Highly Enantioselective Ni(0)-Catalyzed Cascade Reductive *Syn*-Arylative Cyclization for Five-membered Heterocyclics Bearing Chiral Quaternary Carbon Stereocenters of Tetrasubstituted Allylic Alcohols

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Supporting Information Placeholder

ABSTRACT: Construction of chiral quaternary carbon stereocenters is a significant challenge of asymmetric synthesis. Catalytic synthesis of these structures with trisubstituted allylic alcohols is highly important. However, most of reported methodologies required precious transition-metal catalyst. Herein we reported the first highly enantioselective synthesis of five-membered heterocyclics bearing chiral quaternary carbon stereocenters of tetrasubstituted allylic alcohols by cascade reductive *syn*-arylative cyclization of hetereo 1,6-alkynones with aryl boronic acids catalyzed by the earth-abundant Nickel catalysis Ni(cod)2 and *P*-chiral monophosphine ligand **(*S*)-BIDIME** applying proton solvent *tert*-butanol. Various multi-substituted functionalized pyrrolidines and tetrahydrofurans were achieved in high yield (up to 98%), excellent enantioselectivity (>99:1 er) with broad substrate scope. Totally thirty-seven examples were successfully applied for this transformation. The catalytic cycle and the role of proton solvent was proposed, modified and confirmed first time by detailed density functional theory (DFT) calculations, and further clarified the ligand-control for the excellent enantioselectivity initiated by Ni(0) precursor. Ligand effects, gram scale reaction and control experiments were carried out. New reaction design was proposed for further application of this methodology. This developed methodology and mechanism study is anticipated to find wider applications in organic synthesis and chemical biology.

1. INTRODUCTION

Construction of chiral quaternary carbon stereocenters is a significant challenge as the higher steric hindrance of these chiral motifs compared to other chiral units, and research in this field was one of the hotspots for organic chemists.[1] Chiral five-membered heterocyclics is a key area of research in organic synthesis due to their versatile pharmaceutical activities and ligand applications for asymmetric synthesis.[2,3] Allylic alcohols and their derivatives are highly valuable intermediates owing to the enormous synthetic versatility of C=C double bonds.[4,5] Chiral tertiary alcohols are an crucial class of useful building blocks in organic synthesis, and the enantioselective synthesis of these compounds has become one empowered research field as its challenging scientific significance and versatile application perspective.[6,7] Five-membered heterocyclics with chiral tertiary alcohol is commonly found in numerous biologically active pharmaceuticals and natural products (**Figure 1**). (-)-Aspidophylline A was found to reverse drug resistance in drug resistant KB cells.[8] Nifeviroc is a new drug as CCR5 antagonists in clinical development for anti-HIV treatment.[9] Norsecurinamine A showed significant biological activities to central nervous system and potential antitumor cytotoxicity.[10] (+)-Isatisine A was identified as potential strong anti-HIV compound isolated from Chinese Traditional Medicine *Isatis indigotica* Fort. (Cruciferae), which is used for treatment of viral diseases such as influenza, viral pneumonia, mumps, and hepatitis.[11] Cinatrin C_3 was a PLA_2 inhibitor showed potential use as anti-inflammatory

agents.[12] Taxol is one of the most famous anticancer medicines as an effective natural diterpenoid for cancer therapy.[13] Efficient asymmetric synthesis of five-membered heterocyclics bearing chiral quaternary carbon stereocenters of tetrasubstituted allylic alcohols is much more difficult than issues mentioned above, and only a few enantioselective methodologies are reported.

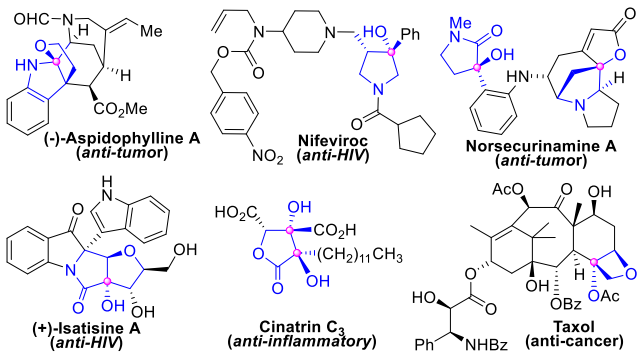
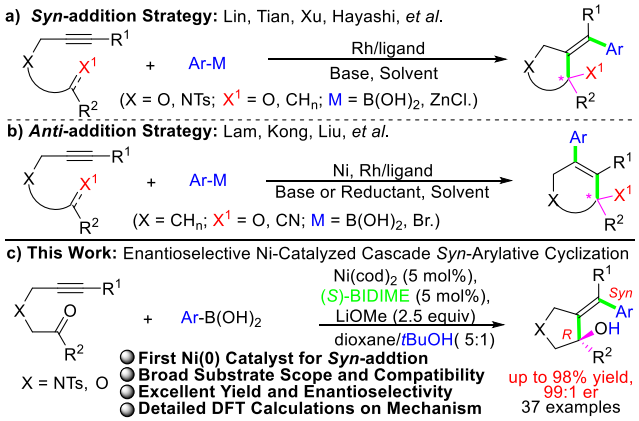


Figure 1. Biologically Active Natural Products and Pharmaceuticals Bearing Five-membered Heterocyclics with Chiral Tertiary Alcohols.

In the past decade, only several catalytic reactions have been developed for enantioselective arylative cyclization to synthesize heterocyclics with chiral quaternary carbon stereocenters. The main [14] and *anti*-arylative cyclization.[15] As illustrated in **Scheme** strategies are *syn*-arylative cyclization **1a**, *syn*-arylative ones includes Rh-catalyzed asymmetric arylative cyclization of *meso*-1,6-dienynes with arylboronic acids,[14a] Rh-catalyzed asymmetric arylative cyclization of alkynones with arylboronic acids,[14b] and Rh-catalyzed enantioselective arylative cyclization of 1,6-enynes with arylzincs,[14c] which involve the aryl insertion to organometallic species and the following *syn*-1,2-addition across an alkyne and alkenyl-metal mediated cyclization. Representative *anti*-arylative ones were shown in **Scheme 1b**, which contains: Nickel-catalyzed enantioselective *anti*-carbometallative cyclizations of alkynyls,[15a] Rh-catalyzed enantioselective arylative cyclizations of alkynyl 1,3-diketones,[15b] Ni-catalyzed reductive coupling of unsymmetrical internal alkynes,[15c] Ni-catalyzed enantioselective desymmetrization of malononitriles,[15d] which initiated by aryl insertion to organometallic species followed by *anti*-1,2-addition to alkyne and alkenyl-metal mediated cyclization. However, approach for synthesizing these structures of tetrasubstituted allylic subunits is limited, and pose a significant synthetic challenge, especially in a regio- and enantio-controlled manner. Only one example of *syn*-arylative cyclization was revealed to date for chemical catalytic enantioselective synthesis of heterocyclics with chiral quaternary carbon stereocenters of tetrasubstituted allylic alcohols.[14b] However, this report presented limited substrates, and required precious transition-metal catalyst, further highlighting the challenges associated with the efficient enantioselective *syn*-arylative cyclization of alkynone with the earth-abundant, inexpensive, and environmentally friendly Ni catalysis.

Scheme 1. Catalytic Enantioselective Arylative Cyclization for Cyclics Bearing Chiral Quaternary Carbon Stereocenters



In light of these impediments, Inspired by the transition-metal-catalyzed alkyne arylative cyclization chemistry[16] reported by the Lam, Liu, Kong and other groups, and the reductive cyclization process developed by Tang and our group,[17] we envisaged that an enantioselective Ni-catalyzed intramolecular reductive cyclization and intermolecular arylative addition cascade strategy could facilitate the desymmetrization of 1,6-alkynones to access five-membered heterocyclics bearing chiral quaternary carbon stereocenters of tetrasubstituted allylic alcohols (**Scheme 1c**). In this article, we disclose a Ni-catalyzed enantioselective cascade *syn*-arylative cyclization of alkyne-tethered ketones with aryl boronic acids to synthesis of tetrahydrofurans and pyrrolidines bearing chiral quaternary carbon stereocenters of tetrasubstituted allylic alcohols under mild conditions. We have discovered that unique *P*-chiral ligand **(*S*)-BIDIME** is very effective for this enantioselective transformation with the cheap Nickel catalysis.

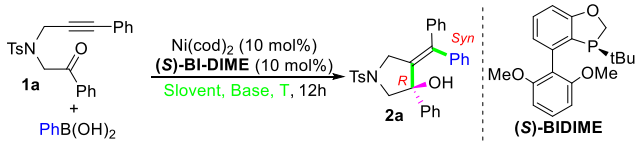
Herein, we reported an efficient enantioselective Ni-catalyzed intramolecular reductive cyclization cascade *syn*-arylative addition of hetero 1,6-alkynones, which concisely synthesize functionalized pyrrolidines and tetrahydrofurans bearing chiral quaternary stereocenters of tetrasubstituted allylic alcohols with up to 98% yield and 99:1 er utilizing *P*-chiral monophosphine ligand **(*S*)-BIDIME**. To the best of our knowledge, this is the first highly enantioselective Ni-catalyzed reductive *syn*-arylative cyclization of hetero 1,6-alkynones with aryl boronic acids for efficient synthesis of various tetrahydrofurans and pyrrolidines with chiral quaternary carbon stereocenters. Furthermore, this strategy is quite different from previous reported arylative cyclizations as it is the first Ni(0) catalyst initiated this type reaction, especially for the key enantio-control steps. The cascade catalytic cycle and clarified mechanism study was first-time proposed, investigated and confirmed by detailed DFT calcu-

lations for this type reaction with alkynones, which will definitely give future guidance for new reaction design and applications.

RESULTS AND DISCUSSION

Reaction Discovery. We selected *N*-1,6-alkynone **1a** as the standard substrate, $PhB(OH)_2$ (phenylboronic acid) as the arylative coupling reagent, The reactivity of the enantioselective Ni-catalyzed reductive *syn*-arylative cyclization were investigated with 10 mol% $Ni(cod)_2$/(***S***)-**BIDIME** (**Table 1**). Following the similar reaction conditions[15a] of Lam group, various solvents were examined, unfortunately, no product was found at all (**Table 1**, Entry 1-3). We randomly speculated that proton solvent might have good effect on this reaction.[14b, 15d] H_2O was initially introduced, but still no product was obtained (**Table 1**, Entry 4). This might because of the water sensitive property of metal precursor $Ni(cod)_2$, which halted the catalytic circle. We then chose the alcohol solvents, and surprisingly, when a small amount of MeOH was added, 35% product was obtained with 82:18 er (**Table 1**, Entry 5), and it was determined as *syn*-arylative cyclization product confirmed by ^1H NMR. When *t*BuOH was applied, a yield of 77% and 89:11er was achieved

Table 1. Solvent and Base Effects [a]

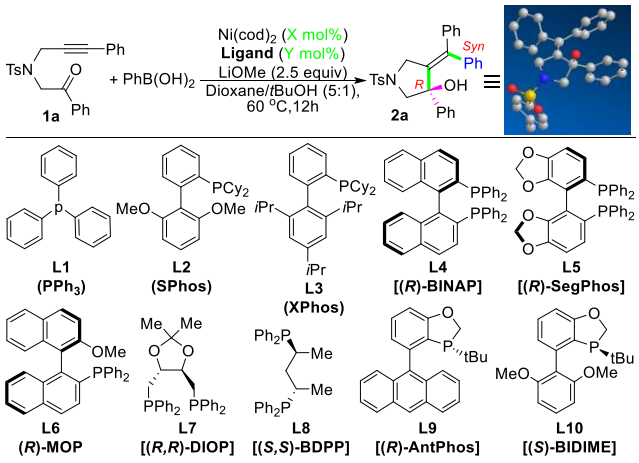


Entry	Slovent	T (°C)	Base	Yield [b] (%)	er [c]
1	THF	80	–	–	–
2	Dioxane	80	–	–	–
3	PhMe	80	–	–	–
4	Dioxane/H_2O	80	–	–	–
5	Dioxane/MeOH	80	–	35	82:18
6	Dioxane/*t*BuOH	80	–	77	89:11
7	Dioxane/*t*BuOH	60	–	68	98:2
8	Dioxane/*t*BuOH	50	–	44	98:2
9	Dioxane/*t*BuOH	60	Et_3N	71	97:3
10	Dioxane/*t*BuOH	60	KOH	–	–
11	Dioxane/*t*BuOH	60	K_2CO_3	53	95:5
12	Dioxane/*t*BuOH	60	NaOMe	78	95:5
13	Dioxane/*t*BuOH	60	KOMe	70	98:2
14	Dioxane/*t*BuOH	60	LiOMe	96	98:2
15	Dioxane/*t*BuOH	60	NaO*t*Bu	68	94:6
16	Dioxane/*t*BuOH	60	KO*t*Bu	73	93:7
17	Dioxane/*t*BuOH	60	LiO*t*Bu	98	92:8

[a]Reaction conditions: under N_2, **1a** (0.2 mmol, 1.0 equiv.), $Ni(cod)_2$/(***S***)-**BIDIME** (10 mol %), $PhB(OH)_2$ (0.4 mmol, 2.0 equiv.), Base (0.5 mmol, 2.5 equiv.), Solvent (1.2 mL), 12h. [b]Isolated yield. [c]Enantiomeric ratio (er) was determined by HPLC with Chiralcel column AD-H.

(**Table 1**, Entry 6). The effect of temperature on the reaction was optimized afterwards, and the enantioselectivity was increased to 98:2 er at a temperature of 60 °C, however, the yield was not good enough (68%, **Table 1**, Entry 7). Thus, a series of alkali additives was used, and several representative organic and inorganic bases were examined (**Table 1**, Entry 9-17). While strong inorganic base KOH stopped the reaction, most of the base does not increase the yield and enantioselectivity until LiOMe and LiO*t*Bu were used to improve the yield to 96% and 98% respectively. Only LiOMe could increase the yield without affecting the corresponding enantioselectivity (98:2 er, **Table 1**, Entry 14). Finally, we chose *t*BuOH as the best proton solvent, LiOMe as the best base for following reaction optimizations.

Table 2. Ligand Screening and Optimizations [a]



Entry	Ligand	X (mol%)	Y (mol%)	Yield [b] (%)	er [c]
1	**L1**	10	10	–	–
2	**L2**	10	10	trace	–
3	**L3**	10	10	trace	–
4	L4	10	5	49	48:52
5	**L5**	10	5	24	39:61
6	**L6**	10	10	30	37:63
7	**L7**	10	5	16	68:32
8	**L8**	10	5	37	14:86
9	**L9**	10	10	86	2:98
10	**L10**	10	10	96	98:2
11	**L10**	0	10	–	–
12	**L10**	10	0	–	–
13	**L10**	5	5	96	99:1
14	**L10**	1	1	28	99:1

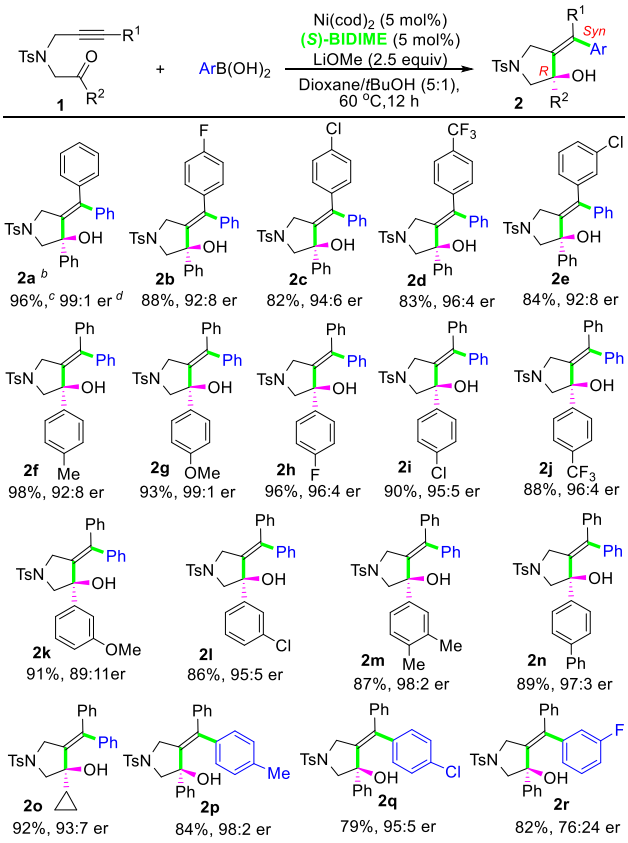
[a]Reaction conditions: under N_2, **1a** (0.2 mmol, 1.0 equiv.), $Ni(cod)_2$ (X mol %), **Ligand** (Y mol %), $PhB(OH)_2$ (0.4 mmol, 2.0 equiv.), LiOMe (0.5 mmol, 2.5 equiv.), dioxane/*t*BuOH(5:1, 1.2 mL), 60 °C, 12h. [b]Isolated yield. [c]Enantiomeric ratio (er) was determined by HPLC with Chiralcel column AD-H.

We then evaluated the effect of different phosphine ligands to see if there is any other ligand applicable to this reaction under the optimal reaction conditions mentioned above (**Table 1**, Entry 14). Various ligands including achiral ligands and chiral ligands were investigated. The reactions were performed under nitrogen in the pres-

ence of a nickel precursor $Ni(cod)_2$ and phosphine ligand with $PhB(OH)_2$ (**Table 2**). As shown in **Table 2**, three achiral mono-phosphine ligands **PPh_3** (**L1**), **S-Phos** (**L2**) and **X-Phos** (**L3**) were firstly used, while **PPh_3** gave no desired product **2a** (Entry 1), **S-Phos** and **X-Phos** could only led to trace product (Entry 2, 3). Then, chiral mono- and bis-phosphine ligands (***R***)-**BINAP** (**L4**), (***R***)-**SegPhos** (**L5**), (***S,S***)-**BDPP** (**L6**), (***R,R***)-**DIOP** (**L7**) and (***R***)-**MOP** (**L8**) were examined. All of them showed low to mediate reactivity with low enantioselectivity (**L4**: 49% yield, 48:52 er; **L5**: 24% yield, 39:61 er; **L6**: 30% yield, 37:63 er; **L7**: 16% yield, 68:32 er; **L8**: 37% yield, 14:86 er; Entry 4-9). It is interesting that the ligand **L4** [(***R***)-**BINAP**], which showed excellent yield and enantioselectivity for the *syn*-arylative cyclization with Rhodium catalysis,[14b] does not work when the transition metal catalysis was changed to Nickel system (Entry 4). When *P*-chiral monophosphine ligand (***R***)-**AntPhos** (**L9**) was applied, the enantioselectivity is also perfect as 2:98 er, but the yield is lower than (***S***)-**BIDIME** (**L10**) (86% compared to 96%, Entry 9-10). This indicated that Tang's *P*-chiral monophosphine ligands are specialized to this type reaction. Furthermore, under the best conditions, with neither $Ni(cod)_2$ nor (***S***)-**BIDIME** (**L10**), this reaction was halted; no product was produced and starting material **1a** was recovered (Entry 11-12). Surprisingly, when the catalyst was reduced to 5 mol %, the enantioselectivity was increased to 99:1 er without the change of the reactivity (96% yield, Entry 13). However, with 1 mol% $Ni(cod)_2$/(***S***)-**BIDIME**, the yield was decreased to 28% (Entry 14). Thus, the *P*-chiral monophosphine ligand (***S***)-**BIDIME** was proved to be the best ligand for this enantioselective Ni-catalyzed intramolecular reductive *syn*-arylative cyclization of **1a** with phenylboronic acids under optimized conditions: N_2, $Ni(cod)_2$/(***S***)-**BIDIME** (5 mol %), $PhB(OH)_2$ (2.0 equiv.), LiOMe (2.5 equiv.), dioxane/*t*BuOH(5:1), 60 °C, 12h, and the best results was 96% yield and 99:1 er. Fortunately, the single crystal of **2a** was prepared by crystallization with solvent heptane/EtOAc (4:1), and its absolute configuration was confirmed unambiguously by X-ray analysis, and the formed chiral center was assigned as *R* (see details in SI).[18]

Substrate Scope. We then sought to evaluate the scope and generality of this enantioselective Ni-catalyzed reductive *syn*-arylative cyclization of hetero 1,6-alkynones with aryl boronic acids. The *N*-1,6-alkynone substrates were then examined with ligand (***S***)-**BIDIME** under the optimized reaction conditions (**Table 2**, Entry 13). Different *N*-1,6-alkynones and aryl boronic acids were found tolerable with excellent enantioselectivities in good yields (**Table 3**, see details in SI). A wide variety of *N*-1,6-alkynones bearing different substituents on the aromatic ring attached to carbonyl or alkyne group were successfully reacted with selected arylboronic acids, providing the corresponding chiral tertiary allylic alcohols

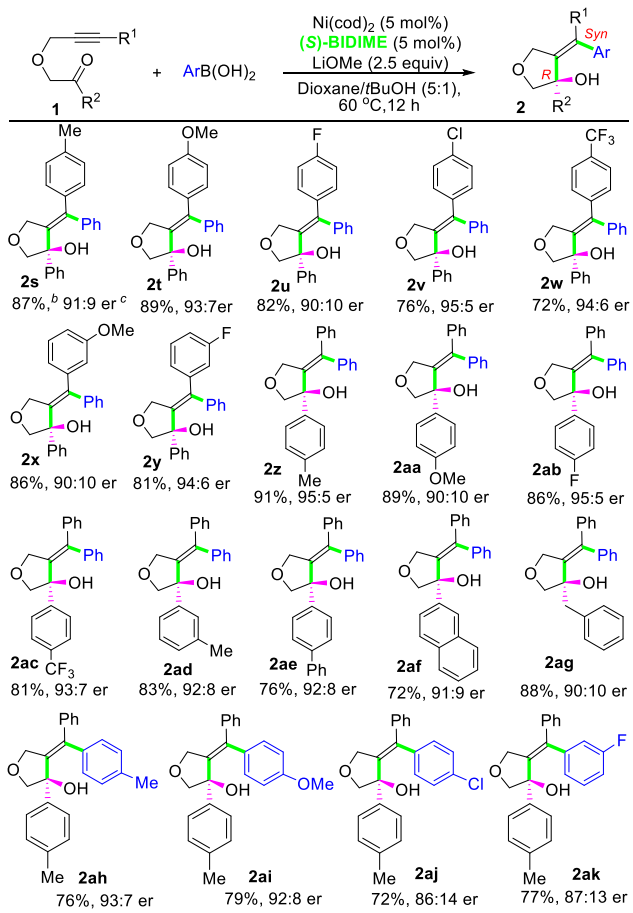
Table 3. Different *N*-alkynone Substrates [a]



[a]Reaction conditions: under N_2, **1** (0.2 mmol, 1.0 equiv.), $Ni(cod)_2$/(***S***)-**BIDIME** (5 mol %), $ArB(OH)_2$ (0.4 mmol, 2.0 equiv.), LiOMe (0.5 mmol, 2.5 equiv.), dioxane/*t*BuOH(5:1, 1.2 mL), 60 °C, 12h. [b]Run in 1 mmol scale. [c]Isolated yield. [d]Enantiomeric ratio (er) was determined by HPLC with Chiralcel columns. The absolute configuration of **2b-2r** was assigned the same as **2a**.

containing a tetrasubstituted olefin and pyrrolidine skeleton **2a–2r** mostly in high yields ((up to 98%) and excellent enantioselectivities (up to 99:1 er). Assuming a similar mechanism, the absolute configurations of the obtained products **2a-2r** were assigned the same as **2a**. The *para*- and *meta*-substituted aromatic alkynes were converted into their desired products in high yields with excellent enantioselectivities (**2a–2e**: 82-96% yield, 92:8–99:1 er). Also, the *para*-, *meta*-substituted aromatic ketones were found to give the pyrrolidines in perfect yields (86%–98%) with excellent enantioselectivities (**2f–2n**: 92:8–99:1 er). Cyclopentane ketone **1o** was also tested, the results is good (92% yield, 93:7 er). Different arylboronic acids were also tested, although *para*-substituted ones could gave the products in high efficiency (**2p**: 84% yield, 98:2 er; **2q**: 79% yield, 95:5 er), *meta*-substituted one gave the product **2r** in good yield with decreased enantioselectivity (82% yield, 76:24 er). Besides the decrease of enantioselectivity for the *meta*-F arylboronic acid, it is interesting that most of the *ortho*- substituted aromatic substrates are not applicable to this transformation. It is probably due to the steric hindrance, and the reason needs further mechanism investigations.

Table 4. Different *O*-alkynone Substrates [a]



[a]Reaction conditions: under N_2, **1** (0.2 mmol, 1.0 equiv.), $Ni(cod)_2$/(***S*)-BIDIME** (5 mol %), $ArB(OH)_2$ (0.4 mmol, 2.0 equiv.), LiOMe (0.5 mmol, 2.5 equiv.), dioxane/*t*BuOH(5:1, 1.2 mL), 60 °C, 12h. [b]Isolated yield. [c]Enantiomeric ratio (er) was determined by HPLC with Chiralcel columns. The absolute configuration of **2s-2ak** was assigned the same as **2a**.

Further evaluation for the compatibility of this method was carried out with different *O*-1,6-alkynones. Different phenyl groups were examined under the same conditions as above mentioned with the best ligand **(*S*)-BIDIME**. Different *O*-1,6-alkynones and aryl boronic acids were found accessible with excellent enantioselectivity and yield (**Table 4**, see details in SI). As summarized in **Table 4**, various *O*-1,6-alkynones bearing different substituents were successfully reacted with selected arylboronic acids, providing the functionalized tetrahydrofurans bearing chiral quaternary stereocenters of tetrasubstituted allylic alcohols **2s–2ak** mostly in high yields ((up to 91%) and excellent enantioselectivities (up to 95:5 er), and the absolute configurations of the obtained products **2s–2ak** were assigned the same as **2a**. Numerous *para*- and *meta*-substituted aromatic alkynes including either an electron-donating or electron-withdrawing one were converted into the desired products in good yields (72%–89%) with excellent enantioselectivities (**2s–2y**: 92:8–99:1 er). Also, the *para*-, *meta*-substituted aromatic ketones with electron-donating or electron-withdrawing one were found to give the tetrahydrofurans in good yields (72%–91%) with excellent enantioselectivities (**2f–2n**: 90:10–95:5 er). Benzyl ketone **1ag** was also tested, the results is good (88% yield, 90:10 er). Four arylboronic acids were examined, although *para*-Me- and *para*-OMe- substituted ones could lead to the products in high yields and enantioselectivities (**2ah**: 76% yield, 93:7 er; **2ai**: 79% yield, 92:8 er), *para*-Cl- and *meta*-F- ones gave the products in good yields with decreased enantioselectivities (**2aj**: 72% yield, 86:14 er; **2ak**: 77% yield, 87:13 er). All of the *ortho*- substituted aromatic substrates are not applicable to this transformation. In view of the decreased enantioselectivities of some *O*-1,6-alkynones and arylboronic acids, and the non-reactive substrates, it is interesting to find the exact underlying reason by further mechanism studies.

Totally, thirty-seven examples of hetero 1,6-alkynones were designed, synthesized and applied for this enantioselective Ni-catalyzed reductive *syn*-arylative cyclization with different aryl boronic acids for the construction of various tetrahydrofurans and pyrrolidines with chiral quaternary carbon stereocenters of tetrasubstituted allylic alcohols. The substrate scope was broad and versatile, and this method may find further utilizations in organo-medicinal chemistry and chemical biology.

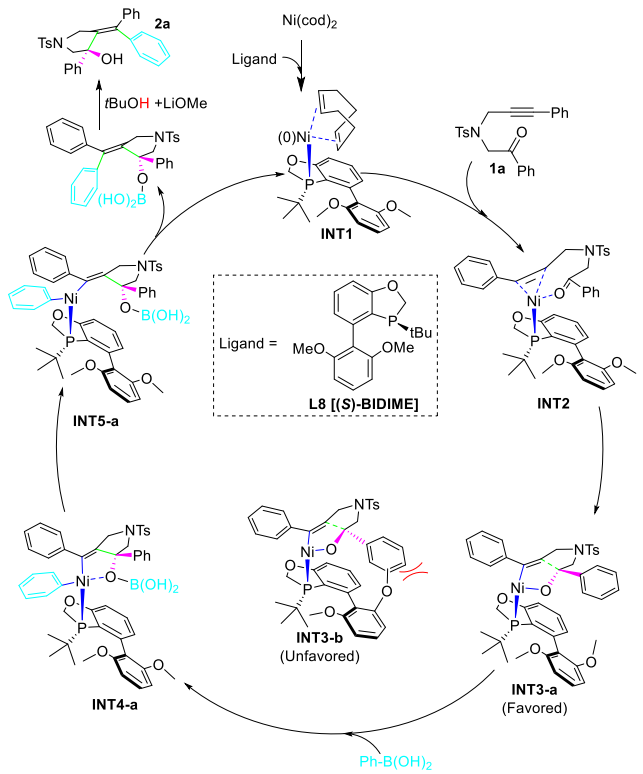


Figure 2. Proposed Mechanism and Stereochemical Model.

Mechanism Study. Based on our previous mechanism studies on Ni-catalyzed alkyne-ketone reductive cyclization,[17] referencing Xu, Lam and Liu's studies on Ni-catalyzed arylative cyclization,[14b,15a,15e] the mechanism of this enantioselective Ni-catalyzed reductive *syn*-arylative

cyclization of hetero 1,6-alkynones with aryl boronic acids was proposed (**Figure 2**). As shown in **Figure 2**, a catalytic cycle of enantioselective reductive cyclization of 1,6-alkynone **1a** with $Ni(cod)_2$ and **(*S*)-BIDIME** is monomeric metallacyclic model. Firstly, coordination of **(*S*)-BIDIME** with $Ni(cod)_2$ formed Ni(0) species **INT1**, and losing one cyclooctadiene. Then substrate **1a** reacted with Ni(0) species **INT1** by cycloaddition to provide Ni(II) metallacycle **INT2** The cyclization process was generated through the dimeric stage **INT2**, further provided Ni(II) metallacycle **INT3**. At this stage, the detailed stereochemical model of Ni(II) metallacycle **INT3**, presented two possible formation with opposite enantiomeric selectivity at tertiary C-O bond position. The enantioselectivity and stereoselectivity is apparently determined at this cycloaddition stage. Conformational analysis of metallacycle **INT3** with **(*S*)-BIDIME** indicates that the conformer **INT3b** is unflavored as its big steric hindrance between the phenyl group of the bicycle ring and the OMe- moiety of **(*S*)-BIDIME**, forming the stable conformer **INT3a**, which is favored, and further generate Ni(II) hydride species **INT4a** by transmetalation with $PhB(OH)_2$. Phenyl boronic acid played important roles as both an arylative reagent to form the aryl-nickel-alkene intermediate and a reductant to keep coordination and δ-bond metathesis and afford the borate intermediate **INT5a.** Finally, additive *t*BuOH and base LiOMe promoted the resulting **INT5a** to yield *syn*-arylative product **2a** by hydrolysis protonation with the *R* configuration, which is in accordance with the X-ray crystallography data mentioned above. The Ni(0) catalyst **INT1** was regenerated at the same time, and started new catalytic cycle then. One thing needs to be notified that the final proton hydrolysis is crucial for this transformation as the product could not be obtained without this step. This catalytic cycle reasonably explained the cause for the reaction discovery.

Computational studies[19] were investigated to gain more mechanistic insights into this Ni(0)-catalyzed enantioselective intramolecular *syn*-arylation cyclization (**Figure 3, 4**). Ni(0) transition states(**INT1**), as the catalytically active species for the reaction, might be formed after a ligand exchange step of $Ni(cod)_2$ with **(*S*)-BIDIME**. Afterward, Ni(0) moiety inserted into triple bond of substrate **1a** to form a Ni(II) complex (**INT2**). Two structural isomers of Ni(II) complexes were considered, in which the benzene ring of benzoyl group kept away from ligand (**INT2-a**) or closed to the methoxyl group of ligand (**INT2-b**). Computational results suggested that the formation of **INT2-a** is more favorable since **INT2-a** is 2.1 kcal/mol lower in energy than **INT2-b**. The geometrical inspections between **INT2-a** and **INT2-b** show that the Ni···O distance of **INT2-a** is considerably shorter than that of **INT2-b**, suggesting the coordination mode in **INT2-a** is more feasible than **INT2-b**.

Our DFT studies also showed that the following intramolecular nucleophilic cyclization is the key enantioselectivity-determining step. Notably, we located the transition state for this step (**Figure 3**). The cyclization proceeded from **INT2** into **INT3-a** through **TS1-a** with an activation free energy barrier of 15.6 kcal/mol and an exothermic free energy of -4.1 kcal/mol (**Figure 4**). For *path b*, the reaction occurred with a relatively higher activation free energy barrier of 20.2 kcal/mol and an exothermic free energy of -1.8 kcal/mol. The steric effect between the ligand and the substrate in both transition states might account for this preference. In the **TS** leading to the minor enantiomer (**TS1-b**), the unfavorable interactions between the benzene ring of benzoyl and the ligand leading to distortion of the substrate away from the ligand. Conversely, In the **TS** leading to the major enantiomer (**TS1-a**), the benzene ring of benzoyl was arranged to occupy the other side of the forming pyrrolidine ring, away from the ligand, which could effectively reduce strain between the ligand and the substrate. Thus, the bridgehead C···C distance of **TS1-a**, which is stabilized to 1.71 Å, is much shorter than that of **TS1-b**. Consequently, the formation of **TS1-a** is more favorable since **TS1-a** is 4.6 kcal/mol lower in energy than **TS1-b**, which is consistent with experimental result.

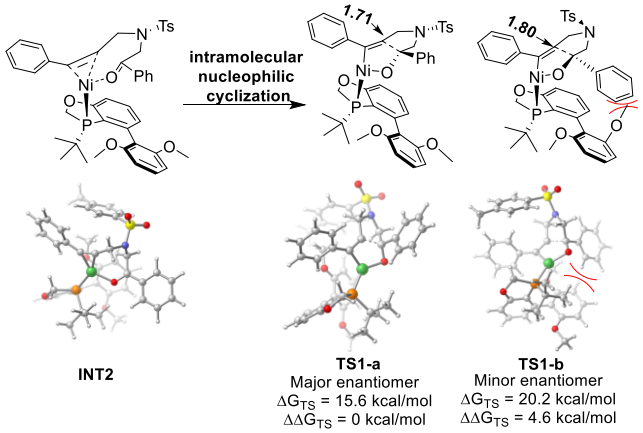


Figure 3. Comparrison of Transition States of Two Enantiomers with Ligand **(*S*)-BIDIME**.

The Ni(II) metallacycle then reacted with phenylboronic acid through an Intermolecular ligand exchange step to produce a new Ni(II) species. The relative free energy of **INT4-b** is 3.3 kcal/mol higher than that of **INT4-a**, which can also be attributed to strain repulsion between the phenyl group on the quaternary carbon centre and the phenyl group of the phosphine ligand. Subsequent reductive elimination rapidly afforded borate intermediate **INT5-a** via transition state **TS2-a** with a free energy barrier of 18.9 kcal/mol. And regenerated the Ni(0) catalyst, which reacted with **1a** to give **INT2** again, A similar process occurred from **INT4-b** into **INT5-b** via transition state **TS2-b** with a free energy barrier of 17.9

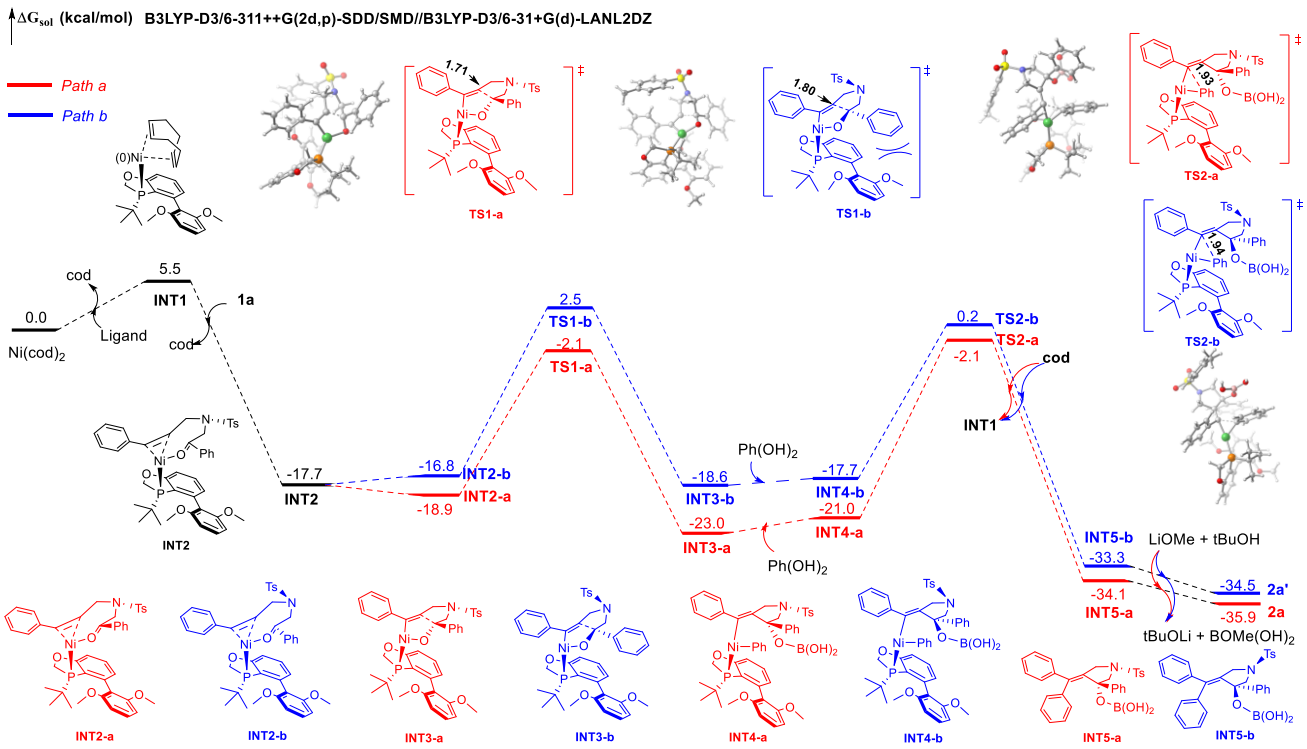


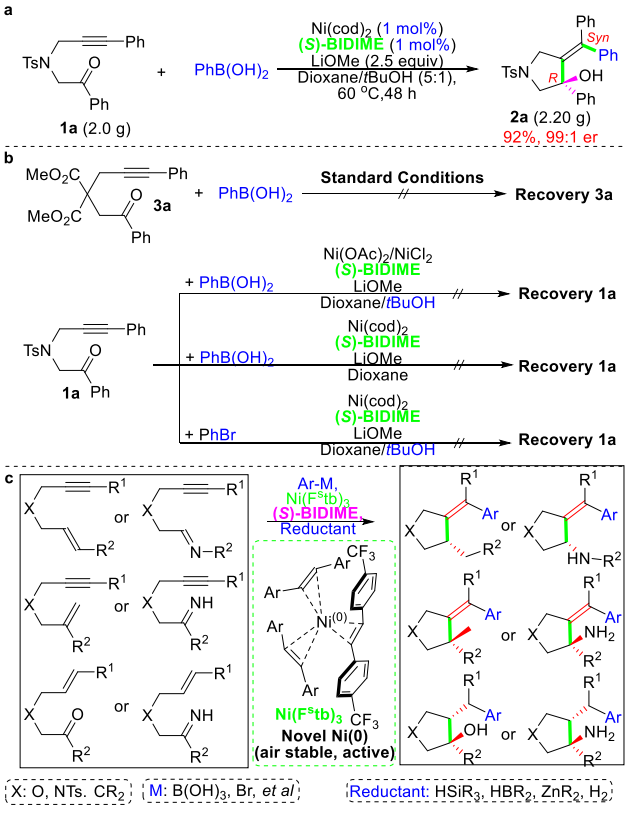
Figure 4. DFT Calculations with Energy Profiles for Mechanistic Pathway, Bond Lengths are Shown in Å..

kcal/mol. Finally, the result borate intermediate was protonated to yield product **3a** or **3b** in the presence of base LiOMe and additive *t*BuOH. A possible mechanistic pathway is depicted in Figure 4.

These reaction mechanism studies partly explain the peculiarities of our reaction. Firstly, proton hydrolysis is the key step for the reactivity. The proton solvent and base accelerate the hydrolysis process, which regenerated the active Ni(0) intermediate, finished the catalytic cycle to provide the desired product. Secondly, the limitation of 1,6-alkynones and boronic acids for *ortho*- substituted aromatic ones and others are possibly due to the steric hindrances of borate intermediate **INT4-a**. Neither the bulky aromatic alkynes nor bulky aromatic boronic acids could not form the transition state **INT4-a** successfully, thus halted the reactions. Thirdly, the enantio-controlled step was mainly rely on the firstly cyclization step, and minorly on the *syn*-arylative insertion step. Thus, the broad substrate tolerance of our previous enantioselective reductive cyclization might be applicable to this enantioselective Ni-catalyzed reductive *syn*-arylative cyclization in case of the optimization for various substitutes of alkynes and boronic acids. A system of reductive *syn*-arylative cyclizations are possibly be developed.

Application and design. With the successful development of this nickel catalyst, we are curious for its practicability of this enantioselective reductive *syn*-arylative cyclization process. Gram scale reaction was carried out starting from N-1,6-alkynone **1a**. As shown in **Scheme 2a**,

Scheme 2. Application and Design. a. Gram-scale Reaction. b. Control Experiments. c. New Reaction Design.



under optimized reaction conditions, a gram-scale *syn*-arylative cyclization of **1a** (2.00 g) was run with $PhB(OH)_2$ (2.0 equiv.) in dioxane/*t*BuOH(5:1) at 60 °C for 48 h in the presence of 1.0 mol% $Ni(cod)_2$ and **(*S*)-BIDIME** with Schlenk tube. Product 2a was obtained (2.20 g) in 92% yield, 99:1 er (**Scheme 2a**). There is no loss of its reactivity and enantioselectivity for this scaled up, which proved that this Ni-catalyzed enantioselective reductive *syn*-arylative cyclization process is practical and efficient. This is very important for the further application of this methodology in other fields.

Having established this successful synthetic methodology and clarified the ligand-control of the mechanism catalytic cycle, attention was then turned to explore how reactions operate in the presence of **(*S*)-BIDIME**, especially the elements for reactivity, stereochemical and enantiomeric control of the chiral product. Based on previous experiments, we reasoned that ligand activation of 1,6-alkynones must play a key role for this process. Several control experiments were carried on to confirm these hypotheses (**Scheme 2b**). Each experiment was run at the standard conditions as above. (1) With all carbon 1,6-alkynone **3a**, no reaction was found, and the starting material **3a** was recovered; this indicated that the substitution and electro-giving group of the substrate is not applicable for ligand activation. (2) Ni(II) precursors $Ni(OAc)_2$ or $NiCl_2$ was applied, ligand **(*S*)-BIDIME** is not enough to generate the active transitional intermediate, **1a** could not be converted to product smoothly, and was recovered. This is possibly due to that Ni(II) precursor could not directly activated alkynone **1a**. (3) Without proton solvent *t*BuOH, no reaction was found, and **1a** was recovered; indicated that both Ni(0) precursor and proton solvent play important roles for this catalytic cycle. (4) When arylative reagent was changed from $Ph(OH)_2$to PhBr, arylative cyclization could not be processed. Thus, we conclude that: while the *P*-chiral monophosphine ligand **(*S*)-BIDIME** and proton solvent is necessary for this Ni-catalyzed enantioselective cascade reductive *syn*-arylative cyclization of hetero 1,6-alkynones, special Ni(0) precursor and substrate is also needed, this reaction is somehow substrate dependent. Although Ni(II) catalyst is not suitable at this time, in view of versatile properties of *P*-chiral monophosphine ligand **(*S*)-BIDIME**, especially with in situ Ni(II) converted Ni(0) active precursor, we proposed that other transition metal precursors (such as Cu., Co., Pd. and Rh. *et al.*) accelerated with **(*S*)-BIDIME** type ligands, and assisted by suitable reductant would start up many new asymmetric reactions.

In case of clarified mechanism studies and many successful examples on the Ni(0)-catalyzed reductive cyclization reaction with *P*-chiral monophosphine ligand, fortunately noticed a newly reported air stable Ni(0)-olefin catalyst **Ni(^{F}stb)$_3$**.[20] we directly propose series of new reactions with **(*S*)-BIDIME** to further explore its applications in different asymmetric synthesis (**Scheme 2c**). Utilizing the newly precursor **Ni(^{F}stb)$_3$** and **(*S*)-BIDIME** with suitable arylative reagents and reductants, various new enantioselective cascade reductive *syn*-arylative cyclization reactions were designed. (1) Linked alkyne-alkene or alkyne-imine substrate is anticipated to construct five membered rings with chiral secondary allylic alcohols or amines of tetrasubstituted olefins. (2) Linked alkyne-alkene or alkyne-imine substrate could be used to synthesis of five membered rings with chiral all carbon quaternary stereocenters or tertiary allylic amines. (3) Linked alkene-ketone or alkene-imine substrate could be converted to five membered rings with two chiral stereocenters of tertiary allylic alcohols or amines. Multiple new arylative reactions might be discovered in view of various substrates and reductants, especially with the novel **Ni(^{F}stb)$_3$/(*S*)-BIDIME** catalyst system.

CONCLUSION

In summary, we have developed a highly enantioselective intramolecular reductive *syn*-arylative cyclization of hetero 1,6-alkynones with arylboronic acids as both the arylative reagent and the reductant catalyzed by a $Ni(cod)_2$ with *P*-chiral monophosphine ligand **(*S*)-BIDIME** applying the proton solvent *t*BuOH. Various pyrrolidines and tetrahydrofurans bearing a chiral quaternary carbon stereocenters of tetrasubstituted allylic alcohols were synthesized in high yields (up to 98%) and excellent enantioselectivity (up to 99:1 er). Totally thirty-seven examples were designed, synthesized and applied for this process successfully, and very broad substrate scope was realized as most of the hetero 1,6-alkynones could be converted to corresponding chiral complex multisubstituted pyrrolidines and tetrahydrofurans with *syn*-arylative tetrasubstituted allylic alcohols. The mechanism of this Ni(0)-catalyzed enantioselective intramolecular cascade reductive *syn*-arylative cyclization of hetero 1,6-alkynones was proposed, modified and confirmed by mechanistic studies with detailed DFT calculations. Computational studies gave clearly mechanistic insights of the catalytic cycle. The results confirmed that the cycloaddition stage Ni(II) metallacycle **INT3** and **INT4** is the enantioselective-determined steps, while ligand **(*S*)-BIDIME** played an important role for providing a large π-conjugated system and steric interactions, the hindrance of alkynone and arylboronic acid taken part in the reductive elimination, and proton solvent promoted the hydrolysis, thus processed excellent yield and enantioselectivity of the desired product. This method has been proved to be a practical pathway for concise synthesis of five-membered heterocyclics bearing chiral quaternary stereocenters of tetrasubstituted allylic alcohols as gram-scale preparation of the chiral pyrrolidine product **2a** was conducted using 1 mol% catalyst loading under optimized reaction conditions from *N*-1,6-alkynone **1a**, convinced the capability and scalability of this methodology. To the best of our knowledge, this is the first highly enantioselective Ni(0)-catalyzed cascade reductive *syn*-arylative cyclization of hetero 1,6-alkynones with aryl boronic acids

using proton solvent as key factor for efficient synthesis of pyrrolidines and tetrahydrofurans with chiral quaternary carbon stereocenters of tetrasubstituted allylic alcohols. Furthermore, this is also the first time detailed DFT calculations were applied in this type reaction of alkynones to clarify and confirmed the mechanism, which will guide the new reaction design and application. Application of *P*-chiral monophosphine ligands in organic synthesis has been proved to be an effective strategy for practical asymmetric transformations. The ligand applied in this study has high potential in many other cyclization reactions. Further exploration on more practical catalyst system, development of various efficient metal-catalyzed asymmetric reactions and chemical biological studies of obtained various chiral cyclized compounds are under investigation in our laboratory.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures and compound characterization (PDF)

X-ray crystallographic data for **2a** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We are grateful to the financial support provided by National Natural Science Foundation of China (22061032), Natural Science Foundation of Inner Mongolia (2020MS02022, 2022QN02005), Science and Technology Program of Inner Mongolia (2020GG0134), Opening-fund from State Key Laboratory of Bio-organic and Natural Products Chemistry of SIOC (21300-5206002), "JUN-MA" High-level Talents Program of Inner Mongolia University (21300-5185121), "Grassland Talents" Program of Inner Mongolia (12000-12102414) and High-level Recruit Program of Inner Mongolia (12000-13000603). Key Project at Central Government Level: the ability establishment of sustainable use for valuable Chinese medicine resources (2060302) is sincerely acknowledged. We gratefully thank Dr. He Meng (Inner Mongolia University) for NMR and HRMS assistance, Prof. Ning Zhu and Dr. Yuanyuan Gao (Inner Mongolia Technology University) for X-ray crystallographic assistance.

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(18) CCDC 2073755 contains the supplementary crystallographic data of **2a** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

(19) See SI for computational details. Substrate **1a** and $PhB(OH)_2$ were employed in computational studies.

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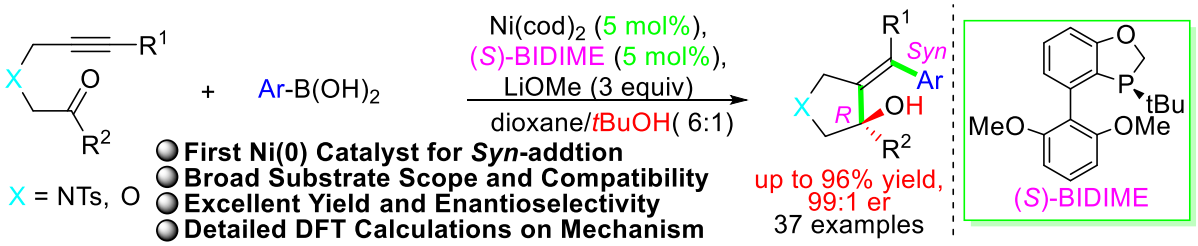

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