Asymmetric Cyclization

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Highly Enantioselective Nickel-Catalyzed Intramolecular Reductive Cyclization of Alkynones**

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Abstract: *The first asymmetric nickel-catalyzed intramolecular reductive cyclization of alkynones is reported. A P-chiral monophosphine and triethylsilane were used as the ligand and the reducing reagent, respectively, to form a series of tertiary allylic alcohols bearing furan/pyran rings in excellent yields and enantioselectivities. This reaction has a broad substrate scope and enabled the efficient synthesis of dehydroxycubebin and chiral dibenzocyclooctadiene skeletons.*

The transition-metal-catalyzed cyclization of alkynals/alkynones has become a powerful method for the efficient construction of cyclic allylic alcohols in current organic chemistry.[1] Recent developments based on the use of transition-metal catalysts, such as Ni,[2] Rh,[3] Ir,[4] Ru,[5] or Pd,[6] in combination with a variety of reducing/alkylating agents have greatly expanded its scope. Among various transition metals, the use of inexpensive Ni in reductive cyclization,[7] as pioneered by the groups of Mori and Sato,[2a–b,9c] Montgomery,[2c–f] and Jamison,[2g–j] is particularly attractive, and with such catalysts, superior reactivities can be achieved in the activation of a variety of functional groups. However, whereas a number of enantioselective cyclizations with chiral Rh,[3c–i] Ir,[4] and Pd[6c] catalysts have been reported (Figure 1), asymmetric Ni-catalyzed cyclizations have hardly been explored.[8] A few examples of asymmetric intermolecular couplings with alkynes and aldehydes/ketones/imines have been described,[8] but a highly enantioselective cyclization of alkynones[9] is yet to be developed. Herein, we report a highly enantioselective Ni-catalyzed intramolecular reductive cyclization of alkynones with triethylsilane as the reducing reagent by employing a chiral monophosphine ligand. A broad range of chiral tertiary allylic alcohols bearing furan/pyran rings were efficiently synthesized in excellent yields and enantioselectivities. This method also enabled the efficient asymmetric synthesis of lignan dehydroxycubebin[10] as well as the facile construction of chiral dibenzocyclooctadiene skeletons.[11]

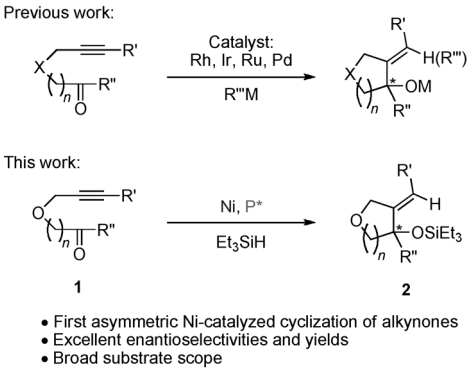

Figure 1. Nickel-catalyzed asymmetric reductive cyclization of alkynones.

Chiral tetrahydrofuran/tetrahydropyran moieties are important substructures found in a broad range of natural products.[12] Although the Ni-catalyzed reductive/alkylative coupling has provided a facile method to obtain these structures as racemic mixtures,[9,2d–f] to the best of our knowledge, no efficient enantioselective reductive/alkylative cyclization of alkynones has been reported. Because of the small size of a nickel atom compared to those of most other late transition metals, it is essential to develop efficient chiral monophosphine ligands for enantioselective Ni catalysis. Early work by Jamison and co-workers[8b] showed that encouraging enantioselectivity could be achieved with a P-chiral ferrocenyl monophosphine for the asymmetric reductive coupling of 1,3-enynes and ketones. We envisioned that the P-chiral biaryl monophosphine ligands developed in our group[13] could be applicable for enantioselective Ni catalysis.

We thus chose **1a** as a substrate to study the Ni-catalyzed intramolecular cyclization of alkynones with triethylsilane as the reducing reagent. As shown in Table 1, no reaction was observed without the addition of phosphine ligands with $[Ni(cod)_2]$ as the catalyst precursor (entry 1). The bisphosphine ligand BINAP also provided no cyclization product (entry 2). In contrast, the monophosphine ligand triphenylphosphine afforded the product in moderate yield (54%, entry 3). Interestingly, using the biaryl monophosphine ligand SPhos led to an excellent yield (98%, entry 4). The high reactivity achieved with SPhos prompted us to explore the performance of the P-chiral biaryl monophosphine ligand (*S*)-BI-DIME, which was developed in our laboratory.[14] Excitingly, BI-DIME provided the desired product in excellent yield and enantioselectivity (97%, 97% *ee*; entry 5). Further screening of the reaction conditions showed the importance of the Ni^0 precursor for the high reactivity, as no product was

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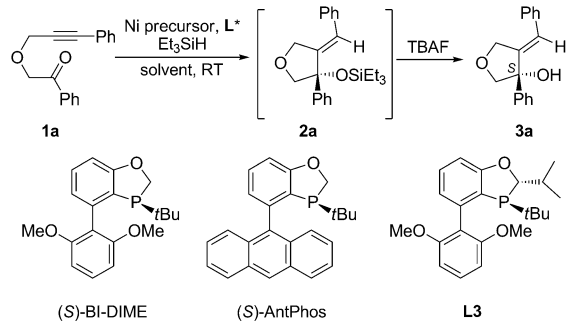
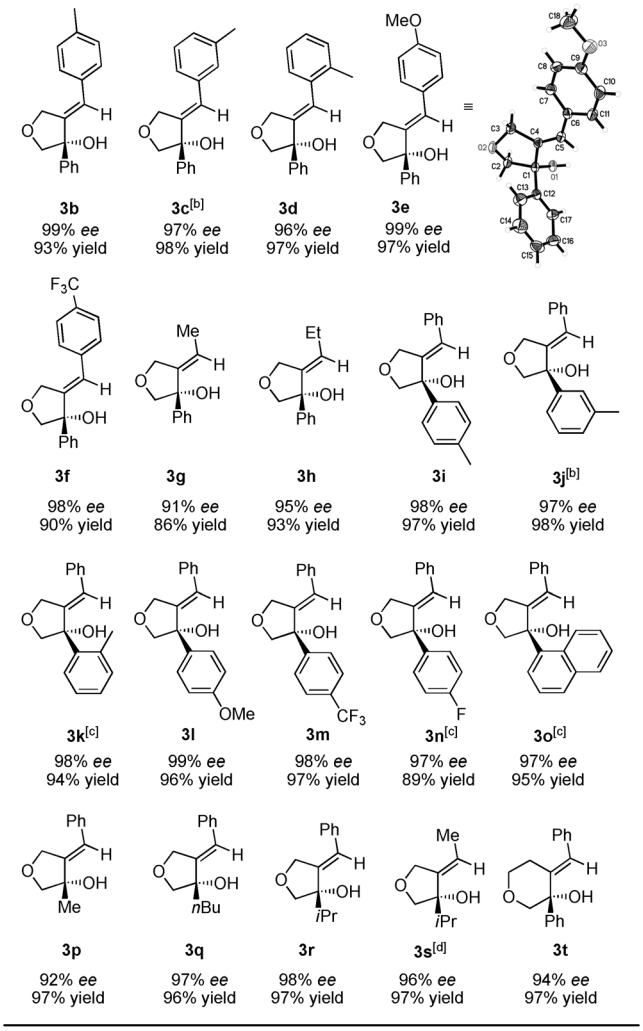
Table 1: Nickel-catalyzed reductive cyclization of alkynone **1a**.



Entry[a]	Precursor	Ligand	Solvent	Yield [%][b]	*ee* [%][c]
1	$[Ni(cod)_2]$	–	dioxane	NR	–
2	$[Ni(cod)_2]$	(*S*)-BINAP	dioxane	NR	–
3	$[Ni(cod)_2]$	PPh_3	dioxane	54	–
4	$[Ni(cod)_2]$	SPhos	dioxane	98	–
5	$[Ni(cod)_2]$	(*S*)-BI-DIME	dioxane	97	97
6	$[Ni(dme)Br_2]$	(*S*)-BI-DIME	dioxane	NR	–
7	$[Ni(cod)_2]$	(*S*)-BI-DIME	THF	93	96
8	$[Ni(cod)_2]$	(*S*)-BI-DIME	MeOH	NR	–
9	$[Ni(cod)_2]$	(*S*)-BI-DIME	EtOAc	18	96
10	$[Ni(cod)_2]$	(*S*)-BI-DIME	CH_2Cl_2	NR	–
11	$[Ni(cod)_2]$	(*S*)-BI-DIME	toluene	46.2	95
12	$[Ni(cod)_2]$	(*S*)-AntPhos	dioxane	98	99
13	$[Ni(cod)_2]$	(*S*)-**L3**	dioxane	NR	–
14[d]	$[Ni(cod)_2]$	(*S*)-AntPhos	dioxane	36	99

[a] Reaction conditions unless otherwise specified: **1a** (0.2 mmol), Ni precursor (5 mol%), ligand (5 mol%), and triethylsilane (2 equiv) in the specified solvent (2 mL) at room temperature under nitrogen atmosphere for 20 h. The absolute configuration of **3a** was assigned by analogy to the absolute structure of **3e**, which was determined by X-ray crystallography.[15] [b] Yields of isolated products. [c] The enantioselectivities were determined by HPLC analysis on a chiral stationary phase (Chiralcel OD-H). [d] $[Ni(cod)_2]$ (2 mol%), (*S*)-AntPhos (2 mol%). BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthene, cod = 1,5-cyclooctadiene, dme = dimethoxyethane, NR = no reaction.

Table 2: Asymmetric nickel-catalyzed reductive cyclization.[a]



[a] Conditions unless otherwise specified: Substrate (0.2 mmol), $[Ni(cod)_2]$ (5 mol%), (*S*)-AntPhos (5 mol%), triethylsilane (2 equiv), dioxane (2 mL), nitrogen atmosphere, room temperature, 20 h. Yields of isolated products are given. [b] (*S*)-BI-DIME (10 mol%). [c] (*S*)-BI-DIME (5 mol%). [d] 48 h.

obtained when $[Ni^{II}(dme)Br_2]$ was employed (entry 6). The solvent also played an important role for the reactivity (entries 7–11), and dioxane was found to be most suitable. Further modification of the chiral ligand showed that chiral AntPhos[14] provided the product with almost perfect enantioselectivity (99% *ee*) and yield (98%, entry 12). It is important to note that the yields of the nickel-catalyzed process compare favorably with those reported for Rh[3i] or Pd[6c] catalysis. The use of ligand **L3**[13c] with an isopropyl substituent led to no conversion (entry 13). This could be due to the increased steric bulk of **L3** rendering substrate coordination to the nickel catalyst difficult. The cyclization required 5 mol% of the Ni catalyst for completion, as only 36% yield was achieved when 2 mol% of the Ni/AntPhos catalyst system were employed (entry 14).

We then studied the generality of this asymmetric Ni-catalyzed reductive cyclization of alkynones. As shown in Table 2, a wide range of cyclic tertiary allylic alcohols bearing furan or pyran rings were efficiently synthesized and isolated in excellent yields (86–98%) and enantioselectivities (91–99% *ee*). For a series of aromatic alkyne substrates, high yields and *ee* values were observed regardless of the substitution pattern and the electronic properties of the aryl ring (**3b–f**). Aliphatic alkynes were also suitable substrates (**3g–h**). Aromatic ketones (**3i–n**) with various substituents and electronic properties were also compatible with the reaction conditions. A 1-naphthyl-substituted ketone was successfully cyclized to provide compound **3o** in 97% *ee* and 95% yield. Various aliphatic ketones were also efficiently converted into chiral 2-alkyl furanols (**3p–r**) in excellent yields and enantioselectivities. An isopropyl ketone with an aliphatic alkyne chain was also smoothly transformed into chiral tertiary alcohol **3s** in 97% yield and 96% *ee*, demonstrating the high tolerance of this method towards various substituents and functional groups. Aside from the tetrahydrofuran products, a chiral tetrahydropyran product (**3t**) was also formed in 94% *ee* and excellent yield (97%).

The high enantioselectivities and yields prompted us to study the mechanism of this catalytic reaction and develop a stereochemical model. Reductive cyclization of **1a** with

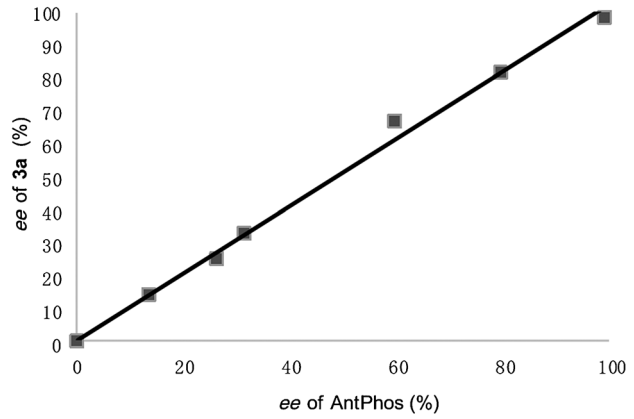


Figure 2. Linear relationship between the *ee* values of the ligand AntPhos and product **3a**.

a scalemic composition of AntPhos revealed the linear relationship between the *ee* values of the ligand and of **3a** (Figure 2), indicating that the reaction is catalyzed by a nickel complex bearing a single AntPhos ligand. To understand whether the cycloaddition of **1a** with the Ni complex takes place prior to the action of $HSiEt_3$, a stoichiometric amount of $[Ni(cod)_2]$was mixed with **1a** in dioxane at room temperature, and the process was monitored by ReactIR (Figure 3). An absorption peak at 1704 cm^{-1} appeared and persisted after the addition of **1a**, indicating the presence of a carbonyl group while the cycloaddition did not proceed without the phosphorus ligand. However, the absorption peak slowly disappeared after the addition of a stoichiometric amount of AntPhos, indicating that the cycloaddition of **1a** with a nickel species bearing an AntPhos ligand has occurred. Based on these results and a kinetic study by Montgomery and coworkers[16] and computational studies by the groups of Houk,[17] Jamison,[17a] and Montgomery[17c,d] on Ni-catalyzed intermolecular or intramolecular ynal reductive cyclizations, we propose the catalytic cycle depicted in Figure 4. Cyclo-

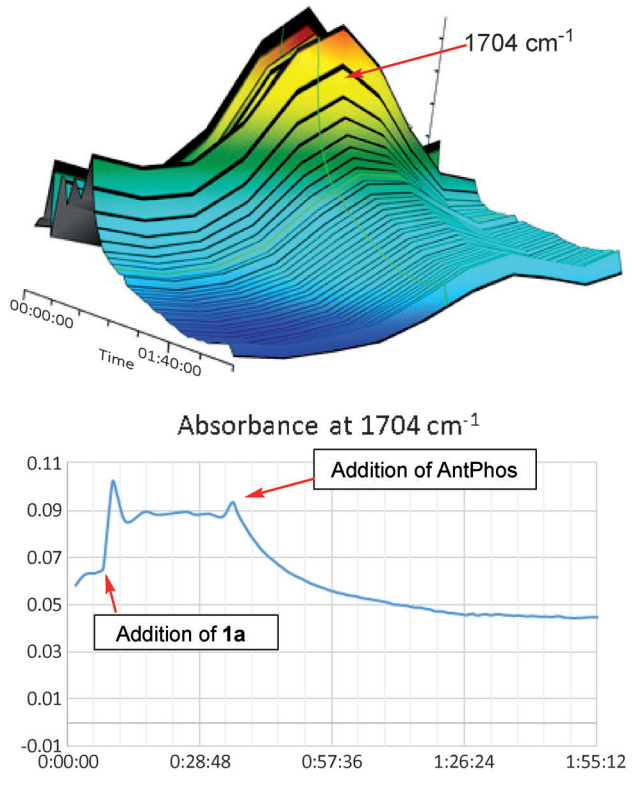


Figure 3. Stoichiometric reaction of $[Ni(cod)_2]$, **1a**, and AntPhos monitored by React-IR.

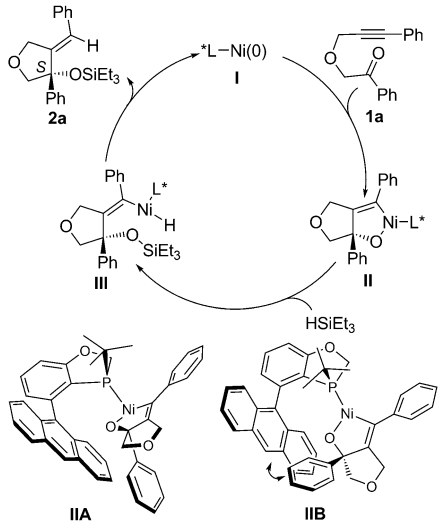
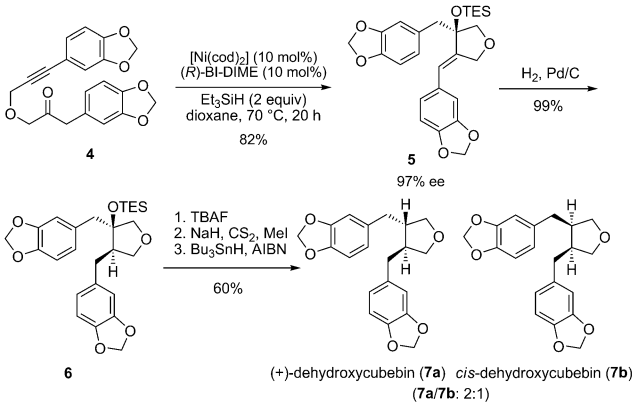


Figure 4. Proposed mechanism and stereochemical model for the asymmetric reductive cyclization of alkynones. L* = (*S*)-AntPhos.

addition of alkynone **1a** with the Ni^0 species **I** provides Ni^{II} metallacycle **II**. This is followed by coordination and σ-bond metathesis of triethylsilane to generate Ni^{II} hydride species **III**. Reductive elimination of **III** provides **2a** and regenerates the Ni^0 catalyst. The stereoselectivity is apparently determined at the cycloaddition stage. Conformational analysis of metallacycle **II** with AntPhos as the ligand indicates that in conformer **IIB**, the steric interactions between the phenyl group on the metallacycle ring and the anthracenyl moiety of AntPhos are greater than in conformer **IIA**. The more favorable conformer **IIA** led to the formation of the cyclization product with the *S* configuration, which is in accordance with the absolute configuration of product **3e**, which was determined by X-ray crystallography.[15]

The highly enantioselective transformation allowed us to synthesize chiral tetrahydrofuran lignans, such as dehydroxycubebin,[10] in a very efficient fashion. Thus, by employing **4** as the starting material and Ni/(*R*)-BI-DIME (10 mol%) as the catalyst, the chiral cyclization product **5** was formed in 82% yield and 97% *ee*. Hydrogenation of the double bond in **5** over Pd/C took place stereospecifically at the opposite side to the OTES group, forming compound **6** quantitatively. TBAF treatment followed by Barton–McCombie deoxygenation provided (+)-dehydroxycubebin (**7a**) and *cis*-dehydroxycubebin (**7b**) in a 2:1 ratio; their spectra were fully identical to previously reported data (Scheme 1).[10d–f]

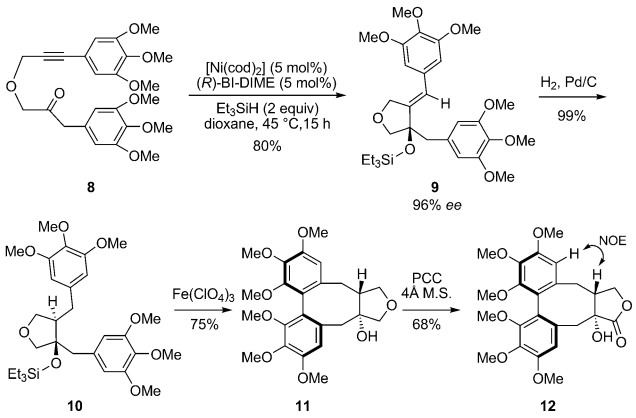
Chiral dibenzocyclooctadiene lignans are members of an important class of natural products with various interesting



Scheme 1. Synthesis of (+)-dehydroxycubebin (**7a**). AIBN = azobisisobutyronitrile, TBAF = tetrabutylammonium fluoride, TES = triethylsilyl.

biological activities.[11] Although their syntheses have been extensively studied, more efficient methods for the construction of chiral dibenzocyclooctadiene skeletons are highly desirable. With Ni/(*R*)-BI-DIME as the catalyst, alkynone **8** was successfully converted into cyclization product **9** in 96% *ee* and 80% yield. Hydrogenation of **9** provided compound **10** exclusively. Stereospecific biaryl coupling mediated by $Fe(ClO_4)_3$ formed dibenzocyclooctadiene **11** as a single diastereomer. Oxidation of the furan ring with PCC provided dibenzocyclooctadiene lactone **12** in 68% yield; its stereochemistry was unambiguously confirmed by NOE experiments (Scheme 2).[18]

In conclusion, the first highly enantioselective Ni-catalyzed reductive cyclization of alkynones was realized by employing a P-chiral monophosphine ligand, namely either AntPhos or BI-DIME. A broad range of chiral tertiary allylic alcohols with various alkyl/aryl substituents bearing furan/pyran rings were efficiently synthesized and isolated with excellent *ee* values and yields. This method further allowed the efficient synthesis of the lignan dehydroxycubebin as well as the facile construction of chiral dibenzocyclooctadiene skeletons. Mechanistic studies demonstrated that the cyclization is catalyzed by a Ni catalyst with a single chiral monophosphine ligand. A simple stereochemical model has been proposed to rationalize the stereochemical outcome. Further applications of this asymmetric cyclization in the synthesis of various lignan natural products are currently being studied, and progress will be reported in due course.



Scheme 2. Construction of the chiral dibenzocyclooctadiene skeleton. M.S. = molecular sieves, PCC = pyridine chlorochromate.

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[15] CCDC 1032269 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[18] See the Supporting Information for details.

