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Bicyclo[4.1.1]octanes via Strain-Storage Cyclobutanone-Alkyne Coupling and Its Enantioselective Strain-Release Transformation to Bicyclo[4.2.1]nonanes

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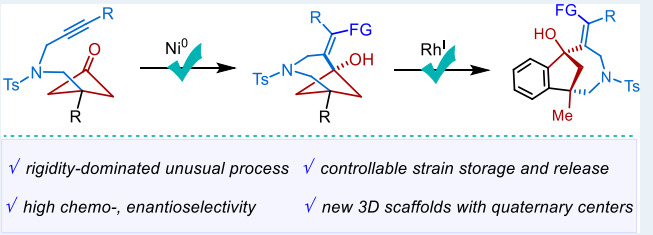
ABSTRACT: Three-dimensional C(sp^3)-rich bicyclic scaffolds are vital saturated bioisosteres and versatile building blocks in medicinal and synthetic chemistry. Notwithstanding the importance and progress, the synthesis of bicyclo[4.1.1] and bicyclo[4.2.1] scaffolds remains challenging. Herein, we unveil a rare nickel-catalyzed strain-storage cyclobutanone-alkyne coupling to prepare various functionalized bicyclo[4.1.1]octanes. Moreover, downstream strain-release transformation of bicyclo[4.1.1] scaffolds via rhodium-catalyzed enantioselective sequential C−C activation and 1,4-rhodium shift was efficiently achieved to fuse a variety of enantioenriched bicyclo[4.2.1] scaffolds with high chemo-, diastereo-, and enantioselectivity. Mechanistic studies revealed the well-tailored spironickelabicyclic intermediate with a rigid endo-cyclic olefin favors the strain-storage cyclometalation over the common strain-release-driven β-carbon elimination.



KEYWORDS: *transition metal catalysis, bicyclo[4.1.1], bicyclo[4.2.1], strain storage and release, mechanistic study*

INTRODUCTION

Three-dimensional (3D) bicyclo[*n*.1.1] (*n* = 1−5) are privileged scaffolds in medicinal chemistry because of their profound bioisosteric applications to enhance the physicochemical and pharmacokinetic properties of bioactive compounds.[1] On the other hand, due to the large strain energies embedded in the 4-membered ring of bicyclo[*n*.1.1] systems, these strained 3D bicyclic molecules frequently serve as important building blocks in organic synthesis.[2] Thus, both aspects have led to extensive researches on designing new practical methodologies to synthesize these strained bridged bicyclic skeletons with highly structural diversity.[3] Recently, radical addition to the central bond of [*n*.1.1]propellane (*n* = 1 and 3) and formal bicyclo[1.1.0]butane cycloaddition with unsaturated π-units have exhibited a wide range of applications in the construction of various bicyclo[1.1.1],[4] bicyclo[2.1.1],[5] bicyclo[3.1.1],[6] and bicyclo[5.1.1][7] systems. However, as an integral part of bicyclo[*n*.1.1] family, bicyclo[4.1.1] scaffold[8] was inaccessible due to the absence of reactivity-matched coupling partners. As our continuous interest in synthesis and transformation of 3D bicyclic scaffolds,[9] we aimed to establish a unique strategy to realize bicyclo[4.1.1] scaffold synthesis and simultaneously investigate their chemical reactivity to produce new polycyclic structures and mimic potential metabolic pathways as a bioisostere.

Transition metal-catalyzed couplings of cyclobutanone derivatives with unsaturated molecules such as alkene,[10] alkynes,[11] and allenes[12] represent an important strategy for synthesis of cyclic compounds, especially the bridged bicycles through an intramolecular coupling manner.[13] Among the metal catalysts, nickel, being a cheap catalyst, has also exhibited a remarkable catalytic reactivity toward such couplings.[14] For example, Dong reported a nickel-catalyzed intramolecular [4 + 2] coupling of cyclobutanones with allenes to form bicyclo[3.2.2] scaffolds.[15] Despite this progress, to date, there exists no report on a strained scaffold using this strategy due to the primary barrier of strain-release-driven C−C cleavage via either originally proposed oxidative cyclometalation and subsequent β-C elimination[16] or recent DFT-established C−C oxidative addition of cyclobutanone and successive migratory insertion (Scheme 1a, left).[17] To promote nickel-catalyzed carbonyl-alkyne coupling over the facile strained C−C oxidative addition, we reckon that the alkyne-substituted cyclobutanones might be competent substrates. When bonded side-on to a nickel center, the alkyne serves as a dihapto, usually two-electron donor. The metallacyclopropanation of nickel with alkyne through strong π-backbonding into the π^* antibonding orbital of alkyne[18] increases the nucleophilicity of alkyne moiety, thus finally accelerating the formal carbonyl-alkyne oxidative cyclometalation over the C−

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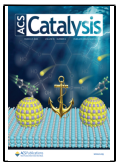

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Scheme 1. Metal-Catalyzed Strain-Storage and -Release Transformations

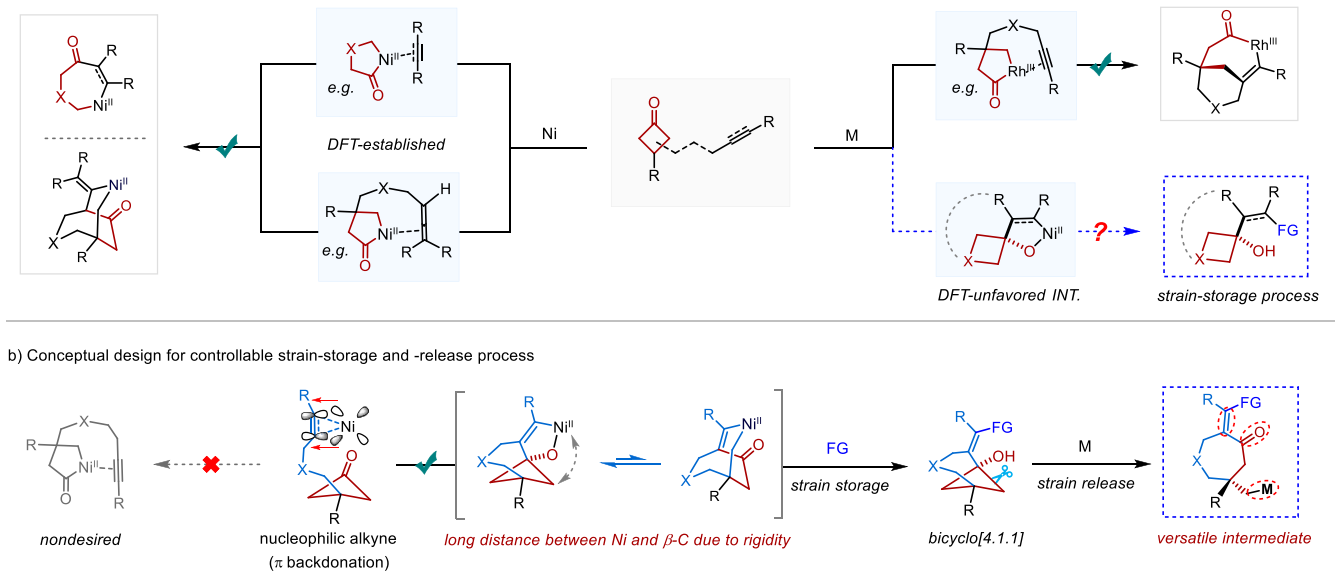
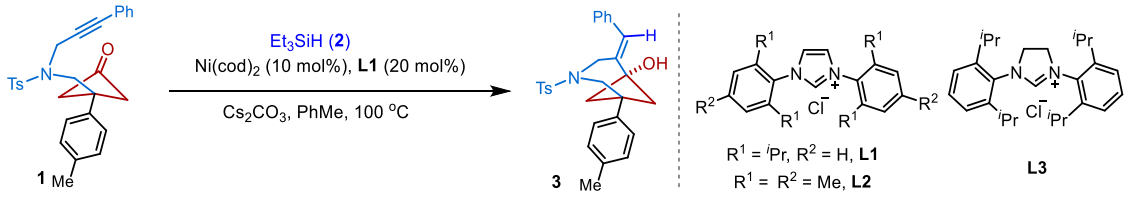


Table 1. Condition Optimization[a]



entry	$Ni(cod)_2$/mol %	ligand/mol %	[H]/equiv	solvent	base/equiv	T/°C	yield/%[b,c]
1	10	L1/20	Et_3SiH/2	PhMe	Cs_2CO_3/2	100	69
2	10	L1/20	B_2pin_2/2	PhMe	Cs_2CO_3/2	100	45
3	10	L1/20	HBpin/2	PhMe	Cs_2CO_3/2	100	27
4	10	L1/20	Et_3SiH/2	PhMe	Cs_2CO_3/2	60	75
5	10	L1/20	Et_3SiH/2	PhMe	Cs_2CO_3/2	25	95
6	10	L1/20	Et_3SiH/2	CyH	Cs_2CO_3/2	25	83
7	10	L1/20	Et_3SiH/2	1,4-dioxane	Cs_2CO_3/2	25	94
8	10	L1/20	Et_3SiH/2	THF	Cs_2CO_3/2	25	72
9	10	L2/20	Et_3SiH/2	PhMe	Cs_2CO_3/2	25	<5
10	10	L3/20	Et_3SiH/2	PhMe	Cs_2CO_3/2	25	98
11	10	L3/20	Et_3SiH/2	PhMe	Cs_2CO_3/0.15	25	32
12	10		Et_3SiH/2	PhMe	Cs_2CO_3/2	25	<5
13[d]	5	L3/10	Et_3SiH/2	PhMe	Cs_2CO_3/2	25	96
14	1	L3/2	Et_3SiH/2	PhMe	Cs_2CO_3/2	25	39
15	5	L3/5	Et_3SiH/2	PhMe	Cs_2CO_3/2	25	84

[a]Conditions: **1** (0.1 mmol), **2** (0.2 mmol), additive (0.2 mmol), catalyst (10 mol %), ligand (20 mol %), and 1 mL solvent. [b]^1H NMR yield with $C_2H_2Cl_4$ as an internal standard. [c]Treatment with TBAF. [d]Isolated yield.

C oxidative addition of cyclobutanone. Moreover, the generation of a rigid spironickelacycle intermediate with an endo-cyclic alkene elongates the distance between the nickel center and β-carbon atom, which inhibits strain-release-driven β-carbon elimination. Thus, the realization of this goal will open a vast opportunity for the strain-storage synthesis of bioisosteric bicyclo[4.1.1] scaffolds (Scheme 1b, left). Beyond strain-storage synthesis, the resulting bicyclo[4.1.1] scaffold could be employed as a strained precursor to undergo transition metal-catalyzed strain-release-driven "cleave and

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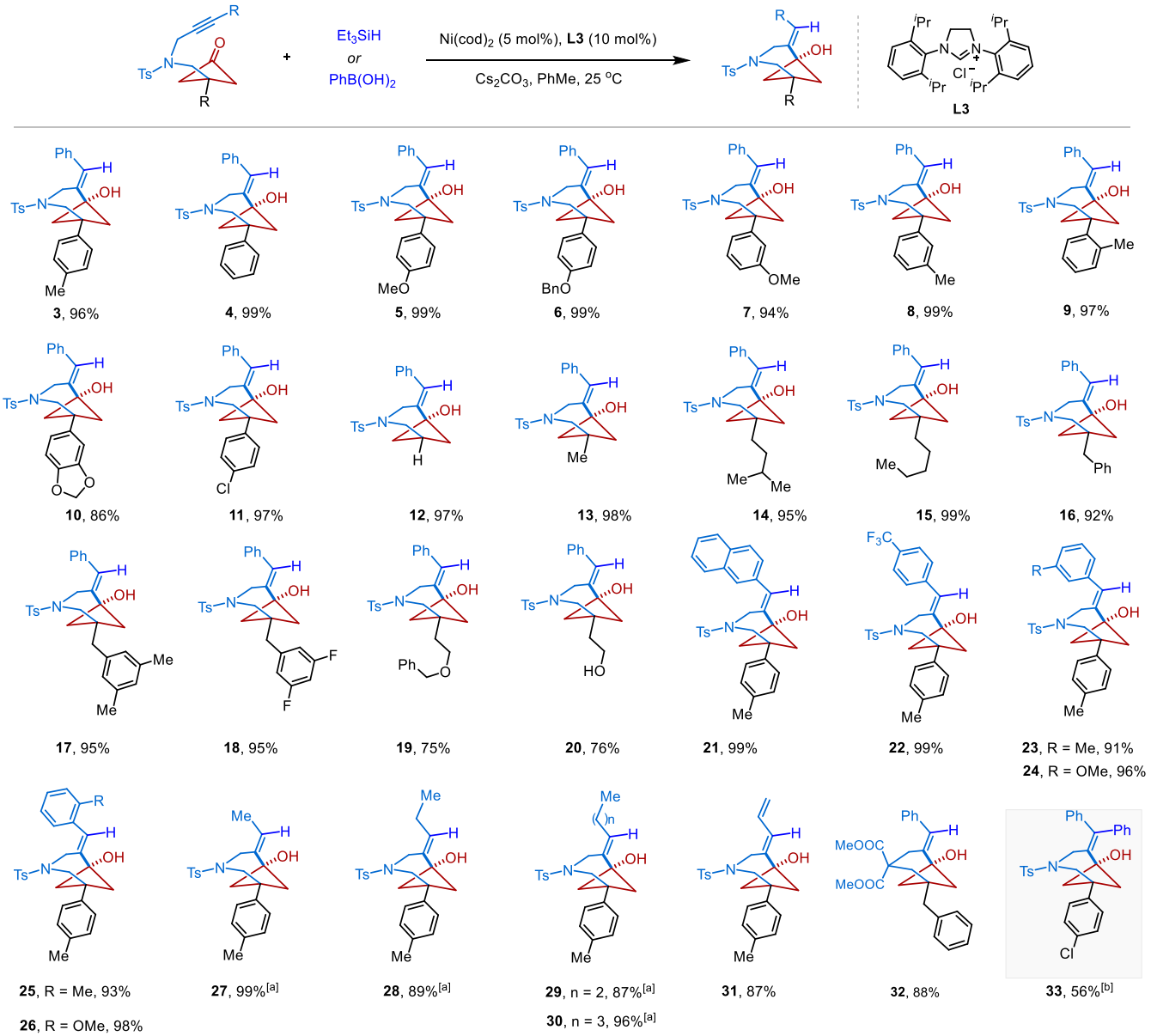
Scheme 2. Scope of Cyclobutanone-Alkyne Cyclization[a−c]



[a]Conditions: **1** (0.2 mmol), **2** (0.4 mmol), Cs_2CO_3 (0.4 mmol), $Ni(cod)_2$ (5 mol %), **L3** (10 mol %), and 1 mL PhMe, isolated yields. [b]Ruphos as a ligand, 80 °C. [c]$Ni(cod)_2$ (10 mol %), Sphos (20 mol %), $PhB(OH)_2$ (2 equiv), 100 °C.

resew" transformations (Scheme 1b, right),[19] thus providing a robust platform to expeditiously assemble new structurally diverse 3D molecules. Herein, we report our findings on nickel-catalyzed chemoselective synthesis of strained bicyclo[4.1.1] scaffold via a well-tailored strain-storage oxidative cyclization of cyclobutanones with alkynes, as well as successive rhodium-catalyzed enantioselective ring expansion of strained bicyclo[4.1.1] to deliver challenging enantioenriched bicyclo[4.2.1]nonanes with excellent enantio- and diastereoselectivity.

RESULTS AND DISCUSSION

Following an extensive optimization campaign, we identified the representative conditions outlined in Table 1. By employing $Ni(cod)_2$ as a catalyst, **L1** as a ligand, triethylsilane as a hydrogen source, cesium carbonate as a base, and toluene as a solvent, we observed a 69% yield of the desired bicyclo[4.1.1] product upon treatment of TBAF solution (Table 1, entry 1). Other silane surrogates such as bis(pinacolato)diboron and pinacolborane showed a lower efficiency (entries 2 and 3). Lowering reaction temperature to room temperature led to an improved yield, and the desired product was isolated in 95% yield (entries 4 and 5). Further evaluation of other NHC ligands and solvents showed that employing **L3** as a ligand and toluene as a solvent gave optimal reaction efficiency (entries 6−10). Control experiments confirmed the necessity of the ligand and a stoichiometric amount of base in this reaction (entries 11 and 12). We also studied the influence of catalyst loading toward the reactivity. An identical reaction efficiency was observed when the amount of Ni-catalyst was reduced to 5 mol %, while further lowering the catalyst loading to 1 mol % gave a dramatically reduced yield (entries 13 and 14). Finally, a nickel-to-ligand ratio of 1:1

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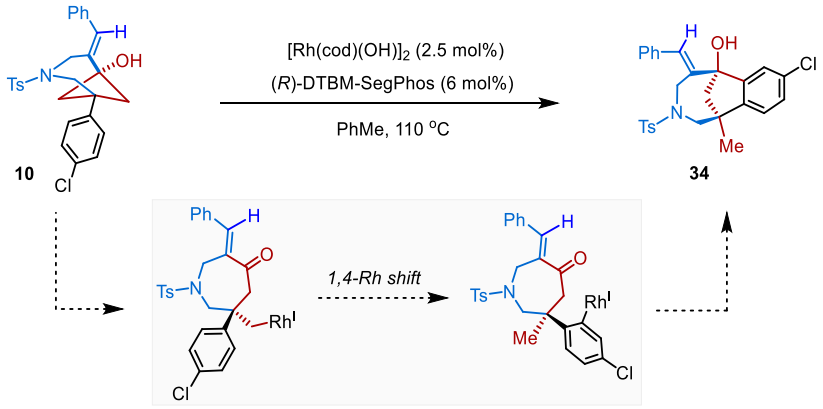
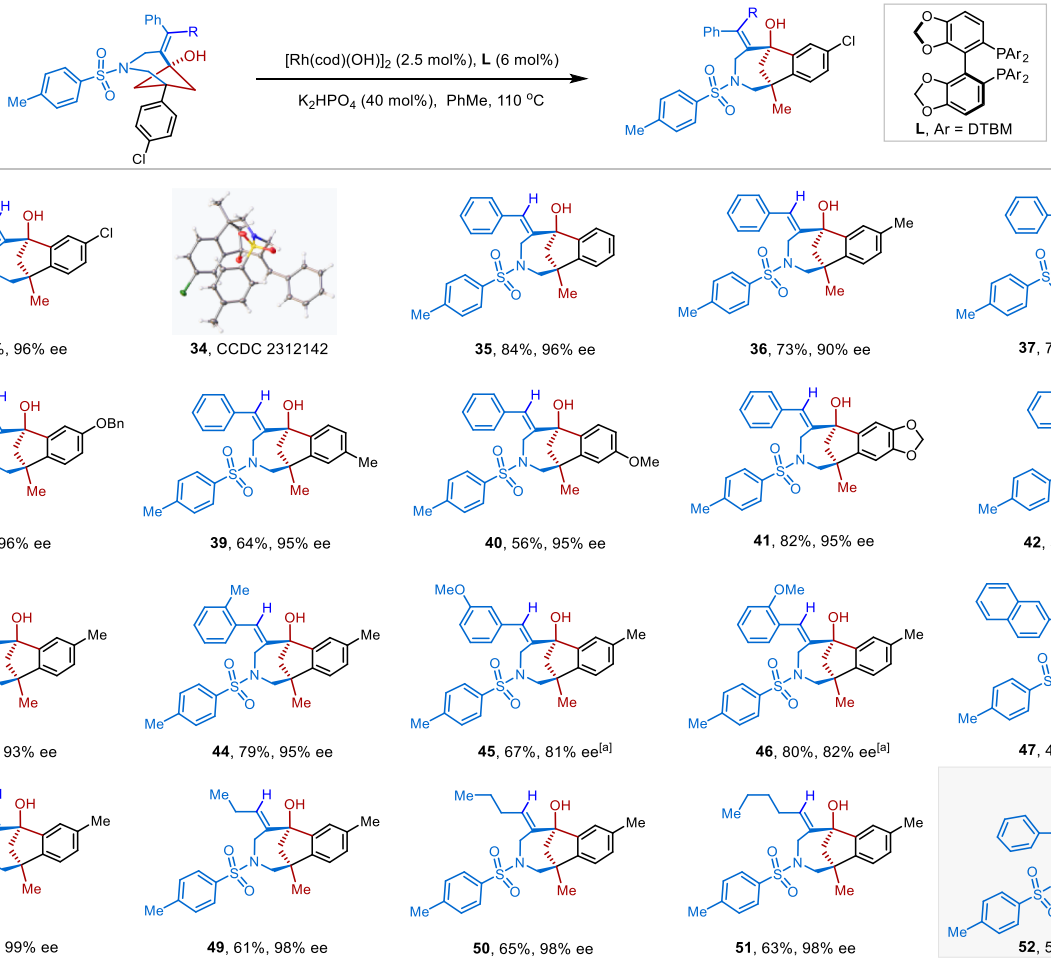
Scheme 3. Rhodium-Catalyzed Enantioselective Transformation of [4.1.1] Scaffold



Scheme 4. Scope of Rhodium-Catalyzed Asymmetric Ring Expansion[a]



[a]Conditions: bicyclo[4.1.1] (0.1 mmol), $[Rh(cod)OH]_2$ (2.5 mol %), (*R*)-DTBM-SegPhos (6 mol %), K_2HPO_4 (40 mol %), and 1 mL PhMe, 110 °C, isolated yields. [b]120 °C.

was investigated, giving a reduced yield of desired product (entry 15).

With the optimized conditions in hand, we began to explore the reaction scope, which was summarized in Scheme 2. We first probed the variations on the cyclobutanone unit in this catalytic system. Aromatic ring attached to cyclobutanone scaffold bearing various electron-rich groups including methyl, methoxy, benzyloxy, and dioxole at the para-, meta-, and ortho-positions were found to be compatible with this transformation (**3**–**10**). Because of the mild reaction conditions, the reactive halogen that was usually explored in Ni-catalyzed cross couplings remained intact in this oxidative cyclization system (**11**), thus leaving an additional reactive handle in the product for further derivatizations. Besides aromatic groups, hydrogen (**12**) and alkyl groups including methyl (**13**), iso-butyl (**14**), *n*-pentyl (**15**), benzyl (**16**–**18**), benzyl ether (**19**), and free hydroxyl group (**20**) at the 3-position of cyclobutanone ring were all well tolerated, affording the desired products in high

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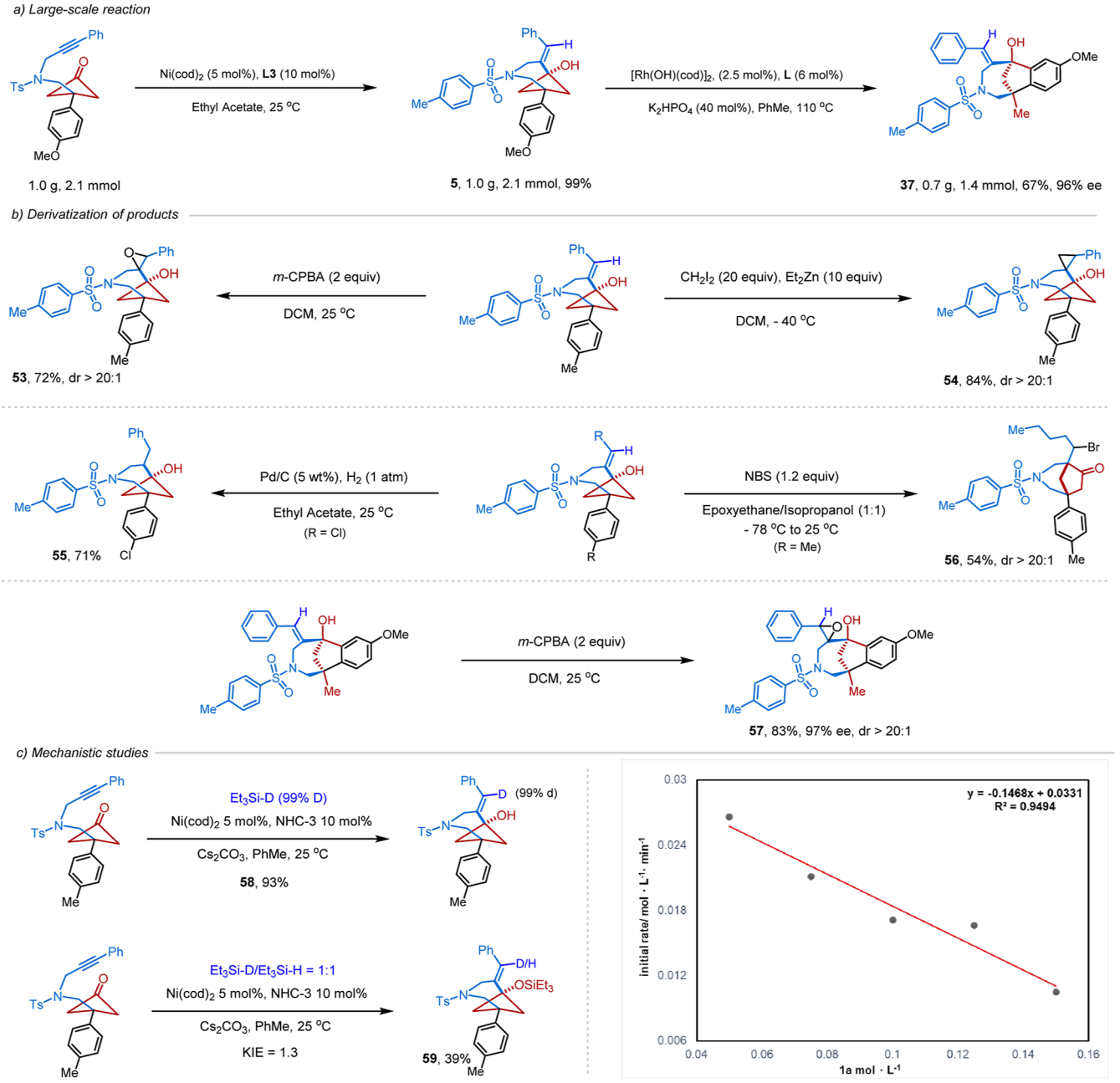
Scheme 5. Derivatization of a Product and Mechanistic Studies



yields. In addition, installing naphthyl (**21**), 4-(trifluoromethyl)phenyl (**22**), 3-(methyl)phenyl (**23**), 3-(methoxy)phenyl (**24**), 5-(methyl)phenyl (**25**), and 5-(methoxy)phenyl (**26**) groups as well as different alkyl groups such as methyl (**27**), ethyl (**28**), n-propyl (**29**), and *n*-butyl (**30**) to the alkynyl fragment all underwent the oxidative cyclization smoothly to construct the desired bicyclo[4.1.1] scaffolds in good yields. The coupling of a substrate derived from 1,3-enyne furnished the desired product (**31**) in 87% yield. This example is particularly noteworthy in that the formed 1,3-diene group could coexist well with the excessive triethylsilane, demonstrating the generality of this catalytic system. The reaction of C-tethered substrate underwent the cyclization smoothly under the standard conditions, affording the product (**32**) in 88% yield. Beyond triethylsilane, phenylboronic acid is an applicable reagent in this Ni-catalyzed oxidative cyclization, and the arylated bicyclo[4.1.1] scaffold (**33**) with a tetrasubstituted alkene moiety was prepared in a good yield.

To examine applications of the concept of controllable strain storage and release, we sought to explore synthetically useful strain-release transformations of this strained bicyclo[4.1.1] scaffold. Since seminal works reported by Murakami et al.[20] and Seiser and Cramer,[21] the rhodium-catalyzed enantioselective *β*-carbon elimination of strained monocyclic alkanol has been an excellent approach for the formation of new monocyclic scaffolds with sterically demanding quaternary stereogenic centers.[22] However, enantioselective transformation of strained polycyclic alkanol to construct more complex 3D bicyclic scaffolds remains elusive due to the inherent tedious synthetical procedures and untamable reactivity of the polycyclic molecules.[23] Inspired by our rapid access to

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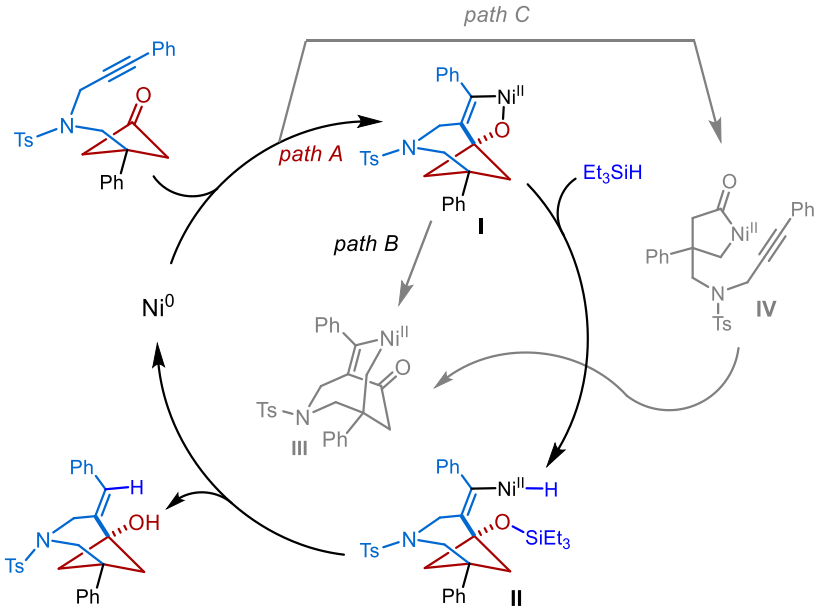
Scheme 6. Proposed Mechanism



bicyclo[4.1.1] scaffold, we envisioned that the sequential rhodium-catalyzed enantioselective β-carbon elimination, stereospecific 1,4-Rh shift, and nucleophilic addition to carbonyl may be an alternative robust strategy for the construction of chiral bicyclo[4.2.1] scaffold, which is a part of biologically active natural compounds such as longifolene and longicamphoric acid (Scheme 3).[24] With this conceptual design in mind, we began to examine the rhodium-catalyzed enantioselective strain-release process. After a careful condition screening (see details in the Supporting Information), the optimal conditions to furnish the chiral 3D azabicyclo[4.2.1]-nonanes were established: $[Rh(cod)OH]_2$ (2.5 mol %), (*R*)-DTBM-SegPhos (6 mol %), K_2HPO_4 (40 mol %), and PhMe solvent. It is noteworthy that this reaction represents a scare strategy for chiral bicyclo[4.2.1]nonane skeleton synthesis[25] via transition metal asymmetric catalysis.

Under the optimized reaction conditions, the generality of the reaction was then evaluated. As depicted in Scheme 4, substituents including chloro (**34**), hydrogen atom (**35**), methyl (**36**, **39**, and **42**), and ether group (**37**, **38**, and **40**) dioxole (**41**) at the para, meta, and ortho-positions of aryl rings all underwent the ring expansion process smoothly, giving the bicyclo[4.2.1] products in good yields with excellent diastereo- and enantioselectivities. The absolute configuration of (1*S*, 6*R*)-**34** was secured by X-ray crystallographic analysis. The *o*-methylphenyl and *m*-methylphenyl substituents on the alkyne moiety (**43** and **44**) showed a marginal influence on the reactivity and enantioselectivity. Installation of an *o*-methoxyphenyl or *m*-methoxyphenyl substituent to the alkyne fragment resulted in a reduced reactivity under the standard conditions, while increasing the reaction temperature to 120 °C afforded the desired product in good yield with good enantioselectivity (**45** and **46**). The substrate with a naphthyl-substituted alkyne (**47**) also gave the desired product with high enantioselectivity, albeit with a moderate yield due to the increased steric hindrance. The substrates bearing aliphatic alkynes (**48**−**51**) were well tolerated, affording the desired products with excellent enantioselectivity. We also examined the rhodium-catalyzed C−C and C−H activation of an arylated bicyclo[4.1.1] scaffold (**33**), efficiently generating azabicyclo[4.2.1]nonane **52** in 57% yield with a dramatically reduced enantioselectivity due to the bulky tetrasubstituted alkene fragment. Unfortunately, when performing this rhodium-catalyzed sequential C−C and C−H activation of compound **16**, the 1,5-rhodium shift did not occur at the current stage with recovery of the starting material.

The synthetic utility of this transformation is shown in Scheme 5. As shown in Scheme 5a, the nickel-catalyzed cyclization reaction and subsequent rhodium-catalyzed enantioselective ring expansion on a gram scale furnished the corresponding products in good yields. To further demonstrate the applicability of this strategy toward formation of more complex sp^3-rich scaffolds, we undertook several useful transformations of bicyclo[4.1.1] product (Scheme 5b). Spirocyclic propagations were performed to access polycyclic skeletons with differently sized rings in high yield with excellent diastereoselectivity via epoxidation (**53**) or cyclopropanation (**54**) of the exocyclic alkene of the product. Treatment of the product with hydrogen and Pd/C provided saturated compound **55** in a 71% yield. Transformation into a synthetically useful brominated 3-azabicyclo[3.2.1]octan-6-one skeleton (**56**) was achieved in 54% yield with excellent diastereoselectivity via NBS-induced semi-pinacol rearrangement. In addition, we performed the oxidation of bicyclo[4.2.1], generating epoxide derivative **57** in 83% yield.

We subsequently performed a series of deuterium-labeling and kinetic experiments to probe the mechanism of this nickel-catalyzed oxidative cyclization process (Scheme 5c). We conducted the cyclization reaction of substrate **1a** with Et_3Si-D under standard conditions, and the deuterium atom was located at the alkenyl position. ^1H NMR analysis of the reaction between substrate **1a** and a mixture of Et_3Si-D and Et_3Si-H indicated that protonation of alkenyl nickel species is not a rate-determining step due to a small kinetic isotope effect (KIE = 1.3) given in the reaction (Scheme 5c, left). To gain further insight into the process of oxidative cyclization, kinetic analyses were performed. The initial rates of nickel-catalyzed oxidative cyclization were investigated at various concen-

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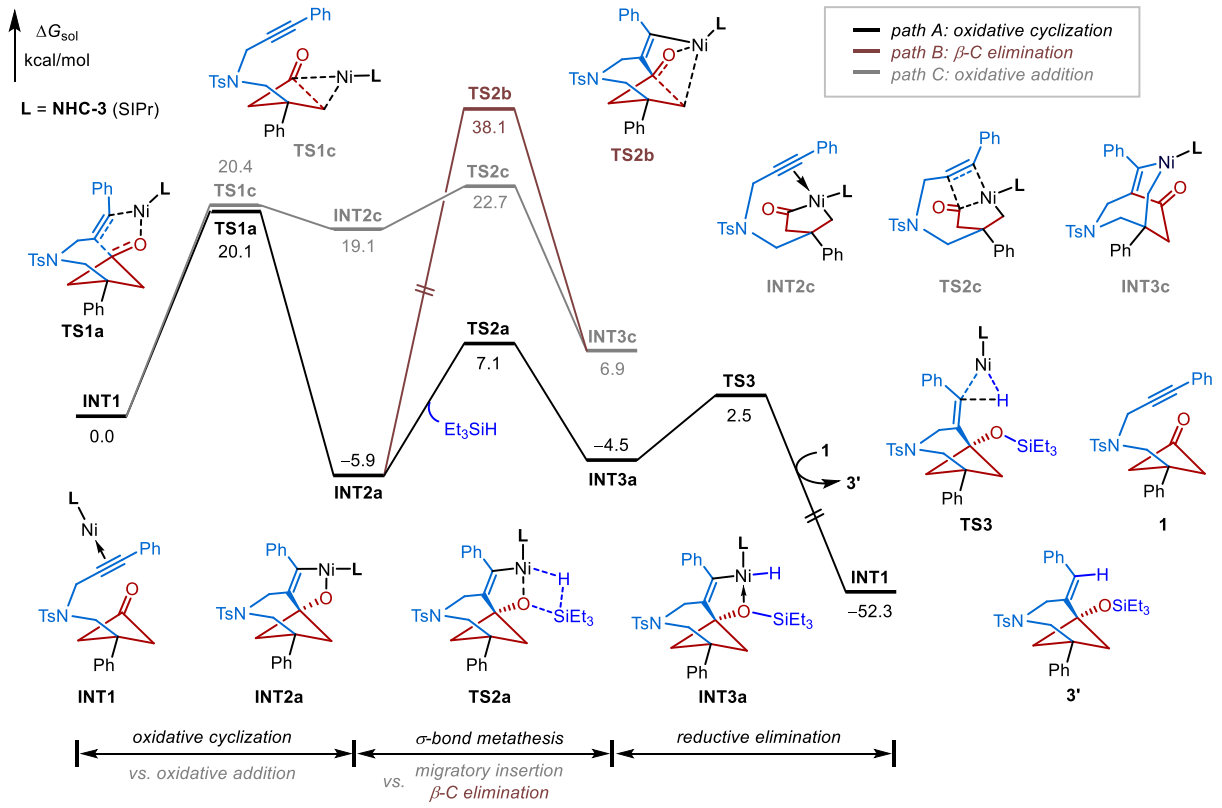

Figure 1. Computed energy profiles for nickel-catalyzed intramolecular annulations of the distally alkynyl-substituted cyclobutanone.

trations of the substrate (Scheme 5c, right). The rates showed a negative first-order dependence on the concentration of substrate **1a**, indicating a strong coordinating interaction between substrate **1a** and the nickel catalyst.

On the basis of previous work[26] and our mechanistic studies, possible reaction pathways were proposed as shown in Scheme 6. In path A, the mechanism commences with an oxidative cyclization of alkyne-substituted cyclobutanone with a Ni^0 catalyst to give rigid bicyclic nickel species **I**, followed by σ-bond metathesis of triethylsilane to generate nickel-hydride species **II**. Reductive elimination provides the desired product and regenerates the Ni^0 catalyst. Furthermore, two competing strain-release pathways commonly proposed in previous work[15,16,17a,26] were also considered. The intermediate **I** undergoes β-carbon elimination to generate rigid nickel complex **III** (path B), which was originally proposed in the previous reductive couplings of cyclobutanone with alkyne.[16] Recent DFT calculations all showed that the strain-release-driven oxidative addition of C−C bond to a nickel center to generate a five-membered nickelacycle is energetically superior to the oxidative cyclization process.[17] Thus, in path C, nickel-catalyzed C−C activation of strained cyclobutanone followed by an alkyne insertion to form bicyclic organonickel intermediates **III** was proposed.

After failing isolation of the oxidative cyclization intermediate, DFT calculations were further performed to investigate these competing pathways to unravel the origins of reaction chemoselectivity. The computed energy profiles are shown in Figure 1. Among a series of possible catalyst-substrate complexes, **INT1** was identified as the most stable one and chosen as the zero-energy reference (see the details in the Supporting Information). The intramolecular oxidative cyclization between alkynyl and cyclobutanone moieties requires a barrier of 20.1 kcal/mol (**TS1a**), forming the spiro-oxa-nickelacycle (**INT2a**). By reaction with Et_3SiH via σ-bond metathesis (**TS2a**, $\Delta G^{\ddagger}$ = 13.0 kcal/mol), the Ni−O bond in **INT2a** is readily cleaved to generate the alkenyl nickel hydride species (**INT3a**). The ensuing C(alkenyl)−H reductive elimination (**TS3**) proceeds smoothly to deliver the strained bicylo[4.1.1] skeleton (**3′**) and regenerate the active catalyst. The relatively low barriers for the steps related to nickel hydride (**TS2a** and **TS3**) are in line with both the deuterium-labeling and KIE experimental results (Scheme 5b).

In this strain-storage annulative reaction, the major competing pathways are the undesired strain-release processes. For the spiro-oxa-nickelacycle intermediate (**INT2a**), the β-carbon elimination is straightforward to release the ring strain. However, this process is less possible due to the extremely high barrier (**TS2b**, $\Delta G^{\ddagger}$ = 44.0 kcal/mol), which is consistent with prior computational studies of nickel-catalyzed annulations of strained cyclic ketones with π components.[17] The difficulty of β-carbon elimination is mostly because of the great rigidity of the spiro-oxa-nickelacycle (**INT2a**), which renders the Ni center away from the β-carbon position, bearing a long Ni···C_β distance (3.76 Å, Figure 2). To approach the β-carbon atom, the alkenyl-Ni moiety in **TS2b** suffers from significant geometric deformations, which is evidenced by the distorted angle of $\angle C_1C_2Ni$ (from 115° in **INT2a** to 143° in **TS2a**, Figure 2). Even after distortions, there is still a relatively long Ni···C_β distance (2.49 Å) in **TS2b**, which is unable to effectively stabilize the negatively charged C_β atom, thus leading to a high barrier. Alternatively, the strain may be released in the initial reaction stage through the oxidative addition of cyclobutanone. Indeed, this oxidative addition requires a relatively low barrier (**TS1c**, $\Delta G^{\ddagger}$ = 20.4 kcal/mol), which is comparable with that of oxidative cyclization (**TS1a**,

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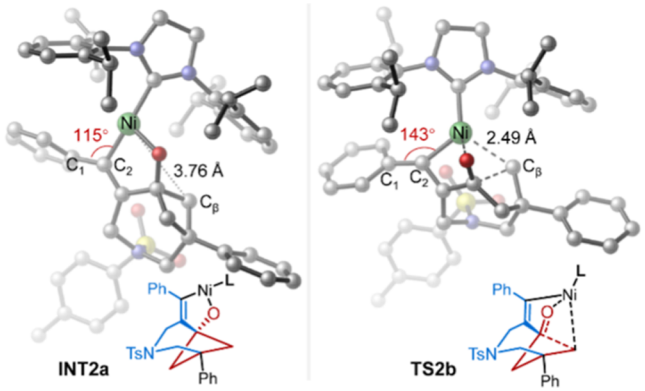

Figure 2. Optimized structures of spiro-oxa-nickelacycle and β-carbon elimination transition state. Hydrogen atoms are omitted for clarity.

$\Delta G^{\ddagger}$ = 20.1 kcal/mol). However, the subsequent alkyne migratory insertion (**TS2c**, $\Delta G^{\ddagger}$ = 22.7 kcal/mol) is less favorable than that of **TS1a**. Thus, either at the initial or intermediate stage, the strain-release process is energetically inferior to the strain-retentive pathway. The efficient capture of spiro-oxa-nickelacycle by Et_3SiH is critical for this strain-storage strategy since other silane surrogates (e.g., HBpin) showcased lower efficiency (entries 3, Table 1).

CONCLUSIONS

In summary, we have unveiled a strain-storage approach for the formation of a strained bicylo[4.1.1] skeleton via formal oxidative cyclization of precisely designed alkyne-substituted cyclobutanones. Mechanistic studies revealed that the rigidity of the nickelacycle generated by oxidative cyclization lengthens the distance between nickel center and β-carbon atom, which hampers the β-C elimination process. Furthermore, the rhodium-catalyzed enantioselective strain-release transformation of bicylo[4.1.1] skeleton was well-established to generate various synthetically and pharmaceutically useful bicylo[4.2.1] scaffolds with excellent chemo-, diastereo-, and enantioselectivity. We anticipate that these reactions will be of forceable value to the medicinal chemistry community by assisting the rapid synthesis of highly functionalized 3D bicyclic scaffolds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.5c00065.

Experimental procedures and physical characterization data (^{1}H, ^{13}C, and ^{19}F NMR spectra) of the substrates and products (PDF)

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Notes

The authors declare no competing financial interest.

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