the construction of the 3,4-dimethyl cyclopentane structure 32 from the easily accessible 3,3-diallyl-butyrolactone 31 in 78% yield. Ring opening of the lactone 32 with ammonia gives amide 33 in 68% yield (88% yield on the basis of the recovered starting material). The 1,3-amino alcohol 34 undergoes dehydrogenative amide formation in the presence of a 10% Ru catalyst\textsuperscript{35} to form pyrrolidone 35 in 93% yield. Alternatively, straightforward protection of the amine by Boc\textsubscript{2}O, followed by oxidation of the alcohol by pyridinium dichromate (PDC) and deprotection of the amine, gives 35 in 86% yield over three steps (Figures S68–S79). The ring opening of 35 by acid to form 36 has been established in the previous synthetic work.\textsuperscript{18} We anticipate that racemic 36 could be readily resolved to provide both enantiomers, which are both valuable for drug discovery.\textsuperscript{36}

**Mechanistic Studies**

Catalyst 5 displays a high chemoselectivity for reductive cyclization, as opposed to redox-neutral cyclosomerization. In addition, the reaction exhibits high diastereoselectivity favoring formation of the trans-disubstituted products. We conducted studies in order to elucidate the mechanistic reasons for this observed selectivity. Monitoring the conversion of 1 to 2 by in situ \textsuperscript{1}H nuclear magnetic resonance (NMR) spectroscopy resulted in a linear time course (Figure 3), revealing that the reaction rate was independent of [1] and [Et\textsubscript{2}SiH\textsubscript{2}]. We attempted to determine the kinetic isotope effect with Et\textsubscript{2}SiD\textsubscript{2}, but the measurements were complicated by H/D scrambling of the silane reagent with the protic solvent and the isopropyl groups of the ligand via cyclometallation, resulting in partial deuterium incorporation to the methyl groups of 2 (Figures S2 and S3). Such cyclometallation is commonplace in transition-metal-catalyzed hydrogenation and hydrosilylation reactions.\textsuperscript{37}
During the course of the reaction, we observed broad $^1$H resonances corresponding to the catalyst resting state. When the catalytic reaction was frozen, the electron paramagnetic resonance (EPR) spectrum showed a Ni-centered radical (Figure 4). The reaction catalyzed by ($^8$-diimine)Ni$^{II}$Br$_2$7 also displayed a Ni radical signal upon freezing (Figure S1). Analyzing the crude reaction mixture revealed that Et$_2$SiH(OCH(CF$_3$)$_2$) and Et$_2$SiH(OiPr) were the resulting silane products when reactions were conducted in HFIP and an acetone/iPrOH mixture, respectively.

The presence of S = 1/2 Ni species, as characterized by EPR spectroscopy, prompted us to isolate possible paramagnetic Ni intermediates. We reasoned that a Ni(II)-alkyl complex could be present. We prepared ($^8$-diimine)Ni(II)Bn 37 by taking advantage of stabilization by a cyclohexyl backbone.38 Addition of Et$_2$SiH$_2$ to complex 37 resulted in an immediate formation of toluene (Figure 5A). When Et$_2$SiD$_2$ was used, the reaction resulted in mono-deuterated toluene. An alternative pathway for product formation involves the protonation of Ni(I)-alkyl species by protic solvents to form toluene and a Ni-alkoxyl complex. To verify this pathway, we dissolved complex 37 in a mixture of acetone-$d_6$ and iPrOH-$d_7$ in a 5/1 ratio. At 50°C, no toluene was formed in 30 min (Figure 5A).

Single-crystal X-ray diffraction established that complex 37 was stabilized by the $\eta^3$-coordination of the benzyl ligand (Figure 5B). Density functional theory (DFT) calculations on the electronic structure of 37 with the use of the ORCA package suggest that the majority of the spin density is delocalized on the $\alpha$-diimine ligand (Figure 5C). This assignment is corroborated by its EPR spectrum, which exhibits an isotropic signal at 22°C with a $g_{iso}$ value of 2.00 (Figure 5D). The superhyperfine splitting patterns are due to the coupling of the radical with the N ($I = 1$) and $\alpha$-H ($I = 1/2$) atoms of the ligand. Thus, the electronic structure of 37 is best described by its valence tautomer 38, featuring a Ni(II) center with a radical delocalized on the redox-active $\alpha$-diimine ligand (Figures 5A).40,41

Figure 4. X-Band EPR Spectrum of the Reaction Mixture of 1 Catalyzed by 5
Temperature = 10 K, solvent = acetone/iPrOH (5/1). Spectroscopic parameters: $g_x$ = 2.38, $g_y$ = 2.34, $g_z$ = 2.00, $A_{XX}$ = 5 MHz, $A_{YY}$ = 93 MHz, $A_{ZZ}$ = 11 MHz. Microwave frequency = 9.380 GHz, power = 0.25 mW, modulation amplitude = 1 mT/100 kHz.
Gaussian DFT calculations on possible Ni(III) intermediates converged to square pyramidal complex 39 (Figure 6), in which the hydride and silyl groups are trans to each other. The spin-density plot calculated with the ORCA package clearly shows a Ni-centered radical. Calculation of the EPR spectrum of complex 39 resulted in g tensors of $g_x = 2.29$, $g_y = 2.24$, and $g_z = 2.03$ and an $A_{iso}$ value of 32.2 MHz.

In order to distinguish two-electron pathways from an HAT mechanism, we prepared radical clock 40 (Figures S80–S87). Reductive cyclization of 40 generated the cyclized product 41 in 30% isolated yield, accompanied by reduced products 42 and 43 (Figure 7A; see also Figures S4, S5, and S88–S93). We attribute this side reaction to the steric hindrance created by the cyclopropyl substituent that inhibited cyclization. Importantly, the cyclopropyl group underwent no ring opening, even when the adjacent C=C double bond was reduced in 43. It is also possible that the reductive coupling proceeds via a classic cycloisomerization, followed by reduction of the unsaturated intermediate. We prepared the correspondingly exo-methylene product 45 and subjected it to our standard conditions (Figure 7B). In HFIP, internal cyclopentane was formed as the major product via migration of the C=C double bond, and cyclopentanes formed in a 2:1 cis/trans mixture as minor products via reduction (Figure 5d). In a mixture of acetone and iPrOH, no reaction was observed.

DISCUSSION

Origin of trans Diastereoselectivity

Several reasonable pathways can be proposed for the reductive cyclization of dienes (Scheme 3). Tandem cycloisomerization and reduction is expected to generate the...
cis product (Scheme 3A). A control experiment in which the cycloisomerization product 45 was subjected to the reductive conditions led to olefin migration as the major product (Figure 7B) and ruled out this pathway. Cycloaddition of the diene with Ni forms a metallocycle, followed by reduction with Et₂SiH₂ to afford the reductive cyclization product (Scheme 3B). This cycloaddition mechanism, however, would give rise to the cis diastereomer, as determined previously with Ni⁴³ and other metals.

HAT pathways via organic radical intermediates have been invoked in recent olefin coupling reactions.¹⁴,²⁵,⁴⁴ Cyclization of diene 1 with Fe led to a mixture of cis and trans diastereomers, with a preference for the cis isomer (Figure 1, entry 1). The formation of the cis product with Fe corroborates previous studies of radical cyclization¹⁴,⁴⁵ and provides circumstantial evidence to exclude a radical cyclization pathway for this Ni system (Scheme 3C). In addition, results from radical clock 40 confirmed the absence of an organic radical intermediate (Figure 7A). Formation of the reduced products 42 and 43 suggests that hydride transfer occurs prior to cyclization, as opposed to formation of a radical intermediate. The observed trans diastereoselectivity is consistent with a classic, organometallic pathway proceeding via hydride insertion,⁴⁶ followed by reinsertion to the second olefin and reductive cleavage of the Ni–C bond by Et₂SiH₂ (Scheme 3D). Previous studies in the context of cycloisomerization reveal that the hydride insertion pathway favors formation of trans products.⁴⁷,⁴⁸

Figure 6. Geometry Optimization and Spin-Density Plot of Possible Ni(III) Intermediate 39 According to DFT Calculations

Figure 7. Mechanistic Study of Ni-Catalyzed Reductive Cyclization
(A) Reaction of radical clock 40 under standard conditions.
(B) Control experiment of cycloisomerization product 45 under reductive cyclization conditions.
Proposed Catalytic Cycle

The transdiastereoselectivity and the radical clock experiment described above provide support for a classic, organometallic mechanism. Our experimental data are consistent with the catalytic cycle shown in Scheme 4, in which formal oxidation states of the Ni intermediates are shown for clarity. Activation of the dimeric catalyst 5 by Et₂SiH₂ gives rise to Ni-H 46, which inserts into the diene substrate, followed by reinsertion to form Ni(I)-alkyl intermediate 48. Oxidative addition of Et₂SiH₂ generates a Ni(III) intermediate 39, which undergoes reductive elimination to form the 3,4-disubstituted cyclic product and Ni-silyl 49. Ni(I)-H 46 is regenerated by the reaction of Ni-silyl intermediate 49 with the protic solvent, HFIP or iPrOH. The formation of the silyl ether by-product is evident after the reaction by NMR spectroscopy.

Analysis of the electronic structure of Ni(I) complex 37 suggests that the α-dimine ligand is redox active, giving a Ni(II) center with an organic radical delocalized to the α-dimine ligand. This assignment is consistent with the EPR spectrum of 37, showing an organic radical at 22°C (Figure 5C). In contrast, the frozen catalytic reaction displays an S = 1/2 Ni species as a rhombic signal at 10 K (Figure 4). The features of the EPR spectrum resemble that of the Ni(III) complexes reported previously 49–53 and are consistent with the calculated EPR spectrum of Ni(III) intermediate 39 (Figure 6). Comparing the EPR spectrum of the catalyst resting state with those of known compounds suggests that the catalyst resting state is a Ni(III) species. This assignment is corroborated by the zero-order kinetic dependence on [diene] and [Et₂SiH₂]. Thus, the turnover-limiting step is the reductive elimination of Ni(III) 39 that occurs after the insertion of the diene and addition of Et₂SiH₂. When (η²-α-dimine)NiBr₂ 7 was used, the frozen reaction mixture exhibits a Ni radical (Figure S1), suggesting

Scheme 3. Mechanistic Pathways for Ni-Mediated Reductive Cyclization of 1,6-Diene

Proposed Catalytic Cycle

A  Cycloisomerization-Reduction

B  Cycloaddition Pathway

C  H-Atom Transfer Pathway

D  Hydride Insertion Pathway
that the Ni(II) precursors can be activated to access Ni(I) intermediates during the reaction. Such a catalyst activation process has been observed recently in the context of hydrosilylation.

**Origin of Chemoselectivity for Reductive Cyclization**

The chemoselectivity of reductive cyclization in relation to cycloisomerization arises from the Ni(I)/Ni(III) catalytic cycle. The electron-rich, formal Ni(I) intermediate \( \text{48} \) undergoes rapid oxidative addition with \( \text{Et}_2\text{SiH} \), which outcompetes β-H elimination to form the unsaturated cycloisomerization product \( \text{51} \) (Scheme 4). This chemoselectivity sharply distinguishes the Ni(I) catalyst from previous Ni(II) catalysts, \(^{10,11}\) which favor β-H elimination rather than reaction with silanes. In addition, the lack of β-H elimination prevents possible olefin isomerization, which could lead to scrambling of the stereocenters. \(^{10,11}\) Characterization of the electronic structure of \( \text{37} \) reveals that the redox-active \( \alpha \)-diimine ligand plays an important role in stabilizing Ni(I) intermediates, such as \( \text{48} \), by forming its valence tautomer \( \text{50} \). The dtbpe ligand lacks conjugated π* orbitals to delocalize the radical on Ni and therefore exhibits lower reactivity than \( \alpha \)-diimine ligands (Figure 1, entry 8).

**Conclusion**

We developed a Ni-catalyzed reductive cyclization reaction of 1,6-dienes and diallyl-amines to form trans-3,4-disubstituted cyclopentane and pyrrolidine derivatives with high diastereoselectivity. This cyclization reaction has found applications in the preparation of biologically active molecules. The trans diastereoselectivity arises from a classic organometallic catalytic cycle mediated by Ni(I) and Ni(III) intermediates. The trans diastereoselectivity distinguishes this reaction from HAT and cycloaddition pathways, which favor cis products. The electron-rich Ni(I) intermediate is
stabilized by the redox-active \( \alpha \)-diimine ligand, and is responsible for the chemoselectivity toward reductive cyclization, as opposed to redox-neutral cycloisomerization observed with previous Ni(II) catalysts. The distinct reactivity of \(( \alpha \)-diimine) Ni(II) highlights the power of ligand control in achieving unprecedented selectivity in organic transformations.

**EXPERIMENTAL PROCEDURES**

Detailed experimental procedures are provided in the Supplemental Information.

**ACCESSION NUMBERS**

Crystallographic data have been deposited in the Cambridge Crystallographic Data Center (CCDC) under accession numbers CCDC: 1548657 for \( 5 \) and 1548656 for \( 37 \).

**SUPPLEMENTAL INFORMATION**

Supplemental Information includes Supplemental Experimental Procedures, 93 figures, and 2 data files and can be found with this article online at [http://dx.doi.org/10.1016/j.chempr.2017.07.010](http://dx.doi.org/10.1016/j.chempr.2017.07.010).

**AUTHOR CONTRIBUTIONS**

Y.K., D.A., and F.M. performed the experiments. J.K. conducted the DFT calculations of intermediate \( 39 \). S.H. performed the EPR characterization of compound \( 32 \). T.D. supervised the project and wrote the manuscript.

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